Blood Flow Measurement: The Cardiac Output and Vascular Resistance

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The maintenance of blood flow commensurate with the metabolic needs of the body is a fundamental requirement of human life. In the absence of major disease of the vascular tree (e.g., arterial obstruction), the maintenance of appropriate blood flow to the body depends largely on the heart's ability to pump blood in the forward direction. The quantity of blood delivered to the systemic circulation per unit time is termed the cardiac output, generally expressed in liters per minute.

**ARTERIOVENOUS DIFFERENCE AND EXTRACTION RESERVE**

Because the extraction of nutrients by metabolizing tissues is a function not only of the rate of delivery of those nutrients (the cardiac output) but also of the ability of each tissue to extract those nutrients from the circulation, tissue viability can be maintained despite a fall in cardiac output as long as there is increased extraction of required nutrients. The extraction of a given nutrient (or of any substance) from the circulation by a particular tissue is expressed as the arteriovenous difference across that tissue, and the factor by which the arteriovenous difference can increase at constant flow (due to changes in metabolic demand) may be termed the extraction reserve. For example, arterial blood in humans is normally 95% saturated with oxygen; that is, if 1 L of blood has the capacity to carry approximately 200 mL of oxygen when fully saturated, arterial blood will usually be found to contain 190 mL of oxygen per liter (190/200 = 95%). Venous blood returning from the body normally has an average oxygen saturation of 75%; that is, mixed venous blood generally contains 150 mL of oxygen per liter of blood (150/200 = 75%). Thus the normal arteriovenous difference for oxygen is 40 mL/L (190 mL/L - 150 mL/L).

The normal extraction reserve for oxygen is 3, which means that under extreme metabolic demand, the body's tissues can extract up to 120 mL of oxygen (3 × 40 mL) from each liter of blood delivered (1). Thus if arterial saturation remains constant at 95%, full utilization of the extraction reserve will result in a mixed venous oxygen content of 70 mL/L (190 mL/L - 120 mL/L) or a mixed venous oxygen saturation of 35% (70/200 = 35%). This is essentially the value found for mixed venous (i.e., pulmonary artery) oxygen saturation in normal men studied at maximal exercise. The relation between cardiac output and arteriovenous O₂ difference is illustrated in Fig. 8.1.

**FIG. 8.1.**

Relationship between arteriovenous oxygen (A-VO₂) difference (broken line) and cardiac index (solid curve) in normal subjects at rest (center) and during exercise (right) and in the patient with progressively worsening myocardial failure (left). (See text for discussion.)

**Lower Limit of Cardiac Output**

The value of 3 for the oxygen extraction reserve predicts that in progressive cardiac decompensation, meeting the basal oxygen requirements of the body demands that oxygen extraction increase as cardiac output falls, until arteriovenous oxygen difference has tripled and cardiac output has fallen to one-third of its normal value (Fig. 8.1). Because the extraction reserve has now been used fully, further reduction of cardiac output will result in tissue hypoxia, anaerobic metabolism, acidosis, and eventually, circulatory collapse. This prediction appears to be quite accurate; clinical investigators have observed for many years that a fall in resting cardiac output to below one-third of
normal (i.e., a cardiac index of $\leq 1.0 \text{ L/min/m}^2$) is incompatible with life.

**Upper Limit of Cardiac Output**

Several studies have indicated that the largest increase in cardiac output that can be achieved by a trained athlete at maximal exercise is 600% of the resting output. If a normal 70-kg man has a cardiac output of 5 L/min or 3.0 L/min/m$^2$, his maximal cardiac output might be as high as 30 L/min (18 L/min/m$^2$). Because cardiac output increases approximately 600 mL for each 100-mL increase in oxygen requirements of the body, an increase in cardiac output of 25 L/min with maximal exercise would suggest an increase in total-body oxygen requirements of 4,167 mL/min, which is approximately an 18-fold increase over the normal resting value of 250 mL/min. The 18-fold increase in total-body oxygen requirements is met by the combined sixfold increase in oxygen “delivery” (i.e., cardiac output) and threefold increase in oxygen extraction (extraction reserve). These relations are illustrated in Fig. 8.1.

**Factors Influencing Cardiac Output in Normal Subjects**

The range of the “normal” cardiac output is difficult to define with precision because it is influenced by several variables. Obviously, body size is important, and the ranges of normal values for cardiac output of 2-year-old children, 10-year-old children, and 50-year-old men are so different that they show only minimal overlap. For this reason, normalization of the cardiac output for differing body size is considered fundamental by all students of this subject, although there is disagreement about the best way to accomplish this normalization. Because cardiac output seems to be predominantly a function of the body's oxygen consumption or metabolic rate (1),(2) and because metabolic rate was thought to correlate best with body surface area (3),(4), it has become customary to express cardiac output in terms of the cardiac index $[(\text{liters/min})/(\text{body surface area, m}^2)]$. Body surface area is not measured directly but is instead calculated from one of the experimentally developed formulas, such as that of Dubois (4).

$$\text{Body surface area (m}^2) = 0.007184 \times \text{weight}^{0.425} (\text{kg}) \times \text{height}^{0.725} (\text{cm}) \quad (8.1)$$

Despite the shortcomings and weaknesses of this approach to normalization of the cardiac output (1),(5), the method has gained nearly universal acceptance by clinicians over the past 40 years and will be employed throughout this book. A chart to aid calculation of body surface area (if weight and height are known) appears in Fig. 8.2.

**FIG. 8.2.**

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Nomogram for calculation of body surface area given the weight and height of the patient. From the formula of Dubois (4).

Although expression of cardiac output as the cardiac index greatly narrows the range of normal values among our groups of 2-year-old children, 10-year-old children, and 50-year-old men, it does not completely abolish the differences in these ranges. In fact, the normal cardiac output appears to vary with age, steadily decreasing from approximately 4.5 L/min/m$^2$ at age 7 years to 2.5 L/min/m$^2$ at age 70 years (1),(6). This is not surprising because it is well known that the body's metabolic rate is affected greatly by age, being highest in childhood and progressively diminishing to old age.

In addition to age, cardiac output is affected by posture, decreasing approximately 10% when rising from a lying to a sitting position and approximately 20% when rising (or being tilted) from a lying to a standing position. Also, body temperature, anxiety, environmental heat and humidity, and a host of other factors influence the normal resting cardiac output (1), and these must be considered in interpreting any value of cardiac output measured in the clinical setting.
Techniques for Determination of Cardiac Output

Of the numerous techniques devised over the years to measure cardiac output, two have won general acceptance in cardiac catheterization laboratories: the Fick oxygen technique and the indicator dilution technique. Both techniques resemble each other in that they are based on the theoretical principle enunciated by Adolph Fick (7) in 1870. The principle, which was never actually applied by Fick, states that the total uptake or release of any substance by an organ is the product of blood flow to the organ and the arteriovenous concentration difference of the substance. For the lungs, the substance released to the blood is oxygen, and the pulmonary blood flow can be determined by knowing the arteriovenous difference of oxygen across the lungs and the oxygen consumption per minute.

