Evaluation of Myocardial Blood Flow and Metabolism

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Measurement of myocardial blood flow for research studies and in clinical practice has enhanced our understanding of the coronary circulation in health and disease. Despite the refinements in measurement techniques of epicardial coronary anatomy provided by quantitative angiographic techniques and, more recently, by intravascular ultrasound, direct measurement of coronary blood flow provides important additional insights into functional aspects of coronary artery disease. In this chapter, we will review the wide variety of techniques that have been used to evaluate myocardial metabolism and blood flow with a focus on catheter-based methods. Particular emphasis will be placed on intracoronary translesional Doppler flow velocity and pressure measurements as simple and safe techniques for determination of coronary artery blood flow that can be clinically applied in the cardiac catheterization laboratory.

MYOCARDIAL METABOLISM

The myocardium relies almost exclusively on oxidative (aerobic) metabolism for its energy needs. Even at rest, transmyocardial oxygen extraction is already near maximal, with coronary venous oxygen saturation (25% to 35%) being the lowest in the body (1). Any increase in myocardial oxygen demand can thus be met primarily by a proportional increase in myocardial blood flow, chiefly mediated by a reduction in coronary arteriolar resistance. Such adjustments in coronary arteriolar resistance in response to alterations in demand (so-called autoregulation) permit the coronary circulation to maintain appropriate myocardial perfusion in the face of varying coronary perfusion pressure and oxygen demand (2,3).

Regional myocardial blood flow tracks mechanical activity by linkage through metabolic substrates: oxygen, glucose, free fatty acids, lactate, amino acids, and ketones. These substrates are critical for the generation of high-energy phosphates [adenosine triphosphate (ATP) and creatine phosphate] (4–6) that supply the energy requirements of the myocardium. At rest, the rate of force development and the frequency of force generation per unit time account for approximately 60% of myocardial energy utilization; myocardial relaxation accounts for approximately 15% of energy utilization; electrical activity accounts for 3% to 5%; and basal cellular metabolism accounts for the remaining 20% of energy utilization (5) (Fig. 18.1, Table 18.1). As workload increases, myocardial contractile function consumes an even greater fraction of high-energy phosphate availability. Any compromise in substrate availability causes the myocardium to minimize energy expenditure on mechanical work and divert the remaining high-energy substrates for the continued maintenance of cellular integrity.

FIG. 18.1.

Basal metabolism, activation energy, tension-related energy, and energy for external work as components of myocardial oxygen consumption in dogs at various levels of cardiac output. (With permission from Ando H, Nakano E, Ueno Y, Tokunaga K. New techniques for analysis of cardiac energetics using a modified Fenn equation. J Thorac Cardiovasc Surg 1989;97:565.)

Under normal aerobic conditions, several substrates contribute simultaneously to meeting myocardial energy needs: free fatty acid (65%), glucose (15%), lactate and pyruvate (12%), and amino acids (5%) (4–6). Under aerobic conditions, glycolysis plays only a minor role. Lactate is extracted by the myocardium, converted into pyruvate, and oxidized by way of the Krebs cycle (6).
In the fasting state, when serum fatty acids are high, myocardial glucose uptake tends to be suppressed by fatty acid utilization. After an oral glucose load, or when a fall in myocardial blood flow or oxygen supply leads to a reduction or loss in mechanical function, glucose uptake is enhanced and fatty acid oxidation declines (6). While glucose metabolism is initially aerobic, as oxygen availability decreases, high-energy phosphate stores are depleted and ATP breakdown products (adenosine diphosphate, adenosine monophosphate, and other nucleosides) accumulate. The myocardium then turns toward enhancing glycolysis and glycolysis to augment ATP production. In doing so, the pyruvate-lactate equilibrium is shifted toward lactate formation, causing net transmyocardial lactate production rather than extraction. Under extreme conditions, increasing cytosolic lactate and hydrogen ion concentrations lead to inhibition of residual glycolysis and deprives the cell of even anaerobic ATP production, a sequence of biochemical events that may lead to complete cessation of energy production with irreversible cellular injury.

REGULATION OF CORONARY BLOOD FLOW IN HUMANS

Coronary blood flow is regulated primarily by the need to keep myocardial oxygen supply in balance with variations in oxygen demand resulting from changes in myocardial work. In the setting of constant aortic pressure, changes in coronary blood flow are modulated by coronary vascular resistance (CVR = coronary pressure/flow). Coronary vascular resistance, in turn, may be considered as the sum of three distinct resistance components (3): \( R_1 \) resides in the large epicardial coronary conduit vessels that function primarily as vascular capacitors and contribute minimally to total coronary vascular resistance in the absence of fixed or dynamic epicardial obstructions; \( R_2 \) resides in the precapillary arterioles and is the major component of coronary vascular resistance; and \( R_3 \) resides in the intramural coronary capillary vessels, where resistance increases markedly during systole due to mechanical compression during ventricular contraction. This phasic variation in \( R_3 \) explains the diastolic predominance of coronary blood flow.

**FIG. 18.2.**

Primary and secondary coronary vasomotion as determined by the simultaneous measurement of coronary blood flow (FLOW) and coronary venous oxygen saturation (CSO₂ SAT). Primary vasodilation causes a rise in flow at constant myocardial oxygen consumption (MVO₂), resulting in lower transmyocardial oxygen extraction. In contrast, in secondary coronary vasodilation, an increase in myocardial oxygen consumption obliges a secondary rise in coronary blood flow with either constant or reduced coronary sinus oxygen saturation. (With permission from Baim DS, Rothman MT, Harrison DC. Simultaneous measurement of coronary venous blood flow and oxygen saturation during transient alterations in myocardial oxygen supply and demand. *Am J Cardiol* 1982;49:743.)

