CRITICAL CARE PHYSIOLOGY

Robert H. Bartlett, M.D.
Professor of Surgery
University of Michigan Medical Center
1500 East Medical Center Drive
Ann Arbor, Michigan
## Critical Care Physiology

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Preface

Fat medical textbooks are often accompanied by a pudgy, pocket-sized small-print prose synopsis for instant reference by the student, resident, or practitioner. As the companion piece to "Critical Care Handbook" this book represents the opposite. Critical Care Handbook is a slim, pocket reference which contains only graphs, charts, tables, and algorithms which are essential for the management of critically ill patients. The Handbook contains no prose, no procedures, no discussion, and assumes a basic knowledge of pathophysiology. This book is the secondary companion piece, compiled to provide the explanations, references, methods, and other supportive information for the essentials presented in the Handbook.

This book is limited to discussion of four organ system (cardiovascular, respiratory, renal, and neurological) and four topics in integrative physiology (oxygen kinetics, fluid and electrolytes, host defenses, and metabolism/nutrition). The focus is specifically on monitoring and management. A basic knowledge of anatomy, normal physiology, and general medicine is assumed. ICU procedures, pharmacology, basic bioengineering, and ICU devices and artificial organs are referred to only briefly, with references to more complete descriptions. The topics are presented as background in support of information for the Critical Care Handbook as described above. The format is generally modeled after the scholarly and encyclopedic "Handbook of Physiology" published by the American Physiological Society. The format includes the assumption of appropriate basic knowledge, selected topics discussed in depth, methods of measurement, classic graphs, charts, and tables from the literature, minimum discussion and concise summary.

Unlike the Handbook of Physiology the facts presented, the interpretations, and the recommendations are the selections and opinions of a single author. Although there are surely more qualified experts on each topic, this presumptuous effort is justified by the fact that whole patient care requires an integrated approach favoring, for example, neither the lungs nor the kidneys, neither the pre-load nor the after-load. Critical care often requires decisions based on risk and benefits, observation, and experience. In this book dogmatic recommendations are based primarily on risks and benefits observed by the author over a period of 30 years. Because of this, many of the opinions and diagrams are based on our own published research, without apology.

Both the Critical Care Handbook and this accompanying text are intentionally over simplified and dogmatic. The methods of monitoring and management described here will be applicable to 95% of critical patient care. The justification for axioms and treatment recommendations is included in the text, but no attempt is made to include all the pertinent references or contrasting theories. There are several excellent exhaustive texts of critical care in which the literature is extensively reviewed. Critical Care Handbook is intended for practical use at the bedside, therefore the emphasis is entirely on physiology, pathophysiology, and macro physiologic management. Intracellular, subcellular, and molecular phenomena are discussed only as they relate specifically to whole organ and whole patient care. This is not to minimize the importance of molecular biology in critical illness, but there are other excellent textbooks, symposia, and entire journals devoted only to those topics. These books are focused on graphic presentations and algorithms based on the assumption that the physiology and pathophysiology of critical illness is best learned
and described through graphic presentation. Most of the graphs, figures, and tables in the Critical Care Handbook are original drawings by the author drawn from dozens of standard sources, usually without reference. For example, the oxyhemoglobin dissociation curves, Frank-Starling cardiac function curve, pulmonary compliance curves, etc. are presented without citing primary sources. The figures in the Critical Care Handbook were selected to be the most descriptive and most useful for quick reference in critical care. Many of the other classic presentations of critical care physiology are presented as figures in the accompanying text. For example a single graph of the bicarbonate buffer system is presented in the Handbook while several classic and common variations on this graph are presented in the text.

All of intensive care is based on measurement, and precise measurement of physiologic variables makes intensive care possible. In this book and in clinical practice, however, precise measurement is not necessary. For example it is not important to measure the arterial blood pressure to 3 decimal places, not even to single units, but it is important to know the blood pressure within about 5% of the precise value. The same is true of blood gases, chemical measurements, and calculated descriptors such as shunt fraction or vascular resistance. Consequently numerical values in this book are usually expressed as round numbers which are easy to remember, rather than precisely accurate numbers. For example normal arterial oxygen content is described as 20 cc/dL, although the precise value is closer to 20.5. Normal cardiac index is identified in graphs and tables as 3 l/m^2/min, although the accurate number is 3.2. Physiologic purists will note that my selection of important constants is, at times, arbitrary, and that conventional notation is sometime ignored. For example the amount of oxygen which 1 gm of hemoglobin can bind is given as 1.36 cc and the solubility coefficient for oxygen is given as .003 cc/mmHg/dL. Many measurements are expressed in terms which make the most sense in teaching the concepts, rather than in proper arithmetic form. In the example just given, oxygen solubility is expressed as cc of oxygen per unit of pressure per unit of volume, rather than k X mmHg^-1 X dL. Standard notation using a dot over a capital V to indicate volume per minute is usually ignored (as in VO2 or DO2), and some new shorthand is invented, particularly m to mean per square meter per minute. N is used to indicate the normal value on charts and graphs.

Although measuring is central to management of the critically ill patient, many of the values are relatively useless without normalizing the values to the size of the patient. For example a cardiac output of 4 L/min may represent shock for a large muscular man and luxuriant perfusion for a little old lady. Hemodynamic variables are usually normalized to body surface area - an unwieldy combination of height and weight which requires a table of values for reference. Drug doses and metabolic variables are usually normalized to kilogram of body weight without regard to relative amounts of fat, water, or lean body mass. Although both of these methods of normalizing are imperfect, they are necessary, particularly when writing a book intended to describe pathophysiology for all adults. Another common approach is to describe physiologic variables as they would be found in a typical 70 kg lean, healthy young man. All of these methods of normalization and example are used in this book.
The emphasis in this two-volume set is clearly on the Critical Care Handbook. Critical Care Physiology merely serves to provide explanation and expansion for the interested reader. Comments, suggestions, and corrections are welcomed by the author.
CHAPTER 1: Oxygen Kinetics: Integrating Hemodynamic, Respiratory, and Metabolic Physiology

Monitoring and management of critically ill patients is an exercise in applied physiology and pharmacology made possible through applied bioengineering. The intensive care unit affords the possibility to monitor a wide variety of physiologic variables continuously, and to use that information to prevent and treat organ failure. Central to the intelligent use of this information is an understanding of homeostatic physiology: integrated cardiac, respiratory, and metabolic physiology (oxygen kinetics), hemodynamics, respiratory physiology, nutrition and metabolism, renal pathophysiology, fluids and electrolytes and host defenses.

Figure 1.1: Oxygen Kinetics. Oxygen Delivery (DO2) is the product of cardiac output (CO) X arterial oxygen content (CaO2). Oxygen delivery is normally 4-5 X oxygen consumption (VO2). m = per minute per square meter

Oxygen Consumption (VO2): The fire of life is maintained by the continuous oxidation of chemical substrates, consuming oxygen and producing carbon dioxide in the process. The oxygen consumed in this process of metabolism is expressed as the volume of oxygen per minute (VO2). VO2 is normally 100-120 cc/m²/min, or 200 cc/min for a typical adult. Resting VO2 is a function of the metabolizing body cell mass, with fine tuning control provided by the level of thyroid and catecholamine hormones and governed by a poorly understood metabolic controller in the hypothalamus. VO2 decreases under conditions of hypothermia, paralysis, and hypothyroidism. VO2 increases during exercise or other muscular activity, hyperthermia, profound hypothalamic injury, hyperthyroidism, catecholamines, and inflammatory mediators, particularly the interleukin cytokines. Metabolism of different organs proceeds at different rates depending on the cell mass and cellular activity, so systemic VO2 is affected to some extent by changes in regional blood flow. Under steady state conditions the amount of oxygen consumed in systemic metabolism is exactly equal to the amount of oxygen taken up in the pulmonary capillaries via the airway (Fick's axiom). This is true regardless of the status of pulmonary function or dysfunction, so we measure VO2 across the lung and assume that this is exactly the amount consumed in systemic metabolism. The efficiency of oxygen uptake across the lung is controlled by the match between perfusion and inflation of alveolar units. As long as normally perfused alveoli are inflated and contain gas with an oxygen concentration of 20% or higher, the perfusate blood will be fully oxygenated.

Measurements of VO2

Assuming Fick's axiom to be correct, oxygen consumption during metabolism in body tissues can be measured in three ways: 1) closed circuit re-breathing, 2) open circuit mixed expired gas analysis, and 3) calculation of arteriovenous oxygen content difference times cardiac output. Closed circuit re-breathing volumetric spirometry is the gold standard method for measurement of oxygen consumption. The subject breaths in and out of a low resistance spirometer equipped with a CO2 absorber. As oxygen is absorbed the volume loss in the closed system can be measured. Oxygen consumption is measured over 5-10 minutes, averaged, and results reported as oxygen consumption per minute after ATPS to STPD conversion. Since the measurement is a direct volumetric measurement any small leak in the system will result in major errors in measurement, therefore this technique can not be used on a patient with a bronchopleuro cutaneous fistula, for
Figure 1.1: Oxygen kinetics. Oxygen delivery (DO2) is the product of cardiac output (CO) X arterial oxygen content (Ca). Oxygen delivery is normally 4-5 X oxygen consumption (VO2). m = per minute per square meter.
example. Complete closure at the mouth and nose is essential. The technique is excellent for intubated patients in whom the airway is totally controlled.

Figure 1.2: Three methods of measuring oxygen consumption. A. Closed circuit re-breathing volumetric spirometry. B. Mixed expired gas analysis. C. Fick equation

The second method of measuring oxygen consumption is by measuring the concentration of oxygen in inspired and expired gas and multiplying the difference times the minute volume. This method requires precise measurement of oxygen concentration in mixed expired gas, precise measurement of exhaled minute volume, and precise measurement (or assumption) of inspired oxygen concentration. Because inspired oxygen concentration is known and constant when the subject is breathing air, mixed expired gas analysis is ideally suited for air breathing patients, during physiologic studies of exercise for example. For the same reason this technique is not well suited for patients who require supplemental inspired oxygen because a very small error in maintaining the constancy or measuring the concentration of inspired oxygen (50.5 versus 51%, for example) can result in large errors in VO2 calculation. Another variable affecting the accuracy of this technique is that the breath-by-breath volume of inspired versus expired gas can be slightly different because the amount of CO2 exhaled may not be exactly equal to the amount of oxygen absorbed from each breath. If the ratio of CO2 produced to oxygen consumed (the respiratory quotient, RQ) is 1.0, then the inhaled and exhaled volumes will be exactly equal hence measuring the exhaled volume alone exactly predicts the inspired volume. However, if the patient is hyperventilating and CO2 production exceeds oxygen consumption, or if the patient is primarily metabolizing fat and the RQ is 0.7, then measuring the exhaled volume alone does not exactly predict the inspired volume from which oxygen was consumed. This problem can be dealt with in one of three ways: assume a constant RQ of 0.8, measuring inspired and expired nitrogen concentrations and correcting minute ventilation assuming that the amount of nitrogen inspired and expired per minute is exactly equal, or assume the RQ is 1.0 and ignore the artifact. In practice the third option is usually followed because the error associated with not correcting for RQ is small. Values are measured ATPS and converted to STPD. When using mixed expired gas analysis VC02 is measured as well as VO2, and RQ is calculated. The RQ should be close to 1.0 to prove that a steady state without hyperventilation existed during the period of measurement (or, the RQ should correspond to the physiologic conditions, such as 0.7 during starvation).

The third method of VO2 measurement is a variation of the Fick equation using the arteriovenous oxygen content difference times the cardiac output measured by thermal or indicator dilution. This method requires accurate measurement of oxygen content in both arterial and mixed venous blood, hence is possible only in patients who have a pulmonary artery catheter in place. Since the measurement of indicator dilution cardiac output is ± 5% at best, and the measurement of arterial and venous oxygen content is ± 5%, the range of error of VO2 calculation using this method is ± 10% at best. Consequently this method is the least accurate and it is used only for rough estimates of VO2 or in circumstances such as large air leaks where closed circuit or mixed expired gas analysis methods can not be used. Because the constants used for calculation of oxygen content from PO2 and saturation are expressed in STPD units, further conversion is not necessary. Whatever
Figure 1.2: Three methods of measuring oxygen consumption. A. Closed circuit-rebreathing volumetric spirometry. B. Mixed expired gas analysis. C. Fick equation
A method is used to measure oxygen consumption, it is important to remember that normal values and calculations are always based on STPD conditions. Conversion from ATPS to STPD may decrease the volume by 15-20%, so careful attention to accurate measurement of temperature and humidity is important.

There are several simple methods for checking the accuracy of VO2 measurements. The RQ should be close to 1.0, or correspond to expected physiologic variations, as mentioned above. Steady state should be assured by checking VO2 measurements each minute during a 5 or 10 minute collection period. Minute to minute variations should be less than 5%. VO2 should correspond to the observed physiologic state. For example if a normothermic sedated patient at rest has a measured VO2 50% above normal levels there is probably a leak in the system or an error in calculation. This can be further checked by calculation of the ventilation equivalent for oxygen or CO2. Under most conditions minute ventilation will be 2.5 to 4 liters for each 100 cc of oxygen consumed or CO2 produced. If the ventilation equivalent for oxygen or CO2 is outside this range an error in measurement is likely. Measurement of VO2 and VCO2 can be done very simply in mechanically ventilated patients by accurately measuring minute ventilation and collecting samples of mixed inspired and mixed expired gas, then measuring oxygen and CO2 concentration in any standard blood gas machine. If all the variables and potential errors mentioned above are accounted for, this method of analysis gives very accurate information at little cost. It is also possible to buy and use very expensive "metabolic carts" which do essentially the same thing.

Once the VO2 is accurately measured it is used in three ways: to determine if the patient is hyper or hypo metabolic, to determine and regulate the relationship between oxygen delivery and oxygen consumption, and to calculate the caloric expenditure of metabolism. Normal VO2 is 100-120 cc/m2/min or 3-5 cc O2/kg/min. VO2 above this range in a resting non-exercising subject indicates active inflammation, usually infection. Changes in metabolism are followed by compensatory changes in oxygen delivery to maintain a DO2 ratio of 5:1. In order to interpret whether oxygen delivery is adequate, inadequate or excessive, it is necessary to know both DO2 and VO2. This is discussed in detail below. VO2 measurement can be converted to the caloric equivalent of substrate for purposes of nutritional planning through calculations known as indirect calorimetry. This is discussed in detail in Chapter 4. A quick summary of the relationship is: 5 kilo calories worth of energy substrate is metabolized for each liter of oxygen consumed.

**Oxygen Delivery (DO2):** Oxygen is delivered from the lung to the systemic tissues via the blood. The amount of oxygen that is delivered to peripheral tissues is the product of the oxygen content in arterial blood times the cardiac output.

![Figure 1.3: Schematic representation of the distribution of oxygen in blood. The amount of oxygen bound to hemoglobin is represented in the flask, in equilibrium with the amount of oxygen dissolved in plasma represented as the small graduated cylinder. (From Bartlett Surgery Annual, 1971).](image)

Normally the oxygen content of arterial blood (CaO2) is 20 cc/dL, and the normal cardiac index (CI) is 3.2 L/m2/min, 5 L/min for a typical adult. Therefore the normal systemic oxygen delivery (DO2) is 20 cc/dL X 50 dL/min = 1000 cc/min.
Figure 1.3: Schematic representation of the distribution of oxygen in blood. The amount of oxygen bound to hemoglobin is represented in the flask, in equilibrium with the amount of oxygen dissolved in plasma represented as the small graduated cylinder. (From Bartlett Surgery Annual, 1971).
Figure 14: The amount of oxygen in blood can be expressed as oxygen content, PO2, or saturation of hemoglobin. In this figure all three measurements are applied to blood ranging from normal (hemoglobin 15 gm/dL) to anemia (hemoglobin 7.5 gm/dL) to plasma (hemoglobin 0). The typical values for normal arterial (A) and venous (V) blood are shown. Notice that PO2 and saturation are normal in anemic blood even though oxygen content is severely decreased.

Although oxygen content is the most important measure of oxygen in blood, PO2 and oxyhemoglobin saturation are more commonly measured in the intensive care unit, hence it is necessary to convert between these measurements. Each gram of hemoglobin can bind 1.36 cc's of oxygen. If the hemoglobin of the blood is normal (15 g/dL) and the hemoglobin is 100% saturated, the amount of oxygen bound to hemoglobin is 20.4 cc/dL. In addition, a small amount of oxygen is physically dissolved in the water which makes up plasma and red blood cells. The solubility coefficient for oxygen is .0031 cc/torr/dL and therefore the amount of oxygen dissolved in 1 dL of blood at PO2 100 torr is 0.3 cc's, making the oxygen content of normal arterial blood 20.4 + 0.3 = 20.7 cc/dL, conveniently rounded off to 20 cc/dL. Through the same arithmetic, the oxygen content of venous blood (CvO2) is 16 cc/dL hence the normal arterial-venous difference is 4 cc O2/dL. The relationship between PO2, saturation, and oxygen content for different concentrations of hemoglobin is shown in Figure 1.3 and 1.4. Notice that the PaO2 and saturation are the same for anemic arterial and venous blood even though the oxygen content is severely decreased.

Measuring Oxygen in Blood: The most common method of measuring oxygen in blood is to measure the partial pressure of oxygen (PO2) in a blood gas machine. Blood gas machines use a system referred to as the Clark electrode developed by Leland Clark over 30 years ago. The principle of the Clark electrode is that the flow of electrical current in a platinum wire is proportionate to the concentration of oxygen. The Clark PO2 electrode includes a platinum cathode and a silver chloride anode held in a KCl solution and encased in glass and covered with a plastic membrane which is permeable to oxygen. When a gas or fluid containing oxygen is applied to the membrane and allowed to come into equilibrium, the resulting current flow can be used to determine the oxygen concentration in the sample when the entire device has been calibrated against known standards. The Clark electrode is accurate ± 1%.

The oxyhemoglobin saturation is measured with an infrared spectrophotometer. Infrared light with two or three specific wave lengths is shined into the blood sample and the amount of reflected light is measured. The wave lengths are chosen to represent a point at which reduced and oxygenated hemoglobin have the same absorbance used as the reference point, and another wave length at which the absorbance of reduced and oxygenated hemoglobin is widely divergent. Accuracy over the full range of absorbance can be further assured by using a third or fourth wave length. The spectrophotometer can be calibrated against an internal standard and does not require separate blood or fluid calibration however there is a tendency to drift in most spectrophotometers so that the calibration should be reset fairly frequently. The spectrophotometer is used to measure the amount of saturation basically by examining the color of the reflected light. By examining the intensity of reflected light the total amount of hemoglobin can be measured. In addition by using other infrared wave lengths the amount of carboxyhemoglobin or methemoglobin can also be measured. Spectrophotometers which make these measurements are referred to as oximeters.
Figure 1.4: The amount of oxygen in blood can be expressed as oxygen content, PO2, or saturation of hemoglobin. In this figure all three measurements are applied to blood ranging from normal (hemoglobin 15 gm/dL) to anemia (hemoglobin 7.5 gm/dL) to plasma (hemoglobin 0). The typical values for normal arterial (A) and venous (V) blood are shown. Notice that PO2 and saturation are normal in anemia blood even though oxygen content is severely decreased.
Oximeters are available using fiberoptic technology to measure the saturation continuously in arterial or venous blood using fiberoptic equipped catheters attached to external spectrophotometers. These devices have proven to be exceptionally valuable for critical care, particularly when applied to continuous mixed venous oximetry. Another very useful variation on continuous oximeter is the application of infrared light to capillary beds in the fingers, toes, or ear lobes. The absorption of infrared light when applied in this fashion shows considerable variation ranging from arterial to venous blood in the capillaries. If the device is programmed with a microchip to display only the highest levels of saturation which occurred during systole when arterial blood surges into the capillaries, the device can be used to provide a reasonable estimation of arterial blood saturation. Devices of this type are referred to as pulse oximeters and the value displayed is commonly referred to as $SpO_2$. Although any factor which minimizes peripheral perfusion can cause artifacts in $SpO_2$ measurement, this monitoring technique is still very valuable for detecting extreme hypoxia or poor peripheral blood flow, and for gross adjustments in mechanical ventilator or supplemental oxygen management. The range of error of the best blood oximeters is $\pm 2\%$ and the range of error of pulse oximeter compared to actual arterial blood saturation is $\pm 5\%$. It is important to note that blood saturation can be calculated based on $PO_2$, PH, and temperature if all three variables are known. Oxyhemoglobin saturation calculated in this fashion assumes that the oxyhemoglobin dissociation curve is normal, which is often not the case in critically ill patients. Consequently reports of oxyhemoglobin saturation on many blood gas machines are simply calculations and may be in considerable error. If saturation is used to calculate oxygen content or to adjust mechanical ventilators or oxygen treatment the saturation should be directly measured with an oximeter rather than calculated from $PO_2$ values.

The measurement of oxygen content is by far the most important measure of oxygen in blood but is the most difficult, therefore the most rarely performed. The classical method for measuring oxygen content is to displace all the oxygen from a precisely measured aliquot of blood through a combination of vacuum and strong reducing agents. The gas thus liberated includes oxygen, CO2 and nitrogen. The total volume of gas is measured then CO2, then oxygen are selectively removed, and the volume of each can be determined by subtraction. This methodology is extremely tedious, time consuming and operator-dependent. It is the method known as the Van Slyke method, with variations designed and described by Sholander, Natelson, and others. The range of error by a very experienced operator is $\pm 3\%$. Direct measurement of oxygen content measured in this fashion is almost never utilized in modern critical care. A second method for direct measurement of oxygen content is the fuel cell. In this system a precisely measured aliquot of blood is exposed to vacuum, oxygen is released and consumed in an oxidative process which results in an electrical signal proportional exactly to the amount of oxygen liberated from the blood. The original fuel cell system was produced by Lexington Instruments and called the Lex-O-Con. Although the fuel cell method is much easier and as accurate as the Van Slyke method, it is still difficult, operator-dependent, and rarely utilized. Because of these difficulties of measurement, even though oxygen content is by far the most important measure of the amount of oxygen in blood, it is almost always calculated from other measurements, rather than measured directly. Oxygen content is calculated by measuring the total hemoglobin in grams per deciliter, the amount of hemoglobin which has oxygen bound to it using an oximeter, and measuring the $PO_2$ of
oxygen dissolved in plasma. These quantities are converted to cc of oxygen using the constants described above, with the final value reported as oxygen content. Realizing that the range of error of PO2 measurement and hemoglobin measurement and saturation measurement is considerable, the numbers derived for oxygen content in this fashion are accurate ±5%.

**Estimating O2 Delivery**

Despite the range of error in all the various measurements mentioned above, it is still very valuable to calculate systemic oxygen delivery in critically ill patients. This is done by measuring hemoglobin and saturation, calculating content (usually ignoring the dissolved fraction if the PO2 is less than 100), then multiplying arterial oxygen content times cardiac output. This calculation gives the oxygen delivery in cc of oxygen per minutes with a range of error ±15%. All physiologic variables should be normalized to body size. By convention oxygen delivery and consumption measurements are normalized to body surface area. To accomplish this the arterial oxygen content is multiplied by cardiac index to give cc of oxygen delivery per minute per m². The normal value is 600. In the graph shown in Figure 1.5, oxygen delivery has been calculated and displayed for a wide range of hemoglobin concentration and cardiac index measurements. The normal point is shown as cardiac index 3 L/m²/min and oxygen delivery 600 cc/O2/m²/min.

Figure 1.5 Estimating oxygen delivery. When the cardiac index and hemoglobin or hematocrit is known, and if the arterial saturation is close to 100%, the systemic oxygen delivery can be quickly estimated using this graph.

Definitions and formulas related to oxygen kinetics are summarized in Table 1.1.

**Autoregulation to Maintain DO2:** The relationships between VO2 and DO2 represent one of the most interesting autoregulation systems in hemostasis. First of all, if one of the three components of oxygen delivery is abnormal, endogenous mechanisms regulate the other two until normal oxygen delivery has been restored. These relationships are shown in Figures 1.6 and 1.7.

Figure 1.6: Oxygen delivery is normally maintained at a level 4 - 5 times above oxygen consumption by changes in endogenous cardiac output. In this figure typical changes in cardiac output to maintain normal delivery in the presence of other variables are demonstrated. The relationships are shown for normal metabolism (DO2=600 ccm) and hypermetabolism (DO2=1200 ccm). Line1 shows the increase in cardiac index required for an increase in VO2 or energy expenditure. Line 2 shows the change in cardiac index required to maintain normal oxygen delivery in the face of progressive hypoxia. Line 3 shows the change in cardiac output required to maintain normal oxygen delivery during progressive levels of anemia.

In compensation for acute hypoxia or acute anemia, (Figure 1.6) cardiac output increases, but only until normal oxygen delivery is re-established. In chronic hypoxia the red cell mass increases until systemic oxygen delivery is normal at normal cardiac output. The mechanism is by generation of erythropoietin from the kidney. In chronic anemia cardiac output increases and remains increased. The mechanism is primarily related to a change in viscosity while arterial tone remains constant. When cardiac output is decreased there is no mechanism to induce super oxygenation or polycythemia. The mechanism in this situation is that oxygen consumption generally continues at the
Figure 1.5: Estimating oxygen delivery. When the cardiac index and hemoglobin or hematocrit is known, and if the arterial saturation is close to 100%, the systemic oxygen delivery can be quickly estimated using this graph.
Figure 1.6: Oxygen delivery is normally maintained at a level 4 - 5 times above oxygen consumption by changes in endogenous cardiac output. In this figure typical changes in cardiac output to maintain normal delivery in the presence of other variables are demonstrated. The relationships are shown for normal metabolism (DO2=600 ccm) and hypermetabolism (DO2=1200 ccm). Line 1 shows the increase in cardiac index required for an increase in VO2 or energy expenditure. Line 2 shows the change in cardiac index required to maintain normal oxygen delivery in the face of progressive hypoxia. Line 3 shows the change in cardiac output required to maintain normal oxygen delivery during progressive levels of anemia.
TABLE 1.1

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<td>CaO₂</td>
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</tr>
<tr>
<td>CvO₂</td>
<td>Oxygen content, venous</td>
</tr>
<tr>
<td>AVDO₂</td>
<td>Arterio-venous oxygen difference</td>
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<tr>
<td>DO₂</td>
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<tr>
<td>VO₂</td>
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<tr>
<td>VCO₂</td>
<td>CO₂ produced</td>
</tr>
<tr>
<td>REE</td>
<td>Resting energy expenditure</td>
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Oxygen Content = (Hbgm/dl X %sat X 1.36 cc/gm) + (pO₂ X .003 ccO₂/mmHg/dl)

Oxygen Delivery = CaO₂ X cardiac index

Fick's Axiom: O₂ consumed via lung = O₂ consumed in metabolism

CaO₂ or CvO₂ = Oxygen Content = ccO₂/dl = O₂ bound to Hb + O₂ dissolved

  O₂ bound to Hb = Hbgm/dl x % sat x 1.36 ccO₂/gm

  O₂ dissolved = pO₂ x .003 ccO₂/mmHg/dl

AVDO₂ = CaO₂ - CvO₂
normal rate of metabolism, and relatively more oxygen is extracted from the flowing
blood, widening the AVO2 difference. (Figure 1.7)

Figure 1.7: The shaded area shows compensation for decreasing cardiac output by increasing the amount of oxygen extracted from each deciliter of flowing blood. Relationships are shown for normal metabolism, \( \text{VO}_2 = 120 \text{ cc}/\text{m}^2 \). Normally only 20% of oxygen is extracted, leaving the venous blood 80% saturated. Increased extraction of oxygen can compensate for low blood flow without physiologic side effects until the ratio of delivery to consumption is decreased to 2:1 or less. At 2:1 ratio the venous blood will be 50% saturated.

The various combinations of these compensatory mechanisms supply adequate oxygen for systemic metabolism through a wide range of variations in oxygen delivery. If oxygen delivery can not be maintained at a level at least twice the oxygen consumption, an unstable state results, described below.

**Autoregulation for Changing VO2:** When there is a change in metabolic rate there is a proportionate change in DO2 which occurs almost immediately, mediated completely by a change in cardiac output. For example, if we go from rest to mild exercise VO2 doubles, followed promptly by an increase of cardiac output (Figure 1.8), re-establishing the ratio of delivery to consumption at approximately 5:1. The mechanism which mediates this change in cardiac output is not fully understood but is probably related to a chemoreceptor on the venous side of the circulation and vasodilation in working muscles. This autoregulation occurs whether the change in VO2 is up or down, and whether it is caused by fever (Fig. 1.9) or exercise, sepsis, catecholamines or other mediators (Fig. 1.8).

Figure 1.8: Change in VO2 (and compensatory change in DO2) related to typical conditions which affect critically ill patients.

Figure 1.9: Change in VO2 (and compensatory change in DO2) related to a change in body temperature.

**Autoregulation for Changing VO2 with Exercise:** As shown in Figure 1.8, conditions causing hypermetabolism in critically ill patients might increase the metabolic rate 20,30,50, or very rarely 100% above normal baseline. Contrast this change in metabolism to the changes associated with exercise. Oxygen consumption doubles with very mild exercise, such as walking. With vigorous exercise oxygen consumption increases 10-20 times normal. As in critical care conditions as outlined above, cardiac output increases as metabolic rate goes up to maintain the ratio of delivery to consumption at 5:1. When the cardiac output has reached maximum, further compensation for increased activity is made up by increased peripheral extraction of oxygen down to venous saturation levels as low as 20%. Maximal oxygen consumption during exercise to the point of exhaustion is referred to in the exercise physiology literature as "VO2 max" and is the method by which being "in shape" is measured. This is somewhat of a misnomer because the limiting factor is not the maximal amount of oxygen consumption but rather the maximal cardiac output which can be generated in response to elevated VO2. In a trained runner VO2 at rest is 0.1 L/m²/min, and VO2 max might be 20 L/m²/min. In a frail patient with cardiac disease resting VO2 might be 0.1 L/m²/min and VO2 max 0.3 L/m²/min. These relationships are shown in Figure 1.10.
Figure 1.7: The shaded area shows compensation for decreasing cardiac output by increasing the amount of oxygen extracted from each deciliter of flowing blood. Relationships are shown for normal metabolism, \( (V_O2=120 \text{ cc/m}^2) \). Normally only 20% of oxygen is extracted, leaving the venous blood 80% saturated. Increased extraction of oxygen can compensate for low blood flow without physiologic side effects until the ratio of delivery to consumption is decreased to 2:1 or less. At 2:1 ratio the venous blood will be 50% saturated.
Figure 1.8: Change in VO2 (and compensatory change in DO2) related to typical conditions which affect critically ill patients.
Figure 1.9: Change in VO₂ (and compensatory change in DO₂) related to a change in body temperature.
Autoregulation for Changing DO2: Conversely, a primary change in oxygen delivery is not followed by any change in oxygen consumption, nor would we expect VO2 to change since there is nothing in the list of controllers of metabolism that includes systemic oxygen delivery. However it is obvious that oxygen consumption can not exceed oxygen delivery, and if DO2 fell below the level of VO2, VO2 would become supply-dependent. In theory this situation would occur when the ratio of delivery to consumption is below 1:1. In actuality, this condition of supply dependency of VO2 occurs when the DO2 falls below twice VO2, i.e. supply dependency occurs when the ratio of DO2 to VO2 is less than 2:1. This relationship is shown in Figure 1.11 which demonstrates the biphasic nature of the VO2/DO2 relationship.

When a state of supply dependency exists, anaerobic metabolism occurs, the patient develops an oxygen "debt", hemodynamic instability eventually results, and if the situation proceeds long enough progressive organ failure occurs and the patient can be said to be in a state of circulatory, ischemic, or hypoxic shock. The same relationships exist when VO2 is elevated during hypermetabolism as shown in Figure 1.12.

Supply dependency exists during hypermetabolism whenever the DO2/VO2 ratio is less than 2:1, although during hypermetabolism this occurs at a higher level of actual DO2 than it does during normal metabolism. The primary goal of intensive care management is to estimate or determine the VO2 and DO2, to maintain the patient near the normal ratio of 5:1, and, if oxygen delivery fails, to intervene before the ratio reaches the critical low level around 2:1.
Figure 1.10: Oxygen consumption and cardiac output compensation during exercise compared to conditions encountered in critical illness. In this example the maximum cardiac output is five times resting level.
Figure 1.11: The normal relationship between VO2 and DO2. The normal point (A) is shown as VO2 120 cc/m²/min and DO2 600 cc/m²/min. If DO2 is increased by transfusion (B) VO2 remains constant. If DO2 is progressively decreased, (A → C) VO2 remains constant until the ratio of DO2/VO2 falls below 2:1. (C → D)
Figure 1.12: DO2/VO2 relationships during normal metabolism (as in Figure 1.11 above), and during hypermetabolism. During normal, hypo or hyper metabolic states the normal ratio of delivery to consumption is 5:1. This results in 80% venous saturation if the arterial blood is 100% saturated. The isobar for the 5:1 ratio is demonstrated in this diagram, as well as the isobar for 4:1, 3:1, and 2:1 ratios. Corresponding levels of venous saturation are shown. A state of decreasing oxygen consumption in which consumption is supply dependent occurs when the ratio is less than 2:1.

**OXYGEN CONSUMPTION/DELIVERY AND SHOCK**

<table>
<thead>
<tr>
<th>DO2/VO2 Ratio</th>
<th>V Sat</th>
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</thead>
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<tr>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
</tr>
</tbody>
</table>

(if Sa = 100)
Figure 1.13: Interpreting the DO2/VO2 diagram. In this diagram the relationships shown in Figure 1.11 and 1.12 are demonstrated without specific numerical values to emphasize the difference between normal relationships, utilization of oxygen delivery reserves, and
(This measurement must be made in mixed venous blood since the relative extraction by organs served by the superior and inferior vena cava and coronary sinus are quite different.) If 80% SvO2 corresponds to a 5:1 ratio, then 75% corresponds to 4:1, 66% to 3:1, 50% to 2:1, and so on. As long as the arterial blood is fully saturated, this observation holds true regardless of the absolute level of DO2 or VO2, as shown in Figure 1.12. If the arterial blood is less than fully saturated, the difference between arterial and venous saturation corresponds to the oxygen extraction, hence the DO2/VO2 ratio. For example if the arterial blood were 80% saturated and the venous blood were 64% saturated the ratio would be 5:1.

All of these inter-relationships were originally pointed out by Fick in 1870. Fick’s axiom is that oxygen consumption via the airway is equal to that in peripheral tissues. His equation for calculating cardiac output is CO = VO2 divided by AVO2, which can also be expressed as AVDO2 times cardiac output equals VO2.

In critically ill patients VO2 may be elevated or depressed, but slight to moderate elevation in VO2 is the most common abnormality in critically ill patients. VO2 will be elevated in proportion to the amount of inflammation (either bacterial or sterile, as in burns and pancreatitis). A febrile patient with significant signs of septic toxicity will typically have VO2 1.5 times normal. (Fig. 1.8) It is very unusual for a critically ill patient to experience VO2 greater than twice normal. This occurs only in situations of severe muscular exercise such as seizures or tetanus. VO2 is decreased in critically ill patients who are hypothermic. In critically ill patients, just as in the normal state, a change in VO2 is followed promptly by a proportionate change in DO2. It is “normal” for a hypermetabolic patient to have a high cardiac output and pulse rate, i.e., to be “hyperdynamic”.

Rarely the hyperdynamic response exceeds the increase in VO2, reflected in a ratio higher than 5:1 and venous saturation greater than 80%. This situation can occur when a large arteriovenous fistula is present, either from direct vascular communication or through hyperperfusion of tissues such as occurs in portal hypertension with excessive perfusion of the splanchnic viscera. Perfusion of non-metabolizing tissue such as re-establishing flow to a long-ischemic leg or "successful" cardiac resuscitation after a long cardiac arrest will result in venous saturation over 90%. Rarely, this phenomenon is seen after cellular poisoning as in carbon monoxide cytochrome intoxication or end-stage sepsis. Abnormally high venous saturation also occurs when normal oxygen delivery is maintained during hypothermia, such as cardiopulmonary bypass for cardiac surgery.

Some patients can not mount an increased DO2 in response to increased VO2, because of any combination of hypoxia, anemia, and myocardial failure. If this occurs, then the DO2/VO2 ratio will be less than 5:1, AVO2 difference widens, SVO2 falls, the amount of oxygen extracted from each deciliter of blood increases and the patient is using up the systemic oxygen reserves. This increased extraction is perfectly adequate compensation, however, and the patient remains stable as long as the ratio is greater than 2:1. When the various mechanisms of delivery cannot maintain DO2 at least twice VO2, supply dependency and shock occurs.

There have been a series of clinical studies claiming that the biphasic relationship is absent and there is a continuous state of VO2 supply dependency in patients with ARDS or sepsis. These studies are marred by artifacts of clinical investigation and not supported by laboratory studies where all the variables can be evaluated. Most investigators agree that "pathologic O2 supply dependency" does not exist. However it appears that the "knee" of
the biphasic curve may be shifted to the right in sepsis making the critical ratio closer to 3:1 than 2:1. This is probably due to the rate of oxygen diffusion from capillaries to mitochondria in edematous tissues rather than a specific abnormality of oxidative metabolism.

Figure 1.14 During certain conditions such as sepsis and peripheral edema the biphasic relationship between DO2/VO2 becomes blunted and the critical DO2/VO2 ratio may be closer to 3:1 than 2:1. The DO2/VO2 curve in a normal hypermetabolic condition (exercise) is shown in the dotted line.

The shape of the oxyhemoglobin dissociation curve shown in Figure 1.3 changes in various conditions, moving to the right during acidosis, hypercarbia, and hyperthermia. Although these changes have physiologic importance (facilitating system oxygen unloading during ischemia and acidosis for example) the effects on oxygen content and relationship to PO2 and saturation are relatively minor compared to the effects of hemoglobin on oxygen content.

**Implications for Patient Management**

For many years Shoemaker has pointed out that patients at risk for multiple organ failure whose cardiac output, hemoglobin, and oxygenation are sufficient to maintain normal DO2/VO2 ratios (in excess of 4:1) have less complications and higher survival rates than patients who can not maintain normal systemic oxygen delivery in relationship to their metabolic rates. Similarly, many investigators have shown that patients who can not mount the response of increased oxygen delivery in response to increased metabolism, and hover around DO2/VO2 ratios of 2:1 have lactic acidosis, multiple complications, and a higher mortality rate.

Clinical research on DO2/VO2 relationships in critically ill patients is notoriously difficult because there are so many variables, many of which can not be controlled, and because complications and outcome relates to many factors including the primary injury or illness in addition to oxygen kinetic physiology. For example many of the clinical studies over the last decade have been conducted on patients in whom the baseline DO2/VO2 ratio was 2 or 3:1. Individual interventions to raise or lower DO2 on these patients who were, in retrospect, on the knee of the DO2/VO2 curve often showed supply dependency. This was interpreted as “pathologic” supply dependency when, in fact, the patients were never brought to normal DO2/VO2 ratios of 4 or 5:1. In the laboratory, controlling all the variables can be done with complex physiologic preparations. In such laboratory studies normal oxygen kinetic physiology was demonstrated in normal animals (Cilley), hypometabolic animals (Sinard), and animals which were hypermetabolic due to exercise (Bongiorno) or sepsis (Hirschl).

In critically ill patients, therefore, it is good management to maintain oxygen delivery greater than four times oxygen consumption. If the patient can not do this through autoregulation, then oxygen delivery should be optimized by transfusion, improved oxygenation via the lung, or increasing cardiac output with inotropic drugs. In addition, the ratio can be optimized by decreasing oxygen consumption by paralysis or cooling. Several studies show that optimizing delivery to consumption ratio in critically ill patients improves outcome (Tuchsmidt, Yu, Boyd, Fleming).

Since continuous venous saturation monitoring is a continuous and direct measurement of DO2/VO2 ratio, it is the ideal monitor to determine when systemic
Figure 1.14: During certain conditions such as sepsis and peripheral edema the biphasic relationship between $DO_2/VO_2$ becomes blunted and the critical $DO_2/VO_2$ ratio may be closer to 3:1 than 2:1. The $DO_2/VO_2$ curve in a normal hypermetabolic condition (exercise) is shown in the dotted line.
oxygen delivery is optimized, and to titrate treatment aimed at optimizing DO2 (transfusion, FiO2, PEEP, inotropes) or VO2 (cooling). Arterial pulse oximetry and mixed venous saturation monitoring nearly eliminates the need for most of the individual measurements of the components of oxygen delivery (cardiac output and blood gases). The ability to monitor these variables continuously with venous saturation allows intervention to maintain normal DO2/VO2 relationships before reaching critically low levels.
Chapter 1 Monographs and Reviews


This chapter has concise descriptions of normal and abnormal respiratory physiology in the setting of critical illness. Several figures from this chapter are included in this text.


Oxygen kinetics is presented as the background for monitoring and management in critical care.


Written in a most unusual style for scientific journals, this editorial points out some common errors related to oxygen kinetics in critical care management.


For two decades Stephen Cain has been the leading experimental physiologist studying oxygen kinetics. This is an excellent review experimental studies, focusing on factors which affect oxygen utilization in peripheral tissues.


The authors review previous reports (including their own) which purported to show pathologic supply dependency, concluding that the DO2/VO2 interactions in many cases represent normal physiologic behavior rather than an abnormal manifestation of impaired oxygen extraction.


An English intensivist concisely summarizes the literature on oxygen kinetics.

Although written with the pediatric patient in mind, this chapter includes references to most of the modern investigation in clinical oxygen kinetics.


This is the proceedings of a symposium on oxygen transport held in Berlin in 1989. The concepts of simultaneous continuous venous and arterial oximetry are well described.


The Vancouver group has conducted many clinical research studies on oxygen kinetics in critically ill patients which are summarized in this review. The discussion of mathematical coupling in clinical research studies is particularly well described.


This paper written by critical care nurse Kathleen White is one of the best descriptions of the use of continuous venous saturation monitoring as a guide to oxygen kinetics.

Chapter 1 Selected Reports

The problems and goals in clinical oxygen kinetic research are enumerated.


Norepinephrine increases oxygen delivery but also increases oxygen consumption in normal dogs. Whenever catecholamines are used to increase cardiac output, a concomitant increase in oxygen consumption can be expected based on primary effects of the drug on systemic metabolism.


This prospective randomized controlled study showed that mortality and morbidity were decreased when oxygen delivery was optimized in surgical patients.

This landmark report was one of the first to characterize oxygen kinetic relationships in detail.


All the variables of oxygen transport were carefully controlled in dog experiments.


The original description of the pO2 electrode.


In normal and endotoxic dogs oxygen delivery was varied by creating transient hypovolemia. Normal oxygen kinetics were demonstrated in both groups.

Fick A: On the measurement of the blood quantity in the ventricles of the heart. Proceedings of the Physiological, Medical Society of Wurzburg, July 9, 1870.

The original "pencil experiment" describing Fick's axiom and Fick's equation for cardiac output measurement.


This prospective controlled randomized study demonstrated better survival and less complications when oxygen delivery was optimized in trauma patients.


Septic dogs with peritonitis were hypermetabolic but had normal oxygen kinetic interactions.

When compared to patients monitored with standard pulmonary artery catheters, patients who had mixed venous saturation monitoring catheters had half as many deleterious hemodynamic events and half as many cardiac output measurements.


One of the first papers demonstrating the value of venous oximetry in critically ill patients.


These authors have reported several useful clinical research studies on monitoring oxygen kinetics. In this study changes in cardiac output in response to metabolic rate were documented by continuous monitors.


This paper points out the problems of mathematical coupling when oxygen consumption and delivery are calculated from the same primary measurements.


This is one of many studies by Shoemaker's group demonstrating that critically ill patients who can maintain (or are treated to maintain) optimal oxygen delivery have better outcome.


Oxygen delivery was controlled by extracorporeal circulation over a wide range during normothermia and hypothermia in sheep.


The original description of the "Swan-Ganz" catheter.

A good description of the principles and applications of arterialized capillary oximetry.


A prospective randomized controlled study showed that optimizing oxygen delivery resulted in decreased mortality in septic shock patients.


Mortality and morbidity were decreased when oxygen delivery was optimized in patients with shock, sepsis, and ARDS. Beneficial effects of optimizing oxygen delivery were demonstrated only on subgroup analysis of the entire population.
CHAPTER 2: Blood Volume, and Hemodynamics

Monitoring and management of systemic perfusion is one of the easier aspects of intensive care. In fact an inordinate amount of attention is paid to blood pressure monitoring and management, sometimes to the exclusion of other more important parameters such as oxygen delivery or metabolic rate. In this section we will review cardiac physiology and pathophysiology, cardiac function in relationship to blood volume and filling pressure, and systemic vascular physiology in the management of hypotension and/or inadequate systemic perfusion.

Cardiac Function

For purposes of understanding physiology it is useful to think of the functions of the right heart and the left heart as related but independent systems. In most circumstances the function of the left heart predominates and the function of the right heart follow passively. This is because the controlling factor of systemic perfusion is the state of contraction or tone in systemic arterioles (commonly referred to as systemic vascular resistance). Similarly “cardiac failure” in adult patients usually refers to left ventricular failure and all efforts at monitoring and managing cardiac function are focused on the left ventricular and systemic circulation. The exception to this general rule are circumstances in which the pulmonary vascular resistance and right ventricular function become the limiting factors in cardiac output. This occurs in acute or chronic pulmonary hypertension caused by primary pulmonary disease, pulmonary embolism, or right ventricular disease or infarction.

Cardiac function is regulated by a complex set of baro and chemoreceptors which continually adjust cardiac rate, strength of contractility, and extracellular fluid volume (by diuresis or antidiuresis), all acting to maintain systemic oxygen delivery at four to five times systemic oxygen consumption. Since normal oxygen oxygen consumption is 120 cc/m2/min and normal arterial oxygen content is 20 cc/dL, normal cardiac output is auto regulated to a level of 3 L/m2/min. If the rate of metabolism increases or decreases, neural and humoral reflexes readjust the cardiac output proportionately. If arterial blood oxygen content falls because of anemia or hypoxemia, cardiac output increases until normal systemic oxygen delivery is re-established. (Figure 1.6). If cardiac output drops because of hypovolemia, increased catecholamine secretion results in increased cardiac rate and contractility to maintain normal systemic oxygen delivery until transcapillary refilling or exogenous treatment returns blood volume to normal. Any or all of these complex interactions may be going on in the same critically ill patient at the same time. To assess these factors in the critically ill patient we estimate cardiac output, blood volume and filling pressure based on physical examination. Specifically we examine the quality and numerical values of the pulse pressure, the adequacy of urine output and brain function, the warmth and perfusion of the skin, and the endogenous autoregulation required to maintain perfusion (tachycardia, chest wall cardiac impulse). All of these findings give us a reasonable estimation of cardiac output. Examination of the lungs for signs of vascular congestion and examination of the visible veins in the neck for estimation of venous pressure give us some determination of filling pressure. Often these physical findings are adequate to establish a diagnosis and institute management. If this level of monitoring is
Figure 2.1: Right and left heart function related to ventricular filling pressure
not satisfactory to solve clinical problems, direct measurement of filling pressure of the right heart (central venous pressure) or the left heart (pulmonary artery pressure) is required. Placement of a pulmonary artery catheter allows us to measure cardiac output by thermodilution and, more importantly, to sample mixed venous blood for saturation measurements which tells us the ratio between systemic oxygen delivery and oxygen consumption. All intrathoracic pressures are measured at the end of expiration (FRC). This may be only a single heartbeat (Figure 2.2).

From all these measurements we can determine if cardiac output is normal for the level of filling pressure of the left ventricle, or if contractility is decreased. In the latter case cardiac output will be lower than predicted for a given level of filling pressure. These relationships are described in the familiar Frank-Starling curve which is shown in Figure 2.3.

Figure 2.3 Starling Curve of cardiac function. The normal relationships are in the shaded area.

If measurements indicate that the patient is in the normal range then myocardial function can be assumed to be normal. If the patient is to the right of the normal range then cardiac function itself is compromised because of valvular disease, extrinsic pressure such as pericardial tamponade, or (most commonly) a decrease in contractility.