Fick's principle is illustrated in Fig. 8.3. In this figure, a train is passing by a hopper that is delivering marbles to the boxcars at a rate of 20 marbles per minute. If the boxcars each contain 16 marbles before passing under the hopper and 20 marbles after passing under the hopper, each boxcar is picking up four marbles and must be taking only 0.20 minute to pass under the hopper, because it would pick up 20 marbles in each full minute under the hopper. If each boxcar takes 0.20 minute to pass by the hopper, the train is moving at a speed sufficient to deliver five boxcars per minute to any point down the line. This could have been calculated as shown in Fig. 8.3:

FIG. 8.3.

Illustration of Fick's principle. A train, representing the circulation, passes by a hopper (the lungs) that delivers marbles (oxygen) to the train's boxcars at a rate of 20 marbles per minute. Because the boxcars each contain 16 marbles before and 20 marbles after passing under the hopper, each boxcar is picking up 4 marbles and must be taking only 0.20 minute to pass under the hopper, since it would pick up 20 marbles in each full minute under the hopper. If each boxcar takes only 0.20 minute to pass by the hopper, the train is moving at a speed sufficient to deliver 5 boxcars per minute to any point down the line. This could have been calculated as

Train's speed (boxcars/min) = marble delivery rate (marbles/min)/“A-V” marble difference (marble/min)

= (20 marbles/min)/(4 marbles/boxcar)

= 5 boxcars/min

If one boxcar is 1 L of blood and each marble is 10 mL oxygen, then we have an arteriovenous oxygen difference of 40 mL/L, an O₂ consumption of 200 mL/min, and a cardiac output of 5 L/min. (Illustration kindly provided by Jennifer Grossman, age 11.)

Train's speed (boxcars/min)

= marble delivery rate (marbles/min)

÷ “A-V” marble difference (marbles/boxcar)

= (20 marbles/min)/(4 marbles/boxcar)

= 5 boxcars/min

If one boxcar is 1 L of blood and each marble is 10 mL of oxygen, then we have an arteriovenous O₂ difference of 40 mL/L, an oxygen consumption of 200 mL/min, and a cardiac output of 5 L/min.

Fick Oxygen Method

In the Fick oxygen method, pulmonary blood flow should be determined ideally by measuring the arteriovenous
difference of oxygen across the lungs and the rate of oxygen uptake by blood from the lungs. If there is no intracardiac shunt and pulmonary blood flow is equal to systemic blood flow, the Fick oxygen method also measures systemic blood flow. Thus, cardiac output = oxygen consumption ÷ arteriovenous oxygen difference.

In actual practice, the rate at which oxygen is taken up from the lungs by blood is not measured, but rather the uptake of oxygen from room air by the lungs is measured, because in a steady state these two measurements are equal. Furthermore, arteriovenous oxygen difference across the lungs is not measured directly. Generally, pulmonary arterial blood (true mixed venous blood) is sampled, but pulmonary venous blood is not sampled. Instead, left ventricular or systemic arterial blood is sampled and assumed to have an oxygen content representative of mixed pulmonary venous blood. Actually, because of bronchial venous and the besian venous drainage, the oxygen content of systemic arterial blood is commonly 2 to 5 mL/L of blood lower than pulmonary venous blood as it leaves the alveoli.

FIG. 8.4.

Measurement of O$_2$ consumption by a polarographic cell technique using the Waters Instruments metabolic rate meter (MRM). A transparent hood fits snugly over the patient's head, resting on his or her pillow. Air enters the hood through holes in a plastic sheet at a flow rate of $V_R$. The patient's inspiratory ($V_i$) and expiratory ($V_E$) flow rates subtract and add to $V_R$ to yield $V_M$, the flow rate leaving the hood and entering the servounit. A blower motor in the servounit adjusts $V_M$ to keep the O$_2$ sensed by a polarographic cell constant. (See text for details.)

**Oxygen Consumption**

Two different methods for measurement of oxygen consumption are widely used today: the polarographic method and the paramagnetic method. The older Douglas bag method is rarely used.

Oxygen consumption may be measured using the metabolic rate meter (MRM) made by Waters Instruments (Rochester, MN) or the Deltatrac II, made by Sensormedics (Yorba Linda, CA). The MRM instrument contains a polarographic oxygen sensor cell (gold and silver/silver chloride electrodes), a hood or face mask, and a blower of variable speed connected to a servocontrol loop with the oxygen sensor (Fig. 8.4). This device is convenient and accurate and represents a significant advance over the older, standard procedure of collecting expired air for 3 minutes in a Douglas bag and measuring volume (Tissot spirometer) and oxygen content. The principle of operation for the MRM involves using a variable-speed blower to maintain a unidirectional flow of air from the room through the hood and via a connecting hose to the polarographic oxygen-sensing cell. As illustrated in Fig. 8.4, room air enters the hood at a rate $V_R$ (mL/min), which is determined by the blower's discharge rate $V_M$ (mL/min), as well as the patient's ventilatory rate ($V_i$, inhaled air in mL/min; $V_E$, exhaled air). The blower speed $V_M$ is controlled by a servoloop designed to maintain the oxygen content of air flowing past the polarographic cell constant at a predetermined value. In a steady state, the average value of $V_M$ together with the oxygen content of room air and of air flowing past the polarographic cell can be used to calculate the patient's oxygen consumption, as follows:

The patient's oxygen consumption $VO_2$ is given by

$$\dot{V}_{O_2} = (F_R O_2 \cdot \dot{V}_R) - (F_M O_2 \cdot \dot{V}_M) \quad (8.2)$$

where $F_R O_2$ and $F_M O_2$ are the fractional contents of oxygen in room air and in air flowing past the polarographic cell, respectively.