**FIG. 8.3.** Mean coronary flow before, during, and after coronary occlusion. Arrow indicates the release of occlusion. Area A represents the flow debt and area B its repayment. (With permission from Gould KL. *Coronary artery stenosis.* New York: Elsevier, 1991:13.)

Changes in epicardial (\( R_1 \)) and arteriolar (\( R_2 \)) coronary resistances during physiologic or pharmacologic stimuli can be considered either primary or secondary vasomotor events (Fig. 18.2). Primary vasodilation signifies an alteration in myocardial vessel tone and perfusion with no preceding change in myocardial oxygen demand. Secondary vasodilation refers to changes in vessel tone and blood flow that occurs in response to alterations in myocardial oxygen consumption (7).

Coronary vasodilator reserve (also known as flow reserve) is the ability of a coronary vascular bed to increase coronary blood flow in response to stimuli that produce a maximal or near maximal hyperemic response. Such stimuli include the reactive hyperemia that follows transient coronary occlusion or the administration of various pharmacologic agents (8) (Fig. 18.3). Coronary flow reserve is expressed as the ratio of maximal hyperemic flow to resting coronary flow-a ratio that averages 4 to 7 in experimental animals and 2 to 5 in man (8),(9). In experimental animal studies, increasing conduit stenosis (\( R_1 \)) produces a predictable decline in coronary flow reserve, beginning at about a 60% artery diameter narrowing. At diameter stenoses of more than 80% to 90%, all available coronary reserve has been exhausted and resting flow begins to decline (10–12). This relationship between increasing stenosis...
severity and reduced available flow reserve has been used to assess the effective physiologic severity of any given coronary lesion and forms the basis of many noninvasive test modalities for ischemia. For individual patients, however, this relationship has been less predictable, given complex three-dimensional anatomy, imprecise correlation between angiographic estimate of diameter stenosis reduction and true lumen cross-sectional area, and thus the uncertain hemodynamic significance of a given lesion. In addition, flow measured in regions proximal to a stenosis in branching systems may not reflect poststenotic flow responses.

Because coronary reserve flow represents a ratio of maximal over basal flow, the level of basal coronary flow also has an important effect on the reserve value (Fig. 18.4) (13). Increases in resting flow will lower the apparent reserve ratio in the absence of any other alterations. When using Doppler flow techniques, poststenotic flow reserve may differ from proximally measured flow reserve, depending on the contribution of prestenotic branch vessel distribution relative to the stenosis.

**FIG. 18.4.**

Resting and maximally vasodilated coronary pressure–flow relationships. Coronary flow reserve, the ratio of maximally vasodilated over resting flow, can be seen to be a complex function of the actual position of the maximally vasodilated and resting flow curves. (With permission from Klocke FJ. Measurements of coronary flow reserve: defining pathophysiology versus making decisions about patient care. *Circulation* 1987;76:1183.)

**MEASUREMENT OF MYOCARDIAL METABOLISM**

Measurement of myocardial metabolism may be performed noninvasively (i.e., positron emission tomography scanning) or invasively by transmyocardial sampling techniques that involve acquisition of simultaneous arterial and coronary venous (i.e., coronary sinus) blood. Specialized blood products commonly used in the determination of changes in myocardial metabolism include serum pyruvate, lactate, oxygen content, and other metabolic or hematologic blood components. The transmyocardial extraction of pharmaceutical agents after systemic or intracoronary delivery can also be determined by the transmyocardial sampling technique. In studies involving ischemic myocardial metabolism, the most commonly measured products are lactate and oxygen. Specialized chilled collection tubes containing an agent (perchloric acid) to stop red cell metabolism and prevent clotting are prepared. Samples should be obtained in pairs and serial containers labeled in advance of the procedure. Measurement assays need to be geared to measuring small differences in “normal” lactate levels across the myocardium. Clinical laboratory tests geared to measuring high lactate levels in lactate acidosis are unsuitable for transmyocardial measurements. Myocardial catecholamines (norepinephrine, epinephrine) and other mediator products, such as prostaglandins, can be measured if sample tubes are placed immediately in ice to prevent platelet activation on withdrawal through a long, narrow catheter lumen. Large-bore (6F) heparin-coated catheters may be required to assess platelet products. In the setup of any measurement system for myocardial metabolism, advanced preparation of the sampling tubes should be made so that the operators can quickly draw and pass the blood to the technicians for insertion into the collection tubes. Additional equipment beyond the specific sample tubes may be needed, such as an iced bath, a centrifuge (in the laboratory), or a series of dilutional tubes. Although the techniques are not complicated, advanced preparation with correct labeling and anticipation of the tubes required during the various maneuvers in the laboratory will facilitate studies of myocardial metabolism without error or unnecessary prolongation of the study.