**Cardiac Function, Blood Volume, and Filling Pressure**

The filling pressure described above and identified in Figure 2.3 reflects the relationship between the cardiac function and the effective blood volume. If cardiac function and anatomy are normal, then blood volume, filling pressure, and cardiac function are related as shown in the normal area of the Starling curve. The intake and output of fluid and salt is auto regulated to maintain the filling pressure of the left ventricle around 10 mmHg. Under normal circumstances it is almost impossible for a healthy person to become hypervolemic. The ingestion of water, even in huge amounts, has minimal effect on blood volume because the water is distributed throughout total body water, only a very small fraction of which is in the blood volume. Moreover diuresis occurs promptly maintaining total body water normal or close to it. Voluntary ingestion of very large amounts of salt and water could result in hypervolemia, but this fluid would be distributed throughout the entire extracellular space, only 1/4 of which is in the plasma volume. In this circumstance diuresis would occur more slowly, responding to volume receptors rather than osmoreceptors. In fact the extracellular space can be overloaded for days or weeks with minimal autogenous diuretic response. However extracellular fluid expansion (generalized edema) is usually associated with a normal blood volume. It is important to remember this fact when considering the critically ill patient with fluid overload. Gross expansion of the extracellular space with all the deleterious effects of tissue edema can and often does exist with perfectly normal blood volume. In other words a pulmonary capillary wedge pressure of 5-10 does not rule out fluid overload as the cause of pulmonary or GI dysfunction, for example. If hypervolemia does occur because of gross expansion of the extracellular space, or because of intravenous infusion of fluids or blood,
Read PAP or PCW at end-expiration

Figure 2.2: Pulmonary artery pressure tracing in a patient on a mechanical ventilator. Pressures are read at end-expiration (FRC). PCW is the "capillary wedged" pressure, measured when the inflow is occluded with a balloon upstream from the tip of the catheter.
Figure 2.3: Starling curve of cardiac function. The normal relationships are in the shaded area.
the result will be an increase in left atrial pressure (reflected in pulmonary artery pressure), central venous pressure, and arterial pulse pressure. These changes are shown in Figure 2.4.

Similar to hypervolemia, hypovolemia rarely occurs in the normal person. However short periods of voluntary starvation, or short periods of acute disease such as diarrhea or vomiting can result in hypovolemia rather quickly. The fluid losses in these circumstances are extracellular losses which are relatively slowly reflected as changes in the blood volume. However even a minor decrease in extracellular fluid volume leads to anti-diuresis as soon as hypovolemia is reflected by decreased atrial filling pressures. (Figure 2.4) Autoregulatory mechanisms increase cardiac output to compensate. In the case of bleeding the change in blood volume is immediate and immediately reflected in these compensatory mechanisms. If the bleeding stops before a critical level of exsanguination occurs, the normal combination of hydrostatic and osmotic forces which control the flow of salt and water at the capillary level results in the net transfer of extracellular fluid back into the plasma volume (so called transcapillary refilling) which restores normal blood volume, albeit with hemodilution.

In critically ill patients our fear of hypotension and ineffective perfusion, although it may be appropriate, usually results in infusion of intravenous salt and water in quantities which exceed losses. Consequently most patients in the intensive care unit have edema (worse in areas of injury or inflammation), anemia, dilutional hypoproteinemia, and compensatory increase in cardiac output. In response to anemia, these patients are tachycardiac, even though blood volume is normal, filling pressures are normal, and total body extracellular fluid is excessive. All of these factors are reflected in the autoregulatory mechanisms designed to maintain systemic oxygen delivery four to five times consumption. If arterial saturation is close to 100%, then cardiac function is "normal" for that patient if the venous saturation is in the range of 75 to 80%.

**Measuring Blood Volume:** Blood volume can be measured by dilution of specific indicators such as tagged albumin or tagged red cells. However from a practical point of view, measurement of blood volume is no longer done in critically ill patients because the exact measurement of blood volume is only important as it relates to cardiac function and this relationship can be determined from the Frank Starling curve shown in Figure 2.3.

Definitions and formulas related to hemodynamics are listed in Table 2.1
Figure 2.4: The effects of changes in blood volume when myocardial function is normal. Hypervolemia results in increasing filling pressures and expanded arterial pulse pressure. Hypovolemia results in decreased filling pressures and narrowed pulse pressure.
### TABLE 2.1

**Definitions and Formulas:**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
<th>Normal</th>
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<tbody>
<tr>
<td>C.O.</td>
<td>Cardiac Output</td>
<td>3.2L/m/m²</td>
</tr>
<tr>
<td>C.I.</td>
<td>Cardiac Index</td>
<td>3.2L/m/m²</td>
</tr>
<tr>
<td>PAP</td>
<td>Pulmonary Art. P</td>
<td>25/10 mmHg</td>
</tr>
<tr>
<td>PCW</td>
<td>Wedge Pressure</td>
<td>5-10 mmHg</td>
</tr>
<tr>
<td>RAP (CVP)</td>
<td>Right Arterial Pressure</td>
<td>2-5 mmHg</td>
</tr>
<tr>
<td>BP</td>
<td>Systemic Art. P</td>
<td>120/80 mmHg</td>
</tr>
<tr>
<td>SV</td>
<td>Stroke Volume</td>
<td>CO + rate</td>
</tr>
<tr>
<td>SI*</td>
<td>Stroke Index</td>
<td>CI + rate</td>
</tr>
<tr>
<td>SVRI*</td>
<td>Systemic Resistance Index</td>
<td>BP - RAP</td>
</tr>
<tr>
<td>PVRI*</td>
<td>Pulmonary Resistance Index</td>
<td>PAP - LAP</td>
</tr>
<tr>
<td>LVSWI*</td>
<td>Left ventricular stroke Work index</td>
<td>PAP - LAP</td>
</tr>
<tr>
<td>RVSWI*</td>
<td>Right ventricular stroke Work index</td>
<td>PAP - LAP</td>
</tr>
<tr>
<td>RPP</td>
<td>Rate Pressure Product</td>
<td>BP X rate</td>
</tr>
<tr>
<td>Fick Equation:</td>
<td>CO =</td>
<td>AVDO₂</td>
</tr>
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</table>

*Use CI to calculate derived parameters*
interarterial measurement system is working correctly, direct arterial pressure measurements are the gold standard in the ICU. It is never necessary, in fact it is usually misleading, to "check" the direct measurement with "cuff" measurements. Originally arterial pressure measurements were made directly in the aorta through catheters placed via the femoral artery. Now, the radial artery at the wrist is most commonly used for continuous pressure measurement because it is easily accessible and the complication rate is very low. Right atrial or central venous pressure is measured by attaching a catheter which has been advanced in the area of the right atrium to a manometer or a transducer. Pulmonary artery pressure is similarly measured by attachment to a catheter which has been placed in a lobar or segmental pulmonary artery. The catheter is guided into this position by observing the sequential pressure changes in the right atrium, right ventricle pulmonary artery and wedged positions. The position is verified by a chest x-ray.

Pressures throughout the cardiovascular system reflect the contractility of the upstream ventricle, the downstream arterial resistance, and to a small extent the viscosity of the blood. In addition the vascular pressures are affected by respiration. The effects of respiration on arterial pressure are minimal and usually ignored, however the effects of respiration on intrathoracic pressures are very important. By general agreement, intrathoracic intravascular pressures are measured at FRC, that is, at the end of an exhaled breath. (Fig. 2.2). If the heart rate is rapid and the respiratory rate is rapid this point of measurement may be only a single heartbeat. For this reason it is necessary to read right atrial pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure from a storage oscilloscope or paper tracing rather than from a digital output which tends to average the pressure over many heart beats and many respiratory cycles. The wedge pressure was originally described by Dexter to indicate the pressure measured when an end hole catheter is advanced in the pulmonary vasculature until it is wedged in a small artery. The pressure at the tip of the catheter is a measure of the pressure in the pulmonary capillaries which in turn is a measure of pressure in the left atrium and the left ventricle at end diastole (if the mitral valve is normal). The measurements of right heart catheterization moved from the cardiac catheterization lab to the ICU bedside when Edwards Laboratories developed a long thin catheter with a small balloon near the tip. Inflation of the balloon (usually) carries the catheter along with the flowing blood through the right heart chambers into the pulmonary artery eliminating the need for fluoroscopy. Edwards' original catheter was tested and described by Los Angeles cardiologists Swan and Ganz and became known as the Swan-Ganz catheter. This device has been so useful and so widely recognized that it has joined our lexicon of noun-verbs. We often hear that a patient is going to be "swaned", or that the Swan readings are such-and-such. Pulmonary artery catheters have undergone many modifications since the original device and it is grammatically and historically more correct to refer to "pulmonary artery catheters" and "Frank-Starling measurements". However we don't object too much, recognizing the importance of acknowledging our heritage.

If the intrathoracic pressure at FRC is higher than atmospheric pressure the condition is referred to as positive end expiratory pressure or PEEP. PEEP is commonly used in the treatment of critically ill patients in an attempt to maintain inflation of alveoli served by small airways which collapse at lower pressures. PEEP levels as high as 25 cm H2O are sometimes used. How should intravascular pressures be measured when PEEP is used? The answer, simply put, is to ignore it and measure and report the pressure
regardless of the level of PEEP. The explanation is that end expiratory pressure measured at the airway is different than, and higher than, pressure measured at the tip of intravascular catheters because the chest is not a closed box, but rather an expansile box with a very floppy bottom (the diaphragm).

In addition to the effects of respiration and expiratory pressure, the position of the patient will affect the reading of intravascular pressures because of the simple weight of blood when the catheter tip is in a dependent position, and because movement of the patient may change the relationship between the tip of the catheter and the electronic transducer. These problems are solved by placing the manometer or transducer at the level of the left atrium when measurements are made. It should be noted that this can and should be done when the patient is in a lateral position, sitting up, or lying prone. It is not necessary to put the patient in a supine position in order to measure hemodynamic pressures.

Measurement of Cardiac Output

Although there are many ways to measure the output of the heart, only two are generally practiced in the intensive care unit: Indicator dilution using cold temperature as the indicator, and the Fick method. In the indicator dilution method a small bolus of a measurable indicator (originally Evans Blue or Indocyanine dye) is injected rapidly in the central venous system (the exact location is not important). The concentration of the indicator is measured continuously downstream, either in the pulmonary artery or in a systemic artery. The ventricle act as mixing chamber to distribute the bolus of injectate into the ventricular volume, typically about 100cc. (Fig. 2.5). If the cardiac output is high, the volume of "dyed" blood will move through the circulation very quickly, so that the concentration at the point of measurement rises quickly to a high peak value then disappears quickly. (The tail of the disappearance curve will be distorted by some of the dye which has gone through the entire systemic circulation and re-circulated to the point of measurement). If the cardiac output is very low the volume of dyed blood will move relatively slowly and the concentration will rise slowly at the point of measurement, then slowly decline as the indicator is washed through. The area under the curve describing the concentration of the indicator is a measure of the total volume of blood into which the indicator was dispersed, from the point of injection to the point of measurement. This is known as the central blood volume. The exact quantity can be calculated by knowing the exact quantity of indicator injected and the extent to which it was diluted. Similarly the time that it took the central blood volume to go past the point of measurement can be measured and described as the mean transit time. Therefore if we know the volume of blood and the time of passage we can calculate the volume of blood which would flow through that ventricle(s) per minute which is, in fact, the cardiac output. At one time part of this measurement was done by cutting out the paper tracing of the dye concentration and balancing in on a straight edge to determine the time when half the indicator had passed the measurement point or the dye concentration halfway between maximal and minimal. This method was reduced to a series of formulas by Stewart and Hamilton who are credited with popularizing the indicator dilution method. The indicator dilution method with central venous injection and systemic arterial sampling was used in intensive care units for many years, but was cumbersome because any dye gradually accumulated in the patient requiring frequent re-calibration achieved by diluting a sample of the injectate with aliquots of blood. This problem was eliminated when it is was
discovered that temperature could be used as the indicator by injecting a small bolus of room temperature or, better yet, iced crystalloid solution. Moreover, by including a sensitive thermistor on the tip of a pulmonary artery catheter the thermal indicator dilution method could be used easily and repeatedly in any patient with a PA catheter in place. Thus, "thermal" cardiac output has been widely used in intensive care units for the past 20 years.

Like any dye dilution method, thermal cardiac outputs are subject to many methodological artifacts. The colder the temperature the more detectable the differences, but iced fluid changes temperature when going through conduit tubing and a warm intravascular segment of catheter. The most accurate results are obtained when the injectate bolus is injected very quickly, but incorporating the injection lumen in the wall of the pulmonary artery catheter necessarily made that lumen very small so that rapid (half second) injection is not possible. The timing of injection related to the respiratory cycle affects the reproducibility of the measurement. Because of these artifacts, the usual practice is to measure three or four indicator dilution curves, discard the curves which show irregularities, and average the results of the remaining curves. The net result of all this is that thermal dilution cardiac outputs are accurate ± 10% under the very best of circumstances. Nonetheless, it is certainly worthwhile to know if the cardiac index is 2.4, or 6 L/min. It is important to remember that all calculations based on cardiac output will simply magnify the errors in measurement. The principles of thermal dilution cardiac output are described in Figure 2.5.

Figure 2.5 Indicator dilution cardiac output measurement using cold solution as the indicator. A bolus of cold crystalloid is injected into the central venous circulation (any central venous catheter will do) and temperature is measured near the tip of the catheter in the pulmonary artery. Typical thermal dilution curves are shown.

The gold standard method for measuring cardiac output is the method described by Adolph Fick. Fick never actually measured cardiac output but simply postulated that it could be done if there were a way to measure mixed venous and arterial oxygen content and oxygen consumption at the airway. By measuring the oxygen consumption per minute, and knowing the AVO2 difference in ccO2/dL of blood, it is simple arithmetic to determine how many dL of blood pass through the lung in the course of a minute. Fick's method works well regardless of the status of lung function, because of Fick's axiom which assumes that the amount of oxygen absorbed across the lung is exactly equal to the amount of oxygen utilized in peripheral tissues. Perhaps a better way to describe the Fick equation would be to divide the AVO2 difference into the amount of oxygen consumed in metabolism in peripheral tissues. Measuring cardiac output via the Fick technique requires getting a sample of mixed venous blood, (hence requires a pulmonary artery catheter) and a sample of arterial blood, (hence an arterial catheter) and accurate measurement of oxygen consumption at the airway. The errors in each of these measurements is a few percent, so that even the Fick cardiac output method has an overall error rate of ± 5%. The principles in measuring cardiac output by the Fick method are described in Figure 2.6.

Figure 2.6 Cardiac output measured by the Fick principle requires measurement of the oxygen content in arterial and venous blood and oxygen consumption at the airway.
Figure 2.5: Indicator dilution cardiac output measurement using cold solution as the indicator. A bolus of cold crystalloid is injected into the central venous circulation (any central venous catheter will do) and temperature is measured near the tip of the catheter in the pulmonary artery. Typical thermal dilution curves are shown.

Figure 2.6: Cardiac output measured by the Fick principle requires measurement of the oxygen content in arterial and venous blood and oxygen consumption at the airway.
More accurate, simpler, or best of all continuous methods of cardiac output measurement would be desirable for managing critically ill patients. Some of the other methods which have been utilized include indicator dilution using radioisotopes with external counting, ultrasonic measurement of the velocity of flow through large vessels or cardiac chambers with calculations based on measured or estimated cross sectional area of the vessel, transthoracic electrical impedance, analysis of the arterial pulse wave form, and continuous thermal dilution using slow infusions or heated wires to produce a temperature gradient. To date none of these methods has been reliable enough to replace bolus thermal indicator dilution as the most commonly used approach.

**Systemic and Regional Blood Flow**

All of this discussion has addressed cardiac output as if blood flow were ideally distributed to each of the various organ systems. In fact, this is usually the case. Even in periods of high cardiac output and low cardiac output the organs which require increased oxygen delivery (i.e. blood flow) get the extra blood flow at the expense of other organs which need it less. This autoregulation is based primarily on the maintenance of total systemic vascular resistance as determined by arteriolar tone in all organs throughout the vascular system. Some organs, such as the heart and the brain, maintain constant blood flow over a wide range of inflow pressure. In other organs (such as the kidney) blood flow is more sensitive to arterial inflow pressure (or to state it more accurately, arteriolar resistance regulates organ blood flow in a fairly active fashion). Management of regional or organ-specific blood flow is rarely possible or even considered in management of the critically ill patient. Notable exceptions are the use of vasopressin and glucagon to selectively increase or decrease splanchnic blood flow, and the use of hypocarbic alkalosis to decrease cerebral blood flow. Low doses of dopamine are said to selectively improve renal blood flow, although this phenomenon may be primarily the result of a generalized increase in cardiac output.

In the context of peripheral circulation a word should be said about vascular resistance. The calculation of "resistance" is a useful shorthand to describe the interrelationships of cardiac output and systemic or pulmonary blood pressure, but it is no more than that. It is impossible to measure resistance. Resistance is simply a calculation in which blood pressure is divided by blood flow. The results should be expressed as Wood units, or millimeters of mercury per liter per minute per square meter. It is naive to apply other laws of fluid dynamic physics which are described for flow of Newtonian fluids through rigid tubes, and it is ridiculous to convert resistance units to dyne-sec-cm\(^{-5}\) as if the resulting number will somehow be more accurate. (Multiplying Wood units \(X 79.9\) to express resistance is common practice but has no rationale). All cardiovascular measurements should be normalized to body weight or body surface area and this is particularly true of resistance calculations. Cardiac index rather than cardiac output should always be used for resistance calculations in order to compare each patient to theoretical normal. For example imagine a 4 year old with a blood pressure of 90 over 60 and a well-trained adult 300 pound athlete with a blood pressure of 110 over 80. Both have a normal cardiac index. The calculated systemic vascular resistance based on cardiac index is the same for both and is normal. If the calculated systemic vascular resistance were based on cardiac output, it would be "pathologically" high in the child and pathologically low in the athlete.

**Management of Hypotension and Hypoperfusion**
Our algorithm for hemodynamic management is shown in Figure 2.7. Despite all of the foregoing discussion, the first sign which brings hemodynamic problems to our attention is often low blood pressure. If we identify a patient who has low blood pressure (or tachycardia, confusion, syncope, or narrow pulse pressure) as a patient who might have inadequate systemic oxygen delivery to meet metabolic needs (i.e. shock), our first response is to make some assessment of venous pressure by physical examination. If the venous pressure is high we presume that the problem is related to the heart or some mechanical obstruction to blood flow. If venous pressure is low we assume that the problem is attributable to hypovolemia or systemic vasodilatation. If the patient does not respond to initial simple management more detailed monitoring is required in the form of a central venous pressure catheter. If simple monitoring provides a diagnosis we can proceed to appropriate treatment. If signs of inadequate blood flow persist despite treatment based on venous pressure measurement, then transfer to the intensive care unit and direct monitoring of pulmonary artery pressure, saturation, and cardiac output are required.

Figure 2.7: Hemodynamic Management (Shock) Algorithm

With pulmonary artery catheter monitoring in place we can determine if delivery is adequate to meet metabolic needs (venous saturation is greater than 65% assuming that arterial saturation is over 95%). If the answer to this is yes, then no further acute treatment is needed. If the answer is no, then an appropriate blood volume expander should be given until the wedge pressure is greater than 10 mmHg. The appropriate blood volume expander may be blood, crystalloid, or plasma substitute, depending on the presumed or proven fluid loss which led to hypovolemia.

If, despite adequate filling pressure, cardiac output is still decreased and/or venous saturation is less than 65% then the cause is probably related to cardiac function and appropriate treatment can be undertaken. If mechanical factors are ruled out and contractility is the limiting factor then inotropic drugs are the appropriate treatment. (Fig. 2.8, 2.9). If cardiac output is high and hypotension persists, the cause may be related to system vasodilatation (caused by sepsis, paralysis, or vasodilating drugs), or the problem may be metabolic in origin (hypoglycemia, hypocalcemia, or Addison's disease).

Figure 2.8: Pressor Drugs increase blood pressure by improving contractility or arteriolar tone or both.

Figure 2.9: Inotrope Algorithm

If blood pressure is normal or high and cardiac output is decreased despite adequate filling pressure, then the problem may be systemic hypertension or systemic hypertension combined with decreased contractility. Only in the latter circumstance is the use of systemic vasodilating drugs appropriate. (Figure 2.10)

Figure 2.10: Drugs used to treat acute hypertension

If the patient is already systemically vasodilated from the primary disease the cardiac output will be high and the blood pressure, (therefore the calculated resistance) will be low. This occurs with loss of vasomotor tone due to anaphylaxis and acute spinal cord injury, but is most commonly due to systemic sepsis. The lipopolysaccharide endotoxin...
Figure 2.7: Hemodynamic management (shock) algorithm
Figure 2.8: Pressor drugs increase blood pressure by improving contractility or arteriolar tone or both.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Contractility (Inotropc)</th>
<th>SA Node Tone (Chronotropc)</th>
<th>Vasodilation</th>
<th>Vasoconstriction</th>
<th>Renal Perfusion</th>
<th>Cardiac Output</th>
<th>Systemic Vascular Resistance</th>
<th>Blood Pressure</th>
<th>VO₂</th>
<th>VCO₂</th>
<th>REE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoprenaline</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
<td>+++</td>
<td>↑</td>
<td>↓</td>
<td>t</td>
<td>t</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td>+++</td>
<td>0 to +</td>
<td>0 to +</td>
<td>↑</td>
<td>t</td>
<td>↓</td>
<td>0 to t</td>
<td>t</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>+++</td>
<td>+</td>
<td>0 to +++</td>
<td>0</td>
<td>T × 4</td>
<td>↑</td>
<td>↓</td>
<td>T × 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>T × 4</td>
<td>T</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>++</td>
<td>+++</td>
<td>0</td>
<td>↓</td>
<td>T × 4</td>
<td>↑</td>
<td>T</td>
<td>t</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ephedrine</td>
<td>++</td>
<td>+</td>
<td>0 to +</td>
<td>↓</td>
<td>↑</td>
<td>T × 4</td>
<td>↑</td>
<td>t</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>0</td>
<td>0</td>
<td>+++</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>t</td>
<td>t</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Inotrope Algorithm

- Hypotension/Perfusion Algorithm

**NOTROPES REQUIRED**

- Dobutamine or Dopamine

- V 5a > 70?

  - Yes
    - T to 15 mcg/Kg/min
  - No
    - Calcium, glucose
    - Epinephrine 0.1 mcg/Kg/min (Limit: tachycardia)
    - Isoproterenol 0.1 mcg/Kg/min (Limit: tachycardia)
    - Levophed + Regtine .1 mcg/Kg/min
    - Aminophylline 10 mcg/Kg/min

**Follow**

1. V 5a (>70)
2. Urine output > 5 cc/kg/min
3. Cardiac Output
4. Blood pressure

**TREAT ACIDOSIS**

- Sodium bicarbonate 50 mEq
- THAM: 30 grams/L, drip

**Not responding**

Reconsider mechanical, chemical problems; use aortic balloon or IAD

---

Figure 2.9: Inotrope algorithm
Figure 2.10: Drugs used to treat acute hypertension
elaborated by most gram negative bacteria is the most common cause of the septic shock syndrome, although it can also be associated with gram positive infection and even yeast infection. Some of the vasodilatation is undoubtedly due to activation of neutrophils and macrophages with systemic production of interleukins, leukotrienes, and platelet-derived cytokines. However the major mechanism is mediated by elaboration of tumor necrosis factor from macrophages. These mediators cause vasodilatation by activating the production of nitric oxide at the arteriolar level. Since vascular resistance is one of the major controllers of cardiac output, when vascular resistance falls, cardiac output increases thus the patient with severe systemic sepsis is most likely to be febrile, tachycardic, hypotensive, alert and awake despite the hypotension, oliguric, with a very high cardiac output, low blood pressure, therefore the calculated resistance will be low. The patient is described as "hyperdynamic" but this is a helpful normal response to systemic infection. It is more worrisome if the septic patient does not have a hyperdynamic response. The hyperdynamic state associated with sepsis or anaphylaxis is similar to the hyperdynamic state associated with extensive exercise. One major difference is that in sepsis the capacitance veins, as well as the arteriolar constrictors are dilated, capillary permeability is often increased, and relative hypovolemia complicates the picture. Because of this a severely septic patient may present with hypotension and a normal or low cardiac output, only to proceed to the classical hyperdynamic state when adequately volume resuscitated.

Hemodynamic treatment of the hyperdynamic state associated with sepsis is somewhat controversial, but rather obvious lessons can be drawn from the treatment of anaphylaxis. The brain, the heart, and the kidney are organs which can auto-regulate blood flow, but need a certain mean pressure to maintain adequate perfusion. The first goal, then is to restore some level of systemic arteriolar tone using alpha agonists such as phenylephrine or epinephrine. Remember that these catecholamines increase oxygen consumption as well as vascular tone and heart rate. The final result could be a decrease in DO2/VO2 ratio. The use of a drug which has primarily inotropic effects to improve cardiac output such as dopamine or isoproterenol is not a good first choice. Turning off the entire hyperdynamic response with beta blockers for example, decreases the pulse rate and cardiac output (therefore appears to increase the calculated resistance) but actually increases mortality in septic inflammatory shock. Of course the most important step in treatment is to find and treat the primary source of infection.

In summary, the principles involved in hemodynamic monitoring and management are simple: make accurate measurements, rely on primary data rather than calculated variables whenever possible, understand the differences between blood volume and extracellular volume, and use the measurements to select and titrate appropriate drugs. Some of these principles are summarized in the list of hemodynamics axioms in Figure 2.11.

Figure 2.11: Hemodynamic Axioms

**Electrocardiography**

Body surface measurement of the electrical potential generated by the conduction system of the heart has not changed a great deal since the time of Einthoven and Wilson. The concept of continuously monitoring the electrocardiogram was introduced by Lown and Levine 40 years ago and remains the mainstay of coronary care units. In any general
Hemodynamic Axioms

1. PCW reflects LV filling pressure (LAP), which depends only on blood volume and myocardial muscle status. LAP = LVEDP if mitral valve is normal.
2. PCW DOES NOT reflect extracellular fluid volume; PCW is generally NOT related to over-hydration.
3. PCW is equal to PA diastolic P if the heart rate is < 90.
4. RAP (CVP) is always lower than PCW, except when pulmonary vascular resistance is grossly elevated.
5. Resistance is just a calculation, not a measurement. The units are: pressure per flow; mmHg per liter per minute per square meter (usually referred to as Wood units). If you multiply Wood units X 79.9, you can express resistance as dyne-sec-cm⁻⁵, but why bother?
6. Use mean pressures and cardiac index to calculate derived parameters (resistance, stroke index, stroke work index)
7. SVRI is almost always caused by low cardiac output, rarely by primary vasospasm. Treat the cardiac output not the "resistance."

Figure 2.11: Hemodynamic Axioms
intensive care unit almost every possible arrhythmia is seen and treated almost every day. There are dozens of excellent books, not the least of which is standard ACLS, and it is not necessary or appropriate to review electrocardiography and arrhythmia management here. The simple practical approach that follows is adequate to recognize and manage 99% of cardiac rhythm problems seen in the intensive care unit. The details of the normal electrocardiogram are reviewed in Figure 2.12. Although the sweep speed and the gain on monitoring oscilloscopes is variable and adjustable, physicians and nurses who spend time in ICUs get quite good at recognizing even esoteric arrhythmias from a glance at the oscilloscope tracing. However to interpret the fine details such as intervals and voltage it is necessary to make a paper printout of the tracing with a property calibrated and timed electrocardiograph. When this is done such elements as the PR interval, the PR segment, the ST segment, etc. can be identified, quantitated, and compared. These intervals are usually measured in lead 2, although placement of electrodes in the ICU can be quite variable. Before any significant diagnosis or treatment is undertaken based on the electrocardiograph, it is wise to have a standard 12 lead electrocardiograph for a look at the electrical heart from all directions. Some of the common drugs and conditions which affect conduction are summarized in Figure 2.13.

Figure 2.12: Elements of the normal electrocardiogram seen in lead 2.

Figure 2.13: Drugs and conditions which affect the myocardial conduction system

Arrhythmias

At the risk of insulting my colleagues who devote their entire career to disturbances of the cardiac rhythm, all of the dysrhythmias which affect patients in the intensive care unit can be classified as too fast or too slow, atrial or ventricular, and hemodynamically important or unimportant. The slow arrhythmias are the result of vagal stimulation, sinus node abnormalities, hypercalcemia or hypermagnesemia, or heart block. The common fast arrhythmias are caused by spontaneous or accelerated firing of parts of the conduction system generated by catechol drugs and hormones, hypokalemia, digitalis, and electrical irritability. (Figure 2.14).

Figure 2.14: Diagram of the common causes of cardiac arrhythmia

These arrhythmias may originate at the atrial level, in the conduction system itself, or at the ventricular level. A list of the common causes of arrhythmias, classified in this fashion, is presented in Figure 2.15.

Figure 2.15: Common causes of arrhythmias classified by site of origin

The treatment of arrhythmias in the ICU always brings to mind the scene from "Raiders of the Lost Ark" in which a villain with a large sword is threatening to kill the hero who has only a small whip. After parrying thrusts of the sword and side stepping ever closer lethal lashes, the hero becomes bored with the encounter, pulls out a gun and shoots the villain. We have a long list of drugs which can be used quite successfully to treat all manner of arrhythmias, but if the drugs fail or aren't working fast enough we simply pull out our DC defibrillator (another Bernard Lown invention) or our handy pacemaker and solve the problem. We almost always win. The algorithm for choice of drugs or electricity is shown in Figure 2.16.
Figure 2.12: Elements of the normal electrocardiogram seen in lead 2.
**ECG**

<table>
<thead>
<tr>
<th>PR</th>
<th>Normal</th>
<th>AV Black</th>
<th>Nodal, WPW</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT</td>
<td>.3-4</td>
<td>↓ Ca, ↓ Mg, ↑ Ca, ↑ K, ↑ Mg Digitalis</td>
<td></td>
</tr>
<tr>
<td>fwave</td>
<td>25 mV</td>
<td>↑ K, Ischemia</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2.13: Drugs and conditions which affect the myocardial conduction system
Figure 2.14: Diagram of the common causes of cardiac arrhythmia
<table>
<thead>
<tr>
<th>Atrial</th>
<th>Vagal stimulus</th>
<th>Sinus bradycardia</th>
<th>Sick sinus</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conduction</td>
<td>Wandering pacemaker</td>
<td>Wenckebach</td>
<td>Toursad de pointes</td>
<td>PVC's</td>
</tr>
<tr>
<td>Ventricular</td>
<td>Standstill</td>
<td>Diastolic arrest</td>
<td>Potassium</td>
<td>V tach</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>V fibrillation</td>
</tr>
</tbody>
</table>

Figure 2.15: Common causes of arrhythmias classified by site of origin
Most of the slow arrhythmias in the intensive care unit are caused by vagal stimulation. Most mysterious intermittent bradyarrhythmias can be solved by finding that an endotracheal tube or tracheostomy tube is near the carina, a nasogastric tube is lying in a particularly irritable area of the nasal pharynx, sutures holding chest tubes are pulling on the chest wall when the patient moves, the stomach or urinary bladder is too full, etc. These simple observations and the use of old fashioned atropine are sometimes forgotten, but they are easier solutions than the insertion of a transvenous pacemaker. Even patients with complete heart block can be managed very successfully with isoproterenol or epinephrine until pacing wires can be electively placed.

Unlike slow arrhythmias, sometimes the best first solution to fast arrhythmias is the defibrillator. Lidocaine will often solve the problem of frequent PVCs, and adenosine or verapamil will usually control supraventricular tachycardias, but, like Harrison Ford in "Raiders", we have our big gun handy and we are justifiably quick to use it if pharmacologic means are not successful.

Figure: 2.16A: Treatment of slow arrhythmias

Figure 2.16B: Treatment of fast arrhythmias
Atrial (sinus bradycardia) Ventricular (block)

Stable

Unstable

Stable

Epinephrine .2 mg

Epinephrine .2 mg

Isoproterenol .2 mg

Atropine .6 mg

Pacer

Figure: 2.16A: Treatment of slow arrhythmias
Figure 2.16B: Treatment of fast arrhythmias
Chapter 2 Monographs and Reviews


This multi-authored textbook contains some excellent sections on hemodynamics and cardiopulmonary interactions in critical care.


A standard reference describing the principles and specific details of pressure and flow monitoring.

Harken AH: "Cardiac Arrhythmias" IN: Care of the Surgical Patient Holcroft J (editor), Scientific American Medicine, New York, Section 1, Chapter 3, 1991.

This is a multi-authored textbook on critical care published by the American College of Surgeons Committee on Pre and Postoperative Care. The chapter on arrhythmias is one of the most practical and concise reviews of this topic.


This classic text is the standard reference describing body fluid compartments and transcapillary fluid kinetics in surgical and critically ill patients.


A review of transcapillary flux by the modern experts.


This multi-authored monograph in Volume 42 in the series "Lung Biology in Health and Disease," edited Claude LeFont and published by Dekker. It is the most complete single reference on cardiopulmonary interactions.

Chapter 2 Selected Reports


A thorough review of the literature on adenosine and the rationale for adenosine as the first drug of choice for atrial tachycardias.

Lown originated the "coronary care unit" and developed DC defibrillation and cardioversion.

Fick A: On the measurement of the blood quantity in the ventricles of the heart. Proceedings of the Physiological, Medical Society of Wurzburg, July 9, 1870.

The original "Pencil Experiment" describing Fick's axiom and Fick's equation for cardiac output measurement.


Hamilton adapted the dye dilution method originally described by Stewart many years before to measure the cardiac output. This paper describes the collaboration between Hamilton and the Cournand-Richards group who were developing the field of cardiac catheterization. The collaboration between Cournand and Hamilton resulted in the comparison of Fick vs dye dilution methods.


One of many studies which shows the primary effect of catacholamines on systemic oxygen consumption.


This clinical study defines the hemodynamic events in septic shock, including response to volume infusion.

Sarnoff SJ: Myocardial contractility as described by ventricular function curves; observations on Starling's law of the heart. Physiologic Reviews. Vol. 35:107, 1955.

Sarnoff provided the bridge from laboratory physiology to bedside practice.


The original description of "Starling's Law" of the heart.

The original description of the "Swan-Ganz" catheter.


This review published in the Society of Critical Care Medicine monograph series New Horizons defines the hemodynamic abnormalities in septic shock and the rationale and results for many of the proposed treatments including the use of inotropic and alpha adrenergic agents.
CHAPTER 3: Respiratory Physiology and Pathophysiology

In the intensive care unit the respiratory system commands an amount of attention and concern which is disproportionate to other organ systems. Respiratory failure is the most common organ system failure in any intensive care unit. Careful management is required to prevent respiratory failure in patients with normal lung function.

Subconsciously we consider acute failure of the heart, kidneys, or liver to be an act of God, but acute respiratory failure somehow always seems like our fault - something we could have prevented or at least treated more successfully. The management of severe respiratory failure can become complex. The treatment itself, used to the extreme, is very damaging to the lung, and requires a bit of art in addition to a lot of science.

The terms describing the respiratory system have precise definitions which are often overlapping, semi synonymous, and frequently used incorrectly. Respiration means the overall process of oxygen getting from the atmosphere to the cells, combining with substrate and the resultant CO2 returning to the atmosphere. Hence respiration might mean gas exchange in the lungs, in the peripheral tissues, or at the mitochondrial or molecular level. Pulmonary respiration has two components: ventilation and gas exchange. Ventilation is the process of moving gas to and from the alveoli through the conducting airways and is synonymous with breathing. Everyone agrees on the definition of a breath, but a breath can be further described as a tidal breath, vital capacity breath, yawn, sigh, assisted or controlled. Pressure is required to breathe, and the pressure is described relative to atmospheric pressure, but when pressure is discussed in relationship to volume, inflating pressure is always considered positive, whether it is negative relative to atmosphere or not. The interrelationships between gas volumes and intrathoracic pressure are lumped under the term pulmonary mechanics. The concept of gas exchange is easy to understand but it is often forgotten that the processes is related to CO2 excretion (breathing) are quite different than the processes leading to oxygenation (VQ matching).

Finally, the mechanical ventilator is such a large, obvious, and potentially dangerous apparatus that the process of mechanical ventilation is over-emphasized in the management of respiratory failure, when attention might be better paid to the simpler but more important issues such as position, fluid balance, nutrition, or anemia. In this chapter we will discuss normal and abnormal pulmonary respiration, and use those principles to define an algorithm for the prevention and management of pulmonary respiratory failure.

Pulmonary Mechanics

The interrelations of gas volumes and pressures involved with ventilation are referred to as pulmonary mechanics. Normal lung volumes are measured by spirometry as shown in Figure 3.1. Tidal volume, inspiratory capacity, total lung capacity, and functional residual capacity are not effort dependent, hence can be measured in any patient who is breathing spontaneously or on a mechanical ventilator. The vital capacity (synonym, forced expiratory volume, FEV) is the amount of gas which a patient can exhale with maximum effort, following a maximal inspiratory effort. The amount of gas which can be forcibly exhaled in 1 second (FEV), or fractions thereof, is an indirect measure of expiratory flow. In critically ill patients, functional residual capacity requires measurement with a relatively inert gas such as helium or nitrogen during 100% oxygen breathing. The methodology is cumbersome, therefore FRC is not commonly measured in the ICU, even though it is by far the most important of the lung volumes. Residual volume is not
actually measured, but the result of subtracting the expiratory reserve volume from the FRC.

Figure 3.1: Lung volumes are measured by having the patient breathe in and out from a spirometer which measures volume changes. Flow and volume spirometry is commonly referred to as "pulmonary function tests." (From Bartlett, Surgery Annual, 1971)

The amount of gas volume that moves in or out of the lungs for a given amount of inflating or deflating pressure is referred to as pulmonary compliance. Compliance is usually expressed as a single number (X cc/cmH2O pressure), but this shorthand can be quite misleading. To understand and describe compliance it is necessary to compare volume and pressure relationships through an entire breath, which is done by plotting volume on the ordinant against pressure on the abscissa, generating a compliance curve as shown in Figure 3.2. In Figure 3.2 expiratory or deflation volume pressure curves are drawn for three normal subjects of different sizes. In each curve the patient has inhaled total lung capacity with an inflating pressure of 60 cmH2O, then pressure is measured continuously as the patient exhales. Exhalation is passive between inflating pressure of 60 and atmospheric pressure, then active exhalation is required between atmospheric and -40 cmH2O in these examples. If the inflation half of the volume pressure curve were shown for these normal individuals, it would be almost the same, but shifted slightly to the right. Notice that full inflation of alveoli to total lung capacity occurs at about 40 cmH2O for a single normal alveolus or a million alveoli, so that the shape of the volume pressure curve is the same for all subjects; only the total lung capacity and FRC are different. The compliance curve for a 70 kg adult who had a left pneumonectomy would look the same as the normal compliance curve for the 40 kg child. The same would be true if the 70 kg adult lost half of his alveolar volume because of atelectasis, pneumonia, or edema. The concept of the functional lung being smaller (not "stiffer") is essential in the understanding and management of severe respiratory failure with a mechanical ventilator.

This concept is described in Figure 3.3. When the full volume pressure curve is graphed out it is easy to see how the decrease in FRC and total lung capacity makes the lung "smaller" in atelectasis. The normal alveoli are inflated and the atelectactic aleveoli are not. However, in clinical practice the full compliance curve is not displayed and the FRC is not measured. Instead, the compliance curve and is displayed with the beginning and end point being atmospheric pressure and the FRC during each breath, rather than related to normal FRC. Therefore it appears that the compliance curve is flatter when alveolar volume is missing and there is a tendency to say that the lung has become "stiffer". At present there is no practical way to readjust the volume baseline for shifting FRC during breath to breath or minute to minute testing, so that the artifact induced by that problem must be understood in order to interpret bedside compliance curves.

What is the best way to measure the compliance curves shown in Figure 3.2 or Figure 3.3? The simplest way is to inflate the lung from atmospheric pressure to total lung capacity (either by voluntary effort or by a mechanical ventilator), then cap the airway, have the subject completely relax, and measure pressure at the mouth. This is referred to as static compliance measurement. It takes about one second for pressure at the mouth to come into equilibrium with the intrathoracic pressure. For our 70 kg adult the pressure at TLC will be approximately 40 cmH2O and the inspiratory capacity will be about 2800 cc, so
Figure 3.1: Lung volumes are measured by having the patient breathe in and out from a spirometer which measures volume changes. Flow and volume spirometry is commonly referred to as "pulmonary function tests."
(From Bartlett, Surgery Annual, 1971)
the static compliance would be 70 cc per cmH2O pressure, or 1 cc/cmH2O/kg. Actually this
would be best described as “static pulmonary compliance at TLC”. If we gradually allowed
exhalation but capped the airway and measured pressure every few hundred cc’s, we
would define several points on the deflation compliance curve which would ultimately
allow us to plot out the entire curve. This method is referred to as quasi-static compliance
testing. A simpler method to define the entire curve is simply measure pressure at the
airway (or in the thorax itself) continuously during deflation and plot the volume versus
the pressure, resulting in the deflation curve shown in Figure 3.3. Notice that the normal
lung is most compliant at pressures close to atmospheric, so that if we expressed
compliance at 10 cm of inflating pressure (rather than 40), we would find that the inflating
volume is 1400 ccc’s, and the compliance is 2 cc/cmH2O/kg.

When a patient is on a mechanical ventilator, volume, pressure, and flow are all
controlled so that measurement and manipulation of pulmonary mechanics is possible, in
fact is the goal. The foregoing discussion of pulmonary mechanics actually refers to a
pressure measured in the chest (by an intraesophageal manometer or by an intrapleural or
intraesophageal monitor) while measuring volume at the mouth. Although this can be
done in a ventilated patient, the common practice is to measure both the volume and the
pressure at the mouth or at some other point closer to the mechanical ventilator. This
practice introduces several variables and artifacts such as pressure gradients between the
intrapleural space and the measuring site, compression and expansion volume related to
the machine and conduit tubing, and the fact that the expiratory pressure may be
intentionally elevated for patient management (PEEP). When compliance is measured
and reported in this fashion it is referred to as "effective compliance" meaning that the
pressures and volumes are measured at the endotracheal tube or on the ventilator, taking
all these variables into account. Hence, if our 70 kg patient has atelectasis and is on a
mechanical ventilator set at inspiratory plateau pressure of 30 cm with 10 cm of PEEP
resulting in a tidal volume of 700 cc, we would say that the effective compliance is 700
cc/20 cmH2O or 35 cc/cmH2O or 0.5 cc/cmH2O/kg.

The relationship of gas flow to pressure is referred to as pulmonary resistance.
Resistance physiology is the major issue in small airway disease or bronchospasm and
bronchodilator drugs are titrated to minimize pulmonary resistance. Actual measurement
of flow for these purposes is achieved with a sensitive gas flow meter attached at the
mouth or at the level of the endotracheal tube. This device is called a pneumotachograph.
Integrating flow with time gives volume, and pneumotachographs are often used as
volume measurement devices in studies of pulmonary mechanics.

Figure 3.2 Volume Pressure Curves. Normal lung volumes for subjects of 10,40, and 70 kg are shown. Static lung
volumes for the 70 kg subject are shown. Notice that full inflation of alveoli to total lung capacity occurs at 40
cmH2O for all sizes of subjects.

Figure 3.3 Volume Pressure Curves in a normal 70 kg man, and the same man with atelectasis. By showing the
end-expiratory volume as zero for each breath, the single breath compliance curve makes the smaller
atelectatic lung appear stiffer.

Effective of position on pulmonary mechanics

All of the foregoing discussion related to normal pulmonary mechanics refers to
normal subjects tested in a sitting position. However most of our patients are supine.
Figure 3.2: Volume pressure curves. Normal lung volumes for subjects of 10, 40, and 70 kg are shown. Static lung volumes for the 70 kg subject are shown. Notice that full inflation of alveoli to total lung capacity occurs at 40 cmH2O for all sizes of subjects.
Figure 3.3: Volume pressure curves in a normal 70 kg man, and the same man with atelectasis. By showing the end-expiratory volume as zero for each breath, the single breath compliance curve makes the smaller atelectatic lung appear stiffer.
When lying supine the weight of the stomach, liver, spleen, and other abdominal viscera presses down on the posterior half of the diaphragm, physically compressing the lung bases and requiring extra effort by diaphragmatic contraction to "lift up" the abdominal viscera off of the compressed lung. (Remember, at FRC, most of the diaphragm is oriented in a coronal rather than a transverse plane). Therefore both FRC and TLC will be significantly decreased in a subject who is supine rather than sitting. In the same subject standing, the weight of the abdominal viscera actually pulls down on the diaphragm (the same is true in a kneeling prone subject). Therefore the FRC is highest in the standing or prone kneeling position. In a subject lying completely prone the viscera press on the smaller anterior parts of the lung bases and abdominal motion is limited so that FRC and TLC are slightly less than in the sitting position. All of these relationships are diagrammed in Figure 3.4.

Figure 3.4 Lung volumes measured at various body positions. The abdominal viscera compress the lung, decreasing FRC in the supine position. (Adapted from the Handbook of Physiology, see references).

The effect of position on lung volume affects lung compliance. In the supine position the FRC is smaller, so greater pressure will be required to achieve full inflation. Moreover force is required to lift the weight of the abdominal viscera. The net effect is that the compliance is considerably lower in a supine subject compared to the same subject sitting or standing. This becomes important when we are trying to wean a patient from mechanical ventilation to spontaneous breathing. Much less effort will be required if the patient is sitting or standing (or, for that matter, kneeling) than when the patient is supine. The same principles must be considered if we are trying to recruit atelectatic alveoli. Atelectasis almost always occurs in the posterior aspects of the lung, partly because of the effects of that posture, and it is always easier to inflate collapsed posterior alveoli with the patient sitting, standing or prone.

In acute respiratory failure, the cause of decreased compliance is almost always associated with a decrease in the functional residual capacity (Figure 3.3). The decreased FRC represents the lost alveoli which are either collapsed or filled with fluid but still perfused with blood. One way of managing ventilation in this circumstance is to stop expiration when pressure is still positive (PEEP). PEEP set at 10 cm H2O, for example, maintains the inflation of alveoli that might close at lower end-expiratory pressures. When that happens the functional lung is bigger and the entire compliance curve shifts back toward the left.

Several measurements must be taken to determine whether positive airway pressure is recruiting collapsed alveoli or simply distending normal alveoli (see Figure 3.5). As collapsed alveoli are reinflated, compliance improves, dead space ventilation decreases, cardiac output is unaffected, oxygenation improves at the same ventilator settings as shunt decreases, and the risk of air leak is minimal. These principles and measurements must be kept in mind during the management of the patient on a mechanical ventilator.

Figure 3.5: When inflating pressure is applied to collapsed lung, the goal is equal inflation of all alveoli (recruitment), but unequal inflation (distension) is possible. (from Bartlett, Respiratory Care of the Surgical Patient, 1980)
Figure 3.4: Lung volumes measured at various body positions. The abdominal viscera compress the lung, decreasing FRC in the supine position. (Adapted from the Handbook of Physiology, see references).
Figure 3.5: When inflating pressure is applied to collapsed lung, the goal is equal inflation of all alveoli (recruitment), but unequal inflation (distention) is possible. (from Bartlett, Respiratory Care of the Surgical Patient, 1980)
Lung damage can be caused by high airway pressure, so that over-distention as shown in Figure 3.2 is not merely inefficient, but actually detrimental. Since the most normal areas of lung have the best compliance, they are the most vulnerable to over-distention, contributing to the steady progression of lung dysfunction in patients ventilated at high peak pressure. Every effort should be made to keep the peak inspiratory pressure under 40 cmH₂O, preferably lower.

Definitions and formulas related to pulmonary mechanics are shown in Table 3.1.

**Gas Exchange**

Gas exchange refers to oxygen and CO₂ transfer between the ventilating gas and the blood. It is best to consider the exchange of these two gases separately. The definitions and formulas related to gas exchange are shown in Table 1.1 and in Table 3.2. The methods of measuring and describing oxygen in blood are discussed in detail in Chapter 1 and diagrammed in Figure 1.2 and 1.3. The PO₂ of dry air is 20.9% of the barometric pressure, or 157 mmHg at sea level. By the time inhaled gas reaches alveoli H₂O is 47 and the PO₂ is 149. The PO₂ in the pulmonary capillary blood is about 40 so at the first instant of inspiration there is a gradient of 109 mmHg between the alveolus and the capillary blood and oxygen diffuses across the alveolar membrane into the blood in response to this gradient. During the rest of the breath oxygen diffuses out of the alveolus into the blood so that at the end of a normal breath (i.e. after 5 or 6 seconds) the PO₂ in both the alveolus and the capillary blood exiting the alveolus is about 90 mmHg. This is true for an alveolus in the middle of the lung, and if all the alveoli had equal ventilation and perfusion the arterial PO₂ would be the average PO₂ during the breath, about 115. However in the sitting position alveoli at the apex of the lung have relatively low blood flow and blood entering the pulmonary veins from those alveoli has an average PO₂ around 120. On the other hand alveoli at the base of the lung have more blood flow than ventilation, and PO₂ in the blood exiting those alveoli is around 80. Blood from all of these alveoli mixes in the left ventricle, so that the resultant arterial PO₂ in a normal person, seated, breathing air is about 90 mmHg. During vigorous exercise ventilation and perfusion both increase and equalize so that the PO₂ during exercise breathing air is normally about 110. Another factor contributing to the normal end tidal gradient between alveolar gas and arterial blood oxygen is the fact that about 3% of the blood arriving in the left atrium comes from bronchial circulation or thebesian veins and is not fully oxygenated (the normal "anatomic" shunt).