As can be seen from Fig. 8.4,
\[ V_M = V_R - V_i + V_E \]  \hspace{1cm} (8.3)

which can be rewritten as

\[ V_R = V_M + V_i - V_E \]  \hspace{1cm} (8.4)

Substituting this in Eq. (8.2) gives

\[
\begin{align*}
V_{O_2} &= F_{RO_2}(V_M + V_i - V_E) - F_{MO_2} \cdot V_M \\
&= F_{RO_2}(V_M) - F_{MO_2}(V_M) + F_{RO_2}(V_i) \\
&\quad - F_{RO_2}(V_E) \\
&= V_M(F_{RO_2} - F_{MO_2}) + F_{RO_2}(V_i - V_E) \\
&= V_M(0.209 - F_{MO_2}) + 0.209(V_i - V_E) \\
&= V_M(0.209 - 0.199) \\
&\quad + 0.209(V_i - V_E) \\
\end{align*}
\]  \hspace{1cm} (8.5)

Since the fractional content of oxygen in room air (\( F_{RO_2} \)) is 0.209, oxygen consumption is given by

\[ V_{O_2} = V_M(0.209 - 0.199) + 0.209(V_i - V_E) \]  \hspace{1cm} (8.6)

Thus in a steady state (where \( V_i - V_E \) is constant), oxygen consumption can be determined by measuring the volume rate of air moved by the blower motor (\( V_M \)) and the fractional oxygen content of air moving past the polarographic sensor. In the MRM, a servocontrolled system adjusts \( V_M \) to keep \( F_{MO_2} \) at a constant predetermined value. In practice, \( F_{MO_2} \) is set at 0.199 so that Eq. (8.6) becomes

\[
\begin{align*}
V_{O_2} &= V_M(0.209 - 0.199) \\
&\quad + 0.209(V_i - V_E) \\
V_{O_2} &= 0.01 V_M + 0.209(V_i - V_E). \\
\end{align*}
\]  \hspace{1cm} (8.7)

For practical purposes, the respiratory quotient (RQ) is assumed to be 1.0; accordingly, \( V_i = V_E \) and \( V_{O_2} = 0.01 V_M \). If the RQ is actually 0.9 (e.g., the patient releases 0.9 L of CO\(_2\) for each liter of O\(_2\) consumed), the error in \( V_{O_2} \) resulting from the assumption of an RQ of 1.0 is 1.6%, and if RQ is 0.8, the error would be 3.2%. The MRM O\(_2\) consumption monitor has a calibrated blower motor in addition to the servocontrol polarographic sensor and gives a readout of oxygen consumption in liters per minute by digital scale (MRM-2) or by meter and paper (MRM-1). The MRM-2 model is calibrated to be highly accurate in the oxygen consumption range from 10 to 1,000 mL O\(_2\) /min and is thus best suited for measurement of resting O\(_2\) consumption in the catheterization laboratory. The MRM-1 model, which is calibrated in the range of 150 to 5,000 mL O\(_2\) /min, is best suited for exercise studies.
The Sensormedics Deltatrac II differs from the Waters Instruments MRM device in several aspects. First, it is more sophisticated than the MRM and measures directly the fractional content of oxygen as well as the concentration of carbon dioxide in expired flow, and thus calculates the RQ of each patient. The Sensormedics device is calibrated prior to each period of use with a cylinder containing a test gas of 95% oxygen and 5% carbon dioxide. The Sensormedics device uses a constant flow rate $V_M$ leaving the canopy or hood and entering the metabolic monitor unit. The sensors in this unit measure oxygen (paramagnetic sensor) and carbon dioxide (infrared sensor), and the unit adjusts for temperature and the partial pressure of water vapor, expressing $O_2$ consumption and $CO_2$ production at STPD (dry gas at $0^\circ$C and 760 mm Hg).

Both the Waters Instruments and Sensormedics devices are relatively easy to use, although a fair amount of attention to detail is required to obtain reproducible readings consistently. A study by Lange et al. (8), however, found that values of oxygen consumption measured by metabolic rate meter (MRM-2, Waters Instruments, Rochester, MN) were significantly lower than those measured using the standard Douglas bag technique (see later discussion).

**Douglas Bag Method**

The older Douglas bag method is rarely used today, and interested readers are referred to earlier editions of this book for details.

**Arteriovenous Oxygen Difference**

The arteriovenous oxygen difference across the lungs must be measured to calculate cardiac output by Fick's principle, and this can be accomplished by the following method. From appropriately positioned catheters, systemic arterial and mixed venous (pulmonary arterial) blood samples are obtained during the period when $O_2$ consumption is being measured. The samples are drawn into heparinized syringes and capped quickly. If the patient has received heparin systemically, the syringes for collection of these blood samples need not be heparinized. If the samples will be analyzed immediately by oximetry, plastic syringes may be used. $O_2$ may diffuse through the walls of plastic syringes, however, and glass syringes are considered preferable by some if there will be a delay in oximetric analysis of the blood. In a test in my laboratory, no appreciable increase in $O_2$ saturation of venous blood could be detected over 2 hours. (Capped plastic 15-mL syringe filled with venous blood sitting at room temperature was sampled every 15 minutes for oximetry.) The samples should be drawn simultaneously and as close to the midpoint of the oxygen consumption determination as possible. Care must be taken to avoid contamination of the blood samples with air bubbles.

Oxygen content (in milliliters of oxygen per liter of blood) can be determined by a variety of methods, the most classic of which (and the one that serves as a standard for all others) is the manometric technique of Van Slyke and Neill (9). The major drawback of the Van Slyke and Neill technique is that 15 to 30 minutes are required to run a single blood sample. The different devices for oximetry measurement have been studied and compared by Shepherd and McMahan (9). The older Van Slyke methodology is rarely used today, and the Lex-O$_2$-Con fuel cell technique is no longer available. Devices in widespread use today are of the cooximeter class and either hemolyze the blood sample (by ultrasonic or chemical techniques) or use whole blood; both types of cooximeter depend on spectrophotometric measurement of the percent oxygen saturation of hemoglobin. Several devices in use today have been demonstrated to be accurate (9), including the Radiometer OSM2 and AVOXimeter 1000 (A-Vox Systems, San Antonio, TX) devices. Using these devices, oximetry of heparinized blood samples is simple and quick and measures the percentage of hemoglobin present as oxyhemoglobin. This percentage, multiplied by the theoretical oxygen-carrying capacity of the patient's blood, yields the calculated oxygen content of that sample (Fig. 8.5). A formula for approximating the theoretical oxygen-carrying capacity in humans is
Calculation of oxygen content and A-V oxygen difference when using the reflectance oximetry method.