**METHODS OF MEASURING BLOOD FLOW: INDIRECT AND NONINVASIVE TECHNIQUES**

Several historically important techniques, including radionuclide clearance techniques and myocardial and coronary videodensitometry, have been described in detail in previous editions of this textbook. Other noninvasive diagnostic techniques such as positron emission tomography and magnetic resonance imaging play an increasingly important role in the determination of myocardial blood flow and function in clinical practice. The focus of this textbook lies in catheter-based methodologies that are reviewed in the following paragraphs.
ANGIOGRAPHIC ASSESSMENT OF CORONARY FLOW

Since its introduction by the Thrombolysis in Myocardial Infarction (TIMI) investigators in 1985 (14), a simple, qualitative grading of coronary flow (grade 0 through 3) to assess the efficiency of reperfusion therapy has become a standard in assessing coronary obstruction and restoration of flow in clinical trials. The reproducible angiographic quantification of coronary artery flow by TIMI grade is now widely accepted as a standard in the angiographic grading of coronary blood flow (15),(16) and TIMI grade 3 flow has been associated with improved outcome (17–19).

According to the TIMI description (14),(20), when assessing TIMI flow, cardiac catheterization should be performed using 6F or 7F diagnostic catheters. Cineangiograms should be filmed at 30 frames per second following administration of sublingual or intravenous nitroglycerin and thus can be incorporated very easily in the routine catheterization. Care should be taken to film vessel filling and emptying completely with careful panning.

The TIMI group defined the observed flow grades as follows: TIMI flow grade 0 represents no perfusion: There is no antegrade flow beyond the obstruction in an occluded artery. TIMI flow grade 1 represents penetration without perfusion: Contrast material passes beyond the area of obstruction but fails to opacify the entire coronary bed distal to the obstruction for the duration of the angiographic panning. TIMI flow grade 2 represents partial perfusion: Contrast material passes across the obstruction and opacifies the coronary artery distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed, or both, is perceptibly slower than the flow into or rate of clearance from comparable areas not perfused by the previously occluded or infarct-related vessel (e.g., opposite coronary artery or the coronary bed proximal to the obstruction). TIMI flow grade 3 represents complete perfusion: Antegrade flow into the bed distal to the obstruction, and clearance of contrast material from the involved bed is as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery.

By nature, TIMI flow grading is qualitative rather than quantitative, and differences in TIMI flow grading by investigators and angiographic core laboratories have been reported (20). Anatomic differences between coronary arteries and global (multivessel) reduction in coronary flow after myocardial infarction contribute further to heterogeneity of coronary flow grading (20),(21). Even a patent vessel with TIMI grade 3 flow may not be able to identify “normal” flow after myocardial infarction (20). The range of velocities that constitute TIMI flow grade 3 is wide (22) and velocities are frequently abnormal in both culprit and nonculprit arteries following myocardial infarction.

TIMI Frame Count

To overcome limitations of the initial TIMI classification, Gibson et al. introduced a quantitative and continuous measure, the TIMI frame count (20). The TIMI frame count is a standardized assessment of coronary flow using a simple continuous index: the number of cineframes required for contrast material to first reach standard distal coronary landmarks in the infarct-related artery. The first frame used for TIMI frame counting is the first frame in which dye fully spans the artery's takeoff. This occurs when three criteria are met: (a) a column of nearly full or fully concentrated dye must extend across the entire width of the origin of the artery; (b) dye must touch both borders of the origin of the artery; and (c) there must be antegrade motion of the dye (Fig. 18.5). If the left anterior descending coronary artery is subselectively engaged and the left circumflex coronary artery is the culprit vessel, the TIMI frame count begins when dye first touches both borders at the origin of the left circumflex coronary artery. The same rule holds for subselective engagement of the left circumflex artery. The last frame is counted or included as one of the frames and is defined as the frame when dye first enters the distal landmark branch. Full opacification of the distal branch is not required. Often the last frame is best determined by running the cinefilm past the initial opacification of the end point branch and then moving frame by frame in reverse until the end point branch disappears. Care must be taken to advance one frame forward once the dye disappears to identify the frame in which dye first appears. The following distal landmark branches are used for analysis: the distal bifurcation of the left anterior descending coronary artery (i.e. the “mustache,” “pitchfork,” or “whale's tail”; Fig. 18.6, top); in the circumflex system, the distal bifurcation of the segment with the longest total distance that includes the culprit lesion (Fig. 18.6, middle); and in the right coronary artery, the first branch of the posterolateral artery (Fig. 18.6, bottom).
Proper panning is essential for counting the number of cineframes required to first opacify the distal artery, particularly with the left anterior descending. The TIMI frame count of the left anterior descending and circumflex arteries often is assessed best in either the right or left anterior oblique views with caudal angulation, and the right coronary artery often is assessed best in the left anterior oblique projection with steep cranial angulation. Because of the frame rate variations in catheterization laboratories, frame counts need to be adjusted to 30 frames per second.

**FIG. 18.5.**

Definitions of the first and last frames used for TIMI frame counting. The first frame used for TIMI frame counting is the first frame in which dye fully enters the artery. This occurs when three criteria are met: (a) A column of nearly full or fully concentrated dye must extend across the entire width of the origin of the artery; (b) dye must touch both borders of the origin of the artery; and (c) there must be antegrade motion of the dye. Dye may initially track down a single wall of the artery as it leaks from catheter before the injection, and these frames are not included in the TIMI frame count. (With permission from Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. *Circulation* 1996;93:879.)