Increasing FiO₂ increases the gradient for oxygen transfer but the same principles of equilibration during a single breath apply. Therefore even though the PO₂ of inhaled gas breathing 100% O₂ is 713, and the PO₂ of end tidal alveolar gas is 673, the normal arterial PO₂ during 100% oxygen breathing is about 600 mmHg.

Oxygen transfer in the lung and the causes of hypoxemia are demonstrated in Figure 3.6. Under normal conditions red blood cells in the pulmonary capillaries become fully saturated and oxygen dissolves in the plasma resulting in blood PO₂ of 100 (after coming into equilibrium at the end of a resting expiration) and saturation.

Figure 3.6: Normal venous blood (pO₂=40, pCO₂=45) perfusing 5 different areas of lung representing different ventilation-perfusion relationships. (from Bartlett, Surgery Annual, 1971).
Inspired Gas
PO₂ 149
PCO₂ 0
PH₂O 47
PN₂ 564

Venous Blood
PO₂ 110
PCO₂ 40

PO₂ 60
PCO₂ 44

PO₂ 40
PCO₂ 40

PO₂ 120
PCO₂ 40

PO₂ 40
PCO₂ 45

Arterial Blood

Figure 3.6: Normal venous blood (pO₂=40, pCO₂=45) perfusing 5 different areas of lung representing different ventilation-perfusion relationships. (from Bartlett, Surgery Annual, 1971).
### TABLE 3.2

<table>
<thead>
<tr>
<th>Definitions &amp; Formulas</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>CₐO₂</td>
<td>Oxygen content, arterial</td>
</tr>
<tr>
<td>CᵥO₂</td>
<td>Oxygen content, venous</td>
</tr>
<tr>
<td>PAO₂</td>
<td>Alveolar PO₂ = (PB-PH₂O)xFI₂O⁻Paco₂</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>AₐDO₂</td>
<td>Alveolar-arterial O₂ gradient</td>
</tr>
<tr>
<td></td>
<td>PAO₂-PaO₂</td>
</tr>
<tr>
<td>PaO₂/FiO₂</td>
<td>Oxygen index</td>
</tr>
<tr>
<td></td>
<td>(bedside shorthand)</td>
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<tr>
<td>CcO₂</td>
<td>Theoretical maximal CₐO₂</td>
</tr>
<tr>
<td></td>
<td>at known FI₂O</td>
</tr>
<tr>
<td>% Shunt</td>
<td>CcO₂-CₐO₂</td>
</tr>
<tr>
<td></td>
<td>CcO₂-CᵥO₂</td>
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### Table 3.1 Pulmonary Mechanics

<table>
<thead>
<tr>
<th>Definitions &amp; Formulas</th>
<th>Normal</th>
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<tr>
<td><strong>Pulmonary Pressure</strong></td>
<td>Relationship of Flow, Volume, &amp; Mechanics</td>
</tr>
<tr>
<td>TLC</td>
<td>Total Lung Capacity</td>
</tr>
<tr>
<td>FRC</td>
<td>Functional residual capacity</td>
</tr>
<tr>
<td>IC</td>
<td>Inspiratory capacity</td>
</tr>
<tr>
<td>ERV</td>
<td>Expiratory reserve volume</td>
</tr>
<tr>
<td>RV</td>
<td>Residual volume</td>
</tr>
<tr>
<td>TV</td>
<td>Tidal volume</td>
</tr>
<tr>
<td>VE</td>
<td>Minute ventilation (exhaled)</td>
</tr>
<tr>
<td>VA</td>
<td>Alveolar ventilation</td>
</tr>
<tr>
<td>VD</td>
<td>Dead space</td>
</tr>
<tr>
<td>PIP</td>
<td>Peak inspiratory pressure</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>EEP</td>
<td>End expiratory pressure</td>
</tr>
<tr>
<td>Compliance</td>
<td>TV/PIP</td>
</tr>
<tr>
<td>Effective compliance</td>
<td>TV/PIP-PEEP on ventilator</td>
</tr>
<tr>
<td>Resistance</td>
<td>Inspiratory flow/pressure</td>
</tr>
<tr>
<td></td>
<td>PaCO2 - PE CO2</td>
</tr>
<tr>
<td>VD/VT</td>
<td>PACO2 (end tidal)</td>
</tr>
</tbody>
</table>
of 100% (3.6-A). This equilibration may be disturbed by hypoventilation in relationship to
the perfusion (VQ mismatch 3.6-B), diffusion block caused by interstitial fibrosis (3.6-C), or
perfusion of non-ventilated alveoli (simply the extreme of hypoventilation 3.6-D).
Diffusion block and VQ mismatch can be almost completely overcome by breathing 100%
oxygen, hence hypoxemia during exposure to high alveolar pO2 is caused by total VQ
mismatch; so-called transpulmonary shunting or venous admixture. Under normal
conditions about 5% of the blood entering the left atrium has been shunted away from the
pulmonary capillaries, either as a result of bronchial nutritive blood flow or through
thebesian veins opening directly into the left side of the heart. This phenomenon,
combined with the normal minor VQ mismatch associated with breathing at rest and
positional effects on pulmonary blood flow, result in the fact that the normal arterial pO2
is 90 mmHg and the normal SaO2 is 99%. The extent to which various degrees of
transpulmonary shunting affect arterial oxygenation is shown in Figure 3.7.

Figure 3.7: Oxygenation measured as PaO2 at various levels of transpulmonary shunt and FiO2.

The shunt fraction is actually calculated by assuming that the capillary oxygenation
in those alveolo-capillary units which are functioning normally is fully saturated and
equilibrated with end tidal gas. The oxygen content in these theoretically perfectly
normal units is calculated by assuming that the blood is fully saturated and fully
equilibrated at the end tidal alveolar pO2. For example if the subject is breathing 100%
oxygen and the PaCO2 is 40 mmHg, then it is assumed that the pO2 in end tidal alveolar
gas and in the blood perfusing those alveolar is 673 at sea level. Therefore oxygen content
in these theoretical optimal units is (Hb X 100% X 1.36) + (.003 X 673). In addition it is
assumed that blood passing through areas of transpulmonary shunt is identical to venous
blood. With these assumptions the fraction of blood passing through the shunt can be
calculated as

\[
\text{QS} = \frac{\text{oxygen content of blood leaving the capillaries of normal alveoli} - \text{oxygen content in arterial blood}}{\text{QT}}
\]

Abbreviated as

\[
\text{QS} = \frac{\text{CcO}_2-\text{CaO}_2}{\text{CvO}_2 - \text{CcO}_2 - \text{CvO}_2}
\]

Sampling arterial and venous blood and going through all the calculations is
somewhat cumbersome, so that shunt fraction is usually estimated from a graph such as
that shown in Figure 3.7. Obviously the effect of venous blood content on the shunt
calculation is considerable, therefore, if oxygen delivery is decreased because of low cardiac
output or low hemoglobin concentration, venous saturation will fall, decreasing the
calculated shunt fraction. This is not a mathematical artifact, but reflects the fact that
autoregulation diverts pulmonary blood flow away from non-ventilated areas at low
cardiac output, but this effect is overridden at higher cardiac outputs resulting in more
shunting (Figure 3.8). The shunt fraction can be calculated at any level of FiO2, but such a
calculation includes components of diffusion block and VQ mismatch when FiO2 is less
than 1.0. The level of lung dysfunction can be similarly estimated by calculation of the
Figure 3.7: Oxygenation measured as PaO2 at various levels of transpulmonary shunt and FiO2.
alveolo-arterial (Aa) gradient for oxygen or the \( \text{PaO}_2 \) divided by \( \text{FiO}_2 \). The Aa gradient is calculated:

\[
\text{AaDO}_2 = (\text{PB} - \text{P}_\text{H}_2\text{O}) \times \text{FiO}_2 - \text{PaCO}_2 - \text{PaO}_2
\]

Figure 3.8: The higher the mixed venous \( \text{pO}_2 \) the greater the shunt. This is because blood flow through non-ventilated lung increases with increasing cardiac output; increasing cardiac output is reflected as higher venous saturation. (from Bartlett, Surgery Annual, 1971)

Where \( \text{PB} = \) Barometric pressure, \( \text{pH}_2\text{O} = 47 \, \text{mmHg} \) at \( 37^\circ \text{C} \), and assuming that alveolar \( \text{PCO}_2 \) is identical to the arterial \( \text{PCO}_2 \) (not necessarily true). With these assumptions, the normal alveolar arterial gradient is approximately 10 mmHg breathing air and 70 mmHg breathing 100\% \( \text{O}_2 \). Aa gradient greater than 500 corresponds to approximately 30\% transpulmonary shunt.

The \( \text{PaO}_2 \) over \( \text{FiO}_2 \) calculation is simply bedside shorthand to characterize Aa gradient without all the calculations. The normal \( P/F \) value is 500 and a value of 100 corresponds to a 30\% shunt. These four methods of characterizing lung dysfunction based on oxygenation are diagrammed in Figure 3.9.

Figure 3.9: Four methods of describing lung dysfunction based on lung oxygenation. For the curves describing saturation and \( \text{PaO}_2 \) it is assumed that \( \text{FiO}_2 = 1.0 \), \( \text{PaCO}_2 = 40 \), \( \text{SvO}_2 = 70 \). For the curve describing Aa gradient and \( P/F \) ratio it is assumed that \( \text{FiO}_2 \) is adjusted to maintain \( \text{PaO}_2 \) at 70 and \( \text{SaO}_2 \) at 95.

Before leaving the discussion of oxygenation, it should be noted that interruption of blood flow to alveoli has no effect on oxygenation, except by diverting blood flow to all the other areas of lung. (Figure 3.6-E). If the remainder of the lung is basically normal then occlusion of pulmonary arteries should have no effect on oxygenation. However we all remember patients with pulmonary embolism who became hypoxic. This occurs because blood flow must increase through areas of VQ mismatch and shunting, and/or right atrial pressure increases to the point where right to left shunting occurs through the foramen ovale, and/or the residence time of red blood cells in pulmonary capillaries becomes so short that the time for oxygenation is inadequate. Of these causes, the latter can be largely corrected with supplemental oxygen, raising the gradient for oxygen diffusion in the pulmonary capillaries.

**CO2 Kinetics: Ventilation and Metabolism**

As mentioned above, oxygen uptake across the lung is related to ventilation/perfusion relationships and alveolar \( \text{PO}_2 \). CO2 excretion, on the other hand, is related to the amount of ventilation. Because CO2 is much more diffusible than oxygen, and because a small amount of hyperventilation excretes a large amount of CO2, the limiting factors controlling oxygenation and CO2 removal are quite different.

The total amount of carbon dioxide produced by systemic metabolism is roughly equivalent to the amount of oxygen consumed (100-120 cc/m² per min, 200 cc/min in a typical adult). The ratio between \( \text{CO}_2 \) produced and oxygen consumed is referred to as the respiratory quotient (R or RQ) and varies slightly depending on the foodstuff being metabolized.

Carbon dioxide in gas is measured with an infrared spectrophotometer. The spectrophotometer is calibrated against the known standard to read out as \% CO2 or partial
Figure 3.8: The higher the mixed venous pO2 the greater the shunt. This is because blood flow through non-ventilated lung increases with increasing cardiac output; increasing cardiac output is reflected as higher venous saturation. (from Bartlett, Surgery Annual, 1971)
Figure 3.9: Four methods of describing lung dysfunction based on lung oxygenation. For the curves describing saturation and PaO2 it is assumed that FiO2 = 1.0, PCO2 = 40, and SvO2 = 75. For the curve describing Aa gradient and PF ratio it is assumed that FiO2 is adjusted to maintain PaO2 at 70 and SaO2 at 95.
pressure of CO₂. pCO₂ in gas can also be measured by injecting the gas to be tested into a conventional blood gas machine containing a CO₂ electrode. The partial pressure of CO₂ in blood (or gas) is measured by CO₂ electrode described by Severinghaus. The electrode is made of a pH electrode surrounded by an electrolyte solution and covered by a gas permeable membrane. The electrode is placed in the test solution and CO₂ equilibrates across the membrane causing a change in pH which is registered as a voltage change. When this electrode is calibrated against known standards the partial pressure of CO₂ can be measured. "Blood gas machines" contain a Clark electrode, a Severinghaus electrode and an uncovered pH electrode. Thus, the primary measurements are pO₂, pCO₂, and pH. The temperature is controlled at 37°. Based on these four controlled or measured variables, the saturation and bicarbonate and buffer base deviation are calculated. If the hemoglobin concentration is known, then the oxygen content can be calculated and the bicarbonate level can be more exactly calculated by taking into account the effects of carbamino compounds. Most blood gas machines in current use purge the blood sample with cleaning solution and inject a calibrating solution automatically, then print out the results which includes three actual measurements, a host of calculations, and even a professional sounding interpretation ("moderate hypoxemia with hypocarbia and mild respiratory alkalosis. This pattern suggests hypoxemia with compensatory hyperventilation.")

CO₂ production is increased or decreased by each of the factors that causes an increase or decrease in VO₂. Most of the carbon dioxide in blood is present as bicarbonate ion which can not change quickly (somewhat analogous to the total blood hemoglobin or red cell mass in relationship to oxygen). However the metabolically produced CO₂ is mostly present as dissolved carbon dioxide, added to the blood in the peripheral tissues and excreted in the lung. The relationships between CO₂ content, bicarbonate, and dissolved CO₂ are shown in Figure 3.10.

Figure 3.10: The distribution of carbon dioxide in blood. (from Bartlett, Surgery Annual, 1971)

Notice that the AVDO₂ difference for CO₂ is 5 cc/dL, the same as that for oxygen. In a steady state the amount of CO₂ excreted through the lung is exactly equal to the amount of CO₂ produced in peripheral tissues. However because the amount excreted is so easily influenced by minor changes in ventilation the assurance of a steady state is particularly important when VCO₂ is measured at the airway. The amount of CO₂ excreted is a function of ventilation of perfused alveoli (i.e. the alveolar ventilation per minute). The relationship between alveolar ventilation and CO₂ excretion is shown in Figure 3.11.

CO₂ Transfer in the Lung: The amount of carbon dioxide excretion is directly related to alveolar ventilation as discussed above. Even if 75% of the alveoli are not inflated, hyperventilation of the remaining 25% can maintain normocarbia in arterial blood, whereas profound hypoxemia will result from 75% shunt regardless of the level of FiO₂ or ventilation of remaining alveoli. These relationships are shown in Figure 3.12, again illustrating that oxygenation is a function of matching blood flow to inflated alveoli,
Figure 3.10: The distribution of carbon dioxide in blood. (from Bartlett, Surgery Annual, 1971)
Figure 3.11: CO₂ excretion related to ventilation for a typical 75 kg adult. (Adapted from Nunn)
whereas CO2 excretion is a function of ventilation or hyperventilation of alveoli with some blood flow. In this example the shunt fraction is 50%. Perfusate venous blood has a saturation of 80%. Half the blood goes to the shunt and exits unchanged. The other half of the blood goes to inflated alveoli and becomes fully saturated so that the resultant saturation is 90% with systemic hypoxemia at pO2 55. The same distribution of blood flow occurs with regard to CO2 exchange, and blood leaves the collapsed alveoli with a pCO2 of 50. However hyperventilation of the functional alveoli reduces the pCO2 to 20, so that the results in arterial pCO2 is 35.

Figure 3.12: O2 and CO2 Exchange During Shunt. (from Bartlett, Respiratory Care, 1980).

Oxygenation can be monitored continuously and on-line by measuring saturation in blood or transcutaneously with a pulse oximeter. Unfortunately there is no effective way to measure blood pCO2 continuously. Several companies have developed micro pCO2 electrodes which are moderately effective but electrical drift and thrombosis on the membrane limits reliability, and a measurement device which is not reliable is worse than no device at all. Consequently, in the current state of the art on-line blood gas measurements are possible but impractical. Since the carbon dioxide in exhaled gas is in equilibrium with pCO2 in blood, and since the pCO2 can be measured with a spectrophotometer at the exact end of a normal breath (end tidal measurements), this measurement of end tidal CO2 can be used to estimate arterial blood pCO2 continuously.

Normally the end tidal CO2 represents mixed alveolar gas which is in equilibrium with pulmonary capillary blood, hence with arterial blood. Therefore the end tidal CO2 and the PaCO2 should be almost identical. The respiratory center is keenly sensitive to the level of PCO2, so that the automatic rate and depth of breathing is regulated to maintain the arterial PCO2 at 40 torr. The end tidal CO2 should be the same or just slightly less. There is no way that the PaCO2 can be lower than the end tidal CO2. If some of the end tidal gas has not been in equilibrium with pulmonary capillary blood, this gas will not contain CO2 and will dilute the CO2 in end tidal measurements, so that end tidal CO2 is lower than PaCO2. This situation will occur whenever there is a significant amount of lung which is ventilated but not perfused, (i.e., dead space) and/or over ventilated and minimally perfused, and/or some of the end tidal gas represents inflation gas which is simply compressed and released, never having reached the alveoli. The latter situation inevitably occurs under any positive pressure ventilation circumstance, but only creates a significant end tidal PaCO2 gradient when peak airway pressures are very high (over 30 cmH2O) and the compression volume is a significant component of each exhaled breath. The end tidal CO2 measurement, then becomes a very useful continuous PaCO2 monitor when the lung is nearly normal, as in ventilator weaning. In addition the gradient between end tidal and arterial CO2, when it is
Figure 3.12: O2 and CO2 exchange during shunt (from Bartlett, Respiratory Care, 1980).
Figure 3.13: End tidal CO2 monitoring. In this example venous, arterial, and airway pCO2 are shown during various breathing patterns. The end tidal CO2 is very close to arterial pCO2 as long as there is no dead space at the alveolar level. Increased alveolar level dead space, (such as emphysematous bullae, honey combing from lung injury, or exclusion of blood flow by fibrosis or low cardiac output) causes the end tidal CO2 to be lower than PaCO2.
large, acts as an indirect measure of non-perfused alveoli and/or compression volume. The details of end tidal CO2 monitoring are diagrammed in Figure 3.13.

**Pathophysiology of Respiratory Failure**

The lung has a limited repertoire of response to injury. Regardless of the specific cause, pulmonary dysfunction can be classified under two headings, (1) **alveolar collapse**, partial or complete, that is, decreased functional residual capacity (FRC) and (2) **pulmonary edema** caused by high hydrostatic pressure, increased capillary permeability, or both.

**Alveolar Collapse.**

Decrease in functional residual capacity is caused by incomplete alveolar inflation related to (1) shallow breathing, (2) partial or complete airway occlusion, which may be generalized (as in bronchospasm) or localized (as in gastric aspiration), (3) absorption atelectasis, which occurs when oxygen is substituted for nitrogen in the inspired gas, or (4) conditions in which air or fluid is occupying potential alveolar space in the chest such as pneumothorax, hemothorax, or pulmonary edema.

Figure 3.14: Causes and effects of alveolar collapse. (from Bartlett, Respiratory Care, 1980)

Pulmonary arteriolar spasm in response to local hypoxia autoregulates pulmonary blood flow and maintains adequate gas exchange during alveolar collapse — up to a point. However, when the loss in ventilation exceeds the decrease in perfusion, a ventilation-perfusion mismatch occurs, which results in incomplete oxygenation of blood perfusing that area of lung. The resultant hypoxemia stimulates an increased rate and depth of breathing, which may serve to re-expand the partially inflated area of lung. If it does not, the hypoxemia will continue, but increased ventilation in other areas of lung will result in excess CO2 excretion, hypocapnia and respiratory alkalosis. This blood gas picture, hypoxemia with respiratory alkalosis, is the most common abnormality of gas exchange in ICU patients and is the hallmark of ventilation-perfusion imbalance.

Oxygenation of blood in the poorly ventilated area of lung can be improved by the increasing concentration of oxygen in the inspired gas. As long as the airways are pinhole patent and the alveoli are inflated at all, the hypoxemia of ventilation-perfusion (V/Q) imbalance can be reversed by provision of supplemental oxygen. Of course, use of supplemental oxygen treats the symptom rather than the basic cause and may actually make the problems worse by adding to absorption atelectasis, depriving the poorly ventilated area of nitrogen to hold alveoli open. This may lead to total alveolar collapse. In that circumstance, blood perfusing the non-ventilated area (transpulmonary shunt) will mix with blood from other areas of the lung, resulting in hypoxemia that does not improve significantly in response to administration of oxygen.

The reasons for this are shown in Figure 3.12. Blood perfusing the atelectatic lung mixes with blood perfusing the more normal lung, resulting in a decrease in oxygenation and an increase in blood carbon dioxide. Increasing the inspired oxygen to 100 per cent may result in a large increase in pO2 in the blood exiting from the normal lung. However, the major increase in pO2 is associated with a very small increase in oxygen content, since the oxygen that raises the pO2 (from 100 to 500, for example) is the small amount dissolved in plasma. The oxygenation of the arterial blood is an average of the oxygen content of blood from the two areas of lung, not an average of the pO2. Therefore, systemic hypoxia
ALVEOLAR COLLAPSE

CAUSED BY:

INCOMPLETE INFLATION

\[ \downarrow \text{VOLUME} \]

BLOCKED AIRWAY

\[ \downarrow \text{O}_2 \text{ ABSORPTION} \]

\[ \uparrow \text{LUNG WATER} \]

LEADS TO:

V/Q IMBALANCE

HYPOXEMIA

\[ \downarrow \text{FRC} \]

\[ \downarrow \text{COMPLIANCE} \]

\[ \uparrow \text{WORK} \]

Figure 3.14: Causes and effects of alveolar collapse (from Bartlett, Respiratory Care, 1980)
will persist regardless of the fraction of inspired oxygen (FiO2). When this hypoxemic hypercapnic blood reaches the respiratory center, the rate and depth of breathing are increased. This will result in hyperventilation of the normal lung but no change in ventilation of the atelectatic lung. This hyperventilation will have a minimal effect on oxygenation of blood exiting from the normal lung for the reasons just outlined. However, it will result in excessive excretion of CO2, leading to respiratory alkalosis, just as in the lesser degrees of ventilation-perfusion mismatch discussed earlier.

Aside from the effects on gas exchange, loss of alveolar space results in changes in the volume-pressure relationships in the lung (that is, pulmonary mechanics). As shown in Figure 3.3, a decrease in functional residual capacity results in a shift in the volume-pressure relationship toward a condition of decreasing compliance. That is, more pressure is required to achieve the same degree of lung inflation. The pressure specified in this graph is alveolar inflating pressure, or transalveolar pressure. This pressure is plotted as positive if it serves to inflate alveoli, whether the relationship to atmospheric pressure is positive (as in mechanical ventilation) or negative (as in spontaneous breathing). This method of expressing volume-pressure relationships is a standard procedure and seems straightforward. However, it can become complex when a patient is breathing spontaneously while positive pressure is applied to the airway. Remember that “negative” pressure applied to the pleural space via the diaphragm and “positive” pressure applied to the airway with a ventilator are additive when volume-pressure characteristics are considered.

**Pulmonary Edema**

The causes of pulmonary edema are (1) increased hydrostatic pressure (left ventricular failure or gross fluid overload), (2) decreased plasma oncotic pressure (rarely a problem unless the concentration of plasma protein is very low), and (3) increased capillary permeability. When fluid begins to collect in the lung interstitium, it migrates to the loose areolar portions of the lung microanatomy that surround the small bronchioles and pulmonary arteries. Edema in these areas has the effect of narrowing bronchi and increasing resistance in the pulmonary vasculature. This will decrease both ventilation and perfusion in the edematous area, but ventilation is often affected more than is blood flow, resulting in a decreased V/Q ratio, with all of its attendant effects on gas exchange. As more fluid collects in the lung, it may compress alveoli and eventually will flood into the alveoli, further decreasing FRC and ultimately leading to transpulmonary shunting.

The interrelationships between lung edema, atelectasis, and gas exchange in ICU patients are often misunderstood. The amount of lung dysfunction (measured as shunt,
A R F: ↑LUNG WATER

CAUSED BY:
- Chemical Damage
- Capillary Leakage
- ↑ L A Pressure
- ↑ ECF

LEADS TO:
- ↑ Pulm. Vasc. Resistance
- ↓ FRC
- V/Q Imbalance
- Infection

Figure 3.15: Causes and effects of pulmonary edema. (from Bartlett, Respiratory Care, 1980)
Figure 3.16: Shunt fraction related to the amount of edema in the lung.
Figure 3.17: Alveolar fluid, interstitial fluid, and pulmonary lymph flow during progressive levels of pulmonary capillary leakage. (from Bartlett, Respiratory Care, 1980)
V/Q imbalance, or decreased compliance) may parallel changes in pulmonary edema or may be totally unrelated. Under normal conditions, there is a net efflux of "filtrate" across the pulmonary capillary bed of about 20 ml per hour. (Figure 3.17). This fluid is entirely cleared from the lung via lung lymphatics. When the amount of transcapillary filtrate increases, for any reasons, the amount of lymph flow increases proportionately, with no net change in the amount of fluid in the lung interstitium. When the lymphatic drainage can no longer keep pace with the amount of transcapillary filtrate, fluid begins to accumulate in the interstitium. This process continues until the interstitial fluid space of the lung is increased by a factor of two or more, then alveolar flooding begins. If the amount of fluid in all the alveoli approaches the amount in the interstitium, the condition is incompatible with life. Significant changes in lung function do not occur until the level of interstitial water is grossly above normal, and at that point, ventilation-perfusion mismatch begins. With slightly more transcapillary filtrate, alveolar flooding and shunting occur. With these relationships in mind, consider the effect of ventilator treatment: Increased airway pressure will tend to hold alveoli open, spread out the space available for water accumulation, and overcome the effects of small bronchial occlusion. (Figure 3.18). These effects will be observed during minimal edema, right up to the point at which the lung is filled with fluid. This is why positive airway pressure improves gas exchange in pulmonary edema. (Positive pressure does not affect the actual amount of edema in the lung, only its manifestations.) This discussion illustrates the point that edema affects pulmonary function only at the extreme, and even then minor changes in pulmonary water can lead to major changes in function. This fact, combined with the observation that any patient may have atelectasis for reasons unrelated to pulmonary edema, leads to confusion and misunderstanding of this aspect of pathophysiology.

RecentlyGattinoni has pointed out that the deleterious effects of interstitial edema are caused, not only by swollen airways and alveolar filling, but also by compression of dependent lung by the simple weight of the edematous lung above it. This phenomenon became obvious when patients with diffuse interstitial edema due to ARDS were examined by CT scan. Although the conventional AP chest x-ray is said to show diffuse homogenous fluid infiltrates throughout both lung fields, CT scan clearly shows that the infiltrates are not diffuse or homogenous at all, but rather consolidated in the most dependent areas of the lung. For most critically ill patients the dependent areas are the posterior areas because the patients are lying supine. Figure 3.19 shows the CT scan of a patient with ARDS. In Figure 3.19A the patient is lying supine and the posterior consolidation involves almost one third of the lung. Blood flowing through this consolidated area does not participate in gas exchange and contributes to transpulmonary shunting. The more anterior lung is relatively normal and accounts for some oxygenation and ample CO2 clearance. Figure 3.19B shows a CT scan of the same patient in the prone position. Notice that most of the posterior consolidation has cleared and the posterior basal segments of the lower lobes are fairly well ventilated. If the patient remains in the prone position for an hour or so the anterior lung, which is now dependent, becomes consolidated. Some of this anterior consolidation can already be seen in Figure 3.19B.
Figure 3.18: The effect of PEEP on interstitial edema
How does this happen? Surely interstitial water can not percolate directly through the lung; there is no anatomic pathway which would allow it. Surely the posterior lung has not been instantly cleared of the edema by lymphatics. There is not enough time for that to happen. We must conclude that the actual amount of water in the interstitium of the lung in the supine and prone positions is the same, it is only ventilation (and to some extent blood flow) which has changed. This leads to the conclusion that it is the weight of the upper lung pushing down on the dependent lung which collapses small airways and alveoli leading to consolidation and transpulmonary shunting.

Conclusive proof of this theory was presented by Gattinoni, using CT scans of normal and ARDS patients. By calculating the Hounsfield number for each cubic centimeter of lung tissue he showed that the amount of water in the interstitium of the ARDS lungs was roughly the same throughout, and much more than in normal lungs. Calculating the weight of this water deeper and deeper into the dependent lung tissue, it is easy to see that posterior lung would be compressed, particularly if the alveoli are somewhat surfactant deficient. Add to this the weight of the abdominal viscera in the chronically supine critically ill patient, and it is easy to see why posterior lower lobe consolidation is characteristic of acute respiratory failure. Some of the data from Gattinoni's paper is shown in Figure 3.20. In other studies the effect of PEEP on lung inflation has been studied by CT scanning. It is interesting to note that once collapsed alveoli become inflated (either by prone positioning or by maximal peak inflating pressure) the amount of PEEP that is necessary to hold those alveoli open generally corresponds to the weight of a water column which could be supported by that level of pressure. This is probably why 5-10 cmH2O PEEP is maximal in a newborn infant, whereas 20-30 cmH2O is maximal in an adult patient. The difference is simply related to the anterior/posterior diameter of the chest when the patient is in a supine position.

Figure 3.19: CT scan of a patient with ARDS. Figure 3.19A shows the patient in the supine position. 3.19B shows the patient in a prone position. Notice that the dependent lung is the most consolidated in both position (from Gattinoni).

Figure 3.20: The amount of fluid in lung slices going from non-dependent (ventral) to dependent (dorsal) as seen with CT scan (from Gattinoni).

The relationship of pulmonary edema to infection and fibrosis is more important than the effect of pulmonary edema on lung function. Atelectasis may exist for weeks with no permanent effects on lung structure. However, just a few days of pulmonary edema — particularly the protein-rich, capillary leakage type of edema — sets the stage for pulmonary infection of rapidly developing fibrosis, or both. The exact mechanisms of cause and effect are not clear. Perhaps the fibrosis is a result of the primary lung injury that also led to edema, or perhaps the fibrosis is the result of treatment given because of the edema. In any case, humoral or airway damage to the lungs sustained over a period of days may lead to pulmonary destruction and fibrosis.

Management of Respiratory Failure

Our algorithm for management of severe respiratory failure is shown in Figure 3.21. For purposes of this discussion severe respiratory failure is defined as the requirement for intubation, mechanical ventilation, and supplemental inspired oxygen. Although routine
Figure 3.19: CT scan of a patient with ARDS. Figure 3.19A shows the patient in the supine position. 3.19B shows the patient in a prone position. Notice that the dependent lung is the most consolidated in both position (from Gattinoni).
Figure 3.20: The amount of fluid in lung slices going from non-dependent (ventral) to dependent (dorsal) as seen with CT scan (fromGattinoni).
ventilator patients can be managed without a pulmonary artery catheter, that device provides essential information for the management of severe respiratory failure and placement of a pulmonary artery catheter is assumed for purposes of this discussion. Whenever a pulmonary artery catheter is placed we use a fiberoptic oximeter catheter (Oximetrix) which provides continuous measurement of mixed venous saturation. We do this because most of the important steps in management of severe respiratory failure are based on mixed venous saturation monitoring.

Although the cause of respiratory failure is usually in the lung interstitium and parenchyma, it is important not to overlook simple mechanical causes such as pneumothorax, hydrothorax, plugged endotracheal tubes, occluded airways, or ascites. Bronchoscopy should be carried out if there is any question of aspiration or if there is any evidence of mucus plugging or impaction in the airways. Although ventilatory management with an indwelling endotracheal tube can be carried out for days or weeks, the incidence of bacterial pneumonia with chronic intubation, the gas flow resistance of endotracheal tubes, and the obligatory linkage of extubation with ventilator weaning all prompt us to recommend tracheostomy rather than chronic intubation for the management of patients with severe respiratory failure. Pulmonary embolism should be considered as a cause of respiratory failure in any patient if the pulmonary artery systolic pressure is greater than 40 mmHg.

Figure 3.21: Respiratory failure management algorithm

Optimizing systemic oxygen delivery in relationship to oxygen requirement is the primary goal of management. Improving oxygenation of the blood itself by improving alveolar inflation is only one of the steps in optimizing oxygen delivery. Equally or more important are treating anemia and optimizing cardiac output. Most ICU patients are anemic, and oxygen delivery is maintained by a compensatory increase in cardiac output. This is an acceptable practice because most patients have adequate cardiac reserve to compensate anemia, and because of the potential infectious complications of blood transfusion. However the patient with severe respiratory failure is at risk of dying from decreased oxygen delivery (or multiple organ failure related thereto), so that the risk of transfusion is minor compared to the risk of the primary problem. This is complicated by the fact that cardiac output may be compromised in these patients, either by the primary disease or by efforts to increase oxygenation by using airway pressure. Accordingly, oxygen delivery in these patients should be optimized first by maintaining a normal hematocrit. Secondly, cardiac output should be optimal (not necessarily maximal) to maintain delivery four to five times consumption. In general this means avoiding those factors which decrease cardiac output, rather than actively trying to increase cardiac output. This includes keeping the airway pressure as low as possible to maximize venous return, avoiding abdominal distention, maintaining appropriate blood volume based on pulmonary capillary wedge pressure in the range of 15 mmHg, and maintaining blood pressure high enough to provide coronary perfusion (over 50 mmHg mean pressure), but not so high as to limit left ventricular function (over 90 mmHg mean arterial pressure). If all of these steps are taken cardiac output will usually autoregulate to maintain delivery at four to five times consumption. If myocardial contractility is inadequate then inotropic drugs such as dopamine or dobutamine should be used, however it should be recognized
Respiratory Failure Algorithm

Acute Respiratory Failure (tube, vent, FiO₂> .5) (Arterial catheter, Oximetry PA catheter)

**Mechanical RX**
- Treat pneumothorax, hydrothorax
- Large ET tube, Tracheostomy
- Bronchoscopy
- Bronchodilators
- Rx ascites
- Consider PE if PA systolic>40

**Ventilator RX**
- Ventilation
  - TV 5cc/Kg rate 10
  - adjust TV, rate to PaCO₂ 40
- Oxygenation
  - FiO₂ .5
  - PEEP 5
  - PEEP to V Sat max
  - FiO₂ to V Sat max

**Systemic RX**
- Maximize O₂ delivery
  - Sat>95%
  - PRBC to Hct>40
- ↑ CO to V Sat>70

**Antimicrobial**
- Common
- Empiric

**Figure 3.21: Respiratory failure management algorithm**
that these drugs increase oxygen consumption in addition to increasing contractility. The overall benefit and titration of inotropes should be based on mixed venous saturation measurements.

Finally, oxygen delivery can be maintained by assuring adequate saturation of arterial blood. This can be done by supplying supplemental oxygen to the airway and by improving inflation of collapsed or poorly ventilated alveoli. FiO₂ is increased to 50 or 60% as the initial step in treating hypoxemia. Alveolar collapse is treated as outlined earlier, cleaning airways, avoiding 100% oxygen, removing fluid from the lung or chest, and finally by the use of end expiratory pressure to hold open those alveoli which have been opened by other measures. The optimal level of PEEP is that level which maintains arterial oxygenation but does not decrease venous return or cardiac output. This optimal level is best determined by monitoring mixed venous saturation. When varying the amounts of end expiratory pressure the position of the patient on the pressure volume curve should be noted, and volume should be decreased if peak airway pressure exceeds 40 cmH₂O. Another step in optimizing lung function is to take advantage of the gravitational effects on pulmonary blood flow by turning the patient prone or to a full lateral position to direct the blood flow to areas of optimal alveolar inflation. (These steps will often result in the opening of closed posterior alveoli which have been compressed by the weight of fluid in the lung).

At the same time that oxygen delivery is optimized, oxygen consumption should be decreased to normal or even below normal if necessary. Treating infection, providing adequate sedation, and establishing muscular paralysis decrease oxygen consumption, and decrease the need for oxygen delivery. The degree of sedation or paralysis, as with other steps in treatment, is based on mixed venous saturation. If oxygen delivery is still inadequate for metabolic needs despite these measures (i.e. venous saturation is less than 60-70%) oxygen consumption can be further decreased by actively cooling the patient, realizing that cooling will result in coagulopathy, and arrhythmias if the temperature is below 33°C.

Optimizing CO₂ removal is usually an easier step than optimizing oxygen delivery. Ventilator rate and tidal volume are adjusted to achieve normal arterial PaCO₂, being careful to avoid peak airway pressure greater than 40 cmH₂O. If PaCO₂ exceeds 45 mmHg the tidal volume and/or rate are increased until PCO₂ is normal. CO₂ production can be minimized by sedation, paralysis, and treating infection. CO₂ production can be further decreased by avoiding heavy carbohydrate loads in the nutritional regimen, and by cooling the patient. If PaCO₂ exceeds 45 despite these measures (and assuming tube or airway occlusion is ruled out), it is permissible to tolerate hypercarbia and achieve acid base balance with bicarbonate or Tham® buffer. This step is preferable to going to extremes of airway pressure over 40 cmH₂O, which will further injure the lung. Some of the other details of mechanical ventilator management are discussed below.

If oxygen delivery or CO₂ excretion are inadequate despite all these measures the likelihood of survival is less than 10%. In this situation it is reasonable to consider extracorporeal circulation with gas exchange (extracorporeal membrane oxygenation, ECMO) as an alternative. In this procedure catheters are placed into large vessels and venous blood is removed, oxygenated, CO₂ is removed, and the blood is returned to the arterial or venous circulation thus providing mechanical support of pulmonary (or cardiopulmonary) function. This procedure requires systemic heparinization and a well-
trained and experienced team. It is often necessary for one to four weeks in such a patient, however the current survival rate is 60-70% in moribund adult patients with severe respiratory failure.

General steps in managing the patient are important throughout the course of severe respiratory failure. In particular, fluid overload should be treated with diuresis or hemofiltration until the patient is returned to dry weight. Successful outcome in the management of severe respiratory failure is correlated with overall fluid balance; fluid overload results in a lower survival rate. As diuresis or hemofiltration is carried out the patient will become hypovolemic. As mentioned above cardiac output must be supported and the combination of diuresis and packed red blood cell transfusion is usually the best approach to maintain normal blood volume in the early stages of severe respiratory failure.

**Mechanical Ventilation**

Mechanical ventilation should be considered when spontaneous breathing is inadequate to maintain gas exchange, or when the effort required to maintain gas exchange is exhausting the patient. Oral tracheal intubation is preferred. Nasotracheal intubation is more uncomfortable, causes sinusitis, and requires the use of a smaller longer tube. The use of oral tracheal intubation for as long as 2-3 weeks is common practice but is probably not wise. Aside from the obvious damage to the larynx and discomfort for the patient, the tube enters the sterile airway through the grossly contaminated pharynx. Despite the best attempts at oral hygiene, the posterior pharynx harbors a slurry of virulent organisms that inevitably track down along the endotracheal tube to colonize the airway, if not the alveoli. Tracheostomy is much more comfortable for the patient, offers much lower airway resistance, and, most importantly, avoids contamination of the lower airway. Having been through the phase of favoring chronic intubation, we now prefer early (Day 1 or 2) tracheostomy for any patient with major respiratory failure.

Figure 3.22: Potential complications related to oral tracheal intubation and tracheostomy are shown. The complications of pressure cuff injury and contamination can occur with either method of airway access, but the contamination from tracheostomy is much less likely with less virulent organisms than contamination through the posterior pharynx. (from Anderson and Bartlett, Respiratory Care, 1991)

**Ventilator Management**

When mechanical ventilation is used because of coma, respiratory depression, paralysis or weakness, or during recovery from prolonged anesthetics and operations, the lungs are normal and the intent of using mechanical ventilation is simply to provide gas exchange and keep the lungs normal until the patient is able to breathe spontaneously. In fact mechanical ventilation is used to prevent atelectasis in patients who are recovering from major operations and might hypoventilate if extubated in the recovery room. Using the ventilator in this basic maintenance or prophylactic mode is easy, and simply requires avoiding ventilator-induced complications. On the other extreme, mechanical ventilation is used for both life support and active treatment of the lung in severe respiratory failure. In this application ventilator management is critical, and it is possible to do more harm than good by applying damaging pressure or oxygen concentrations. Therefore the choice of the mode of mechanical ventilation and the type of ventilator used depends to a large extent on the clinical application. Simple inexpensive ventilators without complicated
Figure 3.22: Potential complications related to oral tracheal intubation and tracheostomy are shown. The complications of pressure cuff injury and contamination can occur with either method of airway access, but the contamination from tracheostomy is much less likely with less virulent organisms than contamination through the posterior pharynx. (from Anderson and Bartlett, Respiratory Care, 1991)
settings and detailed monitoring are perfectly adequate for the routine or prophylactic application. Complex ventilators which allow for monitoring and adjustment of minute details of pressure, flow, and volume are necessary for appropriate management of severe respiratory failure. The descriptive terms and abbreviations that have grown up with mechanical ventilation are confusing and modified almost every year, but it is necessary to learn the language to use the apparatus. The terms and modes of use are best approached by examining the primary and secondary controls on the typical mechanical ventilator (Figure 3.23). This initial discussion will deal exclusively with volume limited ventilation because that is the mode most widely practiced. Later the discussion will turn to pressure limited ventilation which is preferred if not required for the management of severe respiratory failure.

The primary controls, as outlined in Figure 3.23 are FiO2, tidal volume, respiratory rate, end expiratory pressure, and maximum inspiratory pressure safety limit. If the tidal volume is set at 10 cc/kg and the respiratory rate at 10/min, each breath will take six seconds (roughly 2 seconds during inspiration and 4 seconds during expiration). The minute ventilation will be 100 cc/kg/min. This is about 20% more than normal minute ventilation and moderate respiratory alkalosis may result, depending on the VC02. For a person with normal lungs the PEEP is set at zero, although some would say that 5 cc of PEEP is appropriate to compensate for absent glottic control which is absent because of the endotracheal tube. Finally the maximum inspiratory pressure safety limit is set at 40 cmH2O because pressures above that level will over-distend normal alveoli. In a patient with normal lungs each 10 cc/kg breath will require only 10 or 15 cmH2O pressure generated by the ventilator. Most ventilators have alarms which are set by the operator to identify low tidal volume, respiratory rate or apnea, low PEEP level, high PIP level, and mean airway pressure. Using these primary controls and monitors, the ventilator is used in one of the modes identified at the bottom of the figure in 3.23. If the patient cannot initiate spontaneous breathing, then the ventilator is timed cycled resulting in a mode called controlled mechanical ventilation. If the patient can breath spontaneously then the ventilator is adjusted so that a breath is delivered each time the patient initiates a breath. Used in this fashion, ventilation is referred to as assisted ventilation. If there is a backup rate which initiates a mechanical breath if the patient does not initiate a spontaneous breath within a certain number of seconds, this mode is referred to as assist control. This is the mode most widely used because the patient who controls his own rate of breathing will adjust that rate to achieve normocarbia, avoiding the need for frequent blood gas measurements. It is possible to let the patient breath spontaneously from the ventilator without mechanical assistance, allowing the patient to regulate not only his own respiratory rate but also his tidal volume. This mode of spontaneous breathing is usually combined with occasional mechanical assisted large volume breaths delivered 2 or 3 times each minute. This mode of ventilation is known as spontaneous breathing with intermittent mandatory ventilation (IMV). If those large volume breaths are delivered only when a patient initiates a breath, the mode is referred to as synchronized IMV (SIMV).

Figure 3.23: Controls, monitors, and modes of use for mechanical ventilation. (from Bartlett, Mechanical Ventilation, 1994).
<table>
<thead>
<tr>
<th>Controls</th>
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<td>Tidal volume</td>
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<td>Respiratory rate</td>
<td>Respiratory rate</td>
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<td>Positive end-expiratory pressure (PEEP)</td>
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<td>Maximum inspiratory pressure</td>
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<td>Inspiratory flow rate</td>
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<td>Sigh rate, volume, and maximum pressure</td>
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<tr>
<td>Trigger sensitivity for assist and IMV models</td>
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| Modes of Ventilation                         |                     |
| Controlled mechanical ventilation (CMV)      |                     |
| Assist control (AC)                          |                     |
| Intermittent mandatory ventilation (IMV)     |                     |
| Synchronized IMV                             |                     |
| Continuous positive airway pressure (CPAP)   |                     |
| Pressure-controlled ventilation (PCV)        |                     |
| Pressure-controlled inverse-ratio ventilation (PC-IRV) |                 |
| Pressure support (PS)                        |                     |

Figure 3.23: Controls, monitors, and modes of use for mechanical ventilation. (from Bartlett, Mechanical Ventilation, 1994).
There are secondary controls on the ventilator related to the flow rate, flow pattern, trigger sensitivity for assisted breaths and regulation of IMV breaths. When the ventilator is set up and the primary controls and alarms are dialed in, the pressure volume and flow of a single breath typically look like the tracings shown in Figure 3.24. In this example a tidal volume of 750 cc and the timed cycle or control mode of ventilation has been selected. At the beginning of the breath gas flow begins and continues at a pre set rate until the 750 cc volume has been delivered. The pressure rises rapidly in response to this volume inflation, reaching peak pressure of 36 cmH2O. When the 750 cc tidal volume has been reached, gas flow stops but the exhaled valve is still held closed for one second because a one second inspiratory hold has been selected by the operator. During this inspiratory hold the pressures equilibrate so that the pressure used for compliance calculations in this example is 30 cmH2O. Then the expiratory valve is opened and exhalation proceeds passively. Exhalation continues until the next time cycled breath begins which is six seconds after this breath began if the respiratory rate is 10/min. This cycle is repeated breath after breath while the operator examines the lungs with a stethoscope, observes the respiratory effort, or lack of it on the part of the patient, watches the pulse oximeter and the end tidal CO2 monitor, and perhaps measures blood gases in an arterial blood sample. The FiO2 is usually set at 50% at the initiation of mechanical ventilation, then FiO2 is decreased to the level which results in arterial saturation between 95 and 99%, as detected with the pulse oximeter. This is done because oxygen delivery is more than ample at full saturation, and FiO2 should be maintained at the lowest level which allows full saturation to avoid displacement of nitrogen and subsequent absorption atelectasis. Using the continuous non-invasive monitors or pulse oximeter and end tidal CO2 monitoring it is possible to manage patients with normal or near normal lungs for days without measuring either arterial or venous blood gases.

Figure 3.24: Pressure, flow, and volume during a typical breath generated by a time-cycled, volume limited mechanical ventilator. (from Bartlett, Mechanical Ventilation, 1994)

The principles in using the mechanical ventilator for the management of severe respiratory failure are exactly the same, with the realization that the levels of pressure and oxygen which would be necessary to achieve normal blood gases might be very damaging to the lung. Under these circumstances it is safer to accept moderate hypoxemia and hypercarbia than it is to strive for total normalization of blood gases. Suppose that the settings outlined above including FiO2 .5 and tidal volume 10 cc/kg rate 10 are initiated in a patient with severe respiratory failure, but the resulting arterial saturation is only 85% and the end tidal and/or arterial pCO2 is 55. How should the ventilator settings be modified? First of all it is important to realize that adjustments aimed at normalizing oxygenation are quite different than adjustments aimed at normalizing pCO2. CO2 clearance is achieved by increasing alveolar ventilation by regulating respiratory rate and tidal volume taking care not to exceed 40 cmH2O peak inspiratory pressure. Oxygenation is facilitated by increasing peak inspiratory pressure to achieve inflation (but not over 40) and increasing PEEP to hold inflation. These approaches may be mutually exclusive. For example, increasing PEEP while limiting PIP will result in smaller tidal volume. If this is the case it is better to err on the side of adequate oxygenation, allowing hypercarbia.
Figure 3.24: Pressure, flow, and volume during a typical breath generated by a time-cycled, volume limited mechanical ventilator. (from Bartlett, Mechanical Ventilation, 1994)
For the past 25 years, volume limited ventilation has been the preferred mode of ventilation in adult ICUs. Large tidal volumes were the rule regardless of the inflating pressure required to squeeze the volume in. In the last few years it has been widely recognized that this was a mistake. The high pressures over-inflated the most normal alveoli in the lungs resulting in capillary stretching, capillary leakage, more pulmonary edema, alveolar rupture and often pleural rupture leading to pneumothorax. This barotrauma can occur with only a few breaths at high pressure forcing in large tidal volume into partially inflated lungs. (The trauma is actually volutrauma resulting in over distention rather than pressure induced barotrauma). For years this baro/volutrauma was attributed to PEEP, because those patients who were treated with PEEP at fixed tidal volumes at the highest PIP. It is now clear that the injury is caused by peak pressure and over distention rather than mean or end expiratory pressure. Now, in one of the most rapid turnarounds in worldwide intensive care management, peak inspiratory pressure is limited to 40 cmH2O. Some would say that even 40 cm is too high, favoring pressures closer to 30. At any rate it is generally recognized that over-distention must be avoided and if hypercarbia or hypoxemia results, that is a safer situation than using higher pressures or volumes. This practice has reminded us of some elementary facts regarding tolerance to hypercarbia and hypoxia. Respiratory acidosis causes very few side effects. Patients can do very well with PaCO2 of 80 and a pH of 7.1 for hours or days. We have all cared for asthma or COPD patients who do very well despite pC02's in the 60's. Hypoxemia is also well tolerated as long as systemic oxygen delivery is adequate. Using the principles discussed earlier in this chapter, it is much safer to transfuse red cells, use low doses of inotropic drugs, and decrease VO2 by paralysis and hypothermia than it is to raise the FiO2 over 60%. In the early days of cardiac surgery we all cared for perfectly functional children who lived for many years breathing air with arterial pO2s in the 30s.