In several textbooks the constant is given as 1.34, but studies on crystalline human hemoglobin suggest that the correct number may be 1.36 (10, 11). Whatever its correct value, the formula is only an approximation. Figure 8.5 is a flow sheet that may be used to calculate oxygen content of blood samples and arteriovenous oxygen difference when the spectrophotometric oximeter method is used. Oxygen contents of arterial and mixed venous blood samples are calculated as the percentage of oxyhemoglobin saturation of these samples multiplied by the oxygen-carrying capacity (steps 2 to 5, Fig. 8.5). The arteriovenous oxygen difference (step 3 minus step 5, Fig. 8.5) may then be divided into the oxygen consumption to yield the cardiac output. Current oximeters, such as the AVOXimeter 1000, illuminate a very small sample of heparinized blood (volume 50 mL) with light of multiple wavelengths and record the optical density of each transmitted wavelength. This approach allows estimation of total hemoglobin concentration as well as the concentrations of various components: oxyhemoglobin, methemoglobin, and carboxyhemoglobin. This permits instantaneous calculation of oxygen content, which is displayed on the oximeter's liquid crystal display (LCD) screen. This value can then be entered directly in steps 3, 5, and 6 of Fig. 8.5. Arterial blood may be taken from a systemic artery, the left ventricle, the left atrium, or the pulmonary veins. Theoretically, pulmonary venous blood is preferable to peripheral arterial blood for the arteriovenous oxygen difference calculations. However, except in the presence of a right-to-left intracardiac shunt, pulmonary venous oxygen content may be approximated by systemic arterial oxygen content, ignoring the small amount of venous admixture resulting from bronchial and thebesian venous drainage. If arterial desaturation (e.g., arterial blood oxygen saturation <95%) is present, a central right-to-left shunt should be excluded before accepting systemic arterial oxygen content as representative of pulmonary venous blood. Techniques for detecting and quantifying such shunts are described in Chapter 9.

**FIG. 8.5.**

Calculation of oxygen content and A-V oxygen difference when using the reflectance oximetry method.

The most reliable site for obtaining mixed venous blood is the pulmonary artery. Because of streaming and incomplete mixing, using blood from more proximal sites such as the right atrium or vena cavae as representative of mixed venous blood is much less accurate (12, 13). Right ventricular blood is closer to true mixed venous blood and may be substituted for pulmonary arterial blood if necessary.

**Sources of Error**

The techniques described for cardiac output measurement by application of Fick's principle assume that a steady state exists (i.e., that the cardiac output and oxygen consumption are constant during the period of measurement). Therefore strict quiet, calm, and decorum must be maintained in the cardiac catheterization laboratory during this time to encourage the achievement of a steady-state condition. Potential errors in the determination of cardiac output by the Fick oxygen technique may come from a number of sources.

The spectrophotometric determination of blood oxygen saturation may introduce inaccuracies related to carboxyhemoglobin or other abnormal hemoglobin, as discussed previously. This method also may be inaccurate if indocyanine green dye is present in the circulation, although the newer oximeters are not affected by this problem. Reflectance oximetry, as performed on whole blood, is accurate in the range of blood oxygen saturations from 45% to 98% but may not be reliable when blood O2 saturation is less than 40%, as is the case in pulmonary artery blood.
from patients with very low cardiac output or during strenuous exercise.

Improper collection of the mixed venous blood sample (e.g., air bubbles) is a common source of error. Partial contamination of pulmonary arterial blood with pulmonary capillary wedge blood may result in a falsely high mixed venous oxygen content. If the mixed venous blood sample is taken from the right atrium, inferior vena cava, coronary sinus, or similar sites, a falsely low or high value for arteriovenous difference may result. Also, care must be taken not to dilute the blood sample with too much heparinized saline solution.

The average error in determining oxygen consumption has been estimated to be approximately 6% (13). The error for arteriovenous oxygen difference has been estimated at 5% (14,15). Narrow arteriovenous oxygen differences are more prone to introduce error than wide arteriovenous oxygen differences. Thus the Fick oxygen method is most accurate in patients with low cardiac output, in whom the arteriovenous oxygen difference is wide. The total error in determination of the cardiac output by the Fick oxygen method has been established to be about 10% (16).

Does oxygen consumption actually need to be measured? To avoid the technical difficulties and expense associated with measurement of oxygen consumption, some laboratories assume that O_2 consumption can be predicted from the body surface area, with or without a correction for age and sex. Thus, some laboratories assume that resting O_2 consumption is 125 mL/m^2, or 110 mL/m^2 for older patients. The validity of such an assumption has been addressed in a study from the University of Texas at Dallas (17). Cardiac output was determined by the indicator dilution technique, and O_2 consumption was calculated by dividing cardiac output by arteriovenous oxygen difference, which was measured directly. In the 108 patients studied, O_2 consumption index averaged 126 ± 26 mL/min/m^2 (mean ± standard deviation), but there was wide variability as indicated by the standard deviation, and the authors concluded that O_2 consumption varies greatly among adults at the time of cardiac catheterization. In another study from Bristol Royal Infirmary in the United Kingdom (18), direct measurement of O_2 consumption was compared with assumed values in 80 patients (aged 38 to 78 years). Large discrepancies were evident, with more than half the values differing by more than ±10% and several by ±25% or more. Thus, assumed values for O_2 consumption are likely to introduce considerable error.

Indicator Dilution Methods

The indicator dilution method is merely a specific application of Fick's general principle. In the Fick oxygen method, the “indicator” is oxygen, the site of injection is the lungs, and the injection procedure is that of continuous infusion. Stewart (19) was the first to use the so-called indicator dilution method for measuring cardiac output; he used the continuous-infusion technique and reported his first studies in 1897.

There are two general types of indicator dilution methods: the continuous-infusion method and the single-injection method. The single-injection method is the most widely used and is discussed here in detail. The fundamental requirements for this method include the following:

- A bolus of nontoxic indicator substance, which mixes completely with blood and whose concentration can be measured accurately, is injected.
- The indicator substance is neither added to nor subtracted from the blood during passage between injection and sampling sites.
- Most of the indicator must pass the site of sampling before recirculation begins.
- The indicator substance must go through a portion of the central circulation where all the blood of the body becomes mixed.

For the single-injection method, theoretical considerations may be summarized as follows: An injection of a specified amount of an indicator I into a proximal vessel or chamber (e.g., the vena cava or right atrium for the thermodilution method and the pulmonary artery for the indocyanine green dye method) is followed by continuous measurement of the indicator concentration C in blood as a function of time t at a point downstream from the injection (e.g., pulmonary artery for thermodilution technique and radial or femoral artery for the indocyanine green dye method). Because all the injection indicator I must pass the downstream measurement site,
where \( Q \) is the volume flow (in milliliters per minute) between the sites of injection and measurement. Thus \( Q \) (which is the cardiac output in the methods to be described) may be calculated as

\[
I = Q \int_0^\infty C(t) \, dt
\]  
\tag{8.9}

\[
\dot{Q} = \frac{I}{\int_0^\infty C(t) \, dt}
\]  
\tag{8.10}

Numerous indicators have been used successfully, and the history of this subject is reviewed thoroughly by Guyton et al. (1). Indocyanine green previously had enjoyed long-standing acceptance in clinical practice but is rarely used today for routine measurement of cardiac output. Accordingly, it will not be discussed here and the interested reader is referred to previous editions of this textbook. We will only discuss thermodilution (in which “cold” is the indicator), which is now the dominant technique.