**FIG. 18.6.**

**Top:** Anatomic landmarks used for TIMI frame counting in the left anterior descending coronary artery. The distal-most branch in the left anterior descending coronary artery (referred to as the “pitchfork,” “mustache,” or “whale's tail”) usually occurs at the apex of the heart. In a wraparound left anterior descending coronary artery, the branch closest to the apex of the heart is used. **Middle:** Anatomic landmarks used for TIMI frame counting in the left circumflex coronary artery. The branch of the left circumflex coronary artery used for TIMI frame counting is determined as follows: The artery used for TIMI frame counting is the artery with the longest total distance along which dye travels in the left circumflex coronary artery system and yet passes through the culprit lesion. When the culprit lesion is proximal to two arteries with equal total dye path distances, the artery that arises more distally from the left circumflex coronary artery is used. For example, when the culprit lesion is located in the proximal left circumflex coronary artery, the marginal branch with the longest total dye path distance is used, regardless of whether it is the first, second, or third marginal branch. If these second and third marginals have equal total dye path distances, the third marginal branch is the target artery. The target artery is always the first marginal branch when the culprit lesion is in the first marginal and, likewise, always the second marginal branch when the culprit lesion is in the second marginal. In left and balanced dominant systems, the target artery is no further distal than the marginal branch that lies at the border of the inferior and lateral walls, usually the third or fourth marginal. The anatomic end point is the distal-most branch in the target artery. Usually, this end point branch can be found at approximately the midpoint of the distal third of the artery (five-sixths of the distance down the vessel from its origin), but occasionally it is located just before the termination of the artery. **Bottom:** Anatomic landmarks used for TIMI frame counting in the RCA. The distal landmark is the first branch arising from the posterior lateral extension of the RCA after the origin of the posterior descending (PD) artery, regardless of the size of this branch. As shown, this branch will often be located just distal to the bifurcation and may be oriented either superiorly (RU) or inferiorly (RL). In some cases, this branch will lie further along the extension of the distal RCA and either will course superiorly as the AV nodal artery (AV) or will be oriented inferiorly as the right inferior branch (RI). In the event that a very proximal posterior descending stenosis is the culprit lesion, the first branch off the posterior descending artery after the stenosis is the end point. Infrequently, the distal portion of the posterior descending artery is supplied by a proximally arising acute marginal branch, and the proximal portion of the posterior descending artery arises at the base of the heart. In these cases, it is the extension of the distal RCA past the posterior descending artery at the base of the heart and not the proximal acute marginal branch that is used for determining the TIMI frame count. In patients with left dominant anatomy, the TIMI frame count end point is the distal-most branch of the RCA once it is no longer in the atrioventricular groove. (Modified with permission from Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. *Circulation* 1996;93:879.)

**The Corrected TIMI Frame Count (CTFC) for the Left Anterior Descending Coronary Artery**
The initial experience with the TIMI frame count demonstrated that the length of the left anterior descending coronary artery influences the observed frame count. The TIMI frame count in the left anterior descending coronary artery requires recalculation before comparing flow in the three major coronary conduits and is called the corrected TIMI frame count. Anatomically, the left anterior descending is the longest of the three coronary conduits. The approximate distance to the TIMI landmark in the average human left anterior descending coronary artery is 14.7 cm; in the right coronary artery, 9.8 cm; and in the left circumflex coronary artery, 9.3 cm (20). The corrected TIMI frame count (CTFC) accounts for the longer distance dye has to travel to opacify the left anterior descending coronary artery. The frame rate required for full opacification of the distal end point of the left anterior descending is 1.7 times longer when compared with the right coronary artery and the left circumflex coronary artery. The CTFC divides the absolute frame count in the left anterior descending coronary artery by 1.7 to standardize the distance dye and has to travel in all three coronary conduits. TIMI frame count and CTFC reference values are shown in Table 18.2.

FIG. 18.7.

Method of measuring the distance from coronary ostium to the distal TIMI frame count landmark using the guidewire pullback technique. A standard guidewire is positioned with its tip at the TIMI landmark. A Kelly clamp (no. 1) is placed on the guidewire where it exits the Y-adapter. The wire is then withdrawn to the guiding catheter tip. A second Kelly clamp (no. 2) is then placed on the wire. The distance between the two clamps represents the distance from the guiding catheter tip to the coronary landmark. (With permission from Gibson CM, Dodge JT Jr, Goel M, et al. Angioplasty guidewire velocity: a new simple method to calculate absolute coronary blood velocity and flow. Am J Cardiol 1997;80:1536.)

Angioplasty Guidewire Velocity

A new method recently proposed to measure absolute coronary velocity and absolute flow uses TIMI frame counting and a guidewire-derived measure of intravascular distance between ostium and TIMI landmark (23) (Fig. 18.7). Velocity is then calculated using the following formula:

\[
\text{Velocity (cm/sec)} = \frac{\text{Distance separating Kelly clamps (cm)}}{\left(\frac{\text{frame count}}{\text{frames per second}}\right)(\text{sec})}
\]

The angioplasty guidewire velocity may prove useful as a measure of coronary flow. When compared with the CTFC, it may be superior because it takes into account variability in artery length from patient to patient. Usefulness and applicability in clinical practice remain to be evaluated.