When the lung recovers from acute respiratory failure (or when the postoperative patient is fully alert and awake) it is time to think about weaning from mechanical ventilation to spontaneous breathing. Some simple measurements of lung function and pulmonary mechanics assure us that the patient is ready for spontaneous breathing and extubation. Arterial saturation should be greater than 90% at FiO2 .3 or less. The patient should be able to generate an inspiratory force > 20 cmH2O and a spontaneous vital capacity at least twice the tidal volume. If an end tidal CO2 monitor is used, the ETCO2 should be < 40. These weaning parameters are summarized in Figure 3.25.

Figure 3.25: Parameters used to determine when a patient is ready for a trial of ventilator weaning.

When the patient meets these parameters, the patient is disconnected from the ventilator (or the ventilator is adjusted to provide a constant gas flow at no significant inflating pressure) and the patient is encouraged to breath regularly and deeply. The respiratory rate and the pulse rate are monitored, the latter to provide a rough estimate of the work of breathing, because if the patient has to exert a lot of energy to sustain breathing the pulse rate will steadily rise. If the patient is able to breath deeply and spontaneously at a rate < 20 and a pulse rate < 90 than the patient is extubated. It is always easier to breath through the normal airway than through the endotracheal tube, so the respiratory rate and pulse rate will be even lower after extubation. If the respiratory rate is over 30 or the pulse rate is over 100 the patient will probably not tolerate extubation and should be returned to
Weaning Criteria

- Insp. Force > 20 cm H2O breathing
- TV - 5 cc/Kg
- VC - 10 cc/Kg

- VE 1L/10Kg/min on
- SaO2 > 95, FiO2 < 4 PEEP < 5 ventilator

Figure 3.25: Parameters used to determine when a patient is ready for a trial of ventilator weaning.
mechanical ventilation until the problem is identified. If the pulse and respiration are in
the intermediate zone the decision for extubation is based on oxygenation and CO2
clearance measured by pulse oximetry and end tidal measurement or by arterial blood
gases. (Figure 3.26)

Figure 3.26: After a brief period of spontaneous breathing, the patient is extubated if the respiratory rate is
under 20.

Some patients may have adequate or borderline weaning parameters but fail
spontaneous breathing trials or require intubation following extubation. Our protocol for
these difficult weaning patients is shown in Figure 3.27. If a tracheostomy has not already
been done, it is the first and often most important step in managing the patient who is
difficult to wean from the ventilator. Aside from the comfort and bacteriological benefits
of tracheostomy mentioned earlier, in a difficult-to-wean patient the tracheostomy
decreases the dead space or re-breathing space by about 50 cc. It also decreases the airway
resistance considerably because the short tracheostomy tube has much less resistance than
the longer endotracheal tube. Even more important than these principles of physics are
the practical principles of the risk of extubation. "Difficult ventilator weaning "often
means that the patient is being kept on a ventilator simply because if the patient develops
thick secretions or hypoventilation hours or days following extubation, a respiratory
disaster might occur before the patient could be electively or urgently reintubated. So the
patient remains on the ventilator because of the nervousness of the responsible care team.
All this concern is eliminated by tracheostomy. In addition it is much easier to get the
patient out of bed, sitting in a chair, standing, and walking by the bedside. Trials of
spontaneous breathing through the tracheostomy tube are simple and carry no risks.
Trials of spontaneous breathing through an endotracheal tube are exhausting for the
patient and unsettling for the nursing staff. For all these reasons patients who are difficult
to wean often are completely off the ventilator within a day or two following
tracheostomy. The second step in managing the "difficult to wean" patient is to measure
the respiratory quotient and assure that CO2 production is kept to a minimum. Since
ventilator weaning is, in essence, breathing exercise, and since the reason for breathing is
CO2 elimination, the amount of breathing which is necessary as determined by the rate of
CO2 production. Increased metabolic activity such as sepsis or unnecessary muscular effort
should be minimized. Enteral and parenteral feeding should be adjusted so that the
predominant substrate is fat and the total calories are slightly less than the REE. This will
drive the respiratory quotient down to .7 or .8, proportionately decreasing the need for
alveolar ventilation. Metabolic alkalosis is the most common abnormality of acid base
balance in the ICU. This is caused by chronic gastric acid aspiration, diuretics, and the
presence of lactate or acetate in intravenous fluids. If the patient has metabolic alkalosis
and is difficult to wean from the ventilator, the alkalosis should be treated with
intravenous infusions of .1 normal hydrochloride acid until pCO2 40 is associated with pH
of 7.4.

Figure 3.27: Protocol for management of patients who are difficult to wean from mechanical ventilation.
Figure 3.26: After a brief period of spontaneous breathing, the patient is extubated if the respiratory rate is under 20.
Difficult Wean

↑ Airway Resistance
   Risk of Extubation → Tracheostomy

↑ VCO2 → Rx sepsis, ↓ CHO feed

Metabolic Alkalosis → Rx HCl

Lung Parenchymal Disease → Enteral feeding

Strength and Endurance → Tolerate

Conditioning

Sitting
Standing, walking
Protein feeding

Ventilation

Pressure support mode
↓ P based on respirate
Timed trials off when P < 10

Figure 3.27: Protocol for management of patients who are difficult to wean from mechanical ventilation.
After these three practical and metabolic steps are taken, ventilator weaning might be limited by lung parenchymal disease, particularly residual lung injury presenting as honeycombing (alveolar gas space without blood supply), and interstitial fibrosis. These conditions often take months to resolve, and may require that the patient be weaned from a ventilator with moderate hypercarbia and hypoxia. Pulmonary edema should be treated, if present, to maintain the patient at dry weight. Often elderly patients with cardiac disease must be carefully balanced between pulmonary edema and congestive heart failure, requiring a left atrial pressure of 20 cmH2O for adequate cardiac function, but developing pulmonary edema at pressure of 22 or 23. In these patients it is necessary to have a pulmonary artery catheter in place to facilitate ventilator weaning. However in most patients who are difficult to wean, one of the important steps is to remove central PA lines, central venous lines and arterial catheters, this step has three benefits: The patient is much more mobile and can stand or sit at the bedside without risk of dislodging catheters. All of the monitoring focuses on pulse oximetry and end tidal CO2, decreasing the temptation to focus on minor ventilator changes. Thirdly, the patient without monitoring catheters is no longer considered critically ill but rather has graduated to rehab status. This simple change in the perception of the patient, the family, and the care team results in a different approach to management and some evidence of the formerly critically ill patient is now well on the road to recovery.

With all of these preliminary steps in ventilator weaning accomplished, all that remains is strength and endurance training. Although sitting in the bed or at the bedside facilitates breathing, nothing works as well or as quickly as standing. In addition to the postural benefits of standing (Figure 3.4) there is something about using the postural support muscles which enhances the strength and endurance of the respiratory muscles. Standing in this context does not mean a few seconds of pivoting from the bed to the bedside chair but bearing all the weight on the feet for an hour or two at a time. For the elderly or frail patient who has just spent two or three weeks at bed rest, often pharmacologically paralyzed, standing requires the use of a circle bed with a foot board, and gradually progressive tilting to the full upright position. Gradual in this context does not mean week or two, but an hour spent at 50°, then 75, then 80, then fully upright.

One of the least important details of strength and endurance testing is the one which receives the most attention, namely management of the ventilator itself. Pressure limited rather than volume limited ventilation should be used, and the "pressure support" mode available in newer ventilators is preferred. With difficult ventilator weaning the pressure limit is progressively decreased based on maintaining the patient's spontaneous respiratory rate around 20-30 breaths per minute. These adjustments in ventilator pressure, backup IMV rate, etc. should be made by the nursing and respiratory staff based on respiratory rate, end tidal CO2, and pulse oximetry without blood gases and without physician intervention or written orders every time the ventilator is changed. When the pressure limit is down to about 10 cmH2O the patient is ready for spontaneous breathing trials with no supplemental assistance from the ventilator. Spontaneous breathing trials should be done with the patient sitting or standing and should progress rapidly from a few minutes to several hours, then day time breathing, then freedom from the ventilator altogether. When a patient is breathing spontaneously through a tracheostomy (or endotracheal) tube the balloon cuff should be deflated so that if the tube becomes occluded with a mucus plug the patient can still breath around the tube while
getting the attention of the nursing staff. This leads to the dilemma of airway secretions with the tube in place. The patient may be strong enough to wean off the ventilator, but still appears to need ICU care because of the requirement for "frequent suctioning". The presence of an artificial airway, particularly when the cuff is deflated and minor episodes of aspiration frequently occur, causes the accumulation of mucus in the airway which in turn requires frequent suctioning. Usually the best way to deal with this problem is to simply remove the tracheostomy tube altogether. It is possible to suction the patient through the stoma for a few days after the tube has been removed and this simple step often solves the problem.

Learning to Manage Mechanical Ventilators

Although the principles of mechanical ventilation are well standardized, the actual devices appear to be quite different. Each ICU will have a standard ventilator used for most patients, with other ventilators available for special purposes or for personal preferences. In most hospitals in the United States ventilators are maintained and managed by respiratory therapists. Indeed, in most US hospitals touching the controls of a mechanical ventilator has become the exclusive domain of the respiratory therapists (elsewhere in the world ventilators are managed by nurses and physicians). Whatever the policy in a given intensive care unit, the physician charged with managing the patient must be familiar with all aspects of the mechanical ventilator being used in that particular unit. Respiratory therapy is a wonderful resource, and the attending physician should take full advantage of the opportunity to learn from the respiratory therapists all the major and minor details of each ventilator in the unit. The best way to do this is to put yourself on the ventilator using a noseclip and a mouth piece, then run through the ventilator settings until you have a thorough understanding of how that particular ventilator can be adjusted and how it feels to the patient. The best mouth piece is an endotracheal tube with the balloon inflated and held inside the mouth. This gives the physician the feeling the patient has when relying on this long narrow airway for breathing. A similar protocol for self instruction on the use a mechanical ventilator is shown in Figure 3.28. To avoid suffocation, panic, and embarrassment it is best to start with a rubber bag (or better yet an adjustable mechanical test lung available from your respiratory therapy department) to become familiar with the initial settings. Then go through all the modes of ventilation with yourself as the test subject. If it is available, use a continuous pulmonary mechanics monitor to measure your progress.

Figure 3.28: A plan for self instruction in the use of a mechanical ventilator.
### Self-instruction Routine for Ventilator Training

1. Set: FiO₂, VT, rate, PEEP, PIP  
2. Set mode: CMV  
3. Set ranges for alarms: VT, rate, PIP, PEEP  
4. Attach test lung (rubber bag), and ventilate  
5. Measure: VT, rate, minute volume, PIP, PEEP, effective compliance  
6. Limit the bag to simulate poor compliance. Readjust ventilator, and repeat measurements  
7. Set primary controls to ventilate yourself. Rate = 16/min  
8. With a mouthpiece and a nose clip, ventilate yourself. Relax until you are on controlled ventilation. Then, adjust VT (5-20 ml/kg) and PEEP (0-10 cm H₂O) to get the feel, and observe the measurements. Try the sigh mode.  
9. At baseline settings, resist inspiration, cough, and try to hyperventilate. How does it feel? Do the monitors and alarms work?  
10. At baseline settings, turn to the AC mode. Rate = 0/min. Adjust the sensitivity from low to high.  
11. In the AC mode, adjust the inspiratory flow rate and pattern. Which I:E ratio feels comfortable?  
12. Reset mode to IMV, then CPAP. How much work does it take to initiate a breath?  
13. Repeat steps 10-12, but using an endotracheal tube instead of a mouthpiece in your mouth. What are the effects of the added resistance?

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**Figure 3.28:** A plan for self instruction in the use of a mechanical ventilator.
Mechanical Ventilation in Severe Respiratory Failure

As we have frequently emphasized in this chapter, management of the patient with severe respiratory failure includes many factors, the least important of which is the settings on the mechanical ventilator. Improper management of the ventilator will make the respiratory failure much worse rather than better, conversely, there are occasions in which adjustments on the ventilator actually improve lung inflation and function. Simply summarized, the safe limits of mechanical ventilation are FiO2 .5, PIP 30 cmH2O, PEEP 10 cmH2O, respiratory rate 20. If these limits were arbitrarily imposed, deaths from acute respiratory failure in intensive care units would decrease rather than increase. The mortality of exceeding these settings is 40%. (More accurately, the mortality of respiratory failure which the physician perceives as severe enough to require exceeding these settings is 40%). Nonetheless there are some situations in which ventilator adjustments in the high range are necessary and result in recovery.

The principles necessary for managing pulmonary mechanics in patients with severe respiratory failure are summarized in Figure 3.29. Simple volume limited ventilation as discussed above and demonstrated in Figure 3.24 is shown in this figure as the first example described as IMV, CMV, or controlled volume ventilation. In Figure 3.29 the factor which begins the mechanical breath cycle is identified by a triangle. Following this initiating event the ventilator delivers gas into the patient until a limit (identified by an asterik in Figure 3.29) is reached. Then inspiratory gas flow stops, the expiratory valve is held closed if a plateau pressure has been selected, then the expiratory valve opens and passive exhalation follows until the mechanical breathing cycle begins again. Routine ventilation can be done with either volume or pressure limit, but management of the patient with severe respiratory failure is best done with pressure limited ventilation, identified as PCV in Figure 3.29. The reason that pressure limit ventilation is preferred is that one of the major problems is always lung consolidation. In addition to maintaining adequate gas exchange, one of the goals of mechanical ventilation is to recruit the collapsed alveoli in the consolidated areas while avoiding over-distention of the normal alveoli. This recruitment is done during the peak inflation phase of mechanical ventilation, then the recruited alveoli are held open by PEEP, awaiting more recruitment on the next breath. When alveoli are recruited the FRC becomes larger and the compliance is therefore lower. When pressure limited ventilation is used this breath to breath improvement in compliance results in breath to breath increase in the tidal volume recruiting evermore alveoli. (In the volume limited mode the PIP drops as compliance improves, losing any advantage in recruiting more alveoli). Since alveoli are recruited during the time spent at PIP, there is significant advantage to making this time as long as is safe and tolerable. This is done by applying plateau pressure. When plateau pressure is used with pressure limited ventilation, inspiratory flow continues (rather than simply capping the expiratory valve as in volume ventilation). The plateau is set by determining the total inspiratory time that the PIP is applied, rather than the time that the expiratory valve is closed after full inflation. Used in this fashion to best advantage, the inspiratory time maybe equal to, or even considerably longer than the expiratory time, resulting in a reversal of the usual inspiratory:expiratory ratio. This application of pressure limited ventilation has been called "pressure controlled inverse ratio ventilation" or PCRIV. This mode of ventilation is very effective in recruiting collapsed alveoli associated with major respiratory failure. It runs the risk of high mean intrathoracic pressure which may inhibit venous return. It is
unnatural and uncomfortable for the patient, so that heavy sedation or paralysis is usually required. Try it on yourself, but limit your respiratory rate to 5 or 6, otherwise respiratory alkalosis will rapidly occur.

When consolidated lung has been expanded and it is possible to decrease the minute ventilation and think about weaning, the pressure limit is gradually decreased as long as adequate inflation and minute ventilation is sustained. The major problem with pressure limited ventilation is that atelectasis or airway plugs which decrease compliance will immediately decrease the volume of any pressure limited breath, so careful attention must be given to tidal volume monitoring (just as pressure must be monitored during volume limited ventilation). One way of dealing with this problem is the use of a variation of pressure limited ventilation in which the breathing cycle is initiated by the patient, the prescribed pressure limit is reached, but inspiration is limited by gas flow rather than either pressure or volume. This results in a very natural feeling breath and is ideal for weaning patients from mechanical ventilation. This mode of ventilator control is commonly called "pressure support" (PS). Some ventilators include a mode in which the problem of atelectasis with decreasing pressure limited breaths is addressed by continuing the flow, if necessary, until a prescribed volume is reached. This variation is called volume assured pressure support (VAPS).

Figure 3.29: Patterns of mechanical ventilation. All ventilators generate gas flow which starts (cycle, control - control, A) based on a timer or triggered by patient inhalation. Gas flow stops (limit, *) when a pre-set volume or pressure or flow is reached. Volume limited ventilation should always be used with an inspiratory hold or plateau. Two examples show the effect of PEEP. (from Bartlett, Mechanical Ventilation, 1994)

**Treatment of the Interstitial Space.** Most patients with severe respiratory failure have abnormally permeable pulmonary capillaries secondary to local inflammation and infection (in the case of pneumonia) or secondary to systemic factors (such as endotoxemia, intravascular coagulation, etc.). This increased permeability leads to transudation of plasma into the pulmonary interstitium. It is cleared by pulmonary lymphatics, but if the filtration rate exceeds the capability of lymphatics, edema will result. (Figure 3.17). Edema fluid migrates within the lung to the loose areolar tissue surrounding pulmonary arterioles and small bronchi, leading to an increase in pulmonary vascular resistance and decreased ventilation in the edematous area. Changes in lung function do not occur until lung water is more than twice normal; therefore, the patient who is symptomatic from interstitial edema has a major disturbance of transcapillary kinetics. Treatment of edema (Figure 3.30) has two important goals. the first is to improve oxygenation if it is impaired, and the second is to minimize fibrosis and bacterial infection, which often accompany pulmonary edema caused by capillary injury. (Fibrosis and infection are unusual following hydrostatic edema.) The treatment of interstitial edema is to maintain the hydrostatic pressure as low as is compatible with adequate cardiac output and to raise the oncotic pressure selectively in the vascular space. These measures, combined with fluid restriction and diuresis, will decrease the amount of pulmonary edema. Regulating the hydrostatic pressure and cardiac output requires the use of a pulmonary artery catheter and frequent determinations of cardiac output. Simmons et al found that survival in 113 ARDS patients correlated with negative fluid balance (Figure 3.31) Twenty two percent of patients survived. Survivors had weight loss and negative fluid balance (3 kg loss by day 5); non-survivors had weight gain and positive fluid balance (3 kg gain by day 5).
Figure 3.29: Patterns of mechanical ventilation. All ventilators generate gas flow which starts (cycle, control - control, Δ) based on a timer or triggered by patient inhalation. Gas flow stops (limit, *) when a pre-set volume or pressure or flow is reached. Volume limited ventilation should always be used with an inspiratory hold or plateau. Two examples show the effect of PEEP. (from Bartlett, Mechanical Ventilation, 1994)
Since it is desirable to maintain the filling pressure of the left ventricle as low as possible while maintaining a good cardiac output, inotropic drugs to improve left ventricular contractility are helpful. Dobutamine or dopamine should be used, titrated to optimize venous saturation. A Starling curve can be constructed and the optimal combination of filling pressure and inotropic drug determined.

Figure 3.30 Treatment of increased lung water. (from Bartlett, Respiratory Care, 1980)

Figure 3.31: Outcome related to fluid balance on day 4 in ARDS patients (Data from Simmons, AARD, 1987).

Simple extracellular fluid overload may contribute to interstitial edema in the lung. In some centers it is common practice to infuse 5-10 L of salt solution in addition to blood replacement for trauma patients, for example. This is done as an attempt to replace presumed losses into the "third" extracellular space. (The plasma volume and the interstitial fluid are the normal interstitial spaces; the pathophysiologic "third" space is the transient edema in the area of operation or injury.) It should be noted that the third space will expand as long as salt water is poured into the patient, and the difference between what is required and what is actually given is often measured in liters. One might wonder why gross pulmonary edema does not result each time this type of fluid overload occurs. The reason is that the interstitial proteins, as well as the plasma proteins, are equally diluted with colloid-free electrolyte solution, thus maintaining the oncotic gradient across the pulmonary capillary bed. This was demonstrated nicely by Demling et al., who resuscitated animals from hemorrhage with different solutions and measured the composition of the pulmonary lymph. They found that the plasma and lymph protein concentrations decreased at the same rate with progressive hemodilution, maintaining the oncotic gradient across the pulmonary capillary at albumin levels as low as 1.3 g/dl. The fact that most patients will tolerate iatrogenic edema does not mean that this is a good practice. If sepsis occurs in an edematous patient, the increased capillary permeability may lead to pulmonary, myocardial, or brain dysfunction.

As mentioned above, pulmonary edema does not result in dysfunction until the lung water is more than twice normal, but once alveolar flooding begins, small increments of edema cause major dysfunction. For the same reason removal of a small amount of edema from the lung may result in major improvement.

The first step in decreasing pulmonary edema is to decrease the pulmonary capillary hydrostatic pressure as low as is compatible with adequate cardiac output.

Figure 3.32: Relationship between plasma oncotic pressure and plasma proteins

This is done by diuresis and fluid restriction. As the patient falls behind in blood volume, signs of hypovolemia may appear. Blood volume is then replenished with a fluid that stays in the vascular space. Packed red blood cells are ideal for this application. When the hematocrit is normal, concentrated salt-poor albumin should be used. This hyperoncotic fluid replenishes the blood volume by attracting interstitial fluid from throughout the body into the vascular space and supplementing diuresis. This technique is useful even in the septic patient who may have increased capillary permeability and may lose albumin from the vascular space at a rapid rate. Even if albumin "leaks out" at a
Figure 3.30: Treatment of increased lung water. (from Bartlett, Respiratory Care, 1980)
Figure 3.31: Outcome related to fluid balance on day 4 in ARDS patients (Data from Simmons, AARD, 1987).
Figure 3.32: Relationship between plasma oncotic pressure and plasma proteins
rate three or four times normal, the short-term effects of expanding blood volume and decreasing edema will appear. Experience with infusion of albumin solution into patients who are already hypervolemic has led to the mistaken impression that the use of concentrated albumin in the hypovolemic patient may cause problems. On the contrary, it is an efficient way to re-expand blood volume. The use of concentrated globulins would be better yet, but such a preparation is not available. Although furosemide is usually used as the diuretic of choice, mannitol should be mentioned. This drug provides osmotic diuresis as well as a transient plasma hyperosmolarity, “pulling” fluid into the vascular space.

All of the principles of physiology, physics, and common sense discussed in this chapter come together in the management algorithm and the respiratory care axioms (Figure 3.33).

Figure 3.33: Respiratory Axioms
Respiratory Failure Axioms

1. Breathing and ventilation is for CO₂ removal; inflation is for oxygenation.
2. Normalize O₂ delivery, not just PaO₂.
3. Oxygenation management (FiO₂, position, suction, PEEP, inotropes) is based on SvO₂.
4. In apnea, hypoxemia is fatal in minutes. Hypercarbia alone is never fatal.
5. Increasing FiO₂ decreases alveolar nitrogen and causes atelectasis.
6. Mechanical ventilation does more harm than good at high PIP and high FiO₂.
7. Never exceed PIP (plateau) over 40 cm H₂O. Hypercarbia is safer than PIP > 40.
8. Ventilation management (rate, pressure, volume) is based on PaCO₂ or end tidal CO₂.
9. Achieve and maintain dry weight.
10. Don't confuse PC wedge pressure and hydration status.

Figure 3.33: Respiratory Axioms
Chapter 3 Monographs and Reviews


This multi-authored monograph summarizes research and clinical experience in extracorporeal life support for cardiac and respiratory failure.


This classic monograph describes instrumentation and methods in respiratory physiology in great detail. It is an invaluable reference for a critical care physician.


This chapter has concise descriptions of normal and abnormal respiratory physiology in the setting of critical illness. Several figures from this chapter are included in this text.


This multi-authored monograph includes several practical reviews of respiratory physiology and monitoring. Several figures and concepts from the chapter on pulmonary pathophysiology in surgical patients from this monograph are included in critical care physiology.

Bartlett RH: "Use of Mechanical Ventilation," IN: Care of the Surgical Patient 1 Critical Care, Holcroft J (editor), Scientific American Medicine, New York, Section II, Chapter 5, 1993.

Several concepts and figures in critical care physiology are taken from this chapter.


A summary of a series of landmark studies by the Gattinoni group.


Sections on mechanical ventilation are particularly good.

These classic monographs written by the Dean of modern pulmonary physiologists are written for medical students but constitute the best, most concise standard reference in respiratory physiology.


The University of Michigan algorithm for management of severe respiratory failure is described in this chapter.

Chapter 3 Selected Reports


This animal study demonstrated decreased shunting in the prone position.
The animal studies have been repeated in several clinical studies, such as the Gattinoni paper cited above.


This is the first report of the European collaborative (Euroxy) study identifying the epidemiology of ARDS in Europe.


Description of acute respiratory failure which was first to use the description "adult respiratory distress syndrome".


A nine-center study of the epidemiology and natural history of acute respiratory failure in adults. One of the first studies to describe progressive mortality with multiple organ failure.

This is the report of a consensus conference held on ARDS in 1992 which was very helpful to provide definitions, epidemiology and plans for future studies. The same report was published in the Journal of Critical Care in March, 1994.


A series review in which the P/F ratio is introduced.


The first anatomic (CT) description of the effect of prone position on lung inflation.


PEEP acts by lifting up the weight of wet lung which would collapse small airways and alveoli.


Correlation of anatomy with pulmonary mechanics in ARDS.


This paper very nicely demonstrates the difference in pathophysiology between pulmonary edema and transpulmonary shunt. Large shunt can exist without edema (atelectasis), and edema can exist without shunt if the lungs are well ventilated.


This study demonstrates that over distension (not pressure per se) is the cause of high-pressure alveolar change.

The term "permissive hypercapnea" is introduced in this paper emphasizing peak pressure limits.


Improved survival with pressure limitation in ARDS, compared to historical controls and contemporary published series.


High frequency ventilation can clear CO2, but offers no advantages.


Lung injury occurs in normal sheep ventilated at 50 cmH20 for one day. some of the injury may be due to tissue alkalosis.


Prone positioning redistributes blood flow to anterior lung and improves inflation of posterior lung.


A description of physiologic response to pressure-controlled inverse ratio ventilation.


The Geneva score of ARDS is introduced in this experimental study.

ARDS patients had a better result when managed by algorithms intended to lower pulmonary artery pressure and induced diuresis.


This study showed no advantage to low flow extracorporeal CO2 removal (including the learning curve for that technique) when compared to carefully controlled conventional management, with 60% mortality in both groups.


This series includes the "Murray score" of ARDS.


A typical study showing the advantages of continuous end tidal CO2 monitoring in critically ill patients.


These papers describe capillary and alveolar high pressure (over distension) lung injury.


Definition of the regional distribution of water and dependent consolidation in ARDS.


A case report of a patient who had a pCO2 of 375 mmHg and pH of 6.6. The patient was comatose but had an uneventful recovery after appropriate
ventilator treatment. This is one of many articles that demonstrates the benign nature of respiratory acidosis.


Histology of ARDS from the first NIH-ECMO study.


Early tracheostomy was associated with lowered incidence of pneumonia in trauma and critical care patients.


The original description of the Severinghaus pCO2 electrode.


This study of 113 ARDS patients showed that survival was much improved in patients who had significant negative fluid balance during the ICU stay. Although this was not a prospective randomized study, it clearly defines a rationale for achieving dry weight in ARDS patients.


A large panel chaired by Arthur Slutsky defined many aspects of mechanical ventilation including general recommendations for safe use of mechanical ventilators.


The original description of Starling's equation for transcapillary flux.


A 12-center study of the epidemiology and natural history of acute respiratory failure in adults. In 1991 mortality in all categories was decreased by about 20% compared to the 1986 publication.

This epidemiologic paper is included in a very good multi-author review of ARDS. The MGH series and scoring system is described.
CHAPTER 4: Metabolism and Nutrition

Metabolic Requirements

The typical expenditures of energy and protein in normal subjects and critically ill patients are shown in Figure 4.1. Protein and energy requirements are continuous. These are met by endogenous sources during fasting, or can be met through exogenous treatment (nutrition). Energy expenditure is referred to as the basal metabolic rate or the basal energy expenditure (BEE). The basal energy expenditure refers to a near-sleep steady state. More commonly we refer to resting energy expenditure, measured after a brief period of supine rest.

Figure 4.1 Energy and protein expenditure during common clinical conditions. Normal daily expenditure is shown in the shaded area. (from Bartlett, Cardiopulmonary Critical Care, 1986)

The REE is properly expressed in joules, the standard unit of energy, but is more commonly and more practically expressed in calories. The REE decreases with advancing age and varies with sex and body size. It is a function of cellular metabolism, hence of the body cell mass (Fig. 4.2).

Figure 4.2 REE and Size

The REE is usually estimated from a chart combining age, sex, and body size. Such charts are based on or are similar to those originally published by Harris and Benedict.

Estimating and Measuring Energy Requirements

The actual metabolic rate of any given patient can be estimated by modifying the predicted basal rate according to the clinical condition. For example, the metabolic rate is typically decreased by 10% in a starving person and increased by 10% with minor activity. Trauma, stress, sepsis, and surgical operations are all known to increase the metabolic rate. Several authors have proposed tables or formulas for estimating the metabolic rate depending on the degree of physiologic stress. (Figs. 4.3, 4.4). This amount of energy is most conveniently expressed in calories per day. The metabolic rate is normalized to body surface area; however, the actively metabolizing tissue is the lean body cell mass. Consequently, reporting “per square meter” underestimates metabolism in a fat person and overestimates it in a very lean person.

Figure 4.3: Changes in REE associated with common clinical conditions as diagrammed by Kinney.

Figure 4.4: Changes in REE associated with common clinical conditions as diagrammed by Wilmore. Using a straight line, connect the normal basal metabolic rate on the left (25 kal/kg/d) to the clinical condition on the right. Read the estimated caloric requirement from the column in the middle.

Although most of the studies on nutrition in critical illness have been based on estimated energy expenditure, actual measurement is much more accurate and is becoming an important aspect of critical care management. The most commonly used method of measurement is indirect calorimetry. In this method the amount of oxygen absorbed across the lungs into the pulmonary blood is measured over a given period of time. Assuming the patient is at a metabolic steady state during this time, the amount of
Figure 4.1: Energy and protein expenditure during common clinical conditions. Normal daily expenditure is shown in the shaded area. (from Bartlett, Cardiopulmonary Critical Care, 1986)
Figure 4.2: REE and size

Calories/Day

Kg: 20 30 50 70 90 100

m²: .75 1.0 1.25 1.5 1.75 2.0

VO²

REE

100%

50%
Figure 4.3: Changes in REE associated with common clinical conditions as diagrammed by Kinney.
Figure 4.4: Changes in REE associated with common clinical conditions as diagrammed by Wilmore. Using a straight line, connect the normal basal metabolic rate on the left (25 kal/kg/d) to the clinical condition on the right. Read the estimated caloric requirement from the column in the middle.
oxygen absorbed across the lungs is equal to the amount of oxygen consumed in metabolic processes. (This is the basic assumption of Fick's equation and is the reason why O2 consumption is a valid measure of metabolism, even in patients with abnormal lung function.) The energy released by oxidation of various food substrates is known from direct measurements, so that the metabolic rate measured in cubic centimeters of oxygen per minute can be converted to calories per hour or per day if the oxygenated substrates are known. For practical purposes, a conversion factor of 5 kcal of energy per liter of oxygen consumed is a reasonable approximation. It overestimates the metabolic rate slightly, but it is a much more accurate approximation of the actual metabolic rate than a number derived from an arbitrary chart or table.

**Energy Sources**

The major sources of energy are carbohydrates (including ketones and alcohols) and fats. Protein can be oxidized and is often a significant source of energy in critically ill patients. In nutritional planning, we strive to supply energy from non-protein sources, allowing the use of endogenous and exogenous protein for anabolism rather than catabolism. In normal volunteers and surgical patients, protein breakdown is decreased by giving the subject exogenous fuel, be it glucose, fat, or xylitol. This is referred to as the protein-sparing effect. Small amounts of glucose (400 cal/day) provide some degree of protein sparing, but full caloric support is required for maximal effect.

Carbohydrate is the major source of energy during normal, non-starving existence. The brain, the red cells, and possibly other tissues are obligate glucose users. They require glucose as the primary energy source under normal conditions. Other organs also use glucose preferentially as a source of energy. The brain and red blood cells can develop the capacity to use ketones as an energy source, a process called starvation adaptation. When fully oxidized, carbohydrate produces 4.0 cal of energy per gram of substrate, 5.0 cal of energy per liter of oxygen consumed, and 1 molecule of CO2 for each molecule of oxygen consumed. The latter ratio is the respiratory quotient, which is 1.0 for carbohydrate. (Figure 4.5).

Figure 4.5: Caloric (energy) value, RQ, and energy per liter of oxygen consumed in oxidation of the three classes of substrate.

Fat is the most efficient source of energy. Fat produces 9 cal of energy per gram of substrate metabolized, 4.7 cal per liter of oxygen consumed in this oxidation, and has a respiratory quotient of 0.7. Fat is stored as triglyceride, and for each 3 molecules of fatty acid oxidized to produce energy, 1 molecule of glycerol if also oxidized. Endogenous fat is the major source of energy during starvation. The glycogen stores are basically depleted after a day of fasting, and fat becomes the major source of energy, always with protein breakdown.

**Mediators**

The mediators of the hypermetabolic state are incompletely understood. Elevated catecholamine levels have been identified in burn patients. Corticosteroids, glucagon, growth hormone, and thyroid hormone have all been implicated as mediators of the hypermetabolic state in various critical conditions. Interleukin 2 causes both hypermetabolism and protein catabolism. Certain amino acids may play a modulating
<table>
<thead>
<tr>
<th>Substrate</th>
<th>cal/gm</th>
<th>RQ</th>
<th>Cal/L O2</th>
</tr>
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<tr>
<td>CHO</td>
<td>4</td>
<td>1.0</td>
<td>5</td>
</tr>
<tr>
<td>Fat</td>
<td>9</td>
<td>.7</td>
<td>4.75</td>
</tr>
<tr>
<td>Protein</td>
<td>4</td>
<td>.8</td>
<td>4.8</td>
</tr>
</tbody>
</table>

Figure 4.5: Caloric (energy) value, RQ, and energy per liter of oxygen consumed in oxidation of the three classes of substrate.
role. Alanine, for example, has easy access into the gluconeogenic pathway, and it has been suggested that protein catabolism is dependent on the amount of alanine produced. Fischer and others have shown that infusing patients with branched-chain amino acids diminishes protein catabolism, and have proposed the use of solutions rich in branched-chain amino acids for patients in catabolic states. Whatever the mediator of the hypermetabolic state is, it appears best to treat the underlying cause while feeding metabolic fuel to the fire rather than attempting to reverse the hypermetabolism per se.

Protein Metabolism

Estimating and Measuring Protein Requirements. In normal protein metabolism there is a continuous excretion of nitrogen (mostly as urea) equivalent to approximately 50 g of protein each day, matched by protein intake of 50 g/day.

The protein synthesis and breakdown rate is approximately 300 g/day, with most endogenous amino acids being recycled into new protein. In starvation, protein catabolism continues (although at a slower rate) without a corresponding protein intake, leaving the patient in a negative protein balance. This protein flux is most conveniently measured as nitrogen flux; consequently, this condition is commonly referred to as negative nitrogen balance. During critical illness the rate of protein catabolism generally increases while intake stops, resulting in negative nitrogen balance. It is convenient to think of this protein breakdown as “necessary” to produce more glucose through the gluconeogenic pathway when other carbohydrate stores have been exhausted.

Protein Sources. The fact that the nitrogen balance is negative does not mean that protein synthesis stops or slows down. On the contrary, the synthesis of new tissues, inflammatory cells, collagen, coagulation factors, antibodies, and scores of other proteins occurs at an accelerated rate during critical illness. Amino acids derived from muscle tissue or other somatic and visceral proteins become the building blocks for protein in healing tissue and host defenses. The site of a traumatic or surgical wound or area of acute inflammation becomes a protein parasite on other body tissues. Eventually this parasite may overwhelm the host, because proteins that would otherwise strengthen the diaphragm or the myocardium or participate in host defense processes are thrown to the metabolic flames. A large part of the goal of nutritional management is to provide energy sources so that endogenous proteins are not required for energy (i.e., protein “sparing”) and to supply exogenous proteins such that all of the needs of protein synthesis can be met without breaking down endogenous sources. Although oversimplified, a convenient number to remember for basal protein requirement is 1 g/kg/day or 40 g/m²/day.

Mediators

The mediators of protein catabolism appear to be different from the mediators of the metabolic rate. Although energy requirement and protein breakdown often follow similar patterns, there are patients who have major protein catabolism at a normal metabolic rate, and patients who are hypermetabolic while conserving protein. Tumor necrosis factor (TNF) is a specific mediator released from monocytes that stimulates endogenous protein breakdown. This corresponds to clinical observations in which the degree of protein catabolism is generally related to the degree of inflammation and (presumed) neutrophil/monocyte activation.

Vitamins and Minerals

Vitamin stores are plentiful and deficiency states develop slowly, so vitamin loss is not a concern during the early days of critical illness. A hypermetabolic patient will
catabolize vitamins more rapidly than normal and can reach a deficiency state sooner. A patient who is severely malnourished before entry to the ICU may already have a vitamin deficiency. There is some evidence that high doses of vitamins A and C may be beneficial to patients with injuries. Since vitamins are inexpensive and safe, we deal with vitamins in the ICU the same way we do in the clinic — prescribe more than enough for the patient who is not eating. Commercial preparations for enteral or parenteral administration provide gross excesses but do not lead to overdose.

"Trace" metals must be managed more carefully than vitamins, since deficiency can occur sooner and overdose can be deleterious. Calcium, phosphorous, magnesium, and sulfur are more than trace elements. They are lost continuously in the urine, stool, gastric juices, and other drainage. Although there are large body stores (particularly calcium and phosphorous), deficiency can develop rapidly. Enteral and parenteral feeding must include these elements. Serum levels of calcium, phosphorus, and magnesium should be measured at regular intervals. Zinc, copper, chromium, selenium, and manganese must be supplied to patients who are supported with enteral or parenteral feeding for more than 2 weeks. Recommended daily allowances for vitamins and trace minerals and listed in Figure 4.6.

Figure 4.6: Typical adult daily requirements for vitamins and trace metals.

Endogenous Sources of Energy and Protein

In a normal 80 k man, approximately 1000 cal are available as glycogen and other stored carbohydrates. About 140,000 cal are stored as fat. The body contains approximately 6 kg of protein, which could be consumed as an energy source or maintained to do work. Nutritional assessment is the process of measuring the amount of these energy and protein reserves.

Almost all critically ill patients are starving (have no caloric or protein intake) unless we supply feeding for them. Since starvation is such an integral part of critical care physiology, it is a very instructive exercise to calculate the sources, fate, and balance of fat, carbohydrate, and protein in a normal but starving individual. Fortunately George Cahill has done this for us, and published the results in a classic article several years ago. The metabolic consequences of starving for 24 hours as described by Cahill are shown in Figure 4.7. After 24 hours of starvation, liver and muscle glycogen has been depleted and glucose utilized in metabolism is generated from fat, protein, and lactate in the process of gluconeogenesis. The amount of glucose made in this process is 180 grams. At four calories per gram this process supplies 720 calories worth of energy, most of which is used up in the metabolism of the nervous system. The remaining 60% of energy substrate is supplied by ketone bodies and fatty acids from fat breakdown. This source of energy is more than twice as efficient as gluconeogenesis (expressed as calories per gram), as anyone who has tried to lose body fat through starvation can attest. Notice that the protein catabolic rate is 1 gm/kg/day, and remember that this is a normal man, not a hypermetabolic critically ill patient.

If starvation continues untreated there is a gradual shift in the substrates supplying the energy for metabolism. This shift occurs because of the induction of enzymes in nervous tissue to use ketone in addition to glucose as a major energy source. This
**Figure 4.6**

Typical Adult Daily Requirements

| Vitamin A | 3,300 IU | Calcium | 15 mEq |
| Vitamin C | 100 mg | Magnesium | 20 mEq |
| Vitamin D | 200 IU | Phosphorous | 50 mM |
| Vitamin E | 10 IU | Zinc | 5 mg |
| Thiamine B1 | 3 mg | Copper | 1 mg |
| Riboflavin B2 | 3 mg | Manganese | .5 mg |
| Pyridoxine B6 | 4 mg | Chromium | .01 mg |
| Pyridoxine B12 | 5 mcg | Selenium | .06 mg |
| Niacin | 40 mg | Linoleic Acid | 1 gm |
| Pantothenic Acid | 15 mg |
| Biotin | 60 mcg |
| Folic Acid | 410 mcg |

*Figure 4.6: Typical adult daily requirements for vitamins and trace metals*
adaptation decreases the "need" for gluconeogenesis, so that protein breakdown which was necessary to supply glucose can be significantly curtailed. These adjustments represent a marvelous bit of teleological biology, since the chronically starving person would rapidly become too weak to move or breathe if protein catabolism continued at its usual rate. Starvation adaptation facilitates protein (therefore muscle mass) conservation. The metabolic events in this adaptation process were also calculated for us by Cahill and are shown in Figure 4.8. Now the man is adapted to fasting. Notice that the resting energy expenditure is decreased from 1800 to 1500 calories per day presumably because the chronically starving man is much less active. In starvation adaptation, 40% of the caloric energy still goes to the nervous system and blood cells, but now only half of that energy is supplied by gluconeogenesis and the balance by ketones derived from fat. Fat catabolism continues at almost the same rate as it did after 24 hours of fasting, but muscle catabolism has decreased from 75 grams per day to 20 grams per day. Although protein breakdown is significantly decreased in starvation adaptation, it never goes to zero. This "protein floor" (usually expressed as 2 grams of nitrogen or 12 grams of protein per day) represents the least amount of protein intake which is compatible with life over a period of weeks or months. Remember that the critically ill patient may indeed be starvation adapted, but often has other factors such as inflammation which override this adaptive mechanism and cause major increases rather than decreases in the protein catabolic rate.

Figure 4.7: Metabolic events after one day of starvation in a normal man (from Cahill)

**Energy Reserves**

The simplest measurement of nutritional status is body weight in relation to body height. Major changes in weight that are not caused by fluid shifts are related to changes in body fat. Energy reserves are generally estimates of body fat, since the amount of carbohydrate held in reserve is negligible. The first approach to measuring energy reserve is an estimation of caloric balance. The daily resting energy expenditure is estimated as discussed above, and the daily energy intake is estimated from the caloric value of nutrients. The latter estimate is easy for critically ill patients, since the patient is usually receiving nothing by mouth and all calories are supplied through parenteral or tube feeding routes. A 10,000 cal deficit in a critically ill patient is a severe, acute energy deficit although this represents only 5 or 6 days of semistarvation. The problem associated with a 10,000 cal deficit is not the loss of a few pounds of fat, but rather the associated protein catabolism that is commonly associated with this amount of energy deficit. Fat reserves can be estimated by measuring the thickness of the triceps skin fold or by examining changes in body weight, corrected for fluid balance. Measurement of arm circumference includes both fat and muscle mass. Any of these measurements of body fat is at best a gross approximation.

Figure 4.8 Metabolic events after five weeks of starvation in a normal man (from Cahill)

**Protein Reserve**

Since protein is the functional and structural chemical of the body, most nutritional assessment techniques are estimates of protein reserves. The creatinine/height index if basically a measurement of creatinine excreted (as a measure of muscle breakdown)
Figure 4.7: Metabolic events after one day of starvation in a normal man (from Cahill)
Figure 4.8: Metabolic events after five weeks of starvation in a normal man (from Cahill)
TABLE 4.1

ENERGY:

\[ \text{VO}_2 = 100-130 \text{ cc m ST} \]
\[ \text{VCO}_2 = 80-130 \text{ cc m STPD} \]
\[ \text{RQ} = \frac{\text{VCO}_2}{\text{VO}_2} \]
\[ \text{REE} = 25 \text{ cal/kg/d, 960 cal m/d} \]
\[ \text{BEE} = 20 \text{ cal/kg/d, 800 cal m/d} \]

Caloric Balance = Cals IN-REE (measured)

\[ \text{VO}_2/\text{calorie conversion:} \]
\[ \text{VO}_2 \text{ L/min} \times 60 \text{ min} \times 24 \text{h} \times 5 \text{ cal/L} = \text{cal/day} \quad (\text{same as VO}_2 \times 7200) \]
### TABLE 4.2
Protein metabolism is measured and described as elemental nitrogen gain or loss.

**PROTEIN:**

1 gm Nitrogen = 6.25 gm prot.

Nitrogen loss = 5-10 gm/day, 85% as urea

Protein Catabolic Rate (PCR)

Normal = .5-1 gm/Kg/d

with ↑EE = 1.5 -2 gm/Kg/d
normalized for body size. Since muscle is a major source of endogenous protein, muscle wasting is characteristic of the malnourished state. This can be detected by muscle strength and endurance testing. There are few standardized measures of muscle testing that are used as nutritional assessment. One such test is the maximal breathing capacity (also known as the maximal voluntary ventilation). In this test the maximal amount of air that can be moved through rapid breathing over a period of 12 seconds is recorded. The values are expressed as "percentage of predicted" for a given age and sex and size (normal is 80-120 percent). In the absence of significant obstructive or restrictive disease, a low value usually indicates lack of muscular strength and endurance. Inspiratory force is another strength test that is easily and commonly done in the ICU. The normal range is 80-100 cm H2O.

The actual nitrogen balance can be measured by measuring the amount of nitrogen excreted. This is most conveniently done by measuring the amount of urea excreted in the urine, assuming that urea constitutes 85 percent of the total nitrogen excretion. It is better to actually measure the total nitrogen in urine and other fluid losses, since the percentage made up by urea may vary considerably. Knowing nitrogen excretion, the amount of protein catabolized can be estimated and compared with the amount of protein ingested by the patient. Indirect assessments of protein reserves are based on single measurement of body substances that are dependent on rapid protein synthesis for maintenance of normal levels. Conventional serum proteins such as albumin and globulin are not affected by malnutrition until it is very severe. Proteins such as prealbumin and transferrin, which turn over more rapidly, are better indicators of protein status. Lymphocytes are rapidly destroyed and protein is required for the formation of new cells. Consequently, the absolute lymphocyte count is a useful measure of the status of protein reserves. The lymphocyte count, in our experience, is the best single "static" measurement characterizing nutritional status.

Protein is also required for synthesizing the cells and mediators involved in skin test reactivity. Although skin test reactivity is a manifestation of lymphocyte-mediated immunity, its usefulness in patient assessment is probably that of assessment of the inflammatory response rather than lymphocyte activity per se. The McGill surgical research group showed, for example, that neutrophil chemotaxis (or the lack of it) correlates with cutaneous sensitivity to recall antigens. Some chronically and acutely malnourished patients convert from reactive to anergic, and reactivity can be restored by nutritional repletion.

These methods of nutritional assessment are used to classify the nutritional status of patients at the time of injury, operation, or critical illness (Table 4.3). The most important markers are listed in Figure 4.9.

Figure 4.9: Markers of acute nutritional status.