**Thermodilution Method**

A thermal indicator method for measuring cardiac output was first introduced by Fegler (20) in 1954 but was not applied to the clinical situation until the work of Branthwaite and Bradley (21) and Ganz et al. (22),(23). In the initial report by Ganz et al. (22), two thermistors were used: one in the superior vena cava at the site at which the cold dextrose solution was injected into the bloodstream and a second “downstream” thermistor in the pulmonary artery. These two thermistors allowed accurate measurement of the temperature of the injectate \( T_I \) as well as the temperature of blood \( T_B \) downstream from the injectate. Using the basic indicator dilution equation, the cardiac output by thermodilution \( CO_{TD} \) in milliliters is given as

\[
CO_{TD} = \frac{V_I(T_B - T_I)(S_I \cdot C_I/S_B \cdot C_B)60(\text{sec/min})}{\int_0^\infty \Delta T_B(t) \, dt}
\]  
\tag{8.11}

where \( V_I = \) volume of injectate (mL), and \( S_B \cdot S_I \cdot C_B \cdot C_I \) are the specific gravity and specific heat of blood and injectate, respectively. When 5% dextrose is used as an indicator \((S_I \cdot C_I/S_B \cdot C_B) = 1.08\). Most commercially available thermodilution systems use a single thermistor only, placed at the downstream site, and assume that the temperature of the injectate (measured in a bowl before injection) increased by a predictable amount (“catheter warming”) during injection. The calculated cardiac output by the thermodilution equation is multiplied by an empirical correction factor (0.825) to correct for the catheter warming (23). However, a recent report (24) has demonstrated that improved accuracy and precision can be obtained with the thermodilution technique when cardiac output is measured using a dual thermistor catheter system. These investigators used a specialized dual thermistor right heart catheter, constructed with a second thermistor, positioned to measure temperature at the point where the injectate exits the catheter in the right atrium. This takes into account any warming of the injectate that may take place as it travels from the injectate syringe to the point of exit from the catheter in the right atrium. Using this technique there was substantially less measurement variability, and better agreement with simultaneously measured
Fick cardiac output (the latter determined using a 5-minute Douglas bag collection of expired air and paired blood samples from pulmonary and femoral arteries).

The thermodilution method for measuring cardiac output has several advantages over the indocyanine green dye method, and these include the following:

1. It does not require withdrawal of blood.
2. It does not require an arterial puncture.
3. An inert and inexpensive indicator is used.
4. There is virtually no recirculation, making computer analysis of the primary curve simple.

**Sources of Error**

1. The method is unreliable in the presence of significant tricuspid regurgitation.

2. The baseline temperature of blood in the pulmonary artery usually shows distinct fluctuations associated with respiratory and cardiac cycles. If these fluctuations are large, they may approach the magnitude of the temperature change produced by the "cold" indicator injection.

3. Loss of injected indicator ("cold") between injection and measuring sites (vena cava and pulmonary artery) is not usually a problem, but in low-flow, low-output states, loss of indicator may occur because of warming of blood by the walls of the cardiac chambers and surrounding tissues. This concern is supported by the study of van Grondelle et al. (25), who found that thermodilution cardiac output measurements overestimated cardiac output consistently in patients with low output (<3.5 L/min), and this overestimation was greatest, averaging 35%, in patients whose cardiac outputs were <2.5 L/min. This is what might be expected from the equation for calculation of cardiac output by thermodilution, since the change in pulmonary artery blood temperature ($\Delta T_B$) will be reduced if cold is lost by warming of the injectate during slow passage through the vena cava, right atrium, and right ventricle. Because $\Delta T_B$ is the denominator in the equation for cardiac output calculation, reduction in $\Delta T_B$ will result in a rise in calculated cardiac output.

4. The empirical correction factor of 0.825 may be inadequate to correct for deviations in true injectate temperature from the temperature of the injectate bowl or reservoir due to warming in the syringe by the hand of the individual injecting the dextrose solution from the syringe or by catheter warming.

In general, indicator dilution cardiac output determinations have an error of 5% to 10% when performed carefully. The values obtained correlate well with those calculated by the Fick oxygen method.

**Clinical Measurement of Vascular Resistance and Assessment of Vasodilator Drugs**

**Poiseuille's Law**

The French physician Jean Léonard Marie Poiseuille (1799–1869) made many important contributions to the study of hemodynamics. At age 18, he introduced the mercury manometer for the measurement of blood pressure, a technical innovation that continues in use to this day. In 1846 he formulated a series of equations describing the flow of fluids through cylindrical tubes. Although Poiseuille was interested in blood flow, he substituted simpler liquids in his measurements of flow through rigid glass tubes. His discoveries, later modified by others, are expressed in what is regarded as Poiseuille's law (26), which may be stated as follows:

$$Q = \frac{\pi (P_i - P_o) r^4}{8 \eta l}$$

(8.12)

where:
\( Q = \) volume flow

\( Pi - Po = \) inflow pressure - outflow pressure

\( r = \) the radius of the tube

\( l = \) the length of the tube

\( \varepsilon = \) viscosity of the fluid

This relationship applies in the specific circumstance of steady-state laminar flow of a homogeneous fluid through a rigid tube. Under these conditions, flow, \( Q \), varies directly as the pressure difference, \( Pi - Po \), and the fourth power of the tube's radius, \( r \). It varies inversely as the length, \( l \), of the tube and the viscosity, \( \varepsilon \) of the fluid.

Hydraulic resistance, \( R \), is defined by analogy to Ohm's law as the ratio of mean pressure drop, \( \Delta P \), to flow, \( Q \), across the vascular circuit. The various factors contributing to vascular resistance can be illustrated by rearranging Poiseuille's law as follows:

\[
R = \frac{Pi - Po}{Q} = \frac{8 \eta l}{\pi r^4}
\]

(8.13)

It is apparent from this equation that, in the condition of steady laminar flow of a homogeneous fluid through a rigid cylindrical tube, resistance to flow depends only on the dimensions of the tube and the viscosity of the fluid. In particular, the resistance is remarkably sensitive to changes in the radius of the tube, varying inversely with its fourth power.

Vascular Resistance and Pressure-Flow Relationships

The applicability of laws derived from steady-state fluid mechanics in assessing vascular resistance is somewhat ambiguous because blood flow is pulsatile, blood is a nonhomogeneous fluid, and the vascular bed is a nonlinear, elastic, frequency-dependent system. In such a system, resistance varies continuously with pressure and flow and is influenced by many factors, such as inertia, reflected waves, and the phase angle between pulse and flow wave velocities (26–28).