Limitations and Practical Use of the TIMI Flow and TIMI Frame Count

Gibson et al. (20) and Kern et al. (22) suggested that visual estimates of TIMI flow in the usual clinical setting bear little relationship to the more precise TIMI frame count or Doppler flow measurements, and that even noninfarct-related coronary arteries show prolonged flow when compared with normal values. Most likely, prolonged TIMI frame counts are associated with microvascular dysfunction (21), even in the presence of an open artery. Gibson et al. (24) further investigated the predictive value of CTFC on clinical outcome in patients undergoing thrombolytic therapy in the TIMI 4, 10A, and 10B trials. They found that a CTFC of less than 20 frames per second (or brisk flow) was associated with a low risk for adverse outcomes, both for in- and out-of-hospital events (24). This was particularly true for a subgroup of patients with hyperemic flows of less than 14 frames per second. CTFCs of greater than 20 but less than 40 frames per second (the cutoff value for TIMI grade 3 flow) showed a higher risk for adverse outcome (24). Prolonged CTFCs 4 weeks after myocardial infarction appear to be associated with impaired infarct-artery-related flow at 1 year (25) and may give insight into why complete reperfusion by invasive strategies does not uniformly translate into better outcome.
Technique can also impact on the rate of angiographic opacification. For example, the rate of contrast injections can cause variations in CTFCs. Dodge et al. (26) investigated the impact of injection rate on the CTFC. Using standard 7F diagnostic catheters, they found that a mean increase of 1.0 mL/sec of standard hand injections (10th to 90th percentile of left coronary injections: 1.5 to 2.5 mL/sec; right coronary injections: 1.1 to 2.1 mL/sec) induced a decrease of two frames in the CTFC.

In summary, TIMI frame counting is a simple, reproducible method for the assessment of coronary flow that is applicable in virtually every patient and catheterization laboratory. TIMI frame counting provides additional valuable information related to treatment success and clinical outcome.

**CATHETER TECHNIQUES FOR MEASUREMENT OF CORONARY BLOOD FLOW**

**Coronary Sinus Thermodilution and Oximetry**

The measurement of coronary venous flow is inexpensive and can be performed with only right heart cardiac catheterization. Unlike coronary arterial flow, however, coronary venous flow occurs predominantly during systole. Approximately two-thirds of left anterior descending coronary artery flow drains into the great cardiac vein, the continuation of the anterior intraventricular vein as it reaches the atrioventricular groove. The great cardiac vein then becomes the coronary sinus, at the point marked by the valve of Vieuxsens and the oblique vein of Marshall (a left atrial venous remnant of the embryonic left-sided superior vena cava). The remaining portion of left anterior descending venous drainage enters the coronary sinus along with blood from the circumflex territory, by way of the left marginal vein and circumflex venous branches. Great cardiac vein flow thus represents primarily left anterior descending venous outflow, whereas coronary sinus flow represents a mixture of both left anterior descending and left circumflex coronary artery outflow, accounting for 80% to 85% of total left coronary outflow drained by this route (27,28).

Measurement of coronary venous flow is based on the principle of thermodilution, with the principle that the heat loss by blood equals the heat gained by a cold indicator solution (Fig. 18.8). Room temperature fluid (5% dextrose or normal saline) is injected upstream in the coronary sinus for 20 to 30 seconds at a rate of 35 to 55 mL/min (using a 200-mL Harvard pump or angiographic power injector to ensure turbulent mixing with venous blood). Coronary venous flow is then computed according to the following formula (28,29):

\[
Q = F \times C \times (T_m - T_I)/(T_b - T_m)
\]

where \( Q \) is coronary venous flow, \( F \) is the rate of injection of the thermodilution indicator, \( C \) is the ratio of the specific heats of blood and the injectate (equaling 1.08 for 5% dextrose and 1.19 for normal saline), and \( T_m, T_I, \) and \( T_b \) are the temperatures of the mixture, the injectate, and blood, respectively.

**FIG. 18.8.**

Schematic diagram of the thermodilution technique. The thermal indicator (injectate) at temperature \( T_I \) is infused at fixed rate, typically 50 mL/min. The ensuing turbulence causes mixing of the injectate with coronary venous blood at temperature \( T_B \), resulting in a mixture at temperature \( T_M \). The temperatures monitored by the catheter tip (\( T_B \) and \( T_M \)) and injectate (\( T_I \)) thermistors are recorded continuously on a uniform temperature scale. Because the heat lost by blood is gained by the injectate, coronary venous flow can be calculated using the respective measured temperatures, the rate of indicator injection, and a constant derived from the specific heats of blood and injectate. (With permission from Bradley BA, Baim DS. Measurement of coronary blood flow in man: methods and implication for clinical practice. *Cardiovasc Clin* 1985;15:67.)
Coronary venous oximetry, thermodilution flow, and combined flow oximetry catheters (top to bottom). The flow and flow oximetry catheters have the following features in common: two lumina for indicator injection or sampling at the great cardiac vein (see inset) and coronary sinus sites and two great cardiac vein ($T_{GCV}$) and coronary sinus ($T_S$) thermistors for regional flow determinations. The flow catheter additionally has two pacing electrodes. The oximetry and flow oximetry catheters have fiberoptic bundles for the continuous measurement of great cardiac vein oxygen saturation and permits on-line determination of regional myocardial oxygen consumption ($\text{MVO}_2$) (7):

\[
\text{MVO}_2 = Q \times (A_{O_2} - CS_{O_2})
\]

where $Q$ equals coronary venous flow, $A_{O_2}$ is arterial, and $CS_{O_2}$ is coronary sinus oxygen contents, respectively.