Those patients who have both energy and protein depletion at the time of major physiologic stress have a higher morbidity and mortality than those patients with a normal nutritional status. Preoperative nutrition decreases postoperative morbidity and mortality in high risk, malnourished patients. The measurements of fat reserves are not helpful during the acute management of critically ill patients. The measurements of protein reserves are somewhat helpful but will not reflect hour-to-hour or day-to-day metabolic changes. In an excellent study, the McGill group measured body cell mass (the
| Table 4.3. Measurement of Nutritional Reserves |

<table>
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<th>Normal</th>
<th>Mild</th>
<th>Severe</th>
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<td>-5,000 cal</td>
<td>-10,000 cal</td>
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<tr>
<td>Triceps skin fold</td>
<td>-</td>
<td>per table</td>
<td>-5%</td>
<td>-40%</td>
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<tr>
<td>Arm circumference</td>
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<td>per table</td>
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<td>-30%</td>
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<tr>
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<td>variable</td>
<td></td>
<td>-20%</td>
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<tr>
<td><strong>Protein Reserves</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine/height index</td>
<td>&gt;2,000</td>
<td>per table</td>
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<tr>
<td>Lymphocyte count</td>
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<td>1800/mm³</td>
<td>1600</td>
<td>500</td>
</tr>
<tr>
<td>Cumulative nitrogen balance</td>
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<td>0</td>
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<td>168/dl</td>
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<tr>
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</tr>
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<td><strong>Muscle strength</strong></td>
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<td>Inspiratory force</td>
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<td>Maximal volume ventilation</td>
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<td>-------------</td>
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<td>Lymphocytes</td>
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<tr>
<td>Prealbumin</td>
<td>&lt;10</td>
<td>mg/dl</td>
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**Figure 4.9:** Markers of acute nutritional status.
gold standard measurement of nutrition) and found that the depleted state could not be reliably detected based on weight/height, triceps skin fold, midarm circumference, albumin, total protein, hand strength, or creatinine/height ratio. Actual measurements of metabolic rate and nitrogen balance are the best methods of following nutritional status in critically ill patients.

**Energy and Protein Balance**

Energy expenditure is most conveniently measured through the techniques of respirometry and indirect calorimetry discussed in detail in Chapter 1 and 3. Direct volumetric spirometry is the best method for measuring oxygen consumption. This technique also lends itself well to simultaneous measurement of CO2 production. With measurement of oxygen consumption and CO2 production the respiratory quotient can be calculated.

With the respiratory quotient (RQ) the relative amount of carbohydrate and fat that are oxidized can be calculated. The RQ for protein is 0.8. By measuring urinary nitrogen, the amount of protein catabolized can be calculated, and the measured RQ can be "corrected" for the amount of O2 and CO2 involved in protein catabolism. For example, if the urinary nitrogen is 0.5 g/h, then protein was metabolized at a rate of 3 g/h, accounting for 3200 ml O2 consumed per hour and 2560 ml of CO2 produced per hour. This "nonprotein" RQ is used to define the amount of fat or carbohydrate used as energy sources. Ketones have a very low RQ (0.6), so that ketone metabolism will lower the overall respiratory quotient. Conversely, the conversion of glucose to fat generates carbon dioxide, so that the RQ of that reaction is more than 1. Measurement of the RQ is helpful as an internal check on the accuracy of the calorimetry measurements and as a guideline to patient management. For example, if a patient has been receiving only 500 cal/day and has a metabolic rate of 2500 cal/day, one would expect that fat utilization would be maximum and the RQ should be between 0.7 and 0.8. If such a patient is treated with parenteral nutrition utilizing glucose as the major source of energy, the RQ should be 1.0 when the caloric replacement matches caloric losses. If the respiratory quotient exceeds 1.0, then some of the infused carbohydrate is being converted to fat, producing excess CO2 that increases the need for breathing. Hypercaloric feeding with glucose can cause respiratory failure requiring mechanical ventilation, simply by increasing the load of CO2. Energy balance is helpful because it serves to identify the high risk patient. In our studies, acutely ill patients with caloric deficits greater than 10,000 cal had a much higher mortality than those patients with a positive caloric balance.

A typical balance diagram is shown in Figure 4.10. In the balance diagram the intake during a 24 hour period is plotted from the baseline up, and expenditures plotted from that point back down toward the baseline. In the example in Figure 4.10 the intake was 2000 calories worth of food stuffs and the expenditure was exactly 2000 calories resulting in zero balance for that day. On the next day the intake was 2000 but the expenditure was only 1600 resulting in a 400 calorie positive balance. On the third day the intake was 1000 and the expenditure was 2000 taking to the cumulative balance to minus 600 calories. The fourth day is total starvation. With no caloric intake and 2000 calories of expenditure the cumulative balance is now minus 2600. Balance diagrams like this can and should be constructed for critically ill patients for all of the variables which are crucial in patient management including energy substrate, protein, water, sodium, potassium, and other electrolytes in some cases. The metabolic steps involved in protein metabolism are
diagrammed in a different way in Figure 4.11. When renal function is normal almost all the products of protein catabolism appear as nitrogen compounds in the urine, so that measuring total urinary nitrogen provides a direct measure of net protein balance. Notice that the actual rate of protein turnover in muscle, liver and kidney is much higher than the net rate of protein loss.

In renal failure by-products of protein catabolism accumulate in the body rather than appearing in the urine. Although urea is not the only metabolite of protein breakdown it is the one most easily measured. To calculate the net protein breakdown in renal failure it is necessary to measure the urea nitrogen concentration in blood at the beginning and the end of a timed period. Then with some assumptions regarding the extracellular fluid volume and the distribution of urea and other protein breakdown products in extracellular fluid it is possible to calculate a "protein catabolic rate" which approximates net protein loss despite the fact that there is no urine. The methodology for developing this calculation was developed by Sargent.

Figure 4.10: Energy balance for a 70 kg adult ranging from normal intake and metabolism (Day 1) to starvation (Day 4).

Figure 4.11: Events leading to the calculation of net protein breakdown.

Figure 4.12: Diagrammatic representation of events leading to the calculation of net protein breakdown in renal failure.

NUTRITION SUPPLIES
Energy and Protein

The goal of nutritional therapy in critical ill patients is to maintain a positive nitrogen balance and to avoid endogenous protein breakdown. Exogenous protein can be given via the GI tract or parenterally. Parenteral administration is usually done in the form of amino acid solutions, although peptie solutions may be adequate for most conditions. The amino acid compositions of commercially available enteral and parenteral feeding solutions are arbitrarily designed. The original amino acid solution was concocted to resemble hens' egg albumin, for example. The "best" combination of amino acids has not been determined and will probably be different for different disease conditions.

The interrelationship between the amount of protein and the amount of energy supplied to the patient is a matter of some discussion. In the steady state, a 70-kg adult typically consumes 1800 cal and 60 g of protein each day, a ratio of 30 cal/g of protein, or 187 cal/g nitrogen. This would be the appropriate amount of nutrients for a patient who is not nutritionally depleted and is not hypermetabolic — a patient on ventilator support for Guillian-Barre syndrome, for example. If the patient is nutritionally depleted but not hypermetabolic (a patient with esophageal cancer being prepared for surgery, for example), the maximal amount of protein that can be "loaded into" the active body cell mass should be given. The actual amount depends on the simultaneous caloric support, since a greater degree of positive nitrogen balance can be achieved with a given nitrogen supply when a positive caloric balance is achieved at the same time. (Figure 4.13). In such a patient it would be appropriate to give 150 g of protein and 2500 cal daily ( a ratio of 13 cal/g of protein or 85 cal/g of N) realizing that if the bulk of the calories are given as carbohydrate, some of this carbohydrate will be converted to fat thus producing carbon dioxide and
Figure 4.10: Energy balance for a 70 kg adult ranging from normal intake and metabolism (Day 1) to starvation (Day 4).
Visceral Protein

Protein OUT
Measured as Nitrogen x 6

Muscle + Visceral Protein

Anabolism

Catabolism

Liver + Kidney

Balance = IN - OUT

Figure 4.11: Events leading to the calculation of net protein breakdown.
Figure 4.12: Diagrammatic representation of events leading to the calculation of net protein breakdown in renal failure.
raising the minute ventilation requirement. A patient who is actively catabolizing protein because of depleted carbohydrate energy stores combined with a hypermetabolic state (a major burn patient, for example) requires an energy supply to match his or her

Figure 4.13: Nitrogen balance related to energy balance in critically ill patients treated with standard parenteral nutrition solutions with 40 gm amino acid and 1000 cal glucose per liter. (Author's data)

hypermetabolic losses (3500 cal, for example, in a burn patient who is metabolizing 3000 cal/day). An exogenous supply of energy may slow down or turn off protein catabolism, but it may not, and it is current practice to provide gross excesses of protein to these patients. Such a patient would typically receive 3500 ml of a 4 percent protein formula, hence 140 g of protein with 3500 cal, or a ratio of 25 cal/g of protein (160 cal/g N).

Methods of Supplying Nutrition

Feeding by mouth is the most efficient way of providing energy and protein and is feasible in many critically ill patients. Supplying a patient with milk shakes, eggnog, solid candy, or popsicles, is better than supplying water or fruit juices as is the common practice in critical care units. The possibility of oral feeding is one of several reasons why tracheostomy is preferable to endotracheal intubation for long-term management of patients with acute respiratory failure.

Enteral Feeding

If the patient cannot or will not take food by mouth, liquid food should be administered directly into the stomach or intestine through a feeding tube.

Enteral feeding can be accomplished by a tube passed directly into the duodenum or jejunum at surgery, or by a tube passed into the stomach through the nose or mouth. Soft, small-bore feeding catheters with weighted tips are commercially available, but small bore nasogastric tubes can serve just as well. It is generally possible to accomplish tube feeding with gastric infusion. Patients with gastric ileus, such as patients who have just had abdominal operations, can be fed in the jejunum during the period of gastric atony. Formulas for tube feeding range from milk to commercial preparations. Although milk with supplements or blenderized hospital diet is probably the most economical tube-feeding formula, standardized commercial preparations are the most widely used because they are easy to prepare, sterile, and the composition is precisely known. These commercial preparations range from 1.0 to 2 cal/ml and include 3 to 7 percent protein. Most of the calories are supplied as glucose or sucrose, so that the solutions have a high osmolarity. Cramps or diarrhea can result when these high osmolar solutions are placed into the stomach or intestine. Diarrhea is the major complication with most tube feeding formulations, and it can usually be controlled by adding pectin to the feedings. A large amount of pectin may be required. Diarrhea can also be minimized by the use of starch or fat as an energy source in tube feedings. This can be supplied as part of the commercial preparation or added in the form of medium chain triglycerides or other oils. The best results are usually achieved by supplying approximately half of the calories as carbohydrate and half as fat. Although some formulations are advertised as "low residue," almost all of the liquid feeding formulas are completely absorbed in the small intestine. Typical formulas are shown in Figure 4.14.

Figure 4.14: Typical enteral feeding formulas. Commercial names are used.
Figure 4.13: Nitrogen balance related to energy balance in critically ill patients treated with standard parenteral nutrition solutions with 40 gm amino acid and 1000 cal glucose per liter. (Author's data)
<table>
<thead>
<tr>
<th>Parenteral</th>
<th>CHO</th>
<th>Fat</th>
<th>Protein</th>
<th>mOsm/L</th>
<th>Cal/L</th>
<th>mEq/L</th>
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<tbody>
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<td></td>
<td>%</td>
<td>%</td>
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<td></td>
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<td>TPN Solutions</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>10% glucose</td>
<td>10</td>
<td>0</td>
<td>4.25</td>
<td>880</td>
<td>440</td>
<td>47</td>
<td>23</td>
<td>82 mEq acetate</td>
</tr>
<tr>
<td>25% glucose</td>
<td>25</td>
<td>0</td>
<td>4.25</td>
<td>1825</td>
<td>1020</td>
<td>35</td>
<td>40</td>
<td>75 mEq acetate</td>
</tr>
<tr>
<td>Lipid 10%</td>
<td>10</td>
<td></td>
<td></td>
<td>1000</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Criticare HN</td>
<td>22</td>
<td>.3</td>
<td>3.8</td>
<td>650</td>
<td>1060</td>
<td>27</td>
<td>34</td>
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<tr>
<td>Osmolyte HN</td>
<td>14.1</td>
<td>3.7</td>
<td>4.4</td>
<td>310</td>
<td>1060</td>
<td>40</td>
<td>40</td>
<td>tube only</td>
</tr>
<tr>
<td>Isocal</td>
<td>12.6</td>
<td>4.2</td>
<td>3.2</td>
<td>300</td>
<td>1060</td>
<td>22</td>
<td>32</td>
<td>tube only</td>
</tr>
<tr>
<td>Ensure</td>
<td>14.5</td>
<td>3.7</td>
<td>3.7</td>
<td>470</td>
<td>1060</td>
<td>37</td>
<td>40</td>
<td>oral or tube</td>
</tr>
<tr>
<td>Jevity</td>
<td>15.2</td>
<td>3.7</td>
<td>4.4</td>
<td>310</td>
<td>1060</td>
<td>41</td>
<td>40</td>
<td>tube only</td>
</tr>
<tr>
<td>Replete</td>
<td>11.3</td>
<td>3.3</td>
<td>6.2</td>
<td>350</td>
<td>1000</td>
<td>22</td>
<td>40</td>
<td>oral or tube</td>
</tr>
</tbody>
</table>

Figure 4.14: Typical enteral feeding formulas. Commercial names are used.
Whatever formulation is used, there are some tricks to using enteral feeding that are often neglected, which results in regurgitation or diarrhea and termination of the feedings. Feedings should be given by continuous infusion into the stomach rather than large boluses. This infusion should extend over 24 hours. It is rarely necessary to give more than 100 ml/h. When possible, the patient should be situated in a sitting position (or a side-to-side head-up position) to prevent regurgitation along the tube. Gastric residuals should be checked if the patient feels uncomfortable or appears distended, but it is not necessary to check the residual more than once a day. With continuous tube feeding a residual of 2-300 ml is normal.

It is usually recommended to begin with 50 ml/h of diluted (half-strength) feeding formula, followed by an increase in volume and then in concentration until 100-150 ml/h of full strength formula is reached. In the author's experience, it is better to start with a small amount of full-strength formula rather than a large amount of diluted formula. The amount (rather than the concentration) should be gradually increased until the desired volume is reached. Tube feedings can be supplemented by oral intake. The intake of popsicles, hard candy, peanut butter, eggnog, etc., should be encouraged. The volume of feedings can be decreased proportionate to the number of calories taken in by mouth. As noted above, diarrhea can almost always be controlled with pectin. Hypernatremia can result if the tube feeding is rich in sodium. This should be managed by the use of low salt solutions or by the administration of free water. A serious problem with tube feeding is complete cessation of feedings by the nursing staff because of diarrhea or high gastric residual. If the tube feeding needs to be curtailed for any reason, it should be reinstituted the next hour at a smaller volume and gradually increased until the prescribed caloric load is reached again.

Feeding formulas support bacterial growth, and sometimes the diarrhea and cramps represent "food poisoning." The food should be prepared fresh daily and refrigerated until used. A new aliquot should be started every 8-12 hours.

**Tube Feeding to Prevent Intestinal Atrophy and Cholestasis**

Twenty five years ago hypermetabolic critically ill patients who could not be fed, died. With the development of total parenteral nutrition by Dudrick and his colleagues we began to see patients who lived for weeks supported by parenteral feeding alone. Many of these patients recovered from their primary disease, returned to normal eating, and survive today because of the techniques of parenteral nutrition. Along with this marvelous progress came the recognition of intestinal mucosal atrophy and cholestasis, both of which commonly occurred in patients managed for more than a few days with total parenteral support. There is good evidence that the loss of mucosal thickness in these patients may allow absorption of bacterial toxins or intact bacteria. This endogenous source of chronic inflammation compounded by compromised liver function has been postulated at the underlying mechanism for multiple organ failure often seen in patients who have no enteric feeding for a long period of time. Throughout the development of parenteral feeding it has been documented many times that enteral feeding with equivalence of substrate is always better than parenteral feeding. ("Better than" means better liver function, less organ failure, better endurance, and better host defenses in laboratory animals.) This usually translates to shorter ICU stay, less complications, and perhaps better survival in critically ill patients when enteral feeding is compared to
parenteral feeding. Some, if not all of the advantage of enteral feeding can be attributed to avoiding intestinal mucosal atrophy and cholestasis. Recent evidence indicates that the mucosal atrophy can be prevented by small amounts of the amino acid glutamine in the lumen of the intestine. It is interesting to note that all enteral feeding formulas contain glutamine, but standard parenteral nutrition amino acid formulas are notably deficient in glutamine.

All of these factors point out the importance of providing some feeding into the intestinal tract in critically ill patients. Even small amounts such as 5-10 cc/hr can be given safely to patients with ileus or intestinal anastomosis, but this small volume is sufficient to minimize intestinal atrophy. If some fat is included with the feeding (as is the case with almost all feeding formulas) then the risk of cholestasis is further decreased.

Gastrointestinal Bleeding

Bleeding from the stomach or duodenum is a common problem in critically ill patients, and is discussed at this point because the pathogenesis relates in part to the absence of food, buffering, and gastric acid in the stomach. When upper GI bleeding occurs it is due to ulcerations in the stomach or duodenum commonly referred to "stress" ulceration associated with critical illness. This is a gross misnomer because the ulcerations do not occur in patients who experience stress. Rather they occur in patients who experience sepsis. It would put the emphasis in the proper place to refer to septic GI bleeding rather than stress GI bleeding, since the most effective means of prophylaxis is to prevent localized or systemic infection. This is best demonstrated by experience with burned patients. Upper GI bleeding from gastric or duodenal ulcers was so common in burn patients as to have a specific eponym (Curling's ulcer). With older methods of burn surface management, Curling's ulcer was a common occurrence and frequently the cause of death in patients with burns. Now upper GI bleeding is exceptionally rare in burn patients. In the author's experience with over 5,000 consecutive burn patients following a protocol in which systemic sepsis was very rare, significant upper GI bleeding occurred in only two patients. The prophylactic regimen included gastric feedings and avoiding systemic sepsis, but not H2 blockers.

There is one notable exception to the renaming of ICU GI bleeding as "septic" bleeding. Some patients with brain injury produce huge amounts of gastric acid which can result in rapid development of the most extensive duodenal ulcers a surgeon will ever encounter. This phenomenon is referred to as Cushing's ulcer. Prophylaxis is dependent upon continuous neutralization of the acid.

Although it is commonly said that upper GI ulceration never occurs without acid and pepsin, there is some evidence that gastric ischemia, shock, and some medications such as steroids can predispose critically ill patients to gastric ulceration. Therefore efforts to maintain normal systemic oxygen delivery, normal celiac blood flow, and efforts to decrease steroid medications are important aspects of GI bleeding prophylaxis. With that done, and with attention to preventing sepsis, specific prophylactic treatment for the stomach and duodenum includes protecting the mucosal barrier of the stomach with a coating agent like Carafate, and/or maintain the gastric pH above 4 by buffering or prevention of acid secretion. These preventative steps and the risks associated with them are summarized in Figure 4.15. If the gastric pH is maintained in the neutral range by antacids, gastric feeding, H2 blockers, or anticholinergic drugs, bacteria and yeast will grow in the stomach because the normal sterilizing effect of gastric acid is neutralized. As a
result the upper and lower intestine is contaminated with greater numbers of different bacteria than are usually present there. In addition regurgitation of gastric contents with subsequent small amounts of aspiration may predispose to nosocomial pneumonia. In an orally-intubated patient the risk of serious complications of nosocomial pneumonia is greater than the risk of upper GI bleeding in most cases, so that Carafate alone is the best approach to GI bleeding prophylaxis. In a very high risk patient such as a patient with ongoing sepsis, prior history of ulcer disease, or brain injury, additional steps to neutralize gastric pH are indicated, and the best of those is continuous gastric feeding, if such feeding can be tolerated. Although it is somewhat controversial, the preponderance of evidence indicates that antibiotic treatment to the nasopharynx and stomach in this setting minimizes the risk of nosocomial pneumonia (so called selective decontamination of the GI tract).

Figure 4:15: Methods to prevent upper GI ulceration and bleeding, and the risks associated with those methods.

**Parenteral Feeding**

Commercial preparations for parenteral feeding in the United States are currently limited to glucose (5-45 percent) and fat (10-20 percent) as energy sources and amino acid or peptide solutions (2-10 percent) as protein sources. Both parenteral and tube feedings are planned so that total energy requirements can be met through fat or carbohydrate or both. Any protein administered should be available for anabolic processes. Parenteral feeding with carbohydrate is limited by the sclerotic effect of hyperosmolar solutions on veins. Effective parenteral feeding with carbohydrate alone usually requires solutions of at least 1 cal/ml (25 percent sugar). This type of solution must be given into an area of rapid blood flow, generally the superior vena cava. Complications still occur, which are discussed later in this chapter. Fat is a more efficient energy source and can be given through peripheral veins in concentrations of either 10 or 20 percent. The total daily energy requirement can be given as fat or a major portion can be given as fat with the rest as carbohydrate. Both fat and carbohydrate are equally effective sources of energy. The fat has the advantage of peripheral administration, the carbohydrate has the advantage of approximately one tenth the expense. The ratio between fat and carbohydrate energy sources and the ratio between total energy sources and grams of protein varies depending on the clinical state. For example, a patient in cardiac failure may require a solution that is low in volume, low in sodium, but high in calories and protein. A patient with multiple intestinal fistulas may require large volumes, allowing less calories and grams of protein per milliliter. Because of the potential problems with central venous cannulation, the administration of 10 percent glucose, amino acid solutions, and fat through peripheral veins has become popular. Two liters of 10 percent glucose supply 800 cal, and 500 ml of 20 percent lipid supply 1000 cal. The total is ample for most patients who are not hypermetabolic.

Any hospital that routinely cares for critically ill patients should have a standardized approach to parenteral nutrition, including vascular access, catheter management, solution preparation, stock solutions, and protocols for the management of risks and complications. The “standard” solution for total parenteral nutrition is made by mixing equal amounts of 50-percent glucose and 9-percent amino acids. This solution contains the equivalent of 1 carbohydrate calorie per milliliter at a ratio of 25 cal/g of protein. The osmolarity of this solution is 1800 mOsm/l, and it must be given into an area of rapidly
### GI Bleed Prophylaxis

<table>
<thead>
<tr>
<th>Method</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rx sepsis</td>
<td>0</td>
</tr>
<tr>
<td>↑ DO2, anemia</td>
<td>transfusion</td>
</tr>
<tr>
<td>&quot;Protect&quot; stomach</td>
<td>clamp NG</td>
</tr>
<tr>
<td>Carafate</td>
<td></td>
</tr>
<tr>
<td>↓ steroids</td>
<td>steroids needed?</td>
</tr>
<tr>
<td>↑ Gastric pH</td>
<td>pneumonia</td>
</tr>
<tr>
<td>Antacids</td>
<td>clamp NG</td>
</tr>
<tr>
<td>H2 blockers</td>
<td>cost, confusion</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>dry secretions</td>
</tr>
</tbody>
</table>

Figure 4:15: Methods to prevent upper GI ulceration and bleeding, and the risks associated with those methods.
flowing blood. Insertion and care of the catheter must follow sterile technique. The standard solution can be modified for individual patients by raising or lowering the concentration of glucose and amino acids and by varying the electrolyte and trace metal composition. Vitamins and trace minerals are added to the solution at regular intervals, following the general principle of providing more than basal requirements, as discussed earlier. The standard solution is supplemented with intravenous fat to provide at least 100 g of fat emulsion each week to preclude fatty acid deficiency. We favor giving 25-50 percent of the calories each day as fat emulsion. Fat emulsion is usually given through a peripheral vein, although it can be given through a central catheter at the same time as the hypertonic glucose solution. Typical formulas are shown in Fig. 4.16.

Figure 4.16: Typical parenteral feeding formulas (University of Michigan PEN Team, standard solutions).*

The most common complication of total parenteral nutrition is infection on or around the intravascular catheter. Of course, infection can occur with any indwelling vascular catheter, but it is more likely in the presence of hypertonic glucose and protein solutions. If catheter infection is suspected, the catheter must be removed and a new catheter placed. Replacement "over a wire" is sufficient. The second most common complication is hyperglycemia, which can be exacerbated in a septic, insulin-resistant patient. Hyperglycemia is treated with insulin, and by using fat rather than glucose as the primary calorie source. Other complications are largely those of hyperglycemia, that is, hyperosmolar coma, osmotic diuresis, and localized thrombosis. These complications can be caused by running the solution too rapidly. This is prevented by always using a rate-limiting pump when administering hypertonic solutions. It should be noted that the presence of systemic infection is an indication for nutritional support, not a contraindication to placing a central catheter. Other complications are related to disease states and specific amino acids. Aromatic amino acids are neurotransmitter precursors. Symptoms of CNS disturbances (confusion, seizures, coma) occur in total parenteral nutrition (TPN) patients, particularly those with liver dysfunction. These symptoms often cease when amino acid infusion is stopped. A solution low in aromatic amino acids has been proposed for liver failure patients.

The major "trick" to successful clinical use of parenteral nutrition is the development of a precise protocol for all steps in the management of this procedure. Many large hospitals have developed a parenteral nutrition team that supervises the protocol and facilitates the procedure. The presence of such a team minimizes complications and is well worth the expense.

APPLICATION OF METABOLIC ECONOMICS TO THE CRITICALLY ILL PATIENT

Nutritional Status Assessment

Whenever possible, patients who are identified as malnourished through the nutritional assessment process listed above should be returned to normal nutritional status before a major elective operation. Other than this circumstance, however, patients who require hospitalization because of critical illness cannot be nutritionally prepared ahead of time. Each patient admitted to the intensive care unit should be evaluated for nutritional status as summarized in Figure 4.9. Patients who show evidence of malnutrition should be started on a feeding regimen soon after admission. Patients who
### Nutrients

<table>
<thead>
<tr>
<th>Parenteral</th>
<th>CHO %</th>
<th>Fat %</th>
<th>Protein %</th>
<th>mOsml/L</th>
<th>Cal/L</th>
<th>Na mEq/L</th>
<th>k mEq/L</th>
<th>Other</th>
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</thead>
<tbody>
<tr>
<td>TPN</td>
<td>10</td>
<td>0</td>
<td>4.25</td>
<td>880</td>
<td>440</td>
<td>47</td>
<td>23</td>
<td>82 mEq acetate</td>
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</tr>
<tr>
<td>25% gluc</td>
<td>25</td>
<td>0</td>
<td>4.25</td>
<td>1825</td>
<td>1020</td>
<td>35</td>
<td>40</td>
<td>75mEq acetate</td>
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<tr>
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<td></td>
<td>276</td>
<td>1000</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Values per liter of solution.

Figure 4.16: Typical parenteral feeding formulas (University of Michigan PEN Team, standard solutions).*
cannot eat after a few days in the ICU should be started on enteral and parenteral feeding. (Figure 4.17).

Figure 4.17: Guidelines for the timing of institution of enteral and parenteral feeding in critically ill patients. Most ICU patients fall into the moderate or major acute depletion category and should be started on nutrition the first day or two in the ICU. (from Bartlett, Cardiopulmonary Critical Care, 1986)

During the period of critical illness, nutritional and metabolic status should be assessed daily. Daily measurement of caloric and nitrogen balance is routine in many intensive care units. Although estimation from tables or graphs varies considerably from the actual protein and caloric requirements, estimation is better than nothing. The most accurate estimating system is that of Wilmore. (Figure 4.4). Fluid balance can be measured accurately in the intensive care unit and the patient should be weighed daily. Correlation of daily fluid balance with daily weight is an essential step in evaluating nutritional status during critical illness. Along with daily estimation or measurement of caloric balance, periodic measurement of acute-phase, protein-dependent reactants such as lymphocytes is also helpful. Many patients reach the state of hypoproteinemia (i.e., severe protein malnutrition) in the critical care unit. However, this should never happen if appropriate attention is being given to protein and calorie status. Our algorithm for management of nutrition in critical illness is shown in Figure 4.18. We have carried out retrospective studies related to energy balance in critically ill patients with a variety of conditions. In these studies, patients who were in a positive caloric balance at the time of ICU discharge had a higher survival rate than patients in a negative balance. In particular, patients with a 10,000 cal cumulative deficit at the time of ICU discharge had a high mortality. (Figure 4.19). This was true of patients with a variety of illnesses and specific patient groups with chest trauma and acute renal failure. Furthermore, survival was better when feeding was instituted early in the course of critical illness. The management of nutrition in acute renal failure is undergoing major changes, and is discussed in the next section.

Figure 4.18: Nutritional Algorithm

Figure 4.19: Outcome in 56 ICU patients with multiple organ failure correlated with cumulative caloric balance. This is one of the first studies showing that feeding improves survival in ICU patients. (from Bartlett, Surgery, 1982)

Protein and energy nutrition are required in respiratory failure to maintain respiratory muscle strength and bolster the host defenses of the lungs. Patients with pure respiratory failure usually can be fed via the gastrointestinal tract directly. Energy requirements should be measured specifically in these patients, since overfeeding with carbohydrate will result in excess CO2 production through the conversion of carbohydrate to fat. This positive RQ can require continuation of mechanical ventilation when a patient would otherwise be ready for weaning from the ventilator. Furthermore, overfeeding with carbohydrate is a common cause of ventilator weaning failure, so energy sources should be carefully examined in any patient who has borderline respiratory function.

A patient with systemic infection (sepsis) has an elevated metabolic rate and an elevated protein catabolic rate. This patient requires an energy and protein supply to meet these needs. The fact that the patient has a systemic infection should not deter the
Figure 4.17: Guidelines for the timing of institution of enteral and parenteral feeding in critically ill patients. Most ICU patients fall into the moderate or major acute depletion category and should be started on nutrition the first day or two in the ICU. (from Bartlett, Cardiopulmonary Critical Care, 1986)
Nutrition Algorithm

Routine post-op NPO 4-5 days
Depleted patient pre or postop
Risk for MOF NPO 1 day
Any organ failure NPO 1 day

→ Needs full nutrition
  Estimate caloric + protein needs
  30 cal/KG
  1 gm protein/KG

→ Enteral feeding possible?
  Yes
  • while getting access
  • before full support
  • malabsorption
  • diarrhea
  • feeding DC'd

  Full feeding

  Yes
  Needs TPN

  No
  >2000 cal
  central line
  full feeding
  <2000 cal
  peripheral vein?

→ Enteral feeding possible?
  Yes
  • while getting access
  • before full support
  • malabsorption
  • diarrhea
  • feeding DC’d

  Full feeding

1. Measure REE (Daily ICU, 3x/week other) Give REE calories + 10% (approx 1/3 as fat)
   Follow RG, daily + cumulative E balance
2. Measure N balance (Daily ICU, 3x/week other) Give protein loss + 10%
   Follow: daily + cumulative N Balance total lymphocytes, albumin

Figure 4.18: Nutritional algorithm
Figure 4.19: Outcome in 56 ICU patients with multiple organ failure correlated with cumulative caloric balance. This is one of the first studies showing that feeding improves survival in ICU patients. (from Bartlett, Surgery, 1982)
physician from placing a central venous catheter or whatever access is required for enteral or parenteral feeding.

The principles in this chapter are summarized in the algorithm in Figure 4.18, and emphasized in the Nutrition Axioms (Figure 4.20).

Figure 4.20: Nutrition Axioms
# Nutrition Axioms

| 1. | Estimate or measure caloric and nitrogen balance daily. |
| 2. | Use enteral nutrition whenever possible. Even small volumes prevent mucosal atrophy |
| 3. | Treat hypoproteinemia with diuresis when appropriate, then with concentrated albumin or plasma. |
| 4. | Manage nutrition based on balance studies. |
| 5. | Absolute lymphocyte count and pre-albumin are useful markers of acute phase nutrition, but balance studies are better. |
| 6. | Tube feeding diarrhea can always be controlled by changing formula, flora, or fiber. |
| 7. | Don't use antacids or H2 blockers for stress bleeding prophylaxis. The pneumonia risk is higher than the bleeding risk. |
| 8. | When gastric pH regulation is used to treat active bleeding, measure the pH regularly and keep it over 4. Many elderly patients are achlorhydria and don't need pH control. |

Figure 4.20: Nutrition Axioms
Chapter 4 Monographs and Reviews


This review of more than 300 references summarizes the classic and recent literature on this subject.


An excellent recent review of acute phase metabolism.


This paper introduces the concept of repeated insults after initial "priming" as in the pathogenesis of multiple organ failure.


These two "meta analyses" review the same papers and come to opposite conclusions.


This review of the components of enteral feedings includes references to several of the papers showing that luminal glutamine is important to prevent mucosal atrophy.


This review includes the estimated increase in metabolic rate with various types of critical illness, as discussed in this chapter.

One of the classic references on nutrition and metabolism. The standard reference for caloric value of food stuffs, the Weir equation, and detailed study of metabolism.


The classic monograph summarizing the isotopic dissection of fluid spaces in the body conducted by Moore's laboratory over many years.


One of the experts in nutrition and metabolism discusses endocrine and hormonal mediators of metabolism. This book includes a nomogram for predicting metabolic rate in critical illness which is the most accurate predictor, short of actual indirect calorimetry.


This review includes analysis of the cytokine and hormonal mediators of the stress response, specific fluids, and growth factors including the authors extensive experience with growth hormones.

Chapter 4 Selected Reports


Recommended dosages listed in this chapter are based on this publication.


One of the first reports demonstrating the value of managing nutrition based in indirect calorimetry in critically ill patients.


The first study that correlated positive cumulative caloric balance with survival in critically ill patients.

Many modifications of parenteral feeding formulations have been studied in animals and few have had an impact on clinical outcome in patients. This randomized study of branched chain amino acids showed no improvement compared to conventional parenteral solutions.


A classic reference on the effects of starvation and starvation adaptation in normal man.


One of several papers published by the Montreal group relating immune response measured by skin test reactivity in critical illness and malnutrition.


Development of a device for protein balance measurements in the ICU.


One of the first studies to demonstrate pneumonia associated with gastric bacterial overgrowth in the pH-neutral stomach.


This is the classic paper first describing successful total parenteral nutrition in detail.


This is one of the first papers to show that fat can be used as the sole energy source in parenteral nutrition.

The original publication on oxygen consumption and basal metabolic rate in normal volunteers.


Patients who achieved positive caloric balance early in the ICU course had better survival than patients fed in conventional fashion.


Trauma patients fed an enteral diet high in protein, glutamine, and branched-chain amino acids had less organ failure than conventional tube feeding patients.


This classic paper describes the method to define protein in urea kinetics in anuric and oliguric patients.


This study showed that any source of protein can cause an increase in body cell mass in post-operative patients.


Of many studies showing that luminal glutamine avoids mucosal atrophy in parenteral or enteral feeding.


One of the classic papers describing induction of the hypermetabolic protein catabolic state in normal individuals in response to infusion of stress related hormones.
CHAPTER 5. RENAL PHYSIOLOGY AND PATHOPHYSIOLOGY

Renal physiology is simplified and summarized in Figure 5.1. Blood perfuses the renal cortex and extracellular fluid is filtered through the glomeruli at a rate of about 7 L/hr. Almost all (99.4%) of this fluid is reabsorbed in the proximal and distal tubules leaving about 40 cc/hr to run down the ureters into the urinary bladder. The only "reason" for this incredibly over-designed system is to excrete the biproducts of protein metabolism and a few other molecules which cannot be excreted through the lungs or liver. If only 25% of the nephrons are working, blood electrolytes and urea will still be maintained in the normal range. If only 10% of the nephrons are working azotemia will result but life goes on. If less than 5% of the nephrons are working fatal uremia or congestive heart failure will occur unless some type of mechanical renal replacement is undertaken.

Usually nephrons fail altogether, although there are situations in which specific nephron functions are preferentially loss. The most common of these is polyuric or non-oliguric renal failure in which glomerular filtrate is produced but proximal tubular handling of sodium and potassium and urea is abnormal. In this case the patient may make adequate or even very large amounts of urine which is of "poor quality"; high in sodium, low in potassium and low in urea.

Renal function is most commonly characterized by simply measuring urea or creatinine in serum or urine. If these measurements are abnormal, renal function can be more specifically characterized by calculating creatinine clearance, or the fractional secretion of sodium or urea. The definition and formulas for these measurements are listed in Table 5.1.

In the ICU renal function is taken for granted, and is used to forgive gross excesses in salt and fluid administration to patients. All manner of fluid, electrolyte and metabolic disorders will be automatically corrected by normal renal function. We take advantage of this to clear drugs, salt, and metabolites which we often give in excess. In fact kidney physiology comes to our attention only when it fails. Consequently the rest of this discussion is focused on the causes, pathophysiologic consequences and treatment of renal failure.

Figure 5.1: Renal Function

Table 5.1: Definitions and formulas related to renal function

Acute renal failure, by definition, is an abrupt decrease in kidney function that results in accumulation of nitrogenous solutes. Urine output in ARF may be oliguric (urine output less than 400 ml/day) or non-oliguric (urine output is normal or increased while solute clearance is markedly decreased). The mortality of ARF in the intensive care unit is high (50-90%) because ARF is usually just one component of severe multiorgan failure. Mortality from non-oliguric ARF is significantly less than from oliguric, although many patients progress to oliguria and its poor outcome. Regardless of urine output, the sequelae of ARF result from retention of metabolic wastes and are indicated by a progressive rise in blood urea nitrogen (BUN) and serum creatinine concentrations. Hypervolemia and electrolyte imbalances further complicate management of oliguric ARF.
Figure 5.1: Renal Function

Renal Function

Nephron

Water

<table>
<thead>
<tr>
<th>L/Hr</th>
<th>0.4</th>
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<th>7.5</th>
<th>125 ml/min</th>
</tr>
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<tbody>
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<td>1.25</td>
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<tr>
<td>Mosm/day</td>
<td>700</td>
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</tr>
<tr>
<td>g/day</td>
<td>10</td>
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<tr>
<td>mg/dL</td>
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<td>Solute</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Urine/day

Reabsorbed

Glomerular Filtrate

%
<table>
<thead>
<tr>
<th>Definitions &amp; Formulas</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR Glomerular filtration rate</td>
<td>[2cc/kg/min]</td>
</tr>
<tr>
<td>Osm Osmolarity/liter</td>
<td>urine 300-1300 mmOsm/l</td>
</tr>
<tr>
<td>CrCl Creatinine Clearance</td>
<td>$\frac{U_{cr} \times U_{cr}}{P_{cr}}$</td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>
The pathogenesis of ARF is commonly classified as being prerenal, postrenal, or intrinsic parenchymal disease. This discussion is limited to parenchymal disease. Parenchymal abnormalities include acute tubular necrosis (ATN), pigment nephropathy (due to circulating myoglobin and hemoglobin), and nephrotoxic agents (various drugs and contrast material). Other causes of parenchymal renal disease such as acute glomerular nephritis and vasculitis are not typically responsible for ARF in the surgical patient and will not be discussed in this chapter.

**Acute Tubular Necrosis**

Acute tubular necrosis results from ischemia to the renal parenchyma and is the most common pathologic finding of ARF. Under conditions of diminishing renal blood flow, perfusion of the kidneys is first maintained by vasomotor responses, which dilate the afferent arteriole and constrict the efferent arteriole. As continued hypotension is detected by the juxtaglomerular apparatus, the renin-angiotensin system is activated in concert with sympathetic release of other vasoactive hormones. These substances produce vasoconstriction of the afferent arteriole and further exacerbate cortical hypoperfusion. As a result, glomerular filtration rate (GFR) is sharply reduced and the tubules experience profound ischemia. With damage to the tubular system, casts of cellular debris obstruct the lumen and cellular edema occurs. As tubular cells necrose and slough off, glomerular ultrafiltrate leaks back across the proximal tubular membrane into the interstitium. It has recently been suggested that this “back-leakage” of luminal fluid into the peritubular space causes vascular congestion within the renal parenchyma and may contribute to prolongation of ARF. The absence of these glomerular changes in the presence of adequate cortical blood flow may be responsible for the maintenance of urine output in non-oliguric ARF and the recovery phase of oliguric ARF. Thus, ATN is a spectrum of cortical ischemic injury ranging from polyuria with tubular dysfunction, to temporary anuria, to renal cortical necrosis with chronic anuria.

**Pigment Nephropathy**

Pigment nephropathy is a common cause of ARF and may occur after trauma, burn, operation, or hemodynamic catastrophe. With ischemia or blunt injury to large muscle masses, myoglobin is released to the circulation. In the kidney, it is filtered from blood and reabsorbed by the tubule. Although myoglobin is not a direct nephrotoxin, in the presence of aciduria, myoglobin is converted to ferrihemate, which is toxic to renal cells. Rhabdomyolysis should be suspected in patients with burns, trauma, seizures, alcohol or drug intoxication, prolonged ischemia to muscle groups, and extended coma. Diagnosis can be made with elevated creatine phosphokinase and a urine microscopy study that shows prominent heme pigment without red blood cells in the urine sediment. Hyperkalemia and elevated serum creatinine are also consistent with injury to muscle masses. Prevention of myoglobin-induced ARF may include the use of diuretics and alkalization of urine, although the efficacy of this action has yet to be determined. Prophylactic infusion of haptoglobin is also being tested as a means of protection against ARF in burn patients.

**Nephrotoxic Agents**

Drug-induced ARF is responsible for approximately 20% of all cases of ARF. Its pathophysiology differs according to the offending agent. Through normal reabsorption and secretion, the kidney is exposed to high concentrations of drugs and solutes, which
may be toxic. This problem is compounded by hypovolemia, which causes increased reabsorption of water and solutes and exposes the lumen to even higher concentrations of toxins. Although the damage to tubular function can be significant, much drug-induced ARF remains non-oliguric owing to sparing of glomerular function.

Radiographic contrast dye has been documented to cause ARF. The incidence of contrast nephropathy is approximately 1% to 10% and may be predicted according to a number of risk factors. These include contrast load, age, preexisting renal insufficiency, and diabetes, although some of these factors are currently disputed. The incidence in patients with normal renal function is a significantly lower 1% to 2%. Contrast nephropathy is usually experienced as an asymptomatic, transient rise in creatinine but may progress to oliguric renal failure requiring hemodialysis. Induced diuresis with fluids and diuretics prior to contrast injection may decrease the incidence and severity of ARF in high-risk patients.

Management of Acute Renal Failure

In ICU patients, ARF rarely occurs in an isolated fashion. Rather, ARF is only one component of a multiple organ failure syndrome often accompanied by infection. Management of these patients, therefore, should be focused on treatment of the underlying disease process(es). Development of ARF complicates the care of ICU patients by introducing difficulties in fluid, electrolyte, and nutritional management. The adverse effects of renal replacement therapies further compound these problems. A favorable outcome can be accomplished only through aggressive intervention. This includes surgical drainage of septic focus, excision of necrotic tissue, early implementation of effective renal replacement therapy, and full nutritional support.
**General Care of Patients with Acute Renal Failure**

Our algorithm for evaluation and management of renal failure is shown in Figure 5.2. With non-oliguric ARF, treatment may differ little from that required for identical patients with normal renal function. Management of fluids, solutes, and nutrition is usually unaffected by non-oliguric ARF, although BUN may be elevated. The extent of renal dysfunction is limited and almost always reversible. Use of renal replacement therapies (and their inherent complications) is rarely necessary.

![Figure 5.2: Acute renal failure algorithm](image)

Oliguria and anuria pose several management difficulties. In the absence of normal urine output, problems of fluid overload can lead to anasarca, pulmonary edema, and congestive heart failure. The pharmacokinetics of drugs becomes difficult to predict as a result of decreased elimination and increased volume of distribution. In light of these risks, the volume status of patients with ARF must be carefully monitored. Fluid intake and output must be precisely tabulated, and body weight should be measured daily. Pulmonary artery catheterization may be necessary to monitor more closely the hemodynamic status of these patients. Treatment options for hypervolemia consist of fluid restriction or fluid removal with artificial kidney techniques. However, fluid restriction limits intravenous medications and may preclude adequate nutrition.

ARF can create severe derangements in electrolyte and acid-base physiology. Serum electrolytes should be measured daily. Of all the electrolyte abnormalities that might occur with ARF, hyperkalemia is the most serious. Under the conditions of hypercatabolism and tissue necrosis that characterize these patients, large amounts of potassium may be generated and may accumulate over a short period of time. Acute hyperkalemia decreases cardiac excitability, which may ultimately result in asystole. These events are usually preceded by changes in the electrocardiogram that indicate hyperkalemia. These changes include loss of p waves, widening of the QRS complex, and peaked T waves. Immediate treatment of hyperkalemia consists of infusion of glucose-insulin, calcium gluconate, and bicarbonate. These measures, however, cause only transient shifts in potassium from extracellular to intracellular spaces and are of limited value. Removal of potassium must be accomplished with renal replacement therapy or ion-exchange resins. Other electrolyte abnormalities such as hyponatremia, hyperphosphatemia, hypocalcemia, and metabolic acidosis are common with ARF and must be monitored closely. Treatment consists of appropriate additions or restrictions of intravenous solutions and effective use of the artificial kidney.

Although poorly understood, platelet dysfunction and coagulopathy are often associated with ARF. A reproducible platelet defect can be demonstrated experimentally with a BUN of 100 mg/dl. However, the cause of this defect has yet to be identified.

Anemia also accompanies ARF in the surgical patient. In addition to blood loss due to hemorrhage or operation, erythropoietin production has been shown to decrease in direct proportion with decreasing renal function.

**Nutrition and Acute Renal Failure**

The goal of nutritional support in ARF is to provide optimal amounts of calorie and protein substrates to minimize auto-catabolism and allow tissue anabolism, wound healing, and sustained immune function. In any discussion of nutrition and renal failure,
Figure 5.2: **Acute Renal Failure Management Algorithm**

Oliguria

- Rule out urinary obstruction
  - Bladder Catheter
  - Ultrasound

- Blood volume
- Cardiac output
- Dopamine

- Assure good renal blood flow

**Dx1 Renal Parenchymal Disease**

Confirm by urine electrolytes and clearance

**Furosemide 100-500 mg**

- Diuretic Trial

  - Polyuria
  - Oliguria

**Dx1 Some nephrons functional**

- Continue diuretics
- Expect azotemia
- **Full nutrition**
- Intermittent hemodialysis as needed for solute clearance

  - Renal recovery

**Dx1 Some or all nephrons recovered**

**Dx1 No nephrons functional**

- Isolated renal failure
  - **Full nutrition**
  - Intermittent hemodialysis or PD as needed for volume and solute control

  - Chronic renal failure

- Multiple organ failure
  - **Full nutrition**
  - CAVH/CWH for volume
  - CAVHD/CWHD for solute control

  - Chronic dialysis
it is necessary to point out the distinction between acute and chronic renal failure. In chronic renal failure, patients are generally healthy and have energy requirements that differ little from those without chronic renal failure. Protein intake is required only for metabolic turnover and is restricted to minimize production of urea generation and other products of protein metabolism.

By contrast, the metabolic requirements of a patient with ARF are those of a critically ill hospitalized patient. Actual measurement of resting energy expenditure has shown that caloric requirements of multiple organ failure patients with ARF average 50% above normal, healthy individuals. Measured protein requirements are also increased to as much as 2.5g/kg to provide to anabolic wound healing and sustained immune function. For these patients, protein restriction is counterproductive and potentially detrimental. Urea generation will be best minimized by providing enough energy substrates (carbohydrates and lipids) to prevent cannibalization of endogenous protein as an energy source. In recent years, investigations emphasizing energy and protein balance have demonstrated improvement of outcome from ARF.

Positive energy balance may also make management of uremia and hyperkalemia less difficult. When a patient receives fewer calories than those expended, the difference must be made up from endogenous stores. In a well-nourished individual, carbohydrate stores rarely exceed 2500 kilocalories. After this has been depleted, lipid and protein stores are mobilized. In the diseased state, endogenous protein has been shown to be preferentially catabolized as an energy substrate in the absence of readily available glucose. With catabolism of protein, urea is generated. In addition, catabolic wasting of tissues and cells liberates excess potassium. Maintenance of positive energy balance with glucose and lipids should reduce protein catabolism, urea generation, and hyperkalemia. Our group showed that survival in ARF correlates with positive caloric balance (Figure 5.3).

Although protein restriction may be advocated in chronic renal failure, protein requirements in ARF are usually elevated. Abel and colleagues were among the first to suggest improved survival with addition of amino acids to intravenous nutrition. Others have confirmed these findings. The two important concerns regarding protein supplementation in ARF are what type and how much to administer. The rate of protein catabolism reported in various studies ranges from 70 to 200 g/day. In light of this wide range of protein catabolism, actual measurement of protein balance is desirable. In the oliguric patient, the protein catabolic rate of a patient can be reasonably approximated through calculation of the urea generation rate. In this calculation, changes in BUN and fluid balance are recorded for a 24-hour period. Nitrogen content is also determined from collections of dialysate or ultrafiltrate, nasogastric suction, wound drains, and so on, obtained over the same time interval. Assuming that urea produced by protein catabolism is not reused and that it is contained within the extracellular space, the urea generation rate can be calculated. With this information, daily protein balance can be monitored. Maintenance of positive protein balance is the goal, although this may be difficult to achieve. Most investigators have supplemented protein at a rate of 0.5 to 1.0 g/kg/day, and the effects of providing larger amounts have yet to be studied.