To assess both vessel caliber and elasticity, the resistive and compliant characteristics of the vascular system, the concept of vascular impedance has been used (27). Vascular impedance has been defined as the instantaneous ratio of pulsatile pressure to pulsatile flow (28), (29). Because impedance may not be the same for all frequencies, its calculation requires resolution of the harmonic components of both pressure and flow pulsations. The impedance modulus so calculated is then expressed as a spectrum of impedance versus frequency. Although measurement of impedance is important in research studies, it is rarely included in routine diagnostic cardiac catheterization, and the reader is referred elsewhere (26) for a full discussion.

As a consequence of the foregoing considerations and the many active and passive factors that influence pressure and flow in blood vessels, the concept of vascular resistance in its pure physical sense is limited in application. In the context of the clinical and physiologic setting, however, pulmonary and systemic vascular resistances calculated from hemodynamic measurements made during cardiac catheterization have acquired empiric pathophysiologic meaning and are often important factors in clinical decision making.

Estimation of Vascular Resistance in the Clinical Situation

Calculations of vascular resistance are usually applied to both the pulmonary and systemic circulations. Although many authors refer to systemic or pulmonary arteriolar resistance, I prefer the term vascular resistance because it is less committal concerning the anatomic site of the resistance. As has been mentioned, arteriolar tone is only one determinant of vascular resistance to blood flow. To estimate pulmonary and systemic vascular resistances quantitatively, knowledge of both the driving pressure across the pulmonary and systemic vascular beds and the respective blood flow through them is required.
The formulae generally used are:

1. Systemic vascular resistance = \( A_o - RA/Q_s \)

2. Total pulmonary resistance = \( PA/Q_p \)

3. Pulmonary vascular resistance = \( PA - LA/Q_p \) (8.14)

where \( A_o = \) mean systemic arterial pressure, \( RA = \) mean right atrial pressure, \( PA = \) mean pulmonary arterial pressure, \( LA = \) mean left atrial pressure, \( Q_s = \) systemic blood flow, \( Q_p = \) pulmonary blood flow.

In many laboratories, the mean pulmonary capillary wedge pressure is used as an approximation of mean left atrial pressure. This should cause no problem because there is ample evidence that pulmonary capillary wedge pressure, properly obtained, closely approximates the level of left atrial pressure (30–32). The flows are volume flows (as opposed to velocity flows) and are expressed in liters per minute, and pressures are expressed in millimeters of mercury (mm Hg). These equations yield resistance in arbitrary resistance units (R units) expressed in mm Hg per liter per minute, also called hybrid resistance units (HRU). These HRU units are sometimes referred to as Wood units, since they were first introduced by Dr. Paul Wood. They may be converted to metric resistance units expressed in dynes-sec-cm\(^{-5}\) by use of the conversion factor 80. In this system, resistance is expressed as:

\[
\text{Resistance} = \frac{\Delta P (\text{mm Hg}) \times 1332 \text{ dynes/cm}^2/\text{mm Hg}}{Q_s \text{ or } Q_p (\text{L/min}) \times 1,000 \text{ mL/L} \div 60 \text{ sec/min}}
\]

\[
= \frac{\Delta P}{Q_s \text{ or } Q_p} \times 80 = \text{dynes-sec-cm}^{-5} \quad (8.15)
\]

There is no particular advantage to either system, since both express precisely the same ratio. Most pediatric cardiologists use hybrid resistance units, whereas cardiologists with adult practices generally use metric units.

In pediatric practice it is conventional to normalize vascular resistances for body surface area (BSA), thus giving a resistance index. Although this is not commonly done in adult cardiac catheterization laboratories, the practice makes sense because normal cardiac output and therefore vascular resistance may be substantially different in a 260-lb man and a 110-lb woman. The normalized resistance, however, is not obtained by dividing resistance (as calculated in Eq. 8.14) by body surface area. Rather, normalized resistance is calculated by substituting blood flow index for blood flow in the resistance formula. Thus systemic vascular resistance index (SVRI) is calculated as

\[
SVRI = \frac{(A_o - RA) \times 80}{CI} \quad (8.16)
\]

where CI is the cardiac (or systemic blood flow) index. Therefore, SVRI equals SVR multiplied by BSA.

Cardiac output, usually measured by either the Fick or the thermodilution method, is used as mean blood flow. It is important to realize that in conditions of intracardiac shunts or shunts between the pulmonary and systemic circulations, pulmonary blood flow and systemic flow may not be equal, and the respective flow through each circuit must be measured and used in the appropriate resistance calculation.
Normal values for vascular resistance in adults are given in Table 8.1.

**Clinical Use of Vascular Resistance**

As can be deduced from the Poiseuille equation, changes in systemic or pulmonary vascular resistance may result theoretically from one of three mechanisms. Because changes in length of the vascular beds are uncommon after growth has been completed, changes in vascular resistance reflect either altered viscosity of blood or a change in cross-sectional area (radius) of the vascular bed.

There is ample evidence that changes in blood viscosity alter measured vascular resistances. Nihill (33) has shown that an approximate doubling of pulmonary vascular resistance occurs with increases in hematocrit from 43% to 64%. Similarly, low values for measured vascular resistance are commonly seen in patients with severe chronic anemia, although the low vascular resistance in such cases probably represents more than a viscosity effect alone.

With regard to changes in cross-sectional area of the pulmonary or systemic vascular bed, such changes do not invariably imply altered arteriolar tone. In the normal systemic circulation, mean aortic pressure may be 100 mm Hg, whereas right atrial pressure is only 5 mm Hg. Although the greatest part of this pressure drop occurs at the arteriolar level (approximately 60%), about 15% occurs in the capillaries, 15% in small veins, and 10% in the arterial system proximal to the arterioles (27). Thus although systemic vascular resistance is dominated by the caliber of the arterioles, the other components of the systemic vascular bed are by no means negligible. For example, Read and coworkers (34) studied systemic vascular resistance in dogs with constant (pump-controlled) cardiac output and found that a rise in venous pressure consistently caused a fall in resistance. The magnitude of the fall was proportional to the increment in venous pressure rise and was about 20% for an increase in venous pressure of 20 mm Hg. Other studies show no change in resistance when arterial pressure is so manipulated (in the absence of baroreceptor control). These findings have been interpreted by McDonald (28) to suggest that the decline in systemic vascular resistance with increased venous pressure results from dilation of small venous channels, whereas systemic arterioles do not distend passively with increased pressure. Therefore measurement of vascular resistance is not a precise tool for assessing the dynamics of individual sections of the vascular bed, and the term vascular resistance should not be used as synonymous with arteriolar resistance.