**FIG. 18.9.**

Coronary venous oximetry, thermodilution flow, and combined flow oximetry catheters (top to bottom). The flow and flow oximetry catheters have the following features in common: two lumina for indicator injection or sampling at the great cardiac vein (see inset) and coronary sinus sites and two great cardiac vein ($T_{GCV}$) and coronary sinus ($T_S$) thermistors for regional flow determinations. The flow catheter additionally has two pacing electrodes. The oximetry and flow oximetry catheters have fiberoptic bundles for the continuous measurement of great cardiac vein oxygen saturation. (With permission from Baim DS, Rothman MT, Harrison DC. Simultaneous measurement of coronary venous flow and oxygen saturation during transient alterations in myocardial oxygen supply and demand. *Am J Cardiol* 1982;49:743.)

The coronary sinus is located posteriorly and slightly caudal to the tricuspid annulus. Coronary sinus cannulation has traditionally been performed from a left brachial approach because a catheter with a single curve easily enters the ostium of the coronary sinus from the left arm in the majority of patients. Although a right brachial or femoral venous approach is feasible using a reverse loop technique in which the catheter is rotated so that its tip lies posterior to its shaft in the right anterior oblique projection, the easiest approach to the coronary sinus is via the right internal jugular vein. With this approach, the catheter tip is initially pointed laterally toward the right atrial border. The catheter is then rotated counterclockwise and advanced slightly until it just enters the right ventricle (detected by pressure waves or premature ventricular contractions). After slight additional counterclockwise rotation, the catheter is withdrawn slowly until an atrial pressure tracing is restored. Gentle readvancement of the catheter from this position leads to cannulation of the coronary sinus. Should the right ventricle be reentered, the same maneuver is repeated with accentuation of counterclockwise rotation.

Successful coronary sinus entry is confirmed by the maintenance of a right atrial pressure waveform as the catheter is smoothly advanced across the plane of the tricuspid valve. During catheter advancement, catheter resistance suggests impingement on venous branches or the valve of Vieuvesens. If slight catheter repositioning fails to correct the situation, the anatomic obstacle can usually be crossed with a 0.018-inch soft-tipped angioplasty guidewire, allowing advancement of the catheter over this wire to reach the desired sampling site in the great cardiac vein. The coronary sinus is a thin-walled venous structure that can be easily perforated with the application of force. Care should be taken to ascertain correct intravascular position before catheter manipulation.

Reproducible coronary sinus or venous flow measurements require a stable catheter position to avoid variable inclusion of blood entering from venous tributaries adjacent to the temperature thermistor. The proximal (coronary sinus) thermistor needs to be positioned at least 2 to 3 cm from the sinus ostium to avoid reflux of right atrial blood contaminating the coronary sinus temperature profile. Typically, the most stable position for the catheter tip is near the point where the anterior interventricular vein meets the great cardiac vein. This position also provides a selective measurement of left anterior descending coronary artery territory outflow (Fig. 18.10).
Schematic diagram of the cannulated coronary venous system in relation to the coronary artery anatomy: diagonal vein (DV), anterior interventricular vein (AIV), marginal vein (MV), oblique vein of Marshall (OVM), posterior interventricular vein (PIV), and the right, left anterior descending, and circumflex coronary arteries (RCA, LAD, CX, respectively). (With permission from Baim DS, Rothman MT, Harrison DC. Simultaneous measurement of coronary venous flow and oxygen saturation during transient alterations in myocardial oxygen supply and demand. Am J Cardiol 1982;49:743.)

Coronary venous flow measurements are easy to perform, are inexpensive, and can be done at low risk to the patient. The approach allows insights into regional (left anterior descending) myocardial flow and metabolic changes. Serial measurements can be performed to detect transient changes in flow and oxygen extraction. The technique, however, has several limitations. It does not allow assessment of phasic or very rapid changes in coronary flow. Transmural myocardial perfusion also cannot be assessed. Regionality of flow measurements is confined to the left anterior descending territory. The technique is extremely sensitive to alterations in catheter position and is insufficiently validated for flow measurements in severe coronary artery disease. Coronary venous flow data tend to significantly underestimate coronary flow reserve. Rarely, coronary sinus thrombosis has been reported to occur as a result of right atrial and coronary sinus instrumentation, particularly in the setting of heart failure.

**Coronary Arterial Flow: Doppler Guidewire Techniques**

The change in sound frequency as a transmitter moves to or away from a receiver is called the Doppler effect (Christian Johann Doppler, 1803 to 1853). The change in frequency is related to the transmitter's velocity. In practice, a piezoelectric crystal that both emits and receives high-frequency sounds can be mounted on the tip of an intravascular catheter to measure the velocity of red blood cells flowing through an artery (Fig. 18.11). Coronary flow velocity is calculated from the difference between the transmitted and returning frequency (call the Doppler frequency shift), using the following equation:

\[
\text{Velocity} = \frac{(f_o - f_d)(C)}{(2F_0)(\cos \phi)}
\]

where \( V \) is the velocity of blood flow, \( f_o \) is the transmitting (transducer) frequency, \( f_d \) is the returning frequency, \( C \) is a constant (speed of sound in blood), and \( \phi \) is the angle of incidence, respectively.