Figure 5.3: Survival and nutrition in acute renal failure. Patients in oliguric renal failure had better outcome when positive caloric balance was achieved. (from Mault, Acute Renal Failure in Greenfield, 1989).
Figure 5.3: Survival and nutrition in acute renal failure. Patients in oliguric renal failure had better outcome when positive caloric balance was achieved. (from Mault, Acute Renal Failure in Greenfield, 1989).
Much effort has been dedicated to determining the optimum proteins and amino acids to administer to ARF patients. Abel concluded that a solution of only essential amino acids should be given, but subsequent studies have shown that full protein feeding with essential and non-essential amino acids is the important factor.

**Guidelines for Nutrition**

The current recommendations regarding nutrition in ARF are as follows:

1. To minimize protein catabolism, glucose and lipids should be supplied to maintain positive energy balance.
2. Protein should be administered with the goal of achieving positive nitrogen balance.
3. In the absence of conclusive evidence supporting the use of specialized formulations (i.e., essential or branched-chain solutions), use of mixed amino acids is recommended.
4. Daily measurement of protein and energy balance is the best way to plan nutritional therapy.

**Renal Replacement Therapy**

With the first use of hemodialysis by Kolff in 1944, the reversible nature of ARF was recognized. Since that time, hemodialysis has become the standard of care in sustaining the lives of patients who otherwise would have died from kidney disease.

Indications for use of renal replacement therapy include fluid overload (pulmonary edema, congestive heart failure), hyperkalemia, metabolic acidosis, uremic encephalopathy, coagulopathy, and acute poisoning. Three modalities of renal replacement therapy are currently available for treatment of ARF. The features of each of these therapies are contrasted in Fig. 5.4 and described below.

Fig. 5.4: Renal Replacement Therapies. (from Mault Acute Renal Failure in Greenfield, 1989)

**Hemodialysis**

Hemodialysis has been used extensively over the past four decades to manage both acute and chronic renal failure. In the contemporary form of hemodialysis, blood is circulated through a porous hollow-fiber or cellulose membrane that is permeable to solutes of less than 2000 daltons. An isotonic solution surrounds the membrane that provides a concentration gradient for the selective removal of solutes such as potassium, urea, and creatinine while maintaining plasma concentrations of sodium, chloride, and bicarbonate. A roller pump is used to maintain an extracorporeal blood flow of approximately 300 ml/minute via an arteriovenous shunt or a double-lumen venovenous access. The transmembrane pressure gradient created by the pump effects the desired amount of fluid removal. Systemic or regional anticoagulation is required for this procedure, although less heparin may be used on patients with a baseline coagulopathy. Hemodialysis is typically performed every other day for a 3- to 4-hour period but will be required more frequently in catabolic patients with a high urea generation rate. Solute and volume removal are very efficient with hemodialysis relative to the other methods of renal replacement. This property is reflected in the clearance of water-soluble drugs such as aminoglycoside, cephalosporins, and penicillins. Plasma concentrations may be decreased by as much as 50% per treatment; accordingly, these drugs should be administered on a post-treatment schedule with closer monitoring of serum
## COMPARISON OF RENAL REPLACEMENT THERAPIES

<table>
<thead>
<tr>
<th>Description</th>
<th>Peritoneal</th>
<th>Dialysis</th>
<th>CAVH/CAVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access</td>
<td>Hepodialysis</td>
<td>Slow, intermittent</td>
<td>Arteriovenous</td>
</tr>
<tr>
<td></td>
<td>Arteriovenous or Abdominal catheter</td>
<td>Arteriovenous venovenous</td>
<td></td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>Required</td>
<td>None required</td>
<td>Required</td>
</tr>
<tr>
<td>Solute removal</td>
<td>Excellent</td>
<td>Excellent</td>
<td>Good with standard CAVH; excellent with CAVHD</td>
</tr>
<tr>
<td>Fluid removal</td>
<td>Good to excellent</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>Hemodynamic instability</td>
<td>Significant</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Risks of procedure</td>
<td>Hypotension/hypoxemia</td>
<td>Infection/peritonitis; hemorrhage; disequilibrium</td>
<td>Dehydration; hemorrhage; electrolyte syndrome</td>
</tr>
<tr>
<td></td>
<td>intraabdominal adhesions; respiratory distress</td>
<td>intraabdominal adhesions; respiratory distress</td>
<td></td>
</tr>
<tr>
<td>Overall appraisal</td>
<td>Useful for urgent removal of solutes or poisons</td>
<td>Contraindicated with abdominal operation</td>
<td>Allows great flexibility with fluid and electrolyte balance</td>
</tr>
<tr>
<td></td>
<td>Hemodynamic instability</td>
<td>Useful in burn patients and poor vascular access</td>
<td>Solute removal enhanced with CAVHD</td>
</tr>
</tbody>
</table>

Key: CAVH = continuous arteriovenous hemofiltration; CAVHD = Continuous arteriovenous hemodialysis

Fig. 5.4: Renal Replacement Therapies. (from Mault Acute Renal Failure in Greenfield, 1989)
concentrations. Hemodialysis is also the method of choice for rapid removal of life-threatening toxins and poisons.

Although the incidence of complications from hemodialysis is insignificant in the treatment of patients with chronic renal failure, frequent and often profound complications may occur with its use on critically ill patients with ARF. In the acute setting, hemodialysis has been shown to cause hypotension, hypoxemia, and hemolysis and to precipitate cardiac arrhythmias. These events limit the application of dialysis in patients in unstable condition. The major reason for these complications is an acute increase in metabolic rate, (VO2) presumably caused by activation of white blood cells contacting the dialyzer. If the patient cannot mount an increase in DO2, the ratio will fall below 2 and shock results.

**Peritoneal Dialysis**

Peritoneal dialysis is performed by infusion of several liters of a sterile electrolyte solution with hypertonic glucose into the abdominal space. Using the peritoneal membrane as a selective barrier, the dialysate solution creates an osmotic pressure gradient that extracts extracellular fluid and solutes out of the mesenteric circulation and into the peritoneal cavity, which is then drained after an equilibration period of 1 to 2 hours. Extracellular volume removal usually ranges from 0.5 to 1.0 liters/hour, although greater fluid and solute clearance can be accomplished by using larger volumes of dialysate and performing exchange cycles more frequently. Use of automated delivery systems makes this a relatively simple procedure with respect to nursing time and training.

Peritoneal dialysis has several advantages over other methods of renal substitution. This technique does not require vascular access or systemic anticoagulation, making it useful in patients with peripheral vascular disease or risk of hemorrhage. In addition, the slow rate of equilibration and fluid extraction with peritoneal dialysis minimizes the problems of disequilibrium and hemodynamic compromise experienced with conventional hemodialysis.

However, peritoneal dialysis has many risks and complications, particularly in surgical patients. The most frequent and significant of these complications is catheter infection and peritonitis. Rigid peritoneal catheters inserted percutaneously in the acute setting become predictably colonized after 48 to 72 hours. Subcutaneously placed Silastic catheters are associated with a lower incidence of peritonitis (1.6 episodes per patient-year) and should be implanted for prolonged use of peritoneal dialysis. Other access-related complications include visceral injury at the time of catheter placement and formation of intraabdominal adhesions. In light of these risks, peritoneal dialysis is generally the last-choice method of renal replacement after abdominal operation or trauma.

Other complications of peritoneal dialysis include hyperglycemia secondary to the hypertonic glucose of the dialysate and respiratory distress due to reduced diaphragmatic compliance from increased intraabdominal pressure. Finally, repeated lavage of the peritoneal cavity causes protein (not urea) loss of 10 g/day or greater and may exacerbate malnutrition in patients with catabolic ARF.

**Continuous Arteriovenous Hemofiltration**

Continuous arteriovenous hemofiltration was conceived by Kramer and colleagues in 1977 and is specifically intended for treatment of ARF. CAVH is an extracorporeal ultrafiltration technique that removes extracellular fluid (ECF) across a synthetic membrane via the hydrostatic pressure gradient created between indwelling arterial and
venous catheters. With a systolic blood pressure of 80 mm Hg or greater, blood flows through the porous hollow-fiber capillary membrane at a rate of 50 to 150 ml/minute, thus driving plasma water and solutes of up to 10,000 daltons out of the hemofilter at 500 to 700 ml/hour. A replacement solution formulated to resemble ECF without toxic solutes is simultaneously infused into the venous access of the circuit at a rate to achieve a desired hourly fluid balance. This exchange transfusion of 12 to 17 liters of ECF per day provides clearance of approximately 10 to 14 g of urea per day (assuming a BUN concentration of 80 mg/dl). CAVH is illustrated in Figure 5.5. Arteriovenous access is accomplished by percutaneous cannulation of the femoral artery and vein with a low incidence of complications. Although full systemic anticoagulation is not necessary for CAVH, heparinization of the extracorporeal circuit is required, usually at a rate of 500 units/hour. CAVH is run continuously for as many days as renal replacement is required. Hemofilter performance (as monitored by the ultrafiltration rate) decreases over time, requiring replacement with a new hemofilter approximately every 2 days.

Figure 5.5: CAVH Management (from Mault, Surgery, 1987)

Experience with CAVH has demonstrated little or no incidence of hemodynamic instability with treatment of unstable critically ill ARF patients. The stable nature of this therapy is attributed to its slow and continuous fluid and solute removal and to the fact that the membrane (polysulfone) does not induce complement activation when in contact with blood.

With ultrafiltration rates averaging 10 to 12 liters/day, CAVH also allows great flexibility with volume management and eliminates the need for fluid restriction in patients with oliguric ARF. Fluid balance and serum electrolyte concentrations can be titrated to any value in a matter of hours by manipulating the composition and rate of the replacement solution. CAVH facilitates the ability to provide optimum amounts of nutrition to ARF patients. A typical example is shown in Figure 5.6.

Figure 5.6: A young man developed oliguric renal failure and a rectoperitoneal abscess following renal/pancreatic transplantation. CAVH was started on the BUN was 100 mg%. With CAVH at 10 L/day uremia is controlled and protein/caloric feeding is given, resulting in resolution of the abscess and eventual recovery.

Continuous Venovenous Hemofiltration

If arterial access is a problem, continuous hemofiltration can be carried out by actively withdrawing venous blood with the pump, then pumping the blood through a hemofilter and returning to the venous system. This is commonly done with a double lumen catheter. This technique is commonly used in preference to CAVH because it eliminates the need for access into the femoral or brachial artery. It does, however, add the complications associated with a mechanical pump and induces the risk of hemolysis and air embolism. The principles of managing fluid balance in CVVH are exactly the same as in CAVH.

Continuous Hemodiafiltration (CAVHD or CVVHD)

Solute clearance with CAVH or CVVH is limited by the ultrafiltration and replacement fluid exchange rate. In patients with a high urea generation rate, solute
Figure 5.5: CAVH management (from Mault, Surgery, 1987)
A young man developed oliguric renal failure and a rectoperineal abscess following renal/pancreatic transplantation. CAVH was started on the BUN was 100 mg%. With CAVH at 10 L/day uremia is controlled and protein/caloric feeding is given, resulting in resolution of the abscess and eventual recovery.
removal with CH may be inadequate and variations of the technique may be used to enhance clearance. The best of these variations is continuous AV or VV hemodiafiltration. CHD uses the same filter and circuit as CH but additionally employs the use of a dialysate bath to increase solute clearance. The principle is that small molecules solutes will pass from blood to filtrate by direct filtration, but also by convection in response to a concentration gradient. In straightforward CH the concentration of urea and potassium is the same outside the hemofilter tubule as it is in the blood. By rapidly diluting the filtrate with a dialysate solution which does not contain urea or potassium, some of these molecules are removed by convection as blood passes through the hemofilter, just as they are normally cleared during conventional hemodialysis. By adding dialysate to the filtration side of the filter, small solute clearance can be increased by a factor of 3 or 4, increasing clearances associated with increasing rate of dialysate flow. Since the filtration rate is about 600 cc/min dialysate must run through at quite a rapid rate to cause any significant dilution and improved solute clearance. This process is usually limited by the simple mechanical problems of hanging and discarding bags or bottles of fluid in the ICU. We typically run dialysate at a rate of 2 or 3 L/hr, on a continuous basis. A different and perhaps more efficient method is to run through 30 or 40 liters of dialysate over an hour or so once or twice a day. The principles involved in continuous hemodiafiltration are illustrated in Figure 5.7.

Figure 5.7: Adding dialysate to the outside of the hemofilter fibers enhances solute clearance. In this example dialysate runs through at the rate of 2 L/hr, although a more efficient system is to run 30 L dialysate in 1 hr.

**Slow Continuous Ultrafiltration**

Sometimes it is desirable to use continuous hemofiltration to rapidly remove salt and water from a patient who is not in renal failure. Because it is not necessary to achieve clearance of potassium, urea, or other solutes in this circumstance, it is not necessary to design a filtration replacement fluid or a continuous dialysis system. Instead extracellular fluid is simply filtered out of the flowing blood at the rate of 200-400 cc/hr without specific replacement. This approach is commonly called slow continuous ultrafiltration (SCUF). SCUF is usually used in the setting of critical illness with intravenous fluids running in at the rate of 100-200 cc/hr, and urine coming out at a similar rate. With SCUF, therefore, it is possible to achieve a net hourly loss of 100-400 cc of extracellular fluid per hour. The fluid removed is isotonic. If hypovolemia occurs the extracellular fluid is replaced with packed cells or concentrated protein solutions, maintaining the net negative hourly output. It should be noted that, in the absence of specific replacement fluid, this will result in a significant loss of bicarbonate over a period of hours and metabolic acidosis will result.

**Guidelines for Renal Replacement Therapy in Acute Renal Failure**

The current recommendations for renal replacement therapy in ARF are as follows:

1. **Volume** (intravenous fluids, total parenteral nutrition, and so on) should be provided as needed for the patient, independent of method of renal replacement.

2. Renal replacement therapy should be instituted early in the course of ARF, before hypervolemia, azotemia, or hyperkalemia occurs.
Figure 5.7: Adding dialysate to the outside of the hemofilter fibers enhances solute clearance. In this example dialysate runs through at the rate of 2 L/hr, although a more efficient system is to run 30 L dialysate in 1 hr.
3. For severely ill patients with ARF, CAVH or CVVH is the renal replacement therapy of choice (as opposed to hemo or peritoneal dialysis).
4. If solute clearance is insufficient with continuous hemofiltration, convert to continuous hemodiafiltration or supplement with standard hemodialysis.
5. Peritoneal dialysis may be used when vascular access is unavailable or risk of hemorrhage is prohibitive.
6. Hemodynamically stable patients with isolated ARF should be treated with intermittent hemodialysis or peritoneal dialysis.

Prognosis

Survival of patients with ARF is a function of the successful treatment of the primary disease from which the renal failure was derived. The anephric patient supported with renal replacement therapy survives until disease of some other organ system supervenes. In a study of patients with “pure” ATN following renal transplantation, Mentzer and colleagues described the mortality of ischemic ATN without other organ failure as 6%. By contrast, mortality of multiple organ failure complicated by ARF ranges from 50% to 90%.

Investigation of the conditions associated with ARF has identified several prognostic indicators. In a group of 65 patients with postoperative ARF, Cioffi and colleagues found the following variables significantly different between 12 survivors and 53 non-survivors (P < .05): the number of organ systems failed, the interval from onset of ARF to first dialysis, the maximum serum creatinine prior to dialysis, and the presence of cardiac failure. Corwin and colleagues described similar indicators from a group of 151 ARF patients and added that 90% of deaths were attributed to sepsis or multiple organ failure. Both survival and recovery of renal function were significantly better in patients with non-oliguric versus oliguric ARF.

In patients who survive the acute phase of illness, recovery of renal function after ARF is dependent on the type and extent of injury to the renal parenchyma. Renal replacement therapy may be required for several weeks until urine output and solute excretion return to acceptable levels. If renal function has not returned after 6 weeks, recovery is unlikely, and provisions should be made for long-term renal substitution therapy.

Pharmacology and Renal Failure

Many drugs are excreted in whole or in part by the kidney. Serum levels of drugs which depend on renal excretion will become elevated if renal function is compromised. If the drug has toxic side effects this may have deleterious effects. Accordingly drug dosage is modified in renal failure depending on the extent to which the drug is normally excreted by the kidney. A convenient nomogram for dealing with drug dosage in renal failure is shown in Figure 5.8.

Figure 5.8: Drug Dosage in Renal Failure (adapted from Clinical Nephrology, 1977)

Figure 5.9: Renal Failure Axioms
Drug Dosage in Renal Failure (adapted from Clinical Nephrology 7:81, 1977; with permission)

1. Give usual loading dose.
2. Measure or estimate creatinine clearance (Cr). 
3. Look up dosing line (A-H) for chosen antibiotic: e.g. gentamicin is line A.
4. Read dose fraction from graph at that Cr.
5. Dose fraction times dose for patients with normal renal function per 24 hours = maintenance dose per 24 hours.
6. Choose dosing interval you deem appropriate.
7. Additional doses may be required if patient needs hemodialysis (see PDR).

- Acyclovir B
- Amikacin A
- Amphotericin-B G
- Ampicillin B
- Bacitracin/Septa E
- Carbenicillin B
- Cefamandole B
- Cefazolin A
- Cefotaxime D
- Cefoxitin A
- Cephalaxin A
- Cephalothin A
- Chloramphenicol G
- Clindamycin G
- Colistimethate B
- Dicloxacillin E
- Doxycycline H
- Erythromycin D
- Gentamicin A
- Ketorolac H
- Methicillin B
- Metronidazole G
- Minocycline A
- Nafcillin D
- Oxacillin F
- Penicillin-G B
- Piperacillin D
- Sulfisoxazole F
- Ticarcillin B
- Tobramycin A
- Trimethoprim F
- Vancomycin A

Figure 5.8: Drug dosage in renal failure (adapted from Clinical Nephrology, 1977)
Renal Failure Axioms

1. Clearances can be calculated using any timed urine sample. 24 hour collections are ideal, but not necessary.
2. A diuretic trial is indicated if renal parenchymal disease is suspected. Use a big dose.
3. Renal failure is easy to detect, but hard to admit.
4. Full nutrition is systemic treatment for acute renal failure. Don't without protein.
5. When planning renal replacement therapy, managing ECF volume and solute toxicity are parallel but separate goals.

Figure 5.9: Renal Failure Axioms
Chapter 5 Monographs and Reviews

A summary of methods and results with continuous hemofiltration from a 1988 ASAIO workshop.


Kramer invented the technique of continuous hemofiltration. This book describes all of the early studies and the technique.


One of the early symposia on continuous renal replacement in the ICU.


This chapter describes the pathogenesis of acute renal failure and the University of Michigan treatment algorithm.

Chapter 5 Selected Reports

The first paper describing infusion of essential amino acids (compared to no amino acids) in acute renal failure.


A large series of critically ill patients treated with continuous hemofiltration and full nutritional support describing full survival with positive caloric balance and full feeding in acute renal failure.


The original description of acute renal failure following non-renal injury.


These papers describe survival rate in typical series of patients with acute renal failure.


This is the first description of continuous hemofiltration combined with simultaneous dialysis. This is the technique which is now used most widely in intensive care.


This classic paper is the first description of hemodialysis as a treatment for renal failure.


One of the first reports to suggest that mortality in acute renal failure is related in part to withholding protein and caloric support.


A description of the technique of continuous AV hemofiltration in acute renal failure in critically ill patients.


This paper describes the incidence and possible causes of acute renal failure following injection of contrast media.


This is a classic paper that defines the mortality for acute renal failure as an isolated organ injury. The study was done in renal transplant patients who developed acute renal failure (as opposed to rejection). The mortality was 6%.

This classic paper describes the method to define protein in urea kinetics in anuric and oliguric patients.


This classic paper is the first description of hemodialysis used for post-traumatic acute renal failure. This study was done near the front-lines during the Korean war.
CHAPTER 6: FLUIDS AND ELECTROLYTES

Management of fluids and electrolytes is the simplest problem in all of critical care. Management consists of measuring or estimating fluid and electrolyte losses on an eight-hour or 24-hour basis, then simply replacing what has been lost plus any prior deficits and any unusual anticipated extra losses. Normal requirements and losses are well known and a standard set of commercially available fluids are available for infusion. Serum concentration of electrolytes, proteins, and the components of various blood buffers are easily measured, although management is better based on measurements of electrolytes in losses than in serum.

To manage fluids and electrolytes it is important to have an understanding of the anatomy and the kinetic physiology of body fluids and the small molecules that are dissolved therein. Without images of anatomy and physiology the entire fluid and electrolyte problem seems like a complex black box. Once the problem is visualized as anatomic spaces and daily balance diagrams, the black box falls away to reveal a few elementary components in the system. The diagram of anatomy is shown in Figure 6.1 and the diagram of kinetic physiology is shown in Figure 6.4.

Figure 6.1 Body Composition

Body Composition

In the anatomic diagram of body fluids and electrolytes shown in Figure 6.1, it is apparent that the total body water is divided in three anatomic spaces: the blood volume, the interstitial space, and the intracellular water. Within the blood volume, the plasma is part of the extracellular fluid and the red cell volume is part of the intracellular fluid, so that the system can be further divided into two compartments, intracellular water and extracellular water. The percentages of body weight shown in Figure 6.1 are accurate enough for clinical calculation and simple to remember. The extracellular water is 20% of body weight and the intracellular water is 40% of body weight. The blood volume is 7%, the interstitial space 17% and the intracellular water 37% of body weight. (The remaining 40% of body weight is present as skeleton 10%, fat free solids 10%, and fat 20%). It is useful to get in the habit of visualizing patients as if they were forced into this body composition diagram. A well proportioned 80 kg man, for example, can be visualized as 50 kg of water divided into three compartments surrounded by fat and supported by the skeleton. Of the 50 liters of water, 33 liters are in cells. All of the metabolism underway in that patient is taking place within that 33 liters of water. The other 17 liters of water simply serve as the transport system to get gases and nutrients back and forth from the outside environment to the cells. The 16 kgs of skeleton and supporting tissues provide a framework for the metabolizing cells and the 20 kg of fat is the reserve fuel for running the metabolic processes. This mental image is fairly straightforward, but consider a 40 year old woman who is 5 feet tall and weighs 300 pounds. When considered in the body composition diagram, there is a relatively small amount of total body water supporting a relatively small metabolizing cell mass, surrounded by a huge mound of fat. Or consider a 60 year old man with cachexia from carcinoma of the esophagus who is 6 feet tall and weighs only 60 kg. Body fat is only 5% of body weight. The wasted muscle mass has decreased the intracellular volume considerably compared to his normal status. His total body water and
Figure 6.1: Body composition
Figure 6.2: Fluid and electrolyte exchanges between the patient and the environment take place through the extracellular space, almost all through the interstitial component of the extracellular space.
corresponding water compartments represent quite a large proportion of his body weight, but are actually much smaller than they were when he weighed 85 kg.

When visualizing a patient with the anatomic body composition diagram it is useful to remember that the extracellular fluid is basically a sodium chloride solution whereas the intracellular fluid is basically a potassium phosphate solution. The cell membrane and the capillary membrane are identifiable in the diagram and it is easy to imagine the active and passive mechanisms which account for transport of water and other small molecules between the three spaces. When 10 water molecules are injected into the plasma space, for example, within minutes they will establish equilibrium between the three water compartments. Six molecules will be inside cells, three in the interstitial space, and one remaining in the plasma volume. The time to equilibrium and the distribution of other molecules depends on the size of the molecules and active and passive transport mechanisms. Ten sodium molecules will reach equilibrium in 30 minutes (depending to some extent on plasma protein concentration), and one molecule might be intracellular, six in the interstitial space and three in the blood volume. Potassium, phosphate, and magnesium will be mostly in the intracellular fluid. Chloride, bicarbonate and molecules larger than glucose or urea will be in the extracellular fluid.

Fluid and Electrolyte Losses

Once the anatomic spaces and the electrolyte composition of the spaces are visualized, it is easy to consider interaction of the body fluid spaces with the external environment. Under normal conditions almost all interactions take place through the interstitial space. (Figure 6.2) The only exception is loss of water vapor through the skin or the respiratory tract. All normal body losses (urine, stool, tears, vomitus, diarrhea) all leave via the interstitial space, hence all these losses will be sodium chloride losses. Absorption of water, electrolytes, and nutrients occurs solely through the interstitial space in the intestine with excess quantities excreted and inadequate supply made up by endogenous metabolic rearrangement, all under endocrine control. Pathologic losses (bile, tissue fluid, pancreatic juice, pleural fluid, bleeding) also take place through the interstitial space, hence are all variations of isotonic sodium chloride solution. Replacement of pathologic losses however generally takes place through the plasma volume directly in the form of intravenous fluids. One additional form of fluid electrolyte loss that must be considered is fluid temporarily lost to the extracellular compartments, but still inside the patient. This is commonly referred to as “third space” loss (meaning a third extracellular space, the first and second space being the plasma volume and interstitial fluid). Third space loss occurs as (1) localized edema following pancreatitis, thermal burn, or other inflammatory processes, (2) generalized edema following capillary leakage associated with sepsis or complement activation, or (3) fluid sequestered in body cavities such as the pleural space, peritoneum, or lumen of the gut. The electrolyte composition of third space fluid is always that of plasma. The protein concentration is somewhere between plasma and interstitial fluid, usually closer to the latter. Third space losses have to be replaced,
Although extracellular losses are always sodium chloride-based, the electrolyte idiosyncrasies of various fluids are important. A table listing typical electrolyte composition of various specific body fluids is shown in Table 6.1.

**Water and Electrolyte Balance**

A diagram representing the kinetics of water and electrolytes is shown in Figure 6.4. In a balance diagram, the intake over some specific time period (typically 24 hours) is plotted from the baseline up. (Figure 6.3) The output of that same fluid or electrolyte is plotted from the top of the intake line down. This brings the final result back to the baseline. The patient is in zero balance for that item over the 24 hours period. On a day with no intake losses are plotted from the baseline down with the resultant diagram showing negative balance. If there is more intake than loss positive balance will be shown. The balance diagram can be constructed for any substance including water, electrolytes, protein (expressed as grams of nitrogen), or energy, (expressed as calories). In Figure 6.4 a balance diagram is shown for water, sodium, potassium, energy and nitrogen during a period of normal intake and output starving and thirsting, return to normal, and starving and thirsting plus stress or trauma.

Figure 6.3: In a balance diagram the intake is plotted from the baseline up and the output from that point back toward the baseline. In this example for water balance, the intake is 2 liters and the output, made up of urine, stool, and insensible losses, is 2 liters.

In addition to individual daily balance, the balance can be calculated as cumulative balance over a longer period of time. The data from Figure 6.4 are plotted as cumulative balance in Figure 6.5. Both cumulative and daily balance calculations are very helpful in management of patients. It is useful to construct a balance diagram, either on paper or mentally, for each day that a patient is in the intensive care unit. The electrolyte composition of external losses can be estimated or actually measured in the laboratory. The electrolyte composition of fluids given to the patient is known exactly. With this information the physician should keep the running balance diagram in mind daily. For example it is useful to know that a given patient is in positive balance for 4 liters of water and 500 mEq of sodium and chloride over a one week period, or, that a patient is in daily negative nitrogen balance despite some change in the nutritional regimen.

Figure 6.4: Balance diagram for water, sodium, and potassium and energy during a normal period followed by a period of starving and thirsting.

Figure 6.5: Cumulative balance diagram. The data from 6.4 are replotted with a different scale.

**Fluid and Electrolyte Replacement**

Fluids that are commonly used for intravenous infusion are listed in Table 6.2. Normal saline has the designation “normal” because it is isotonic with human extracellular fluid. (It is not “normal” in the classical chemical sense of one gram equivalent per liter). Normal saline is a solution of 9 gms of sodium chloride in 1 liter of water. This 0.9% NaCl solution has 154 mq/L of sodium and chloride. Therefore it has 308 mOsm/L (actually just slightly hypertonic). Although this solution is isotonic, it is
Table 6.1: Electrolyte Composition of Various Extracellular Space Fluids

<table>
<thead>
<tr>
<th>Extracellular Fluids</th>
<th>mEq/L</th>
<th>mEq/L</th>
<th>mEq/L</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>20-120</td>
<td>15</td>
<td>130</td>
<td>H + 60</td>
</tr>
<tr>
<td>Bile</td>
<td>140</td>
<td>5</td>
<td>140</td>
<td>HCO3 44</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>140</td>
<td>5</td>
<td>70</td>
<td>HCO3 70</td>
</tr>
<tr>
<td>Ileostomy</td>
<td>120</td>
<td>20</td>
<td>100</td>
<td>HCO3 40</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>100</td>
<td>40</td>
<td>100</td>
<td>HCO3 40</td>
</tr>
</tbody>
</table>
Figure 6.3: In a balance diagram the intake is plotted from the baseline up and the output from that point back toward the baseline. In this example for water balance, the intake is 2 liters and the output, made up of urine, stool, and insensible losses, is 2 liters.
Figure 6.4: Balance diagram for water, sodium, and potassium and energy during a normal period followed by a period of starving and thirsting.
Figure 6.5: Cumulative balance diagram. The data from 6.4 are replotted with a different scale.
Table 6.2: Electrolyte composition in one liter of common parenteral fluids

<table>
<thead>
<tr>
<th>IV Fluids</th>
<th>Glucose</th>
<th>600 mOsm/L</th>
<th>450 mOsm/L</th>
<th>Lactate 28, Ca3</th>
<th>Acetate 75,1825 mOsm/L</th>
<th>Acetate 82,880 mOsm/L</th>
<th>H+100</th>
</tr>
</thead>
<tbody>
<tr>
<td>D5 .9NaCl</td>
<td>154</td>
<td>0</td>
<td>154</td>
<td>50g</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D5 1/2 NS, D5 .45NaCl</td>
<td>77</td>
<td>0</td>
<td>77</td>
<td>50</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hartman (D5 LR)</td>
<td>130</td>
<td>4</td>
<td>109</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard TPN</td>
<td>35</td>
<td>40</td>
<td>53</td>
<td>250</td>
<td>4.25g</td>
<td>Acetate 75,1825 mOsm/L</td>
<td></td>
</tr>
<tr>
<td>Peripheral TPN</td>
<td>47</td>
<td>23</td>
<td>35</td>
<td>100</td>
<td>4.25g</td>
<td>Acetate 82,880 mOsm/L</td>
<td></td>
</tr>
<tr>
<td>.1 Normal HCl</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
certainly not normal in the sense of electrolyte composition. However it is very effective as an extracellular replacement, realizing that an excess of chloride ion is given with each infusion.

A common solution which more closely resembles extracellular fluid is Hartman’s solution, also known as Lactated Ringer’s solution. Ringer himself was a turn of the century physiologist who devised this electrolyte solution by trial and error as a sustaining medium for the study of organs. By chance, the final composition turned out to be quite close to human extracellular fluid, solving the chloride excess problem by substituting sodium bicarbonate for 20% of the sodium chloride. Ringer’s solution was used as an intravenous fluid, but it was not shelf stable because of the presence of bicarbonate ion. A New York pediatrician named Hartman had the wise idea of using sodium lactate instead of sodium bicarbonate to make up Ringer’s solution. This solution is shelf stable for a long time, but the lactate molecules takes up a hydrogen ion in the process of metabolism, so that it acts physiologically like bicarbonate. Thus lactated Ringer’s solution or Hartman’s solution (often referred to as balanced salt solution) is the mainstay of intravenous therapy when a large amount of extracellular fluid losses must be replaced. It should be noted that Dr. Hartman could have picked any small carbohydrate molecule which takes up a hydrogen ion during metabolism such as acetate, citrate, or maleate. Presumably he picked lactate because sodium lactate was easily available to him. He never suspected that lactic acid accumulates during metabolic acidosis due to ischemia or hypovolemia. This leads to the paradox of treating lactic acidosis with infusion of lactated Ringer’s solution, leading to the eternal confusion of medical students everafter.

On many occasions it is necessary to give water without electrolytes intravenously to match hypotonic losses. However infusing water intravenously results in prompt and fatal hemolysis. This dilemma was solved (allegedly by Coller) by using an isotonic solution of dextrose. This infusion can be given without fear of hemolysis; as the dextrose is metabolized, “free” water is left to equilibrate in total body water. A solution of 50 grams of dextrose in 1 liter of water is isotonic. This is not called “normal” dextrose as one might expect, but rather 5% dextrose in water commonly abbreviated D5W. An alternative way of infusing hypotonic electrolyte solution is to use one half normal saline which contains 4.5 grams of sodium chloride per liter or 77 mEq of sodium and chloride per liter. This solution has 152 mOsm/L, which is just at the borderline of hypotonicity which red cells will tolerate. Because of the risk of hemolysis, half normal saline is always given as 5% dextrose in half normal saline or D5 HNS. Obviously, the osmolarity of D5 HNS is 452 mOsm/L, one and one half times normal. Hypertonic fluids, however, do not cause hemolysis and are well tolerated. Fluids with an osmolarity >800 mOsm/L are painful and irritating to peripheral veins and cause local thrombosis. For this reason, solutions with a tonicity >800 mOsm/L which require chronic infusion are given into areas of rapidly flowing blood, particularly into the superior vena cava or right atrium. The observation that very hypertonic fluids can be safely given into an area of rapid blood flow is attributed to Stanley Dudrick and his colleagues, and forms the basis for all of parenteral nutrition.

**Patient Management**

By comparing Table 6.1 and Table 6.2, it is obvious that simply keeping track of fluid and electrolyte losses, and using well characterized solutions for replacement, can result in any desired daily balance result for any of the various components. Managing fluids and
electrolytes then becomes simply an exercise of measuring output, estimating deficits, and new losses, and matching intake to loss.

If losses of specific body fluids are excessive and not replaced, hypovolemia will eventually result, although all of the operative homeostatic mechanisms serve to maintain the blood volume at the expense of other body fluid compartments. The oncotic gradient created by proteins in the plasma space maintains salt and water in the vascular space whenever capillary perfusion pressure dips below the oncotic pressure. Small amounts of hypovolemia trigger aldosterone and ADH production, conserving water and sodium while selectively excreting potassium. In this fashion a very long period of starving, thirsting, and catabolism is endogenously managed, with the hyperkalaemia unloading the potassium produced by cellular breakdown. During starvation fat is metabolized, producing 1020 cc H2O for each kg of fat metabolized, providing an endogenous source of water (albeit electrolyte free water which will gradually dilute extracellular fluid electrolyte concentration). In addition to simple hypovolemia, extracellular fluid losses can lead to specific electrolyte deficiencies depending on the fluids which are lost. For example bile contains 44 mEq of bicarbonate per liter so that an extensive bile loss may lead to systemic acidosis from loss of bicarbonate buffer. This situation is exacerbated if bile loss is replaced by sodium chloride solutions. Similarly, gastric juice typically contains over 100 mEq of hydrogen ion and 15-20 mEq of potassium ion, all present as the chloride salt. Therefore prolonged vomiting leads to hypokalemic, hypochloremic, metabolic alkalosis. This situation would be exacerbated if gastric losses were replaced by D5W. The various combinations of high or low concentrations of sodium, potassium, chloride, and magnesium are discussed in great detail in standard textbooks. A single measurement of serum electrolytes will characterize the clinical picture, then management by simply calculating intake, output, and deficit replacement proceeds easily. Although measuring serum electrolytes is useful for identifying abnormal or deficit states, it is generally not useful or necessary in managing the fluids and electrolytes in a routine patient. If laboratory measurements are to be made it is much more useful to measure the electrolyte composition in external losses (urine, wound drainage, diarrhea, vomitus) then it is to try to guess what the actual losses were based on changes in serum electrolytes.

Figure 6.6: To calculate the type and dose of intravenous fluids, categorize and sum the requirements, then the replacement solutions.

Using all of this information to manage fluids and electrolytes on a typical patient is demonstrated in Figure 6.6. The first step is to calculate the requirements for the next 24 hours with regard to water, sodium potassium, chloride, calories, and protein. In each of these categories determine the basic daily maintenance, the deficit replacement if any, expected losses if any and special nutritional requirements. As step two, sum the quantities in each category to determine the total requirements for 24 hours. In step three calculate the amount and type of replacement fluid to achieve these requirements, in each of the categories of fluids and electrolytes. Include oral intake, parenteral nutrition, specific replacement, and complete the total water requirement with D5 1/2 normal saline. Step four, sum the quantities in each category to determine the total intake for 24 hours. Of course the rate and type of fluid infusion may have to be adjusted as the day progresses.
**Fluid and Electrolyte Management Algorithm**
*(75 Kg estimated dry weight) Typical example*

1. Calculate requirements for 24 hours

<table>
<thead>
<tr>
<th></th>
<th>H₂O</th>
<th>Na</th>
<th>K</th>
<th>Cl</th>
<th>Cal</th>
<th>Prot</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic daily maintenance</td>
<td>2250</td>
<td>75</td>
<td>37</td>
<td>60</td>
<td>1875</td>
<td>75</td>
<td>Urine + insensible</td>
</tr>
<tr>
<td>Deficit Replacement</td>
<td>1000</td>
<td>140</td>
<td>10</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>GI loss</td>
</tr>
<tr>
<td>Expected losses</td>
<td>1000</td>
<td>140</td>
<td>5</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>Third space</td>
</tr>
<tr>
<td>Nutrition</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Total Requirements

|                      |     |    |   |    |     |      |

3. Calculate Replacement Fluids

<table>
<thead>
<tr>
<th></th>
<th>H₂O</th>
<th>Na</th>
<th>K</th>
<th>Cl</th>
<th>Cal</th>
<th>Prot</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral, Enteral Nutrition</td>
<td>1000</td>
<td>35</td>
<td>18</td>
<td>53</td>
<td>1000</td>
<td>4.25</td>
<td>(standard TPN)</td>
</tr>
<tr>
<td>Parenteral Nutrition</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DSLR</td>
</tr>
<tr>
<td>Specific Replacement</td>
<td>1000</td>
<td>130</td>
<td>4</td>
<td>109</td>
<td>200</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Balance D5 1/2 NS</td>
<td>1000</td>
<td>77</td>
<td>0</td>
<td>77</td>
<td>200</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

4. Total Infusion

|                      |     |    |   |    |     |      |

Simple starter:
D5 1/2 NS + 20KCl @ 1 cc/Kg/hr =
24 cc/Kg H₂O/day
1.8 mEq Na/Kg/d
.5 mEq K/Kg/d
4.8 cal/Kg/d

Figure 6.6: To calculate the type and dose of intravenous fluids, categorize and sum the requirements, then the replacement solutions.
depending on actual losses. A simple method for uncomplicated fluid and electrolyte replacement is to use D5HNS + 20 mEq potassium chloride per liter at 1 cc/kg/hr. This will supply 24 cc H2O/kg/day, and 1.8 mEq of sodium, .5 mEq potassium and 4.8 calories per kg per day. Typical basic maintenance H2O volume is shown in Fig. 6.7.

Figure 6.7: Maintenance water requirements based on lean body weight

Acid-Base Physiology

Acid base relationships as related to the bicarbonate buffer system are shown in Figure 6.8 Since the bicarbonate buffer is the dominant buffer in body fluids, acid base relationships are always shown in this fashion. Henderson and Hasselbach derived an equation based on the pK of the bicarbonate buffer which basically states that the pH of a bicarbonate buffer solution will be 7.44 when the ratio of bicarbonate ion to carbonic acid ion is 20:1. All of the various diagrams and nomograms describing acid base physiology are basically variations on the demonstration of the Henderson-Hasselbach equation. Five of these variations are shown in Figure 6.8, 6.9, 6.10, 6.11, and 6.12. The expression of the equation shown in Figure 6.8 is currently the most valuable because the pH and pCO2 variables are always reported as part of modern blood gas measurement (the bicarbonate measurement with this system is calculated rather than measured). Since the PCO2 represents the carbonic acid concentration, fluctuations in pH at various levels of PCO2 represent respiratory alkalosis or acidosis, whereas fluctuations in pH at constant PCO2 represent metabolic alterations.

Figure 6.8: Bicarbonate buffer system plotted as pH and pCO2

Figure 6.9: The bicarbonate buffer system presented as nomogram by Singer and Hastings (1948).

Figure 6.10: The bicarbonate buffer system in a plot representing pCO2, bicarbonate, and pH in a single figure prepared by Astrup, 1957.

Figure 6.11: The bicarbonate buffer system plotted as bicarbonate and pH by Davenport (1958).

Figure 6.12: The bicarbonate buffer system presented as a nomogram by Siggard-Andersen. The "base excess" is introduced in the Siggard-Andersen nomogram (1963).

There are two archaic bits of terminology that persists into the modern era without much justification: "Base deficit", and "anion gap". Base deficit is a way of describing the difference between the measured serum bicarbonate and the normal value of 27 mEq/L. (27 mEq/L actually represents the ionic equivalent of all the CO2 in blood including the bicarbonate and carbonic acid). This measurement system was used by Sigaard-Anderson in the 1960's when he was particularly interested in metabolic alkalosis. (Figure 6.12) The patients he was studying had serum bicarbonate in the 30-40 range, so he expressed the abnormality as 3-13 mEq/L "base excess". The concept of describing the difference between the measured bicarbonate and the normal value is a very useful bedside shorthand to characterize acid base disorders, so this terminology persisted. However research interest shifted from alkalotic states to acidotic states, particularly metabolic acidosis caused by
Figure 6.7: Maintenance water requirements based on lean body weight
Figure 6.8: Bicarbonate buffer system plotted as pH and pCO2
Figure 6.9: The bicarbonate buffer system presented as nomogram by Singer and Hastings (1948).
Figure 6.10: The bicarbonate buffer system in a plot representing pCO2, bicarbonate, and pH in a single figure prepared by Astrup, 1957.
Figure 6.11: The bicarbonate buffer system plotted as bicarbonate and pH by Davenport (1958).
Figure 6.12: The bicarbonate buffer system presented as a nomogram by Siggaard-Andersen. The "base excess" is introduced in the Siggaard-Andersen nomogram (1963).
inadequate tissue perfusion and anaerobic metabolism, with accumulation of hydrogen ion and lactate, as discussed earlier. In order to describe the condition of metabolic acidosis, authors borrowed Sigaard-Anderson's convenient terminology, which unfortunately translated to "negative base excess" when referring to acidosis. This terminology persists in the modern era, although it would be much better to describe such abnormalities as "buffer base deviation", as several authors have proposed.

If one adds together the easily measureable cations (sodium and potassium), and the easily measureable anions (chloride and bicarbonate), then subtracts the anions from the cations, the difference is approximately 10 mEq/L. This difference is correctly assumed to be the anionic charges on protein molecules (give or take a few of the lesser salts and minerals). If an acid accumulates in the blood, the hydrogen ion is not accounted for on the cation side, but the decrease in bicarbonate buffer compensation would appear as a bicarbonate deficit on the anion side. Suppose that a patient had 10 mEq/L of hydrogen ion because of lactic acidosis with ischemia, or sulfuric and phosphoric acid because of renal failure, or acetylsalicylic acid because of toxic overdose. The calculated "anion gap" would be 20mEq/L. Thus, metabolic acidosis can be described in terms of an "increased anion gap", which is simply another way of saying that the serum bicarbonate is less than 27 mEq/L.

The treatment of acid base abnormalities is always correctly said to be to treat the underlying cause of the problem. Replacing deficits, compensating for continuing losses, and resuscitation from hypovolemia is the appropriate first-line treatment for obstructing duodenal ulcer, intractable diarrhea, hemorrhagic shock, etc. These maneuvers will, in time, correct any acid base abnormality assuming that the patient's kidney function is normal and the basic anatomic or physiologic problem is corrected. However there are situations in which it is not safe to wait for endogenous compensation and to treat acid base abnormalities directly. Treating respiratory acidosis or alkalosis is simply a matter of adjusting alveolar ventilation. Treating metabolic acidosis or alkalosis is accomplished by the infusion of bicarbonate or other buffers to treat acidosis, and infusion of acid to treat alkalosis.

The treatment of metabolic acidosis, at one time thought to be essential for normal cellular functioning, is now controversial. It is clear that acidosis per se is not detrimental to otherwise normal people, even to the extreme. We have all seen patients with pH 6.8 to 7.0 for 12 hours or more who are in severe respiratory acidosis who recover promptly and without organ dysfunction as soon as their PCO2 is normalized. Conversely a patient with metabolic acidosis below 7.0 for an hour or two develops multiple organ failure and usually dies. The cause of organ failure and death is obviously not the acidosis but the ischemia or hypovolemia which led to it. Nonetheless resuscitation from profound hypovolemia seems to proceed more quickly and response to inotropic and vasopressor drugs seems greater when pH is normalized. For this reason it is common practice to give sodium bicarbonate solution as a temporizing treatment in severe metabolic acidosis. (For reasons of shelf stability sodium lactate or sodium acetate can be used, although the carbohydrate molecule must be metabolized before any buffering effect is realized.) To determine the amount of bicarbonate required to treat acidosis assume that the bicarbonate is distributed in the extracellular space only. This will obviously be an underestimation of the amount of buffer required since the hydrogen ion is distributed throughout total body water. The amount of bicarbonate that will bring the bicarbonate concentration back to 27
can be roughly calculated as the buffer base deviation times 25% of the body weight. If this amount of buffer is given as sodium bicarbonate a considerably heavy sodium load will be infused. If sodium overload already exists or if the patient is in renal failure an alternative is to use Tris buffer (Tham®). Tham® is prepared as 36 gm/L and has buffering properties of approximately 1 mEq/cc in this concentration.

Metabolic alkalosis requires treatment only if the pH is >7.7 (to treat tetany or seizures), or if the patient is being weaned from a mechanical ventilator and has a significant metabolic alkalosis. The amount of hydrochloric acid infusion required is determined in the same fashion as the dose of bicarbonated acidosis, that is buffer base deviation in mEq/L times 25% of the body weight. Hydrochloric acid is usually given as 0.1 normal HCL which has 100 mEq hydrogen ion and chloride ion per liter.

Figure 6.13: Fluid and Electrolyte Axioms
**Fluid and Electrolyte Axioms**

1. Normal ECF losses are replenished with half-normal saline. Excess sodium causes edema.
2. Replace crystalloid with crystalloid; plasma with plasma; blood with blood.
   Corollary: Saline replacement of blood/plasma loss requires 3:1 replacement and causes anasarca.
3. Four organs malfunction when edematous: lung, brain, gut, and heart
4. Abnormal losses are variations of ECF, hence can be replaced with saline solutions.
5. For accurate management, measure electrolytes in fluid losses, not serum.
6. When saline solutions are used to replace "third space" losses, the third space will be as big as the amount of fluid given.
7. Don't confuse the extracellular space with the blood volume.
   Corollary: Pulmonary capillary wedge pressure is not a measure of fluid overload or underload.

*Figure 6.13: Fluid and Electrolyte Axioms*
Chapter 6 Monographs and Reviews

This landmark publication introduces the term homeostases and includes all the appropriate references to Pfluger, Bernard, Haldane, Henderson, Gamble, and others who developed the concept.


This classic monograph made acid-base physiology understandable to every generation of medical students and physicians since it was first published in 1947. Even today it remains mandatory reading in any critical care curriculum.

Fabri PJ: Fluids and electrolyte physiology and pathophysiology, IN: Physiologic Basic of Modern Surgical Care, Miller TA (editor), C.V. Mosby, St. Louis, 1989.

A recent review of fluid physiology


The classic original description of body fluid spaces and their composition described in "Gamblegrams".


This is the summary of all the work on isotopic dilution of body fluid spaces by Francis Moore's research group and is the classic reference on the methods and the results.


The classic reference on normal and abnormal body spaces, fluids and electrolytes. Although the text refers to surgical patients the discussion is applicable to all critically ill patients.

Chapter 6 Selected Reports

Description of the pH L05 pCO2 graph.

Treatment of metabolic alkalosis is only necessary when pH greater than 7.7 leads to tetany, or when weaning a patient from a ventilator. This paper describes experience with hydrochloric acid infusion to buffer metabolic alkalosis.


The use of 5% dextrose is proposed as a way to give water without sodium to postoperative patients.


Experiments on sheep, the oncotic gradient between plasma and interstitial fluid is maintained during progressive hemodilution until the albumin is less than 1.5 gm/dl.