**Systemic Vascular Resistance**

The minute-to-minute control of vascular resistance, at least in the systemic bed, is an amalgam of autonomic nervous system influences and local metabolic factors. Hypotension or reduced cardiac output generally triggers increased systemic resistance by means of the baroreceptors, alpha-adrenergic neural pathways, and release of humoral vasoconstrictor hormones, but these influences may be opposed by metabolic factors if the hypotension or low cardiac output results in decreased tissue perfusion with local hypoxia and acidosis. This latter circumstance is commonly seen in congestive heart failure or shock.

Knowledge of changes in systemic vascular resistance is also important in evaluating the hemodynamic response to stress tests, such as dynamic or isometric exercise (35). In this regard, there is ample evidence that normally, the systemic vascular resistance falls in response to dynamic exercise, but pulmonary vascular resistance is unchanged (at least with supine bicycle exercise). Transient elevations in systemic vascular resistance have been provoked by infusions of vasopressor drugs in an effort to evaluate the left ventricular response to a sudden increase in afterload (36).

Low systemic vascular resistance may be seen in conditions in which blood flow is abnormally high, such as may occur in patients with arteriovenous fistula, severe anemia, and other high-output states. It is important to realize that in these circumstances there may well be regional differences in vascular resistance (e.g., very low in the arteriovenous fistula but normal or increased in other vascular beds), and calculations based on mean pressure and flow in the entire systemic circulation must be interpreted with caution.

**Total Pulmonary Resistance**
Calculated as the ratio of mean pulmonary artery pressure to pulmonary blood flow, total pulmonary resistance expresses the resistance to flow in transporting a volume of blood from the pulmonary artery to the left ventricle in diastole, neglecting left ventricular diastolic pressure. This relationship is obviously influenced by alterations in left atrial pressure and will not consistently provide useful information about the condition of the pulmonary vasculature. Although widely used 25 years ago, this parameter is less commonly used today, and in general should be used primarily in the patient where measurement of left atrial or pulmonary capillary wedge pressure is not possible.

Pulmonary Vascular Resistance

Sometimes (inappropriately) called pulmonary arteriolar resistance, pulmonary vascular resistance expresses the pressure drop across the major pulmonary vessels, the precapillary arterioles, and the pulmonary capillary bed, and is more precise in assessing the presence and degree of pulmonary vascular disease than is total pulmonary resistance. Simple calculation of pulmonary vascular resistance provides general information about the pulmonary circulation, but this must be interpreted in the context of the clinical situation and other hemodynamic data obtained during cardiac catheterization. The pulmonary vasculature is a dynamic system and is subject to many mechanical, neural, and biochemical influences.

Measured pulmonary vascular resistance may be increased by hypoxia, hypercapnia, increased sympathetic tone, polycythemia, local release of serotonin, mechanical obstruction by multiple pulmonary emboli, precapillary pulmonary edema, or lung compression (pleural effusion, increased intrathoracic pressure via respirator). Pulmonary vascular resistance may be decreased by oxygen, adenosine, isoproterenol, alpha antagonists such as phentolamine or tolazoline, inhaled nitric oxide, prostacyclin infusions, and high doses of calcium channel blockers. These vasodilators may be used to test for fixed, irreversible pulmonary hypertension. A practical approach used in many laboratories to test for responsiveness and determine therapeutic dosage, uses intravenous epoprostenol (Flolan, Glaxo Wellcome, Research Triangle Park, NC), starting at 2 ng/kg/min and increasing by increments of 2 ng/kg/min every 15 minutes until dose-limiting pharmacologic effects (such as nausea, headache, or hypotension) are seen.

The tolazoline test for fixed pulmonary hypertension is rarely performed at present, and the interested reader is referred to earlier editions of this textbook for details as to its use. Oxygen inhalation may be of value in assessing pulmonary vascular reactivity. Patients with high pulmonary vascular resistance (i.e., greater than or equal to 600 dynes-sec-cm⁻⁵) in association with a central shunt (e.g., ventricular septal defect) should be given 100% oxygen by face mask before concluding that the changes are fixed. Older patients with a combination of left heart failure and chronic obstructive lung disease may have considerable pulmonary vasoconstriction due to alveolar hypoventilation and its resultant hypoxia. Inhalation of 100% oxygen in such cases may result in a dramatic fall in pulmonary arterial pressure and vascular resistance.

Most studies demonstrating the usefulness of tolazoline or oxygen inhalation in the assessment of pulmonary vascular disease associated with central shunts were carried out in patients living at high altitudes. The usefulness of such assessment in patients living at sea level is less certain.

Pulmonary Vascular Disease in Patients with Congenital Central Shunts

The decision as to whether a patient with congenital heart disease would profit from corrective surgery often hinges on the calculated pulmonary vascular resistance. Although each case must be evaluated on its own characteristics, many criteria for operability have been proposed (37), (38). It has been suggested that the ratio between pulmonary vascular resistance and systemic vascular resistance (resistance ratio, PVR/SVR) be used as a criterion for operability in dealing with congenital heart disease (37). Normally, this ratio is less than or equal to 0.25. Values of 0.25 to 0.50 indicate moderate pulmonary vascular disease, and values greater than 0.75 indicate severe pulmonary vascular disease. When the PVR/SVR resistance ratio equals 1.0 or more, surgical correction of the congenital defect is considered contraindicated because of the severity of the pulmonary vascular disease.

The resistance ratio has the value of factoring in miscellaneous neural, hormonal, and blood viscosity influences that may be affecting both pulmonary and systemic vascular beds and that may be primarily related to the patient’s immediate clinical status more than to intrinsic pulmonary vascular changes. Many patients with left ventricular
failure and low systemic output (from any cause) have associated high systemic and pulmonary vascular resistance, but the resistance ratio will be normal in the absence of intrinsic vascular pathology.

We have reported (37) three patients with congenital heart disease (two with atrial septal defect and one with patent ductus arteriosus) having cyanosis and pulmonary arterial hypertension at nearly systemic levels. Each of our patients (37) had PVR/SVR ratios of less than 0.50 and net left-to-right shunts, despite severe pulmonary hypertension (e.g., pulmonary artery pressure 110/55 mm Hg). Each patient had progressive improvement in pulmonary vascular resistance toward normal following operative closure of the shunts. These cases illustrate the importance of increased blood viscosity associated with the polycythemia of cyanosis (hematocrits in the 56% to 66% range), which may contribute substantially to the measured increase in pulmonary and systemic vascular resistances. As mentioned earlier, studies in dogs showed that calculated pulmonary vascular resistance doubled when hematocrit was raised from 43% to 64%. Accordingly, elimination of severe cyanosis with return of hematocrit to normal may lead to a 50% reduction in pulmonary vascular resistance. This influence of viscosity, as well as the generalized vasoconstriction often seen in patients with advanced cardiac disease, will be factored out by the ratio of PVR/SVR.