**FIG. 18.11.**

Diagram of the Doppler concept. High-frequency ultrasound \((f_o)\) is emitted from the Doppler crystal and is reflected off the moving red cell at frequency \(f_d\). The difference between these two frequencies is termed the Doppler shift and is directly related to the velocity of red cells moving. (With permission from Kern MJ, Aguirre FV, Bach RG, Caraccio EA, Donohue TJ, Labovitz AJ. Fundamentals of translesional pressure-flow velocity measurements. Cathet Cardiovasc Diagn 1994;31:137.)

When the transducer beam is nearly parallel to blood flow and \( \phi \) is zero \((\cos \phi = 1)\), velocity can be measured optimally with changes in blood flow velocity reflected by changes in the Doppler frequency shift. Intracoronary Doppler has several advantages for the assessment of coronary blood flow. It measures red blood cell velocity directly so that indicator-dilution markers are not required. Volumetric blood flow can be calculated as the product of angiographically measured vessel cross-sectional area and mean flow velocity with a correction factor for parabolic
flow profile across the vessel. When the vessel cross-sectional area remains constant, however, changes in Doppler
coronary flow velocities can be used to represent changes in absolute coronary flow. Technical advances using
spectral signal analysis and guidewire-mounted Doppler crystals have improved the reliability and safety of
intracoronary blood flow velocity measurements.

### Intracoronary Doppler Guidewire

The advent of a Doppler-tipped guidewire (FloWire, Endosonics, Rancho Cordova, CA) has overcome the limitations
of catheter-based determination of intracoronary Doppler velocity measurements. The flowire is an 0.014- to 0.018-
inch diameter, 175-cm-long, flexible and steerable guidewire with a 12- to 15-MHz piezoelectric ultrasound
transducer integrated onto the tip (Fig. 18.12). The forward-directed ultrasound beam diverges at 27° from the
Doppler transducer so that the Doppler sample volume is approximately 0.65 mm thick by 2.25 mm in diameter
when range-gated to 5.2 mm beyond the transducer (31). The signal transmitted from the piezoelectric transducer is
processed from the quadrature Doppler audio signal by real-time spectral analyzer using on-line fast Fourier
transformation providing a scrolling gray scale spectral display (Fig. 18.13).

**FIG. 18.12.**

Diagram of coronary Doppler flowwire placed in the proximal segment of a coronary artery through a diagnostic
catheter. The 12-MHz transducer has a sample volume located approximately 5.2 mm from the tip with a beam
spread of 27°. The angle of incidence (theta) is less than 17°. Magnitude and direction of flow are easily determined
blood flow velocity dynamics in angiographically normal and stenosed arteries before and after endolumen

**FIG. 18.13.**

Comparison of coronary spectral flow velocity by two Doppler techniques. **Top:** Flow velocity spectra in a normal
coronary artery using the intracoronary Doppler guidewire. **Bottom:** Flow velocity in the left anterior descending
artery obtained with transesophageal echocardiography. Note the similarities of phasic pattern, although the direction
of flow is inverted for the transesophageal Doppler signal. Scale for top panel: 0 to 160 cm/sec. Scale for bottom
panel: 20 cm/division. Peak flow velocity for both signals is approximately 50 cm/sec.

Poststenotic regional flow velocity can be accurately recorded. Since the Doppler guidewire has a minimal cross-
sectional area of 0.164 mm², it tends to be nonobstructive within any but the tightest coronary lesion and to create
less disturbance of the flow profile distal to its tip, even when placed within small coronary arteries. The physical
properties of the Doppler guidewire are designed for crossing intracoronary arterial obstructions and maintaining a
stable position in the distal coronary artery during coronary angioplasty and other interventional procedures. Easily
recognized phasic coronary flow velocity measurements are readily incorporated into a typical angioplasty procedure
without adding new or unnecessary complex technical maneuvers.

The Doppler guidewire has been validated during intravascular measurements of coronary arterial flow velocity by
Doucette et al. (31), who found an excellent correlation ($r^2 = 0.936$) between Doppler spectral flow velocity using
the guidewire and electromagnetic flow probes in proximal coronary arteries in dogs. The Doppler guidewire
accurately measures phasic flow velocity patterns and linearly tracks changes in flow rates in small, predominantly
straight coronary arteries.

Setting up of the guidewire system usually takes less than 10 minutes. It is easily incorporated into routine
angioplasty procedures and provides additional physiologic information on lesion severity and responses to balloon
occlusions; it also monitors flow in the postprocedural period without the need for frequent contrast injections.

### Measurement of Translesional Velocity

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Complete assessment of an epicardial stenosis utilizing arterial flow velocity requires access to both proximal and poststenotic flow velocity data. After diagnostic angiography and before angioplasty, the Doppler guidewire is passed through a standard angioplasty Y-connector attached to either an angiographic or guiding catheter. The flowwire is then advanced into the target artery. Baseline flow velocity data are obtained at least 1 cm proximal to the target lesion. The flowwire is then advanced distally by a distance equivalent to approximately five to ten times the arterial diameter (2 cm) beyond the stenosis. Placement in any side branch is avoided. Distal flow velocity data are then obtained in a similar manner. If the ratio of proximal-to-distal flow velocity integral is more than 1.7:1, the stenosis is significant (see later discussion).