The description of the bicarbonate buffer system on which the Henderson Hasselbach equation is based.


The classic original description of lactate as the acid accumulating in metabolic acidosis.


A report describing the incidence of the most common abnormality of acid-base balance in the intensive care unit, including introduction of the term "buffer-base deviation".


The original description of isotope dilution techniques in humans; the basis for body composition research and the beginning of nuclear medicine.

One of the first papers demonstrating improvement in pulmonary function with forced diuresis in ARDS.


The Siggaard-Anderssen nomogram describes deviation from normal pH as base excess.


One of the nomograms describing the bicarbonate buffer system.


A very well controlled clinical study of colloid versus crystalloid replacement of blood loss during aortic operations. Patients were resuscitated to a standardized wedge pressure. Crystalloid replacement required three times the volume of colloid, but colloid resuscitation required fine tuning to avoid congestive heart failure.


Wangensteen's classic paper on intestinal decompression and intravenous fluid management in intestinal obstruction.
CHAPTER 7: NERVOUS SYSTEM

Viewed in its simplest terms, the entire purpose of intensive care is to keep the brain alive and healthy during impairment or failure of other organ systems. Our treatment of the nervous system is aimed almost entirely at maintaining adequate function of the other vital organs. Aside from treating CNS infection and avoiding brain ischemia and high intracranial pressure, our attention to the nervous system is primarily monitoring to be sure it is still functioning well, and assuring adequate function of the other organ systems.

The issues of brain and spinal cord disorders, and management of peripheral neuropathy in critically ill patients are all beyond the scope of this handbook. The physiology and pathophysiology of brain function and malfunction are not discussed in any detail here. The figures in the handbook and supplementary discussion in this chapter are intended to provide a readily accessible reference to neurologic localization and a beginning approach to the management of cerebral perfusion, seizures, coma, and traumatic head injury.

Level of Consciousness

The Glasgow Coma scale has become the standard method of describing the level of consciousness. Calculating the score involves the simple evaluation of the best motor function, best verbal response, and best eye response. A normal alert awake person who can respond to commands with eyes open at rest gets an arbitrary score of 6 for motor response, 5 for verbal response, and 4 for eye responses, totalling 15. A flaccid, comatose person who is in coma with eyes closed, no response to verbal commands, and no motor function gets a score of 1 in each category for a total of 3. Neurologic conditions which corresponds to a score from 1 to the highest score in each category are listed in Figure 7.1. This score is converted to commonly observed clinical situations in Figure 7.2. In general

Figure 7.1: Physical exam findings, correlated with brain level and Glasgow Coma Score.

Figure 7.2: Typical Glasgow Score Range

a patient with a Glasgow Coma score of 9 or above responds to stimuli and appears close to consciousness. A patient with a Glasgow Coma score of 8 or less is comatose and unresponsive with variable responses to pain. Verbal responses scoring 3 or 5, and motor responses 5 or 6 require that the patient be able to speak. Obviously a patient who is intubated or has a tracheostomy in place cannot speak, so the score is assigned based on the observer's best estimate of how the patient could respond verbally if able, or given the lower score with a T attached to indicate that full evaluation was not possible.

Evaluation of the causes of coma in patients with a Glasgow Coma Score of 8 or less are illustrated in Figure 7.1 and Figure 7.3. The first differentiation in the comatose patient is to separate coma due to anatomic brain injury from coma due to drugs, uremia, liver failure or other metabolic causes. This differentiation is initially made on the basis of pupillary reflexes, dolls' eyes reflex, and nystagmus in response to cold stimulation of middle ear. If all three of these pons and brain stem functions are intact, then coma is most likely of metabolic origin. If all of these reflexes are absent major brain injury at the level of the upper brain stem is present. If the eye and nystagmus reflexes are equivocal
<table>
<thead>
<tr>
<th>Level of Consciousness</th>
<th>Brain level</th>
<th>Motor</th>
<th>Verbal</th>
<th>Eye</th>
<th>Defect</th>
<th>Metabolic</th>
<th>Anatomic</th>
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</thead>
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<tr>
<td>Alert, responds, opens eyes</td>
<td>All normal</td>
<td>6</td>
<td>5</td>
<td>4</td>
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<td></td>
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<tr>
<td>Confused, disoriented</td>
<td>Cortex</td>
<td>5</td>
<td>4</td>
<td></td>
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<tr>
<td>Inappropriate words</td>
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<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Eyes open to sound</td>
<td>Cortex</td>
<td>3</td>
<td></td>
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<tr>
<td>Withdraws to pain</td>
<td>Cortex</td>
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<td>Makes sounds, no words</td>
<td>Cortex</td>
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<td></td>
<td></td>
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<tr>
<td>Eyes open to pain</td>
<td>Cortex</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Eyes closed, no response to sound</td>
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<td>1</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Decorticate (flexor) posture</td>
<td>Midbrain</td>
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<td></td>
<td></td>
<td></td>
<td>Present</td>
<td>Absent</td>
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<tr>
<td>Pupillary reflex</td>
<td>Midbrain</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decerebrate (extensor) posture</td>
<td>Pons</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Dols eyes reflex</td>
<td>Pons</td>
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<td></td>
<td></td>
<td></td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Cold nystagmus reflex</td>
<td>Pons</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Flaccid to pain</td>
<td>Medulla</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous respiration only</td>
<td>Medulla</td>
<td>1</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Figure 7.1: Physician exam findings, correlated with brain level and Glasgow Coma Score
Glasgow Score Range

Alert, awake, oriented, eyes open  15
Confused, speaks, opens eyes to sound  12
Unconscious but responds to stimulus  
  (moves, opens eyes, makes sound)  10
Unconscious, withdraws or grimaces to pain  6
Unconscious, flexes to pain only  5
Flaccid  3

Figure 7.2: Typical Glasgow Score Range
or indeterminant, the cause of the coma may be a combination of metabolic and anatomic injury such as hypoxic-ischemic injury following cardiac arrest or profound hypoxia. In addition, equivocal findings may occur in coma secondary to trauma, intracranial bleeding, or infection such as meningitis or viral encephalitis. In this circumstance lumbar puncture or fluid sampling, electroencephlogram, CT, and MRI imaging are required to determine the cause of coma. Some of the common causes of coma are categorized and is summarized in Figure 7.3.

Figure 7.3: Common causes of coma

**Spinal Cord Levels**

ICU patients may have spinal cord or peripheral nerve injury present or suspected, making understanding of the sensory dermatomes and motor innervation at different levels of the cord important for the intensive care physician. These cord levels with appropriate sensory and motor correlates are outlined in Figure 7.4.

Figure 7.4: Sensory and motor levels in the spinal cord.

**Cerebral Blood Flow**

Blood flow is remarkably well auto-regulated over a wide range of blood perfusion pressure to the brain. The relationship between perfusion and cerebral blood flow under normal conditions and during hyper and hypo ventilation are shown in Figure 7.5. The cerebral perfusion pressure is the mean arterial pressure minus the intracranial pressure. Obviously it is necessary to measure the intracranial pressure in order to calculate the cerebral perfusion pressure. This is done by insertion of a catheter or a pressure sensitive device through the skull into the epidural space, subdural space, brain parenchyma, or lateral ventricle. The normal intracranial pressure varies with respiration, therefore is properly measured at FRC. Usually the respiratory effect is minimal and the intracranial pressure is expressed as mean intracranial pressure by damping out the respiratory variation. The normal intracranial pressure is less than 10 mmHg (13.6 cmH2O). Normal mean arterial pressure is 80 mmHg, so that normal cerebral perfusion pressure is around 70 mmHg. Under these conditions cerebral blood flow is normal (50 ml/100 grams of brain tissue per minute). Autoregulation maintains this level of normal cerebral blood flow despite wide swings in arterial blood pressure and during moderate elevation of intracranial pressure. This is shown in Figure 7.5. However if the arterial pressure is low and the cerebral pressure is high some regions of the brain may experience decreased cerebral blood flow which can result in ischemia or infarction. In conditions where elevated intracranial pressure is suspected (like head trauma, subarachnoid hemorrhage, encephalitis, meningitis, Reye’s syndrome) it is worth the small risk of infection to place an intracranial pressure monitor and follow the intracranial pressure, allowing calculation of cerebral perfusion pressure. Elevated intracranial pressure is treated by osmotic agents which do not cross the normal blood brain barriers such as urea or manitol, and by elevating the head, minimizing intrathoracic pressure.

Figure 7.5: Autoregulation maintains cerebral blood flow constant over a wide range of cerebral perfusion pressure. CO2 acts as a vasodilator on the resistance arterioles of the brain.
Causes of Coma

Medications
   Sedatives, analgesics, anesthetics

Metabolic and Toxic
   Hypoglycemia, Hyperglycemia
   Hyponatremia, Hypernatremia
   Uremia
   Liver failure
   Alcohol, other drugs
   Anoxia, hypercarbia

Microbiological
   Meningitis
   Encephalitis

Mechanical
   Trauma, ↑ ICP
   Venous thrombosis, occlusion
   Arterial embolus, thrombus, bleed
   Hydrocephalus
   Subdural, epidural hematoma
   Meningioma and benign tumors

Malignancy
   Primary brain tumors
   Metabolic tumors

Figure 7.3: Common causes of coma
<table>
<thead>
<tr>
<th>CORD LEVELS</th>
<th>Sensory</th>
<th>Nerves</th>
<th>Motor</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4</td>
<td>Shoulder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C5</td>
<td>Outer Arm</td>
<td>musculocutaneous</td>
<td>biceps</td>
</tr>
<tr>
<td>C6</td>
<td>Thumb</td>
<td>radial</td>
<td>extensors</td>
</tr>
<tr>
<td>C7</td>
<td>Middle Finger</td>
<td>median</td>
<td>flexors</td>
</tr>
<tr>
<td>C8</td>
<td>Little finger</td>
<td>ulnar</td>
<td>interossei</td>
</tr>
<tr>
<td>T1</td>
<td>Inner Arm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Nipple</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T10</td>
<td>Umbilicus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T11</td>
<td>Gonads</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1</td>
<td>Hip</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L2</td>
<td>Thigh</td>
<td>obturator</td>
<td>adductors</td>
</tr>
<tr>
<td>L3</td>
<td>Knee</td>
<td>femoral</td>
<td>quadriceps</td>
</tr>
<tr>
<td>L4</td>
<td>Inner Calf</td>
<td>tibial</td>
<td>gastroc</td>
</tr>
<tr>
<td>L5</td>
<td>Big Toe</td>
<td>peroneal</td>
<td>toe extensors</td>
</tr>
<tr>
<td>S1</td>
<td>Little Toe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S4</td>
<td>Anal</td>
<td></td>
<td>anal sphincter</td>
</tr>
</tbody>
</table>

Figure 7.4: Sensory and motor levels in the spinal cord.
Cerebral Perfusion Pressure

Figure 7.5: Autoregulation maintains cerebral blood flow constant over a wide range of cerebral perfusion pressure. CO2 acts as a vasodilator on the resistance arterioles of the brain.
Seizures

When seizures occur in patients in the intensive care unit the cause is most commonly related to hypoxia, hypoglycemia, or electrolyte imbalance specifically hyponatremia. In metabolic disorders continuous or irregular muscle twitching and vasculature can resemble seizures, and sometimes electroencephalography is required to differentiate neuromuscular excitation from brain-induced seizures. Benzodiazepines like Valium® or Atavan® are usually effective in stopping seizures acutely. Dilantin and barbiturates are used for both acute and chronic control.

Figure 7.6: An algorithm for treatment of acute seizures in the ICU.

In surgical ICU's, head trauma is a common problem. Sudden deterioration in brain function following trauma may be caused by a hematoma which demands urgent surgical drainage. However the CT scan has replaced exploratory drill holes and runs to the operation room. Any hospital which treats trauma patients should be organized to do emergency head CT scanning in minutes on Emergency Room or ICU patients. An algorithm for treatment of head injury is shown in Figure 7.7.

Figure 7.7: An algorithm for evaluation and management of head trauma.
Seizure Algorithm
Metabolic Causes - Hypoglycemia, Hypoxia
Diazepam (Valium) 10-40 mg IV
Phenobarbital 1 mg/kg IV up to 10 mg/kg total
Phenytoin (Dilantin) 500 mg IV up to 15 mg/kg total

Figure 7.6: An algorithm for treatment of acute seizures in the ICU.
Figure 7.7: An algorithm for evaluation and management of head trauma
Chapter 7 Monographs and Reviews

A recent concise review of brain problems in the critically ill patient.


A brief update on the Glasgow Coma Score in intensive care.


An excellent review of intracranial pressure monitoring and management techniques.


An excellent review of the literature on prolonged neuromuscular blockade with and without steroids, associated with recommendations for monitoring and prevention.
Chapter 7 Selected Reports


These two papers describe the likelihood of recovery after severe brain injury.


Evoked potentials as a way to evaluate injury and prognosis in coma.


A report of three cases and literature review of 15 similar cases implicating the steroidal muscle relaxants (pancuronium and vecuronium).


An excellent study of caloric and protein energy and metabolism in 76 patients with head injury.


The original description of the Glasgow Coma Scoring System
Injury and infection are problems for every critically ill patient, either as the cause of the illness or as a potential complication. Normal physiologic systems which stop bleeding, prevent infection, and heal tissues are constantly at work in the critically ill patient. Malfunction of these systems is manifested as bleeding, infection, too much or too little inflammation, and too much or too little fibrosis. The three host defense systems of thrombosis, inflammation, and healing are inter-dependent and balance themselves through a remarkable network of inter-cellular chemical mediators which act locally but may produce systemic symptoms. The timing of events following tissue injury is fascinating. The activation and response of platelets occurs in seconds, fibrin formation in minutes, inflammation in hours, fibrinolysis (and infection, if it occurs) in days, fibrosis and healing in weeks. This complex system may be activated by direct tissue injury, sterile inflammation (as in pancreatitis, thermal burns, or shock), bacterial or viral induced inflammation, or chronic inflammation and fibrosis without apparent cause (rheumatoid arthritis). In the care of critically ill patients we have a good understanding and appropriate management for bleeding problems. We can culture the full spectrum of infectious microorganisms, and we have drugs to kill most of them (the drugs are so effective that we sometimes forget about drainage and debridement). We are just beginning to understand the chemical phenomena underlying the systemic response to inflammation. Although many drugs to inhibit these mediators are on the horizon, the only potent inflammatory inhibitor currently available (corticosteroids) does more harm than good in most critically ill patients. We pay little attention to the tissue healing phase of host defense. This is probably because we have no effective way of enhancing healing when it is defective, and no safe method to inhibit healing when it is excessive.

To serve as an example of host defenses in the critically ill patient let us consider the case of a young man who has been stabbed in the right flank. The knife wound went through the skin, abdominal wall, right colon, and inferior vena cava. Through a separate midline incision the vena cava was repaired, stool washed out from abdomen, and a double barreled diverting colostomy was done. The patient received 5 units of packed red blood cells, and 7 liters of salt solution. He has received one prophalactic dose of cephalosporin and aminoglycoside. He is now admitted to the ICU with stable vital signs.

**Bleeding and Clotting**

As soon as the knife cut through blood vessels activation of platelets began, stimulated by two mechanisms: shear stress caused by a disruption in the normal laminar flow of blood, and contact with collagen in the vessel walls and tissues. Shear stress causes a conformational change in the phospholipid surface of the platelet, exposing adherent molecules called the G32A receptors. Collagen causes a similar conformational change exposing adherent molecules called 1A receptors. These receptors stick to the collagen in the cut and raw surfaces outside the endothelium resulting in platelet adhesion. An intermediary protein molecule known as von Willebrand factor (VWF) facilitates this adhesion. When the platelet has adhered, materials from the granules in the platelets are expelled through the platelet membrane. These granules contain many compounds including thromboxane, serotonin and bradykinin, (all of which cause local vessel constriction), and the platelet factor, PF4 which stimulates adhesion of other platelets. Like tissue thromboplastin factor, PF4 initiates the activation of factor 10 to 10A in the
fibrin formation sequence. Each successive platelet undergoes a similar adhesion and activation reaction, and a sizable platelet aggregate forms all around the cut surfaces.

In the plasma surrounding the platelets in the aggregate, a sequential series of enzymatic reactions takes place leading in a minute or so to the formation of fibrin, a gluey, ropey polymer which attaches to and stabilizes the platelet aggregate as it grows (by activation of platelet receptor 2B3A). The enzymes in this sequence are named by roman numeral and also by specific names describing their function or discoverer. Any one of the enzymes can be deficient or inhibited, leading to delay or inhibition of fibrin formation. As noted above the fibrin formation sequence is initiated by platelet thromboplastic factor and/or tissue thromboplastic factor, both of which are activated locally when a vessel is cut. This sequence of enzyme activation leading to fibrin formation is referred to as the "extrinsic" system because the stimulus for initiating the process is extrinsic to the blood vessels. The process can also be initiated by exposure of blood to a non-endothelial surface (such as a dialyzer or vascular prosthesis). This activates a protein called Factor XII or Hageman factor. The activated form is called Factor XIIa. This series of enzymatic reactions proceeds through four steps leading to activation of the extrinsic system at the level of factor X to XA activation. This system of contact activation is referred to as the "intrinsic" system. These components of thrombogenesis are summarized in Figure 8.1.

Figure 8.1: Summary of events in fibrin formation and platelet activation resulting in thrombosis. Tests to measure parts of the system are shown in the center, and conditions which inhibit the system are shown on the sides.

Red cells, white cells, and other components of plasma are enmeshed in the platelet-fibrin aggregate as it grows at the site of the disrupted blood vessel. If the blood vessel is very small and the pressure is low (as in a capillary or venule) the platelet-fibrin plug fills the hole and stops the bleeding. The small vessel becomes occluded and nutrient supply to the tissues continues through collateral circulation. Blood which leaked out before the platelet-fibrin plug stopped the bleeding becomes a large platelet-fibrin aggregate, or clot. If the injured blood vessel is large and the pressure is low (as in the inferior vena cava in our example), blood leaks out, forming clots, but the platelet-fibrin aggregate adherent to the cut surfaces does not grow large enough to occlude the opening. When the pressure caused by the surrounding clot equals the pressure in the vein, bleeding stops and the platelet-fibrin plug (including the clot outside the vessel) seals the hole. If the vessel is large and the pressure is high (an artery) each systolic pulse pushes more blood through the hole into the surrounding clot, and the clot may never reach a point where pressure outside the vessel equals arterial pressure, hence bleeding will continue despite the progressive formation of platelet-fibrin aggregate, until it is stopped by local pressure, surgical intervention, or systemic hypotension equalling the clot pressure around the artery. In arteries, the distance that the platelet-fibrin aggregate has to bridge is minimized by spasm of the smooth muscle in the arterial wall. Arterial spasm can prevent bleeding from large arteries for minutes or hours, if the vessel is totally transected. In our case example, bleeding capillaries, venules, and arterioles stopped bleeding within a minute through these mechanisms. Small arteries in the wall of the bowel and the muscle of the abdominal wall stopped bleeding when a combination of spasm and local tissue pressure facilitated the completion of the platelet fibrin plugs. A 4 mm artery in the mesentery and
### Host Defenses

**Coagulation/Thrombosis**

<table>
<thead>
<tr>
<th>Deficiency Inhibitors</th>
<th>Fibrin Formation</th>
<th>Measure</th>
<th>Measure</th>
<th>Platelets</th>
<th>Deficiency Inhibitors</th>
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<tr>
<td></td>
<td>Non-Endothel</td>
<td>ACT</td>
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<td>Complement</td>
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<td>XI (extrinsic)</td>
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<td>Proth (II)</td>
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<td>Thrombus</td>
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<td>↓Temp</td>
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</tr>
</tbody>
</table>

**Figure 8.1:** Summary of events in fibrin formation and platelet activation resulting in thrombosis. Tests to measure parts of the system are shown in the center, and conditions which inhibit the system are shown on the sides.
the 1 cm hole in the wall of the vena cava bled freely into the peritonium until the venous pressure was zero and the arterial pressure was 50 mmHg. At that point the platelet fibrin plug had sealed the holes, but only after 30% of the blood volume (1500 cc) had leaked into the peritoneum and clotted.

**Tests of Thrombosis**

**Platelets:**

Platelets are made in the bone marrow by budding off of megakaryocytes. This process is stimulated by a hormone called thrombopoietin. Each platelet circulates for an average of 11 days, then is removed from circulation in the fixed reticoendothelial system, particularly in the spleen and liver. The balance of this generation and removal system results in approximately 300,000 platelet per mm3 in circulating blood. As with most body systems, this number of platelets is 5-10 times higher than the number actually needed for basal homeostasis and hemostasis. Thrombocytopenia itself may account for bleeding when the platelet count is less than 20-30,000/mm3. Platelet function, although critically important, is notoriously difficult to measure. This is because almost every test of platelet function involves inadvertent activation of the platelets before the test is done (in the process of drawing blood, injecting the blood into test devices, separating the platelets for analysis, etc.) For this reason in-vitro tests of platelets are so insensitive as to be relatively useless for clinical purposes. These tests include aggregation in response to stimulation by ADP, epinephrine, or collagen, and adherence to glass beads or other surfaces. It is possible to measure some of the products released from platelet granules including platelet factor 4, thromboxane and beta thromboglobulin. However these tests have little practical value aside from research applications to evaluate the effectiveness of platelet inhibiting drugs. Platelets are important in facilitating the tightening of fibrin polymers long after a clot has formed, resulting in the process of clot retraction. Hence the loss of retraction when a clot is observed over several hours is suggestive of thrombocytopenia or thrombocytopathia. The only test of platelet function which is uniformly used is bleeding time. In this test a small standardized incision is made in the finger or ear lobe and the time required for formation of the platelet fibrin plug, i.e. cessation of bleeding) is measured. This test is obviously crude and affected by so many other factors that it is essentially useless in the critically ill patient.

**Fibrin Formation:**

The various components of the fibrin formation sequence are measured by adding various activators to liquid blood or plasma, and measuring the time until the liquid becomes gelatinous. All of these tests can be done on fresh unanticoagulated whole blood, but are almost always done on plasma from blood which has been anticoagulated with a calcium chelator such as citrate or EDTA. This approach is taken for standardization, since it is possible to compare results to a large pool of anticoagulated plasma from normal people, and also for convenience, since a large number of fibrin formation tests can be run electively in a central laboratory. Because the plasma is anticoagulated with the calcium chelator, an excess of calcium is added at the same time as the activator to allow the fibrin formation reaction to run to completion. All of these tests are done in an incubator at 37°. In the so-called screening tests, the time from liquid to gelatin is measured after the addition of thrombin (the thrombin time), (standardized tissue thromboplastin), (the prothrombin time), or kaolin and lipid from rabbit brain (the partial thromboplastin time or accelerated partial thromboplastin time). In measuring the clotting time or activated
clotting time (ACT) only the intrinsic system (factor 12) is activated by contact with glass or other silicates such as diatomaceous earth. Of course the intrinsic system is also activated in the other screening tests by the glass or plastic in which the test is done, but this reaction proceeds so much more slowly than that of the other activators that the intrinsic system is not significant in the final result of TT, PT, and PTT. If all of these screening tests are normal (when compared to a pool of plasma from normal people) then it can be said that all of the fibrin formation sequence is normal.

If all of the screening tests are equally prolonged the problem could be a lack of fibrinogen or the presence of an anticoagulant. If the thrombin time is normal but the prothrombin and PTT are prolonged, one or more factors above the level of fibrinogen is deficient. If the PT and TT are normal but the PTT or clotting time is prolonged there is most likely a deficiency of some factor above prothrombin in the sequence. In the latter case the specific factor deficiency is identified by repeating the PTT after various quantities of specific clotting factors are added to the test serum. In this fashion a specific factor defect can be both identified and quantitated, the latter expressed as percentage of normal amount of the factor involved. In addition to these tests which measure the time to fibrin formation, it is possible to separate and measure the actual amount of the various factors. Usually this is done for fibrinogen. The normal value is 300 mg/dL.

The screening tests are also used to titrate anticoagulant dosage. Coumadin inhibits prothrombin formation in the liver and the level of prothrombin deficiency is estimated by the prolongation of the prothrombin time. Heparin combines with circulating antithrombin to form thrombin-antithrombin complexes, inhibiting fibrin formation at that level. Heparin also acts to inhibit other enzymatic reactions in the sequence. Consequently heparin effect can be measured as a prolongation of the PTT or ACT. Although it is common practice to titrate heparin by measured defect on PTT in plasma, the result can be quite misleading. Heparin interacts with red cells, white cells, and platelets, which in turn interact with the fibrin formation system as described above. For that reason, a person who is severely thrombocytopenic, for example, might be over-anticoagulated when the plasma PTT alone is used as the measurement of heparin effect. The best way to titrate heparin dosage is to measure whole blood activated clotting time on fresh blood at the bedside or on chelator anticoagulated blood in the central laboratory. Some laboratories report the heparin concentration in blood. This value is usually not a specific measurement of heparin but rather an estimation of the amount of heparin that would be required to achieve a given level of PTT in normal plasma. Because of the various factors discussed above, the actual amount of heparin in blood is irrelevant compared to the heparin effect, so whole blood activated clotting time remains the best method to regulate heparin dosage.

Tests of Fibrinolysis

Whenever fibrin is formed, plasminogen in the surrounding plasma is activated to plasmin (fibrinolysin). This activation takes place relatively slowly and results in clot lysis beginning at approximately 12 hours at room temperature. There is no specific assay for plasmin. A test called euglobulin lysis time can be done in which a standardized gelatinous fibrin clot is exposed to test plasma and the time required for liquidification is measured. This test is rarely necessary because the only clinical circumstance associated with isolated excess fibrinolysis is associated with systemic absorption of urine, which is usually obvious for other reasons. In all other clinical circumstances in which fibrinolysis
may be occurring, it is associated with previous or on-going coagulation, so that the effect of fibrinolysis is most easily measured by measuring the amount of fibrin degradation products (FDP) or fibrin split products in circulating blood. Normally there are no fibrin degradation products in circulating blood, so any presence of these molecules is a sign of clot lysis with absorption of the breakdown products. Notice that clot lysis anywhere in the patient causes elevated FDP. It is NOT an indication of intravascular coagulation.

Bleeding and Clotting Abnormalities in Critical Care Patients

When an ICU patient is bleeding we must decide whether the problem is simply related to vascular injury or caused by an underlying coagulopathy. Of course both may exist simultaneously, for example a patient with consumption coagulopathy who has a duodenal ulcer eroding into the gastroduodenal artery. Such a patient requires an emergent trip to the operating room to stop the bleeding while returning the coagulation status to normal. As a rule of thumb, direct surgical intervention should be used whenever the blood loss is one half the blood volume in 24 hours or less. In a patient with severe coagulopathy, a modification of this rule of thumb is half a blood volume in 24 hours after the coagulopathy has been successfully treated. As noted in the example, operation may be required before coagulopathy has been corrected.

Major blood loss is treated with infusion of clear fluids, colloid fluids, and blood products. Because platelets and clotting factors are consumed (or physically lost) in the process of bleeding and because the fluids do not fully replace the lost materials, the most common abnormality of coagulation measurements associated with major bleeding is loss or consumption combined with dilution. In this situation there are usually blood clots in the patient which are being broken down and absorbed while the bleeding and dilution is going on. Consequently blood tests will show a decrease in platelet numbers, an increase in the fibrin screening times, and significant levels of fibrin degradation products (FDP). Absorption of broken down red cells may cause elevated plasma hemoglobin. This pattern of coagulation tests occurs with any type of bleeding treated by transfusion. It also occurs when clotting and lysis is taking place simultaneously at some point within the vascular system (localized intravascular coagulation, LIC), such as abruptio placenta or in massive hemangiomas (the Keisselbach-Merritt syndrome). The same test results are seen in disseminated intravascular coagulation (DIC). DIC (essentially the same as thrombotic thrombocytopenic purpura, TTP) is exceptionally rare compared to bleeding with transfusion or localized intravascular coagulation. DIC can occur when factor 12 is activated by antigen-antibody complexes, bacterial endotoxin, or certain toxins such as snake venom. The term DIC is often incorrectly used. It is purely a pathologist's diagnosis based on the finding of intravascular thrombosis in multiple tissues. "Consumption coagulopathy with fibrinolysis" is a much better description of this particular pattern of coagulation abnormalities. These patterns of laboratory tests are shown in Figure 8.2.

Figure 8.2: Abnormalities in coagulation tests associated with various clinical conditions. Notice that the pattern for internal bleeding with transfusion and DIC are the same.

Specific factor defects can be identified by a combination of screening tests and specific factor tests. Deficiency of fibrinogen or any of the protein coagulation factors can be treated with fresh frozen plasma, given in quantities sufficient to return the screening tests
<table>
<thead>
<tr>
<th>Condition</th>
<th>Platelet Count</th>
<th>Bleeding Time</th>
<th>Fibrinogen</th>
<th>PTT or ACT</th>
<th>PT</th>
<th>TT</th>
<th>FDP</th>
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<tr>
<td>External bleeding &amp; transfusion</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
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<tr>
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<td>↓</td>
<td>↑</td>
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<td>-</td>
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<td>N</td>
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<td>N</td>
</tr>
</tbody>
</table>

**Figure 8.2:** Abnormalities in coagulation tests associated with various clinical conditions. Notice that the pattern for internal bleeding with transfusion and DIC are the same.
to normal. Reconstituted cryoprecipitate is a more concentrated solution of plasma proteins which is rich in clotting factors. It is more complicated to prepare than plasma, therefore more expensive. Cryoprecipitate is used when existing hypervolemia makes fresh plasma infusion dangerous. Specific coagulation factors are available for specific factor deficiencies, such as antihemophilic globulin (concentrated factor 8) for hemophilia A.

Platelet rich plasma is given when bleeding is caused by thrombocytopenia, or when platelet dysfunction is suspected. Platelet transfusion is indicated when the platelet count is less than 30,000/m3, or when the bleeding time is grossly prolonged. The latter is usually not measured by standardized lancet incision, but more commonly by simply observing the nature of bleeding after other coagulation factors have been returned to normal. Platelet rich plasma typically contains 400-600,000 platelets/mm3 in 50 cc of plasma. If the blood volume is 5 liters, and if platelet loss has stopped, infusion of 50 cc of plasma containing 600,000 platelets/mm3 will raise the actual platelet count 6000/mm3. It is common practice to give six units of platelet rich plasma at a time, which should be expected to raise the platelet count by 36,000/mm3 (given the assumptions above). Platelets which have been separated from donor blood, stored, then transfused are expected to be less active than normal platelets and have a much shorter half life. Consequently a patient who is being transfused with platelets for thrombocytopenia will require progressively larger and larger amounts of platelet transfusion to maintain a given peripheral blood platelet count. Finally, it is very important to note that neither platelets nor the enzymes of the fibrin formation cascade work well when cold. Even moderate hypothermia (34-36°F C) will result in severe coagulopathy. With bleeding and transfusion in a paralyzed or comatose patient it is common to find temperatures in the range of 33-34°F C. No amount of fresh frozen plasma or platelets will stop bleeding in such a patient. Remember that the coagulation tests are done at 37°C, so coagulation testing may appear to be perfectly normal in a patient who has hypothermic coagulopathy. Our algorithm for evaluation and management of bleeding is shown in Figure 8.3.

In our case example, we expect to find clot and liquid blood in the abdomen and retroperitoneum. We avoid dislodging retroperitoneal clot until we can control aortic and caval inflow and outflow. We are careful to maintain core temperature over 36°C. If red blood cell replacement exceeds one blood volume (8-10 units PRBC) we give some fresh frozen plasma and six units of platelets to replace presumed (or measured) consumption and loss. One to two days following operation we expect to find moderate thrombocytopenia, slight elevation of PT, PTT, TT, and moderately high levels of FDP. The intern calls this DIC, but he is incorrect.

Figure 8.3: An algorithm for management of active bleeding. Prevention of hypothermia is an essential step.

Inflammation

Whenever endothelium is injured or denuded from the underlying basement membrane, circulating white blood cells adhere. Most prominent is the neutrophil, but lymphocytes and mast cells and monocytes stop at the site of injury and expel their cytoplasmic contents such as histamine, lysosomal enzymes, and superoxide and hydroxyl radicals. Oxides combine instantly with chloride, then adjacent proteins to form
Figure 8.3: An algorithm for management of active bleeding. Prevention of hypothermia is an essential step.
chloramines. These activated leukocytes also produce a series of small peptides called interleukin cytokines because their primary function is to provide "communication" to other white blood cells. The net result of this local slurry of unusual chemicals is to increase capillary permeability permitting fluid and intact white blood cells to go through the capillary walls to the interstitial fluid. The change in capillary permeability is not enough to result in bleeding, or even loss of large proteins (in most cases) but does cause extravasation of water, electrolytes, and other molecules up to the size of albumin. The fluid itself is detectable as edema. The neutrophils phagocytize bits of red cells and platelets when the clot lyses. Local vasodilatation results in increased blood flow causing warmth and redness. Systemic absorption of interleukins may result in fever. These signs of inflammation are usually minimal if the injury is not associated with bacterial contamination, foreign bodies, or tissue necrosis. T-lymphocytes which initiate the antibody response cycle, monocytes which generate proteolytic cytokine TNF, and complement which speeds up all these processes, are "alerted" by the family of interleukins, but are not activated unless there is antigenic material at the site of injury. Some of these events are summarized in Figure 8.4.

Figure 8.4: Some of the cellular and molecular events stimulated by bacteria in tissues.

In our case example the clots in the abdomen and all the tissues which have been opened are contaminated with feces which includes all manner of animal and vegetable debris and billions of bacteria. The grossly visible particles have been removed at the time of operation and the free floating bacteria have been diluted by irrigation and killed with topical antiseptics. Antibiotics have been given intravenously with the hope that they will permeate the edema fluid, but despite all these measures we know that the tissues in the peritoneum, vena caval wall, stab wound, and surgical incision are loaded with a wide variety of bacteria. These bacteria are in a medium rich in protein and sugar at 37°C. They grow as fast as they can, producing endotoxin, exotoxin, or just more bacteria depending on the species. The surface antigens and toxins speed up every aspect of the inflammatory process. Now T-cells carry the antigens to local lymph nodes where antibody producing B-cells are activated. Monocytes and fixed tissue histiocytes generate enough TNF to cause systemic proteolysis. Neutrophils produce enough interleukins to be systemically absorbed causing fever and hypermetabolism. Activated complement, histamine, and other mediators may cause generalized capillary permeability. Bacteria are phagocytized, killed, and expectorated by neutrophils, resulting in turbid fluid called pus which stimulates the process of inflammation even faster. Now we have more than inflammation, we have inflammation with infection. The same level of inflammation occurs at the interface between necrotic but sterile tissue and healthy tissue, and is exaggerated if necrosis is caused by a toxin or enzyme, as in pancreatitis or snake bite.

Local inflammation results in a remarkable example of neoplasia at the interface between healthy tissue and infected (or necrotic) tissue. This interface is referred to as granulation tissue and is actually an active neoplasm several millimeters thick. This remarkable tissue is primarily composed of capillaries, bringing a non-stop supply of new leukocytes to the infection. Meanwhile fibroblasts are laying down a barrier of collagen between the healthy tissue and the granulation tissue, preventing the further invasion of
Figure 8.4: Some of the cellular and molecular events stimulated by bacteria in tissues.
growing bacteria. In this fashion the infection is partially isolated from the rest of the body. The pus is said to be "walled off" and the entire process is described as an abscess.

What happens to the abscess is determined by the balance between the number and type of bacteria and the number and activity of leukocytes. If the white cells predominate the fluid will be rendered sterile and eventually re-absorbed. If the bacteria predominate, toxins and intact bacteria will be absorbed into the capillaries causing septicemia and dysfunction of other organs. If the patient survives this continuing septicemia the non-stop production of pus will push aside the tissues which offer least resistance, ultimately resulting in the abscess presenting in the subcutaneous tissue ("pointing"), ultimately leading to external drainage through the skin. When the abscess is externally drained (either by spontaneous rupture or placement of a drainage tube) - or if the abscess is small and the fluid is rendered sterile and re-absorbed - the neoplastic granulation tissue slowly but miraculously disappears, leaving only the empty space surrounded by a thick collagen scar. Over a period of months the collagen scar contracts as the polymer cross links more and more, obliterating the space and leaving only a little scar tissue.

An interesting experiment of nature illustrates the differences between bacterial infected inflammation and systemic symptoms created simply by on-going inflammation. Patients with an expanding abscess (pus under pressure) have intermittent fever, rigors, metastatic infection, bacteremia, leukocytosis, tachycardia, hypermetabolism, ileus, and proteolysis. These are also signs and symptoms of systemic or non-walled off infection such as meningococemia, streptococcal septicemia, or fresh peritonitis. After the abscess has been drained, fever, rigors, bacteremia, metastatic infection, hypermetabolism, and tachycardia disappear in a day or two. Leukocytosis and proteolysis continues, particularly if the granulation tissue wall is thick. These symptoms are typical of isolated monocyte and neutrophil activation and continue until the granulation tissue has healed and resolved. If an abdominal abscess is externally drained but granulation tissue is continually activated by an enteric fistula or smoldering pancreatitis, the process can continue for months. With drained infection ileus resolves and it is possible to resume enteric feeding but cachexia, weakness, and catabolism persists until the granulation tissue has resorbed and healed.

If the organ affected by extensive inflammation with bacteria or tissue necrosis malfunctions during any of these phases, then death or morbidity may result. For example if the primary problem is in the lung, brain, or myocardium, acute or chronic dysfunction may be irreversible.

One aspect of inflammation of major importance to intensive care patients is the normal interfaces between bacterial colonization and internal tissues. These interfaces occur at the skin, the conjunctiva, the oropharyngeal mucosa, the respiratory mucosa, the vagina, and the entire gastrointestinal tract, particularly the ileum and colon. The skin is transgressed by surgical incisions and a variety of tubes and catheters placed for monitoring blood sampling and drainage. Any organisms on the skin can and will find their way along these catheters, drains, and incisions. Bacteria normally present in the eyes, nose, and mouth proliferate and may cause local infection, particularly in the eyes and sinuses. The respiratory tract is normally sterile below the level of the vocal cords, but aspiration of oral fluids, with or without endotracheal intubation contaminates the lower airway with mouth organisms. Pneumonitis, sinusitis, parotitis, and infection of the fibrin sheath surrounding intervascular catheters are all examples of nosocomial or hospital-acquired
infections. All the principles of infected inflammation listed above apply to these circumstances. Even more interesting is the barrier between the grossly contaminated intestinal tract and portal blood circulation. Diseases which cause damage to the lower intestinal epithelium such as colitis, diverticulitis, protozoan colitis, salmonella, shigella, and typhoid often lead to direct absorption of bacteria and bacterial toxins into the portal venous blood. These bacteria may be cleared by the reticoendothelial system in the liver, may result in liver abscess, or may result in systemic bacteremia and septicemia. Other conditions which occur in critically ill patients such as shock, intestinal ischemia, and intestinal atrophy associated with lack of enteral feeding result in a change in permeability of the intestinal mucosa which may lead to absorption of exotoxins and endotoxins (if not live bacteria) causing the septic syndrome even if bacteria are not cultured from the blood stream. This phenomenon can be produced experimentally in animals, and is certainly likely to occur in humans. Some investigators are convinced that this always occurs, referring to the gut as the motor of the systemic inflammatory response syndrome (SIRS) and the cause of multi-system organ failure. However this is certainly not a universal phenomenon, and efforts to prevent it are not always effective. Nonetheless it makes good sense to clear the intestine of gross feces in critically ill patients, provide some non-absorbable intestinal antibiosis or antisepsis, and prevent intestinal mucosal atrophy as much as possible by providing some enteric feeding. The amino acid glutamine seems to be particularly important in this regard.

Tests of Inflammation and Infection

After the vital signs, the white blood count and differential count is the starting point for evaluation of infection. Inflammation is usually associated with leukocytosis and increased percentage of neutrophils, but very severe infection or necrosis can deplete the circulating leukocytes faster than they are replaced from the bone marrow resulting in neutropenia. A very detailed differential count identifying specific categories of lymphocytes is done through a process known as flow cytometry. In this process T-cells, B-cells, and a variety of subclassifications can be identified and quantitated. This is particularly important in the evaluation of patients treated with immunosuppressive drugs which are specifically designed to deplete subsets of the T-cell population. It is also important in patients with AIDS. In that condition the extent of immunosuppression can be evaluated by the CD4/CD8 ratio. (Normal 1.8 to 2.2)

Tests of white cell function are available on a research basis but are rarely used clinically, probably because these tests generally require separating white cells into various types, then incubating them with bacteria, dyes, or other chemicals to determine phagocytosis, intracellular bacterial killing, and chemotaxis. Aside from complexity and expense, another reason these tests are not used clinically is because there is, as yet, no practical means of improving white cell or RE function if it is found to be deficient. The only test of white cell function that has found wide-spread application is the skin test reactivity tests of cell mediated immunity in critically ill patients introduced by the McGill surgical research group. In this test five common antigens are innoculated into the deep dermis and the inflammatory response is measured 24 and 48 hours later. This is exactly like a tuberculin skin test and in fact tuberculin is one of the five antigens, along with trychophyton, streptococcal antibody, candida, and mumps. These antigens were picked because it was assumed that most adults would have developed antibodies to most of them. Local wheal, induration, and erythoma in at least three antigen sites is considered a
normal response. No response at all is considered a sign of anergy. Although this is a test of cell mediated immunity, it is used as a test of the entire inflammatory response with particular emphasis on the ability to respond to bacterial infection. Anergy is associated with malnutrition, acute illness, cancer, and increased incidence of bacterial infection and mortality in critical illness or following major operations. If skin test reactivity converts from anergic to reactive status following nutrition or recovery from critical illness, mortality is reduced. Because there are other simpler methods of evaluating acute nutritional status in critically ill patients, skin test reactivity is not generally used in critically ill patients. However it is helpful in evaluating patients who are being considered for major elective operations to determine whether pre-operative nutritional treatment is likely to be beneficial.

Like the circulating white cells, the fixed tissue reticuloendothelial system can be evaluated by clearance of injected particles or substances from the blood. However these tests are generally reserved for research studies, because there is no specific way to treat RE system malfunction if detected.

Measurement of the chemical products of inflammation are moving from clinical research to clinical practice. All of the several interleukins, leukotrienes, adhesion molecules, and products of abnormal oxidative metabolism can be measured in blood, sputum, and other body fluids. Of all of these molecules, measurement of TNF is emerging as the most important for practical clinical testing because it is a final common denominator for all types of inflammation and because it has significant physiologic effects. However, to date, measurement of these mediators does not predict or even correlate with outcome in inflammatory syndromes.

Measurement of bacteria by culture and antibiotic sensitivity is the mainstay of planning antibiotic or antiseptic treatment. Gram stain is useful for immediate general classification of bacterial infection, and qualitative and quantitative cultures identify specific organisms. The choice of antibiotic drugs is initially based on a guess as to the most likely cause of infection, and drug choices modified after culture and antibiotic sensitivities are available. (Figure 8.5).

There is an assay for the lipopolysaccharide endotoxin produced by most gram negative organisms, but it is not often used in clinical practice. This assay is called the limulus assay because the reagent is blood from the horseshoe crab (limulus). The assay consists of a color change in the copper based pigment of limulus blood induced by endotoxin. Since bacterial endotoxin appears to have physiologic effects only by TNF stimulation and release, direct measurement of TNF is replacing endotoxin measurement even in research studies. Some specific toxins elaborated by bacteria are useful as clinical tests, particularly the identification of clostridium difficile toxin in the evaluation of infectious diarrhea.

Applications in Critical Care Patients

The primary treatment for inflammation and infection is external drainage, if possible. For symptomatic sterile inflammation this may require the removal of necrotic
Figure 8.5: Typical sensitivities, dosage, and relative cost of common antibiotics. Dosage and cost relate to typical parenteral doses in severe infection. The drug of choice for specific species is the author's preference.

<table>
<thead>
<tr>
<th>Family</th>
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<th>IV Dose</th>
<th>Relative Cost/4</th>
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<th>MRSA</th>
<th>Strep A,B</th>
<th>Enterococcus</th>
<th>H. Flu</th>
<th>Bacteroides</th>
<th>Clostridium P</th>
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<th>Pseudomonas</th>
<th>Staphin</th>
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* = Usually sensitive
° = Drug(s) of choice
or ischemic tissue such as burn eschar or drainage of the inflammatory source such as the lesser omental space in acute pancreatitis. For infectious inflammation this may require removing the source of infection such as endocarditis on a tricuspid valve, or draining localized infection such as empyema or abscess. If the infection is not localized or is not amenable to resection or surgical drainage, as in bacterial pneumonia, then antibiotics become the mainstay of treatment. It is important to keep these priorities in order, however. No amount of antibiotics will sterilize a pus-filled gallbladder, pleural space, subcutaneous abscess, or necrotizing fascitis. If antibiotics are necessary for treatment, the choice of antibiotics is determined initially by an informed guess regarding the species of bacteria involved, then a change in antibiotics if necessary when the specific species and antibiotic sensitivity have been identified. A list of common bacteria and commonly used antibiotics is shown in Figure 8.5.

Multiple Organ Failure/Systemic Inflammatory Response Syndrome

Every patient in the intensive care unit is there because of an inflammatory or infectious disease, or is at risk for infection. Much of the ICU monitoring is intended to detect the earliest stages of inflammation or infection, and to measure the response to treatment. Although many assays of the inflammatory process are available as mentioned above, current practice depends on simple measurements like temperature, white blood count, differential, pulse rate, cultures, and of course physical examination. This is appropriate because it is the response to inflammation and infection that we wish to measure, not the mediators themselves. For example suppose we find that blood levels of TNF, IL6 and IL8 are going up while a patient is clinically significantly improving from an episode of pancreatitis or bacterial pneumonia. We might worry about pancreatic abscess or empyema, but we had that worry anyway. We would not change our course of treatment based on measured levels of mediators, just as we would not change insulin dose based on measured levels of serum insulin when the blood sugar is normal. However measurement of mediators and treatment based on those measurements will undoubtedly become an important part of the management of the systemic inflammatory response syndrome (SIRS).

A common problem in any intensive care unit is the patient who has fever, leukocytosis, tachycardia, elevated metabolic rate, and protein catabolism - all the signs of bacterial infection - but cultures are negative and no source of infection can be found. These patients often have an abnormal increase in capillary permeability which may lead to specific organ dysfunction in the lungs (adult or acute respiratory distress syndrome, ARDS), in the kidney (acute tubular necrosis, ATN), in the gut (lack of peristalsis or ileus), in the heart (myocardial edema resulting in decreased contractility or "myocardial depression"), the liver (cholestatic jaundice), or the brain (confusion, disorientation, stupor, coma, known collectively as "metabolic encephalopathy"). These patients are often referred to as "septoid", ARDS, multiple organ failure (MOF), or most recently systemic inflammatory response syndrome (SIRS). The latter term is the most appropriate, because the manifestations all result from systemic responses apparently caused by cells and mediators which are usually locally activated. If a primary source of infection or inflammation can be identified and treated, the distant organ manifestations of the syndrome usually disappear promptly - adding evidence to the theory that MOF or SIRS is driven by a local inflammation or infection. As discussed above, the intestine is often referred to as the "motor" of SIRS. This is certainly true in cases of severe primary
intestinal disease such as toxic megacolon, and may well be true in many other cases of critical illness. It makes sense to evacuate and attempt to sterilize the colon and lower small intestine in the patients whose primary problem is pneumonia, trauma, liver failure, or hemorrhagic shock.

Another application of the knowledge of the physiology of inflammation is the attempt to decrease the incidence and severity of the effect of systemic inflammatory mediators and cells by the use of drugs designed to inhibit specific components of the inflammatory response. For example, generalized inhibition of inflammation by huge doses of corticosteroids has been advocated in the treatment of sepsis, septic shock, generic ARDS, pancreatitis, burns, and pulmonary bone marrow (fat) embolism. The latter is an excellent example because it is a pure sterile inflammation at the level of the lung capillaries. Large doses of steroids can prevent the capillary leakage associated with fat embolism when given before the event in an experimental preparation, or even after the event if given within the first hour or so. Steroids given hours after fat embolism blunt the pulmonary response, but inhibit the total inflammatory response so completely that the risk of bacterial infection and poor healing overrides any potential benefit. This same problem has led to the conclusion that steroids are more harmful than helpful in all of the conditions listed above. As new inhibitors of the inflammatory response reach clinical trials, we must read these papers carefully, with the concern that preventing ARDS, for example, may be possible but lead to other complications so that overall morbidity and mortality is not affected.