In his classic description of the Eisenmenger syndrome, Wood pointed out that attempted surgical repair of the shunt defect was a major source of death in these patients (38). He stated that in patients with pulmonary blood flow of less than 1.75 times systemic flow or with total pulmonary vascular resistance greater than 12 Wood or “hybrid” units (960 dynes-sec-cm⁻²), ordinary surgical repair of the defect should not be attempted. Others have suggested similar criteria for special instances or conditions. In my opinion, surgical repair should be limited to patients in whom the net shunt is left-to-right and the pulmonary vascular resistance is less than systemic vascular resistance, preferably with a resistance ratio of less than 0.50.

**Pulmonary Vascular Disease in Patients with Mitral Stenosis**

Marked elevations in pulmonary vascular resistance may also be seen in acquired heart disease, notably in mitral stenosis. The effect of mitral valve replacement in patients with mitral stenosis and/or regurgitation associated with pulmonary hypertension has been evaluated (39),(40). Most patients experience significant reduction in pulmonary vascular resistance following successful repair of the mitral valve lesion. Although some degree of pulmonary hypertension may persist postoperatively, significant palliative benefit usually occurs, and the decision regarding surgery must be made in light of information regarding left and right ventricular function as well as the degree of pulmonary hypertension.

Currently, percutaneous balloon mitral valvuloplasty is used widely as an alternative to surgery for treating patients with advanced mitral stenosis. The procedure results in an immediate improvement in mitral valve area and in pulmonary hypertension. Its effects on pulmonary vascular resistance have been studied in a cohort of 14 patients with critical mitral stenosis and severe pulmonary hypertension (41). Balloon mitral valvuloplasty resulted in an immediate improvement in mitral valve area (0.7 ± 0.2 cm² to 1.6 ± 0.7 cm², p < .01), mean left atrial pressure (26 ± 6 mm Hg to 15 ± 5 mm Hg, p < .01), mean pulmonary artery pressure (51 ± 17 mm Hg to 40 ± 14 mm Hg), and pulmonary vascular resistance (630 ± 570 dynes-sec-cm⁻² to 447 ± 324 dynes-sec-cm⁻², p < .01). At an average of 7 months follow-up, repeat catheterization showed that pulmonary vascular resistance had declined further and now averaged 280 ± 183 dynes-sec-cm⁻². Of note, two patients who showed substantial restenosis to mitral valve areas of less than 1.0 cm² exhibited a return of pulmonary vascular resistance to prevalvuloplasty values (41). The decline in pulmonary vascular resistance after balloon valvuloplasty is not offset by the bronchopulmonary stresses associated with thoracotomy and general anesthesia, making mitral balloon valvuloplasty appealing as either an alternative to surgery or a preparatory procedure before surgery in patients with mitral stenosis and advanced pulmonary hypertension.

**Assessment of Vasodilator Drugs**

Cardiac catheterization provides an ideal opportunity for assessing the potential response of a patient to a change in medical regimen, particularly with regard to vasodilator drugs. In recent years, vasodilator drugs have assumed a major role in the treatment of patients with congestive heart failure. There is, however, great variability among currently used vasodilator agents, and the relative effects of a particular drug on resistance and capacitance vessels is...
of major importance in predicting its hemodynamic effects (42). This problem may become complex when a particular drug may have different effects, depending on the level of resting tone in resistance and capacitance beds. For example, nitrate preparations are well known to influence venous capacitance; this influence is presumably responsible (at least in part) for the fact that ventricular filling pressures and pulmonary congestion are consistently improved when nitrate therapy is given to patients with congestive heart failure. Despite this consistent effect on preload, the effect of nitrates on forward cardiac output has been variable (43–45), and studies have reported decreases, increases, or mixed effects on cardiac output in normal subjects and in patients with heart failure.

Goldberg and colleagues (46) studied 15 patients with chronic congestive heart failure who were given an oral nitrate (erythrityl tetranitrate) at the time of cardiac catheterization to identify predictors of nitrate effect on cardiac output. There were significant reductions in right atrial, pulmonary capillary wedge, and mean arterial pressure in nearly all patients. Augmentation in cardiac output by >10% occurred in eight patients (thereby defined as “responders”), but no change or decline occurred in seven patients (“nonresponders”). The level of peripheral vasoconstriction, as reflected by resting systemic vascular resistance, was significantly higher for the responders than for the nonresponders (2,602 ± 251 versus 1,744 ± 193 dynes-sec-cm⁻⁵, p < .02). Furthermore, a significant reduction in systemic vascular resistance occurred only in responders, and the decline was a linear function of resting resistance (Fig. 8.6).

**FIG. 8.6.**

The change (Δ) in systemic vascular resistance following administration of erythrityl tetranitrate plotted as a function of resting systemic vascular resistance in 15 patients with congestive heart failure. Patients with the greatest degree of vasoconstriction at rest demonstrated the greatest fall in resistance in response to the nitrate. (From Goldberg et al. Nitrate therapy of heart failure in valvular heart disease. Am J Med 1978;65:161, with permission.)

Thus, although reductions in arterial pressure and left and right ventricular filling pressures are a constant result of nitrate therapy, significant augmentation in forward cardiac output is likely only in patients with the most intense resting peripheral vasoconstriction. The design of a catheterization protocol in a patient with congestive heart failure can include assessment of vasodilator therapy based on these principles. For example, if the resting cardiac output is low and if right and left ventricular filling pressures as well as systemic vascular resistance are high, a long-acting nitrate or a balanced agent (e.g., sodium nitroprusside or an angiotensin-converting enzyme inhibitor) might be expected to be particularly beneficial and can be tested while the catheters are still in place. On the other hand, if the output is low and resistance is high but filling pressures are near normal, a nitrate might not help because the lowered resistance may be offset by the fall of the already normal preload, with the result being no increase in output. In such a patient, a selective lowering of resistance would be desirable, and hydralazine could be tested before removing the catheters. If the cardiac output is low but resistance is normal, neither a nitrate nor a converting enzyme inhibitor is likely to increase output and should be tested only if filling pressures are high and symptoms of congestion are a prominent part of the clinical picture. In such patients, the combination of an inotropic agent and a nitrate may be particularly helpful and could be tested at the time of catheterization. Finally, if the output is low but filling pressures and systemic vascular resistance are normal, vasodilator drugs will probably do more harm than good, and a therapeutic trial of preload elevation (administration of colloid) with or without an inotropic agent could be tested during the catheterization.

These examples are presented merely to illustrate the principle of using cardiac catheterization parameters (i.e., resistances, flows, and filling pressures) to design a therapeutic regimen and then, while the catheters are still in place, put it to the test. We have found this most useful with regard to the patient with heart failure, and cardiac catheterization in such patients should include full right and left heart catheterization with measurement of cardiac output, left and right heart pressures, and systemic and pulmonary vascular resistances.