Nosocomial infection is a major problem in intensive care patients. Intravascular catheters and bacterial pneumonia are the most common nosocomial infections, followed by clostridium difficile colitis, acalculus cholecystitis, urinary tract infection, and closed space infections such as sinusitis and otitis. Prophylaxis is obviously the best approach to this problem, and includes thorough cleaning and antiseptic agents applied to transcutaneous catheters and oropharyngeal hygiene in intubated patients. The most important step in avoiding infection in transcutaneous catheters is frequent physical cleaning with soap and water. It is a myth that patients with transcutaneous tubes or catheters should not bathe or shower, or that fresh incisions or catheters should always kept dry. On the contrary, bathing, showering or local cleaning is the best way to prevent catheter or drain tract infection. Placement of antiseptic ointment and the use of antiseptic impregnated catheters can be used as an adjunct to local cleaning.

Similar principles apply to the airway. Nosocomial pneumonia is clearly related to oropharyngeal organisms tracking along the endotracheal tube. The number and type of bacteria finding their way into the lower airway is best minimized by keeping the oropharynx clean by frequent mouth care, lavage, and topical antiseptics in the mouth. This is difficult in the patient with an oral endotracheal tube, and impossible in the patient with a nasotracheal tube because nasal and sinus mucosa is inaccessible on the side of the tube placement. In addition to the mouth organisms, bacteria and yeast normally killed in the stomach by the presence of stomach acid may proliferate and appear in the mouth as regurgitated fluid in patients who are rendered achlorhydic by histamine blockers or antacid drugs. For this reason the incidence of nosocomial pneumonia is much higher in patients who maintain a neutral gastric pH. Steps that can be taken in the intensive care unit to prevent nosocomial pneumonia in intubated patients include careful and frequent oral hygiene, application of topical antiseptics or non-absorbable antibiotics in the mouth.
and throat, and avoidance of gastric acid neutralization unless absolutely necessary. (The use of a gastric coating agent such as carafate is as effective as antacids in preventing stress bleeding, and minimizes the risk of nosocomial pneumonia in intubated patients.) Rather than, or in addition to this emphasis on oropharyngeal decontamination is a use of tracheostomy rather than endotracheal intubation for patients who are going to require mechanical ventilation for more than a few days. The use of tracheostomy for management of respiratory failure patients (which we prefer) assumes that tracheostomy can be done routinely without complications.

Management of the immunosuppressed patient follows all the principles outlined above. If an immunosuppressed patient has a life threatening infection, consideration should be given to stopping the immunosuppression. For example a patient with a kidney transplant or pancreas transplant can be returned to mechanical or pharmacologic treatment if the grafts are rejected because of stopping immunosuppression. This is not true of a liver, heart, or lung transplant patient. A patient who is immunosuppressed because of chemotherapy for cancer who is dying of infection is in a lethal dilemma, the solution to which relates more to the mode of dying rather than chances of survival. Immunosuppressive drugs used for transplantation (aside from steroids) are designed to inhibit lymphocyte function primarily, so that infections in these patients are usually viral or protozoan. The same applies to patients with primary lymphocyte disorders such as AIDS. Patients who are immunosuppressed because of malnutrition or bone marrow toxicity or subject to both viral and bacterial infections. Granulocyte transfusions and generic bone marrow stimulants have not proven practical in the presence of severe infection.

In our case example, we give oxacillin and gentamycin empirically before, during, and two days after operation. We irrigate the abdomen with four liters of Dakin's solution before closing the peritoneum. We do not culture the feces in the abdomen. We close the fascia, and leave a Dakin's pack in the open subcutaneous space. We do a colostomy to eliminate the risk of colon leak. Postoperatively we expect fever and, leukocytosis, ileus and hypermetabolism for the first four to five days. We start full parenteral nutrition on post-op day one, and gastric feeding with Magnacal® 20 cc/hour on day two.

**Healing and Fibrosis**

The final stage of the host defense system is healing, characterized by fibrosis, or collagen scar formation. This process begins three or four days after the initial injury as fibroblasts begin to secrete collagen precursors, and continues for a year or more, finally resulting in an avascular contracted collagen scar. The healing process is essentially the same whether the injury is a sterile surgical incision, an infected abscess wall, or pulmonary parenchymal destruction from bacterial or viral infection. The first event in wound healing is coagulation, as the injured tissues are "glued together" with fibrin. Fibrin formation seals the area from external bacterial contamination and maintains the site of injury closed unless the fibrin is dissolved by bacterial infection or the edges are physically pulled apart. Tensile strength of the fibrin bond is very low, so that minimal force is required to pull the fibrin bonded area open. The next event in healing (after the neutrophil and monocyte inflammatory process begins as described above) is the activation of fibroblasts to begin to produce elementary collagen known as tropocollagen. At the same time new capillaries are formed, bridging from one side of the fibrin sealed injury to the other. By 5-7 days after injury the collagen molecules have begun to
polymerize and the entire area is supplied by a new and rich capillary network. At 7 days all the elements of healing are well in place and functional. The tensile strength, however, is only about 10% of similar normal tissue (skin, bowel, muscle, fascia). Fibroblasts continue to form collagen and the collagen cross-links into thick polymer bundles. Both collagen formation and collagen lysis both occur in actively healing wounds. Total collagen content (usually measured as the amount of hydroxy proline, the predominant amino acid in collagen) reaches a maximum of 3-5 weeks after injury. If the injury includes skin wound, this process is easily visible as an elevated indurated purple colored (because of the capillary vascularity), epithelium-covered early scar. At six weeks the tensile strength is approximately 60% of normal tissue and the entire healing area has a dense new capillary network. This is why re-operation in a healing area 1-2 months following injury or operation is notoriously difficult.

Over the next 12 months the collagen becomes more and more heavily cross linked, eventually closing off the capillary network and pulling the collagen strands tightly together resulting in wound contracture. Approximately 12 months after injury only a small collagen ball or band remains in the area of the injury. The tensile strength is approximately 70% of normal. At one year the skin wound should appear as a fine white line with no capillary blush. The sequence of events in healing is shown in Figure 8.6.

Figure 8.6: Chemical events in wound healing correlated with tensile strength. Typical relative values for skin and fascia are shown.

Healing is inhibited by infection, foreign body reaction, radiation, corticosteroids, scurvy, uremia, liver failure, and diabetes mellitus.

Tests of Healing in Fibrosis

Aside from laboratory and clinical research studies there are no routine clinical tests to evaluate the activity of the healing process. In a critically ill patient a deficiency of healing is usually obvious as continuing infection, draining wounds, fistula formation. Excess healing with obliteration of normal tissue structure by fibrosis is most commonly seen as total obliteration of lung architecture in response to generalized lung inflammation in ARDS or lung infectious diseases. The same process can also account for obliteration of liver structure and function following severe or repeated liver injury (cirrhosis), or bilateral renal cortical necrosis and fibrosis following acute renal failure.

Application to Critically Ill Patients

One of the remarkable aspects of metabolic physiology is that inflammation proceeds to healing and fibrosis in critically ill patients, even if the face of protein catabolism, negative energy or caloric balance, and despite the influence of systemic illness and a variety of drugs. The wound is said to act as a parasite on normal body protein metabolism, and indeed it is. Even severely cachetic or debilitated patients will heal sterile wounds and sterile tissue injury in the lung, liver, and other organs. If the area of injury exists because of infection, as in necrotizing pneumonia, or becomes secondarily infected as in a pancreatic abscess, collagen is often destroyed more quickly than it is laid down, neovasculature may thrombose under the influence of bacterial toxins or other procoagulants, and the healing process is delayed or disrupted. At the interface between infected tissue and healthy tissue, granulation tissue forms at a rapid rate, but if the margins of the area of injury are separated by a collection of pus, tissue closure can not
Figure 8.6: Chemical events in wound healing correlated with tensile strength. Typical relative values for skin and fascia are shown.
occur. Once the pus is externally drained, coughed up, or reabsorbed, the scar formation
continues, with the collagen in the walls of the injured area eventually contracting to
obliterate the space altogether. This is the process that results in pneumatoceles and
"honeycombing" following severe pulmonary infection, and also the process that explains
the disappearance of pneumatoceles over 6 to 12 months following clearance of the
infection.

ICU patients are often treated with medications that impede healing, particularly
corticosteroids. Steroids act to impede wound healing by inhibiting the inflammatory
process in general, and by causing protein catabolism. Collagen formation and tensile
strength are significantly impeded in patients treated with cortic steroids (or patients with
diabetes mellitus). Immunosuppression does not interfere with wound healing, except for
increasing susceptibility to bacterial infection. There is some experimental evidence to
indicate that topical or systemic treatment with large quantities of vitamin A restores
healing toward normal in patients being treated with corticosteroid drugs. Aside from
this, and despite the investigation of many materials, there is, as yet, no way to speed up
the healing in an injured area.

The management of open wounds is a common problem in the surgical intensive
care unit and merits some specific discussion. Open wounds usually refers to surgical
incisions or injuries which have been closed to promote healing at the level of the
underlying muscle fascia, but the subcutaneous tissue and skin are left open. Since the
most common wound infections are localized to the subcutaneous fat, by leaving wounds
open (or opening infected wounds) the potential for abscess is automatically eliminated.
Fat, fascia, and skin edges are covered by dressings. The wound-dressing or wound-air
interface acts as foreign body stimulus, and the inflammatory process proceeds rapidly,
leading to visible granulation tissue formation within a few days after the injury. Within
a week or two the entire exposed open wound is covered by red velvety granulation tissue
which acts as a good barrier to bacterial invasion (although not as good as intact skin), and
provides a richy vascularized bed which can be skin grafted, allowed to heal by contracture
and the migration of skin epithelium over the surface, or pulled together in apposition
with the hope of healing (so called delayed primary closure). Dealing with open wounds
introduces one other factor which inhibits healing - drying out or dessicationation of the
tissues. The best way to manage an open wound is quite simple: Keep it wet, keep it
clean, keep it as sterile as possible. Keeping the wound wet will eliminate dessicationation and
microthrombosis at the surface of the granulation tissue. The wound can be maintained
wet with an isosmotic solution, such as saline or with a hydrophlic water soluble cream.
(The wound can also be kept wet with a hydrophobic ointment but this may have the
added effect of a foreign body and result in maceration of the wound.) Aside from the
positive effects on wound healing, a wet wound is not painful. Keeping the wound clean
toils daily inspection and physical debridement of necrotic, infected, or dessicated areas.
This can be done by sharp surgical debridement or by topical application of collagenase or
other proteolytic enzymes. The process of packing a wound with gauze in order to remove
debris when the aherent gauze is removed is painful, ineffective, and unnecessary in the
management of open wounds. The purposes of packing is simply to maintain the wound
edges open so that the tissue can drain and ultimately heal before the skin heals. A
secondary purpose of packs is hold moisture and antiseptic drugs at the active granulating
surface.
The third principle is to keep the wound as sterile as possible. This is best accomplished by physical washing in a tub, shower, or at the bedside. After thorough washing, if there is no necrotic tissue in the wound, bacterial counts are decreased to the first or second power and the wound is close to being sterile. Any bacteria present will grow following a typical bacterial logarithmic growth curve, so that bacterial counts over $10^5$ per gram of tissue (usually defined as characteristic of wound infection) occur after 48 to 72 hours. Therefore if an open wound is washed clean every 24 hours it can be maintained in a nearly sterile condition. This process can be enhanced by the application of a topical antiseptic (not antibiotic) agent. Iodine compounds, mercuric compounds, silver compounds, and other chemicals such as formaldehyde have strong antiseptic characteristics. Antiseptics kill all types of bacteria, viruses, yeast, and fungi on contact, as opposed to antibiotics which require metabolism of the toxic agents by bacteria. All of these antiseptics can quickly sterilize a granulating surface. The problem is that most of them injure local tissue or inactivate neutrophils, monocytes, and fibroblasts at the same time. The best antiseptic, and one which renders all others unnecessary is Dakin’s solution and its modifications. Dakin’s solution is 1/2% sodium hypochlorite. (Laundry bleach is 5% sodium hypochlorite). The solution acts by ionization to hypochlorous acid. The hypochlorous acid combines quickly with proteins to produce chloramines which are toxic to bacteria but not to normal tissues. Tissues tolerate chloramine probably because this is the mechanism of action by which neutrophils kill bacteria, and normal tissues are tolerant of this event. Dakin’s solution can be painful on application. This side effect is eliminated by using a solution of oxychlorosene (Cloractin,) in which an organic molecule is substituted for the sodium. The release of hypochlorite is even better than with Dakin’s solution and bacterial killing is enhanced, gram for gram of active agent.

Based on these principles, the best way to manage an open wound is frequent surgical debridement if necessary associated with extensive local washing followed by loose gauze packing soaked regularly in oxychlorosene solution. This process is repeated daily. More frequent dressing changes are unnecessary unless the wound is grossly infected or fed by a deeper fistula. These principles apply to open wounds at the level of the skin and subcutaneous tissue, and also to deep wounds such as packed open abdominal abscesses, areas of burned skin, and deep open abscesses such as extensive wound infections.

A variation of open wounds are deep infections which have been externally drained but are not amenable to total opening and packing. Examples are pleural space infections, liver abscesses, ischiorectal abscesses, and deep intra-peritoneal abscesses. In these conditions free and open drainage is the primary intent, facilitated by catheters, tubes, or suction drains. Drainage catheters must be large enough to accommodate any particles of debris or granulation tissue in the abscess cavity. The inflammatory margin of granulation tissue (in these examples, the abscess walls) are not accessible for surgical debridement but can and should be soaked with Dakin’s solution equivalent on a regular basis by irrigating through the drainage catheter or through a separate adjacent catheter placed specifically for irrigation.

In our case example, we started parenteral and enteral feeding very early. We left the skin open for five days, then did a delayed primary closure with loose sutures. We used running monofilament polypropylene suture on the fascia to avoid intestices where bacteria could grow, supplemented with interrupted heavy absorbable sutures to prevent evisceration in the event of dehiscence. Beginning on the third day, we bathe the patient...
daily in the tub or shower, taking care to wash thoroughly over the open abdominal
wound, around the colostomy, IV sites, and bladder catheter. We evacuate stool from the
colon proximal and distal to the exteriorized colostomy by using Dakin's solution lavage.
We tell the patient to avoid heavy lifting and straining for six weeks. We wait three
months before closing the colostomy.

The important points in host defense physiology and management are summarized
in Host Defense Axioms (Figure 8.7).
1. "Massive" blood loss is half a blood volume in 24 hours or less.
   Corollary: Surgical intervention is indicated for massive blood loss.
2. The most common cause of postoperative bleeding is silk-o-penia.
3. DIC is very rare; localized bleeding with consumption coagulopathy and fibrinolysis is very common.
4. When bleeding persists despite appropriate treatment, implicate platelet function.
   Corollary: There is no good way to measure platelet function except persistent bleeding.
5. No infusion of platelets or coagulation factors will stop bleeding when the body temperature is less than 35°.
6. External drainage is always the first treatment of choice for infection.
   Corollary: Antibiotics will not treat undrained infection.
7. Antiseptics are better than antibiotics for topical prevention and treatment of surface or body cavity infection.
8. Feed a fever. Full nutrition is the treatment for sepsis.
9. Living on steroids is like living with cancer.
10. Open wounds: Dakin's solution is all you need to know.
11. Wash open wounds, catheter sites, and fresh incisions to avoid infection.
Chapter 8 Monographs and Reviews


This multi-authored monograph emphasizes research on cytokines and other mediator molecules in the pathophysiology and treatment of systemic sepsis and shock.


This is one of the most concise and well referenced reviews of thrombosis and hemostasis in the modern literature.


The results of Dakin's experiments on topical antiseptics.


A thorough review of this problem by one of the first investigators in the field.


These two reviews summarize the background, modern literature, and current usage of heparin and oral anticoagulant drugs.


A thorough literature review of events in wound healing with emphasis on growth factors and hormones in the enhancement of wound healing.


A review of the discovery and study of the most important cytokine identified to date.


This pocket sized summary of infections and antibiotics prepared by J. Sanford is widely distributed to physicians and medical students by Merck and
Company. Because of its wide distribution it has become the standard reference for antimicrobial drugs in intensive care.


This is a thorough review of the most recent research describing the adhesion of platelets to endothelium and formation of the platelet plug.


This excellent review of neutrophil function as it relates to tissue injury includes the description of inactivation of oxygen radicals by chloride and protein to form chloramines.


A review of several studies examining the hypothesis of the intestine as the motor of multiple organ failure. The importance of glutamine in the lumen of the gut is emphasized.

Chapter 8 Selected Reports


This study demonstrates bacterial translocation following shock in the rat and suggests that the same phenomenon may take place in patients.


This prospective randomized study demonstrated that corticosteroids are not beneficial when given acutely to patients with ARDS. More recent studies suggest that steroids may be helpful in minimizing fibrosis in late ARDS.


One of several excellent studies on nutrition and infection with host defenses measured by skin test reactivity.

An excellent summary of the recent literature.


One of the early clinical papers describing progressive multiple organ failure.


This exhaustive literature review describes most of the research related to gut, ischemia, and its relation to systemic infection.


This prospective randomized double blinded study of 445 patients showed no difference in survival between the two groups, and no difference in the incidence of pneumonia although the diagnosis of pneumonia was not based on cultures. The patients included a diversity of diagnoses.


This is a thorough literature review of laboratory methodology related to coagulation, with emphasis on changes during consumption coagulopathy.


This is a recent review and literature summary on this common ICU problem.


This review of 15 published studies on this topic concluded that cimetidine and antacids were equally effective in preventing upper GI bleeding.


The author summarizes the many contributions of the Montreal group using delayed hypersensitivity as a way of evaluating metabolism, nutrition, and response to infection. The delayed hypersensitivity test is one of the few
practical tests of host defenses which can be used to guide management in critical illness.


This classic paper describes the physiologic and cytokine effects of endotoxin infusion into normal healthy volunteers.


Significant decrease in nosocomial pneumonia with oral-GI antibiotics. This study has fewer patients but tighter control than the multi-center French study (Gastinne, et. al.)


An excellent study documenting significant coagulopathy from moderate hypothermia.


A "meta analysis" of 16 prospective trials of antibiotic selective decontamination of the GI tract. 15 of the 16 show reduced infection. The problems associated with blinded randomization are discussed. See the editorial by Fink in this issue of Critical Care Medicine which points out that although infection is decreased in all of these studies, no beneficial effect on survival has been reported.
APPENDIX

I. Basic Physics

A. Gases

1. Boyle's Law: At constant temperature \( P_1V_1 = P_2V_2 \)

2. Charles' Law (or Gay-Lusac's Law): At constant pressure \( V_1/V_2 = T_1/T_2 \)

3. Ideal Gas Law: At constant volume \( P \) varies directly with \( T \)

\[
P_1V_1/T_1 = P_2V_2/T_2
\]

or

\[
PV = nRT
\]

where

\[
R = 0.02 \text{ L} / \text{°K} \text{ and } n = \text{ moles}
\]

Using the ideal gas law, the volume of 1 mole at STPD is 22.4L

STPD = standard temperature and pressure dry = 0°C (273°K), 760 mmHg, dry

4. Henry's Law: At constant temperature, when a gas and liquid are at equilibrium, the amount of gas dissolved in the liquid is directly proportional to the partial pressure of the gas

5. Solubility (Bunsen) coefficient at 37°C

\[
\begin{align*}
\text{O}_2 & : 0.023 \text{ ml/ml/Atm} = 0.003 \text{ ml/dl/mmHg} \\
\text{CO}_2 & : 0.456 \text{ ml/ml/Atm} = 0.006 \text{ ml/dl/mmHg} \\
\text{N}_2 & : 0.0127 \text{ ml/ml/Atm} = 0.001 \text{ ml/dl/mmHg}
\end{align*}
\]

B. Hydrodynamics

1. Poiseilles' Law

Flow = \( P \pi r^4/8\mu \)

or

Resistance = \( 8 \mu l/\pi r^4 \)

where

\[
P = \text{ perfusion pressure gradient}, \ r = \text{ vessel radius}, \ 8 = \text{ constant}, \ l = \text{ length of the vessel}, \ \mu = \text{ viscosity of the fluid}
\]

Even though Poiseilles' Law applies to the flow of uniform fluids like water through rigid pipes, the principles can be used to understand the factors which control the interrelationships between blood flow and pressure, or gas flow through airways related to pressure. The key factors are that flow is directly and linearly related to pressure gradient, and inversely and linearly related to length and viscosity, but directly related to the fourth power of the radius of the vessel.

2. Pascal's Law

Pressure applied to a liquid (organs) is equally distributed in all directions.

3. Starling's Law of Capillary Permeability

\[
Q_f = K_f (P_v - P_l) - \delta (COP - TOP)
\]

where \( Q_f \) is the net water flow through a capillary bed, \( P_v - P_l \) is the hydrostatic pressure gradient from the inside to the outside of the capillaries, \( COP - TOP \) is the pressure gradient created by osmotic pressure inside the capillary minus COP in tissue fluid, \( K_f \) is a constant describing the water permeability of the capillary network to water, and \( \delta \) is the reflectance coefficient, a constant describing the semipermeable nature of the capillary membrane to molecules. Like Poiseille's law, Starling's law is rarely used for actual
calculation, but is very helpful to understand the variables which control transcapillary filtration of water and small molecules (another way of saying lymph production).

C. Conversion Factors

1. Temperature

\[ ^\circ F = \frac{9}{5} ^\circ C + 32 \]

\[ ^\circ C = \frac{5}{9} (^\circ F - 32) \]

\[ 0 ^\circ C = 273 ^\circ K \]

2. ATPS (ambient temperature and pressure saturated) to STPD (standard temperature and pressure dry)

\[ V_{STPD} = V_{ATPS} \times \frac{273}{T+273} \times PB - PH2O/760 \]

Factors to Convert Gas Volumes from ATPS to STPD

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<th>28°</th>
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<td>.901</td>
<td>.891</td>
<td>.881</td>
<td>.871</td>
<td>.860</td>
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</tbody>
</table>

Factor × volume$_{ATPS} =$ Volume$_{STPD}$

The factor for converting volume at BTPS (body temperature and pressure saturated, 37°C, 760 mmHg, PH$_2$O 47) is 0.8261. Therefore $V_{STPD} = V_{BTPS} \times .8261$.

3. Pressure

1 mmHg = 1 torr = 1.36 cmH$_2$O = .133 kPa

1 Pascal = Pa = 1 newton/m$^2$
1 kilo pascal = kPa = 1000 N/m²
1 kPa = 7.6 mmHg
1 newton = N = force which accelerates 1 kg 1 m/sec
1 dyne = force which accelerates 1 gm 1 cm/sec
1 atmosphere = 760 mmHg = 14.7 lbs/sq. in. = 101.3 kPa

4. Temperature correction factors for blood gas measurements

Blood gases are measured at 37°C. At the cooler temperatures more gas is dissolved in water, hence the measured partial pressure will be lower than that measure at 37°. The opposite is true for temperatures higher than 37°. The effect of change in temperature on the partial pressure of CO₂ and the bicarbonate dissociation curve causes a change in pH with higher pHs at lower temperatures and vice versa. A table describing these factors is:

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<th>Patient's temperature</th>
<th>pH</th>
<th>PCO₂</th>
<th>PO₂</th>
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<td>°C</td>
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</table>

5. Basic chemistry conversions
1 mole = 1 gram molecular weight = 6.023 × 10²³ molecules
1 molar solution = 1 gram molecular weight per liter
1 equivalent = 1 mole divided by valence
1 gram equivalent = weight which will combine with 8.00 gm O₂ (1 equivalent of O₂)

6. Osmolarity
A. Osmolality = Osmoles/kg solvent
   Osmolarity = Osmoles/liter solvent
   1 mole/liter depresses freezing point of water 1.86°C
   number of mOsm/L = Δ freezing point/.00186
   1 Osmole = molecular weight/particles per molecule
   1 Osm/L = 1000 mOsm/L
   1 Osm NaCl = 58.5 gm/2 = 29.25 gm NaCl = 1000 mOsm/L
   Normal toxicity = 300 mOsm/L = .9 gm/dl NaCl
A quick bedside estimate of Osmolality is:
plasma osmolality = 2 x (Na+K) + BUN/2.8 + Glucose/18

B. Osmotic pressure (same as ideal gas law)
P = nRT/V
where
P = pressure in mmHg, n = moles, R = .02, T = °K, V = volume

Colloid osmotic P = pressure generated by small changed molecules
electrically obligated to remain close to large changed protein
molecules.

7. Standard international units
In the "system international", concentration is expressed as moles (or
nanno, micro, or millimoles) per liter. Despite the efforts of many editors, it has not been
adopted in the United States. (Campion E, A Retreat from SI units, N Eng J Med 327:49,

II. Body Surface Area
DuBois formula: BSA = w.0425 x H.725 x 71.84.
A nomogram based on this equation follows:

III. Equations
A. Alveolar air equation
PAO2 = FiO2 (713) - P aCO2 (FiO2 + 1 - FiO2/R)
The alveolar air equation is used to calculate the percentage of oxygen (or the
partial pressure of oxygen) in end tidal alveolar gas, when the inspired oxygen
concentration and the arterial PaCO2 (or end tidal pCO2) is known. A simplified version
of the alveolar air equation used for most clinical circumstances is:
PAO2 = PiO2 - PACO2
where
PAO2 = end tidal alveolar pO2, PiO2 = FiO2 (PB - PH2O), and PACO2 = arterial pCO2 or end
tidal pCO2 if lung function is nearly normal. PH2O at 37° is 47 mmHg, so that at normal
barometric pressure at sea level PB - P H2O = 760 - 47 = 713.

If the volume of O2 absorbed is exactly the same as the volume of CO2 excreted
(VCO2/VO2 is 1.0, RQ = 1.0), then the alveolar air equation is correct as stated above.
However if the respiratory quotient is more or less than 1, then the alveolar pCO2 part of
the equation must be corrected to account for this small volume change. The correction
factor is FiO2 + 1 - FiO2 divided by RQ. If the RQ is 0.8 (as is commonly assumed), the
correction factor is 1.2. When the PACO2 is multiplied by 1.2, the final calculation of PAO2
is affected by a few mmHg.

The derivation of this correction factor is based on the fact that the amount of
nitrogen gas in inhaled and exhaled air is exactly the same, although the concentration of
nitrogen in exhaled gas might be slightly higher in exhaled gas, therefore:

VA inspired (1 - FiO2 - FiCO2) = VA expired (1 - FAO2 - FACO2)
When actual values for O2 consumption and CO2 production are substituted into this
equation, the correction factor results.

For clinical purposes, and even for most clinical physiologic studies, the
barometric pressure is assumed to be 760 mmHg, the temperature is assumed to be 37°
(hence the PH2O 47 mmHg), and the RQ is assumed to be 1.0. At actual elevations up to
- HEIGHT - (CENTIMETERS)
- SURFACE AREA (SQUARE METERS)
- BODY WEIGHT (POUNDS)
- BODY WEIGHT (KILOGRAMS)
1,000 feet above sea level the barometric pressure typically ranges from 740-770 mmHg. The patient's temperature, or the temperature of the exhaled gas for end tidal CO2 is measured might range from 30-40°C. The respiratory quotient in most ICU patients who are being provided appropriate nutrition should be 1.0, however it may range from 0.6 in a starving patient to 1.3 in a patient who is being fed an excess amount of carbohydrate. Another potential source of error is the inspired carbon dioxide concentration is not zero, as is assumed in the alveolar air equation, but is some fraction slightly above zero, representing the amount of carbon dioxide in the conducting airways at the time the patient initiated an inspiratory breathe. An additional potential source of error is the fraction of inspired oxygen, which is rarely measured to two decimal places, which would be required for absolute accuracy. Even if all of these potential sources of error were precisely measured and appropriate calculated, the effect on the calculated PAO2 would be small (perhaps 5-10 mmHg). Therefore the simplified version of the alveolar air equation, without all the technically proper correction factors, is used most of the time. Correction for altitude is made if the location is more than 1000 feet above sea level. Although many textbooks advocate using a correction factor for RQ assuming that RQ is 0.8, this assumption is no more accurate than assuming that the RQ is 1.0.

B. Pulmonary shunt
The formula for calculating transpulmonary shunt is:

\[ \frac{Q_S}{Q_T} = \frac{C_CO_2 - C_aO_2}{C_CO_2 - C_VO_2} \]

where

- \( Q_S \) = Blood flowing through the lung without participating in gas exchange
- \( Q_T \) = cardiac output
- \( C_CO_2 \) = content of blood leaving pulmonary capillaries after equilibrating with alveolar air
- \( C_aO_2 \) = arterial oxygen content
- \( C_VO_2 \) = venous oxygen content

The derivation of the shunt equation is as follows:

Fick's axiom is that oxygen consumption (VO2) across the functioning pulmonary capillaries is equal to the amount of oxygen consumed in peripheral tissue metabolism, therefore, using the Fick equation

\[ Q_P = \frac{VO_2}{C_cO_2} - \frac{C_vO_2}{C_cO_2} \]

where

- \( Q_P \) = blood flow through ideally functioning pulmonary capillaries in which the content of exiting blood is equilibrated with alveolar gas. The oxygen content of this idealized pulmonary venous blood, designated CcO2 is calculated as hemoglobin, concentration, (gm/dl) times percent saturation plus PAO2 x .003 cc/dl/mmHg. The saturation is always 1.0 if the subject is breathing more than 20% O2, 136 is the O2 binding capacity per gram of hemoglobin, PAO2 is the PO2 and alveolar gas derived from the alveolar air equation, and .003 is the solubility coefficient for O2 at 37°.

Also using the Fick equation,

\[ Q_T = \frac{VO_2}{C_aO_2} - \frac{C_vO_2}{C_aO_2} \]

where

- \( Q_T \) = total blood flow through the systemic or pulmonary circulation (i.e., the cardiac output.)
The amount of blood flowing through the pulmonary circulation, but not through functional capillaries (the transpulmonary "shunt") is, therefore, \( QT - Qp \).

Therefore the ratio of the shunt flow to the total flow is:

\[
\frac{Qs}{QT} = \frac{QT - Qp}{QT}
\]

substituting the definitions for \( Qp \) and \( QT \),

\[
\frac{Qs}{QT} = \frac{VO_2/C_aO_2 - CvO_2 - VO_2/C_cO_2 - CvO_2}{VO_2/C_aO_2 - CvO_2}
\]

this equation simplified becomes

\[
C_cO_2 - C_aO_2 / C_cO_2 - C_vO_2
\]

It is worth noting that in Julius Comroe's classic textbook on the lung the shunt equation is derived in a different fashion and the final result is \( C_aO_2 - C_cO_2 \) divided by \( C_vO_2 - C_cO_2 \) so that the calculation is always done with negative values but the final ratio is the same as with the classic derivation as above.

C. Respiratory Dead Space

The formula is:

\[
V_D = (FACO_2 - FE_{CO_2}) \times VE \text{ divided by } FACO_2
\]

The derivation of this equation is as follows:

\[
VE = VA + VD
\]

where

\( VE \) = volume of exhaled gas, \( VA \) = the volume of gas which came from alveoli and \( VD \) is the volume of gas which came from dead space. Dead space here is considered to be the conducting airways plus any alveolar space which is ventilated without any gas exchange.

The amount of gas \( G \) in these volumes is

\[
FEG \times VE = FAG \times VA + FIG \times VD
\]

The concentration of any gas in the dead space is:

\[
FDG = FIG
\]

therefore

\[
FEG \times VE = FAG \times VA + FIG \times VD
\]

therefore

\[
FEG \times VE = VAG (VE - VD) + FIG \times VD
\]

and

\[
VD = [FAG - FEG] \times VE / FACO_2 - FE_{CO_2}
\]

when the gas is carbon dioxide \( FIG = 0 \) and the final equation becomes

\[
VD = FACO_2 - FE_{CO_2} \times VE \text{ divided by } FACO_2
\]

The concentration of \( CO_2 \) in alveolar gas is assumed to be the same in arterial blood. Therefore the equation can be restated

\[
V_D/VE = PaO_2 - FE_{CO_2} \text{ divided by } PaO_2
\]

Mixed expired \( PCO_2 \) is typically 26 mmHg at STPD, therefore in a normal person

\[
VD = 40 - 26 \text{ divided by } 40 = 34\%
\]

D. Harris-Benedict equation for basal metabolic rate

Men: \( EE = 66.5 + 13.7 \times W + 5.00 \times H - 6.78 \times A \)
E. Wier equation for indirect calorimetry

The simple equation for indirect calorimetry assumes that the respiratory quotient is 1.0, and the caloric value of all substrates consumed in metabolism is 5 k/L O₂ consumed, therefore the simple equation for indirect calorimetry is VO₂ in l/min x 60

\[ \text{VO}_2 \text{ in l/min \times 60 min/hr} \]

\[ \text{min/hr} \times 24 \text{ hr/day} \times 5 \text{k/L O}_2 = \text{k/day} \]

or

\[ \text{VO}_2 \text{ L/min \times 7.2 = k/day} \]

This equation oversimplifies several factors. The oxygen consumption value of carbohydrate is 5 cal/L O₂, but the O₂ consumption for protein is 4.8 cal/LO₂ and fat is 4.7 cal/LO₂. Furthermore the RQ for carbohydrate is 1, for protein 0.8, and for fat 0.7. The amount of protein substrate which is metabolized can be calculated from the amount of nitrogen in urine during a timed collection. For example if a 24 hour urine sample contains 10 grams of nitrogen, then 62.5 grams of protein were metabolized to produce this amount of nitrogen (most of it as urea). The metabolism of 62.5 grams of protein would consume 52 cc O₂ and produce 42 cc CO₂. If the total amount of oxygen consumed and CO₂ produced is measured, then the amount account for by protein metabolism can be subtracted, and the amount due to carbohydrate and fat metabolism can be calculated from these corrected values. Therefore the exact amount of protein, fat, and carbohydrate which went to make up the overall metabolism can be calculated, and the exact values for conversion for VO₂ to calories can be calculated. All of these variables are included into the Wier equation as follows:

\[ \text{cal/day} = (3.941 \times \text{VO}_2) + 1.106 \times \text{VCO}_2 - (2.17 \times \text{gm Urinary N/d}) \]


F. The Sargent equation for calculation of protein catabolic rate. Patients in renal failure do not maintain a stable blood urea nitrogen, but the change in blood urea nitrogen concentration during a period of time can be used to calculate the amount of protein metabolized to produce that amount of urea nitrogen. The concentration of urea must be corrected for the fact that urea is diluted in extracellular fluid, so that an estimate of change in extracellular fluid must be taken into account when making this calculation. The Sargent formula, taking all these variables into account, is as follows:

\[ \text{Protein catabolic rate} = (N_{\text{excreted}} + N_{\text{accumulated}}) \times 6.25 \]

where

\[ \text{Nitrogen excreted} = \]

Urea N excreted (typically 8-10 gm/day)

+ non urea N (typically 1.5 gm/d)

and

\[ \text{Nitrogen accumulated} = \]
\[ BUN_2 \times TBW_2 - BUN_1 \times TBW_1 \]

where

- \( BUN_2 \) = Urea nitrogen in gm/dl at time 2
- \( TBW_2 \) = Total body water in dl at time 2
- \( BUN_2, TBW_2 \) = same at time 1
- \( TBW \) = best estimate of TBW
- Lean, dry = 58% weight
- Obese = 40% weight
- Fluid overloaded = 58% dry weight + Kg over dry

\[ 6.25 = \text{gm protein/gm N} \]


**G. Henderson-Hasselbach equation.** This equation is basically the equilibration equation for the carbonic acid/bicarbonate buffer system. The equation is:

\[ \text{PH} = \text{pK} + \log_{10} \left( \frac{(A-)}{(HA)} \right) \]

\[ = 6.1 \log \left( \frac{\text{HCO}_3}{\text{CO}_2} \right) \]

where \((\text{CO}_2)\) is the sum of dissolved \text{CO}_2 and carbonic acid.

IV. Scoring Systems

A. Trauma Scores

1. Acute Injury Score (AIS-85)

<table>
<thead>
<tr>
<th>Score</th>
<th>Head neck</th>
<th>Face</th>
<th>Thorax</th>
<th>Abd</th>
<th>Extrem</th>
<th>External</th>
</tr>
</thead>
</table>

Range: 0 = Normal, 1 Min or, 2 Moderate, 3 Severe not life threatening, 4 Severe life threatening, 5 Critical survival uncertain

LD50: Covert to Injury Severity Score (ISS)


2. Injury Severity Score (ISS, Baker)

Score: Square AIS for each region, then sum

Range: 0 (Normal) to 75 (arbitrary maximum)

LD50: 35

Example: Mild closed head injury 3-9
Rupt. spleen 4-16
Fracture femur 3-9

3. Trauma Score (Champion)

<table>
<thead>
<tr>
<th>Score</th>
<th>Resp Rate</th>
<th>+Effort</th>
<th>BP</th>
<th>Capillary Refill</th>
<th>Glasgow</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>0-1</td>
<td>0-4</td>
<td>0-2</td>
<td>1-5</td>
<td></td>
</tr>
</tbody>
</table>

Range: 0 = critical
high = normal

LD50: 10


4. TRISS (Boyd) The TRISS (Trauma/Injury Severity Score) is a mortality prediction score based on ISS and age and an admission physiology score and type of injury. LD 50=50 points.


5. 24-hour ICU point system (Sacramento)

<table>
<thead>
<tr>
<th>Points</th>
<th>GCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>13-15</td>
</tr>
<tr>
<td>1</td>
<td>9-12</td>
</tr>
<tr>
<td>2</td>
<td>6-8</td>
</tr>
</tbody>
</table>
B. Acute Physiology Scores

1. APACHE

There are three versions of the Acute Physiology and Chronic Health Evaluation described by Knaus. Only APACHE II and APACHE III are now in use. APACHE II is described below, and is intended as an ICU admission one-time scoring system. APACHE III is based on similar information collected and analyzed daily, and reported as mortality risk on that day compared to the thousands of patients in the central registry. APACHE III requires a computer program and participation in the central registry.

The APACHE II Score: Acute Physiology Score plus age factor plus past history factor
Range: 0(normal) to 56
LD50: 20-25


2. Concomitant Organ Failure (NIH ECMO, 1975-78)

Respiratory Only: 40% mortality risk
2 organ failure: 55
3 organ failure: 75
4 organ failure: 85
5 organ failure: 100


Respiratory 22% mortality
Renal 38% mortality
Liver 27% mortality
Cardiac 67% mortality
Infection 28% mortality


4. Systemic Inflammatory Responses/Sepsis Definitions

SIRS .2 or more:
### The APACHE II Severity of Disease Classification System

<table>
<thead>
<tr>
<th>Physiologic Variable</th>
<th>High Abnormal Range</th>
<th>Low Abnormal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature - rectal (°C)</td>
<td>≥ 41°</td>
<td>39.4°-40.9°</td>
</tr>
<tr>
<td>Mean Arterial Pressure-mm Hg</td>
<td>≥ 160</td>
<td>130-159</td>
</tr>
<tr>
<td>Heart Rate (ventricular response)</td>
<td>≥ 180</td>
<td>140-179</td>
</tr>
<tr>
<td>Respiratory Rate (non-ventilated or ventilated)</td>
<td>≥ 50</td>
<td>35-49</td>
</tr>
<tr>
<td>Oxygenation:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. PaO₂ ≥ 20.5 recorded Aracho₂</td>
<td>≥ 500</td>
<td>350-499</td>
</tr>
<tr>
<td>b. PaO₂ ≥ 20.5 recorded only Aracho₂</td>
<td>180</td>
<td>150-179</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>≥ 7.7</td>
<td>7.6-7.69</td>
</tr>
<tr>
<td>Serum Sodium (mMol/L)</td>
<td>≥ 160</td>
<td>155-159</td>
</tr>
<tr>
<td>Serum Potassium (mMol/L)</td>
<td>≥ 7</td>
<td>6.9</td>
</tr>
<tr>
<td>Serum Creatinine (mg/100 ml)</td>
<td>≥ 3.5</td>
<td>2.4</td>
</tr>
<tr>
<td>(Double point score for acute renal failure)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>≥ 26</td>
<td>25-29</td>
</tr>
<tr>
<td>White blood count (total/mm³)</td>
<td>≥ 40</td>
<td>20-39</td>
</tr>
<tr>
<td>Glasgow Coma Score (GCS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score 1-5: actual GCS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A Total Acute Physiology Score (APS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sum of the 12 Individual variable points</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum HCO₃⁻</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(venous-mMol/L)</td>
<td>≥ 24</td>
<td>21-23</td>
</tr>
<tr>
<td>(not preferred, use if no ABGs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B Age Points: Assign points to age as follows:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>Points</td>
<td></td>
</tr>
<tr>
<td>≤ 44</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>45-54</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>55-64</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>65-74</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>≥ 75</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>APACHE II SCO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sum of A + B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A APS points</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B Age points</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C Chronic health points</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total APACHE II</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Definitions

**B Age Points:**

Assign points to age as follows:

- Age (yrs) ≤ 44: 0 points
- Age (yrs) 45-54: 2 points
- Age (yrs) 55-64: 3 points
- Age (yrs) 65-74: 5 points
- Age (yrs) ≥ 75: 6 points

**C Chronic Health Points:**

If the patient has a history of severe organ system insufficiency or is immunocompromised assign points as follows:

- a. for nonoperative or emergency postoperative patients - 3 points
- b. for elective postoperative patients - 2 points

**Cardiovascular:** New York Heart Association Class IV.

**Respiratory:** Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction, i.e. unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40mmHg), or respiratory dependency.

**Renal:** Receiving chronic dialysis.

**Immunocompromised:** The patient has received therapy that suppresses resistance to infection, e.g., immunosuppressive, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is insufficiently advanced to suppress resistance to infection, e.g., leukemia, lymphoma, AIDS.

---

**APACHE II SCO**

- Sum of A + B
- APS points
- Age points
- Chronic health points
- Total APACHE II
Temp > 38 or < 36
Pulse > 90
Resp > 20
WBC > 12 or < 4,000

Sepsis
SIRS plus positive culture
Severe sepsis
Sepsis with organ dysfunction
Septic shock
Sepsis with hypotension despite treatment
"Culture-negative sepsis": Definitions as above on antibiotics with negative cultures

Organ Dysfunction
Respiratory
Renal
Coagulopathy
CNS
P/F < 175, CXR, PCW < 18
2.0 mg/dl ↑ creatinine
25% ↓ platelet count and ↑ PT
Glasgow coma score


5. SIRS/Sepsis Score

|   | Mortality | "Culture Negative"
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SIRS</td>
<td>12%</td>
<td>NA</td>
</tr>
<tr>
<td>Sepsis</td>
<td>16%</td>
<td>10%</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td>Septic shock</td>
<td>46%</td>
<td>46%</td>
</tr>
</tbody>
</table>


C ARDS Scoring Systems
1. Murray Lung Score (1988)

<table>
<thead>
<tr>
<th>X-ray</th>
<th>PaO2/FiO2</th>
<th>Compliance</th>
<th>PEEP</th>
<th>Score</th>
<th>Approximate</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt;300</td>
<td>&gt;1.0</td>
<td>&lt;5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1 quadrant</td>
<td>255-299</td>
<td>.4-.9</td>
<td>6-8</td>
<td>1</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>2 quadrant</td>
<td>175-224</td>
<td>.4-.7</td>
<td>9-11</td>
<td>2</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>3 quadrant</td>
<td>100-174</td>
<td>.2-.4</td>
<td>12-14</td>
<td>3</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>4 quadrant</td>
<td>&lt;100</td>
<td>&lt;.2</td>
<td>&gt;15</td>
<td>4</td>
<td>90</td>
<td></td>
</tr>
</tbody>
</table>

2. Geneva Score (Morel 1985)

<table>
<thead>
<tr>
<th>X-ray</th>
<th>AaDO2/FiO2</th>
<th>Compliance</th>
<th>PAP</th>
<th>Score</th>
<th>Approximate</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;300</td>
<td>&gt;1.0</td>
<td>&lt;20</td>
<td>0</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Interstitial</td>
<td>300-375</td>
<td>.6-.9</td>
<td>20-25</td>
<td>1</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>≠ Interstitial</td>
<td>375-450</td>
<td>.5-.7</td>
<td>25-30</td>
<td>2</td>
<td>75</td>
<td>90</td>
</tr>
<tr>
<td>Consolid.</td>
<td>450-525</td>
<td>.3-.5</td>
<td>30-35</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≠ Consolid.</td>
<td>&gt;525</td>
<td>&lt;.3</td>
<td>&gt;35</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


3. Euroxy Study (Artigas 1991)

<table>
<thead>
<tr>
<th>X-ray</th>
<th>PaO2</th>
<th>FiO2</th>
<th>PEEP</th>
<th>Tidal Volume</th>
<th>Score</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltrate</td>
<td>&gt;75</td>
<td>.5</td>
<td>5</td>
<td>10cc/kg</td>
<td>Hypoxic</td>
<td>38</td>
</tr>
<tr>
<td>Infiltrate</td>
<td>&lt;75</td>
<td>.5</td>
<td>5</td>
<td>10cc/kg</td>
<td>Severe</td>
<td>69</td>
</tr>
</tbody>
</table>


4. Massachusetts General Hospital Score (Zapol, 1991)

<table>
<thead>
<tr>
<th>X-ray</th>
<th>Vent</th>
<th>Oxygen</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal</td>
<td>+ - Intube</td>
<td>FiO2 &lt; .5</td>
<td>Mild</td>
</tr>
<tr>
<td>Panlobular</td>
<td>PPV</td>
<td>FiO2 &gt; .5</td>
<td>Moderate</td>
</tr>
<tr>
<td>Bilateral</td>
<td>PPV+PEEP</td>
<td>FiO2&gt;6</td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or PaO2&lt;50</td>
<td></td>
</tr>
</tbody>
</table>


D. Liver Failure (C.G. Child, 1960)

<table>
<thead>
<tr>
<th>Class</th>
<th>Bilirubin</th>
<th>Albumin</th>
<th>Ascites</th>
<th>Encephalopathy</th>
<th>Malnutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>&lt;2</td>
<td>&gt;3.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>2-3</td>
<td>3-3.5</td>
<td>Mild</td>
<td>Mild</td>
<td>Mild</td>
</tr>
<tr>
<td>C</td>
<td>&gt;3</td>
<td>&lt;3</td>
<td>Severe</td>
<td>Severe</td>
<td>Severe</td>
</tr>
</tbody>
</table>


E. Pancreatitis (Ranson, 1974)

<table>
<thead>
<tr>
<th>Admission</th>
<th>48 hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;55</td>
<td>Hematocrit φ 10%</td>
</tr>
<tr>
<td>Glucose &gt;200 mg/dl</td>
<td>BUN ≠ 5 mg/dl</td>
</tr>
</tbody>
</table>
### Myocardial Infarction (Killip 1967)

<table>
<thead>
<tr>
<th>Class</th>
<th>Cardiac Failure</th>
<th>Ejection Fraction</th>
<th>Mortality (1967)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>None</td>
<td>.47</td>
<td>8</td>
</tr>
<tr>
<td>II</td>
<td>Mild</td>
<td>.36</td>
<td>30</td>
</tr>
<tr>
<td>III</td>
<td>Pulmonary edema</td>
<td>.31</td>
<td>44</td>
</tr>
<tr>
<td>IV</td>
<td>Cardiogenic shock</td>
<td>.12</td>
<td>80+</td>
</tr>
</tbody>
</table>


### Cardiogenic Shock (Balakumaran 1986)

<table>
<thead>
<tr>
<th>Approx Mortality</th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Class IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate</td>
<td>70-85</td>
<td>85-100</td>
<td>90-110</td>
<td>&gt; 110</td>
</tr>
<tr>
<td>BP System</td>
<td>&gt; 90</td>
<td>80-90</td>
<td>60-80</td>
<td>&lt; 60</td>
</tr>
<tr>
<td>PCW</td>
<td>&lt; 12</td>
<td>12-14</td>
<td>14-18</td>
<td>&gt; 18</td>
</tr>
<tr>
<td>CI</td>
<td>&gt; 3</td>
<td>2.5-3</td>
<td>2-2.5</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>LVWI</td>
<td>&gt; 270</td>
<td>200-270</td>
<td>120-200</td>
<td>&lt; 120</td>
</tr>
<tr>
<td>SWI</td>
<td>&gt; 3000</td>
<td>2000-3000</td>
<td>1200-2000</td>
<td>&lt; 1200</td>
</tr>
<tr>
<td>Approx Mortality</td>
<td>10%</td>
<td>25</td>
<td>40</td>
<td>60</td>
</tr>
</tbody>
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