**Pharmacologic Agents Used to Induce Maximal Hyperemia**

Stenosis severity can be assessed more accurately using flow measurements during maximal hyperemia. Widely used vasodilator agents are dipyridamole, papaverine, and adenosine. The hyperosmolar ionic and low-osmolar nonionic contrast media have also been used, but they do not produce maximal vasodilatation. On the other hand, maximal hyperemia can be obtained by intracoronary injections of adenosine (8 to 18 µg in the right coronary artery and 12 to 18 µg in the left coronary artery), or papaverine (10 to 12 mg). Papaverine (8 to 12 mg) produced a response equal to that of an intravenous infusion of dipyridamole in a dose of 0.56 to 0.84 mg/kg of body weight but can occasionally cause ventricular arrhythmias. Nitrates also cause similar increases in volumetric flow, but since these agents also dilate epicardial conductance vessels, the increase in coronary flow velocity is less pronounced.

Intracoronary papaverine, which produces maximal coronary vasodilation, has been reported to increase coronary blood flow velocity four to six times over the resting value in patients with normal coronary arteries. In these series, however, a highly selected patient population was studied, with the exclusion of patients with myocardial hypertrophy, previous myocardial infarction, or any other condition known to increase baseline flow (such as anemia, hyperthyroidism). Pharmacologically induced coronary flow reserve measured in normal arteries in the cardiac catheterization laboratory more realistically ranges from 2.5 to 3.5.

The hyperemic response after intravenous or intracoronary adenosine is comparable to that of intracoronary papaverine. The time to peak hyperemia, as well as the total duration of the hyperemic response with adenosine, however, is four times shorter than that of papaverine. Intracoronary adenosine has an extremely high safety profile in low doses and has become the pharmacologic stimulus of choice in the cardiac catheterization laboratory.

**Impairment of Coronary Blood Flow Reserve**

Coronary flow reserve is computed as hyperemic flow velocity divided by basal mean flow velocity (Fig. 18.14). Work by Gould and colleagues has established coronary flow reserve as an excellent parameter by which to assess the severity of a stenosis located in a major epicardial vessel, with reduction in flow reserve serving as an objective indicator of stenosis severity.

**FIG. 18.14.**

Method of measuring coronary vasodilatory reserve using flow velocity. Spectral flow velocity signals are displayed in a continuous strip along the top panel with heart rate and systolic and diastolic blood pressure displayed in the upper left corner of the top panel. The phasic signal demonstrates a normal hyperemic velocity with a small systolic component and large diastolic component. Systolic and diastolic periods are demarcated by the S and D, respectively. The lower panel is split into two sections: baseline and hyperemic response. Baseline average peak velocity (BAPV) is 14 cm/sec. The peak hyperemic flow velocity obtained 25 seconds later after 18 µg of intracoronary adenosine is peak average peak velocity (PAPV) of 53 cm/sec, producing a coronary vasodilatory reserve ratio of 3.9. The diastolic to systolic velocity ratio (DSVR) for the peak hyperemic response was 3.6; that is, diastolic to systolic velocity ratio with a maximal peak velocity (MPV) was 75 cm/sec and the peak velocity integral, which is the average velocity integral over two cycles during maximal hyperemia, was 39 units.

Although physiologically attractive, the coronary flow reserve concept has certain limitations. Coronary flow reserve...
is influenced by microcirculatory responses independent from the hydrodynamic characteristics of the stenotic lesion. Thus changes in basal resting flow without changes in hyperemic flow or vice versa will affect coronary flow reserve calculations. Basal systemic hemodynamic variables (e.g., heart rate, preload) and myocardial composition (e.g., hypertrophy, microvascular disease) will affect the hyperemic pressure–flow relationship and modify the flow reserve, thus possibly altering the assessment of lesion severity independent of lesion-specific factors (36). To minimize the influence of coexistent microvascular disease and elevated baseline resting flow on coronary flow reserve, the additional determination of coronary flow reserve in a reference vessel may contribute to a more lesion-specific index. The ratio of coronary vasodilator reserve in the target to coronary vasodilator reserve in a normal reference zone (37), (38) provides both, a lesion-specific index and information on the cardiac microvascular function.

Normal Coronary Flow Velocity

Because the microvascular circulation is subject to biologic variations between individuals, the range of normal coronary flow velocities at baseline and during hyperemia is variable. In one study, simultaneous flow velocity measurements were performed in 55 angiographically normal proximal and distal coronary arteries (right coronary artery = 12, left circumflex artery = 19, left anterior descending coronary artery = 24) (39). Coronary hyperemic flow was produced with intracoronary administration of 8 to 18 µg of adenosine. The normal proximal left anterior descending and circumflex time-averaged peak velocity was approximately 25 to 30 cm/sec with peak diastolic velocity ranging from 40 to 50 cm/sec and peak systolic velocity ranging from 10 to 20 cm/sec. In the right coronary artery and in some distal left coronary locations, flow velocity values may be reduced by 15% to 20%. There was no difference in proximal and distal velocities in normal arteries at baseline or during hyperemia, with a diastolic predominant pattern (diastolic/systolic flow velocity ratio of more than 1.5) in all arterial segments.

Limitations of Intracoronary Doppler Measurements

Intracoronary Doppler velocity measurements have important limitations that should be recognized by the operator. The method may be affected by the stenosis geometry, intracoronary velocity profile, and angle between the piezoelectric crystal and the flow vector of the blood (40). In addition, the sample volume is small and may fail to capture the maximal velocity of the bloodstream (40). Doppler methods measure coronary blood flow velocity, not absolute volumetric blood flow. The use of flow velocity as a surrogate for coronary blood flow assumes that the cross-sectional area of the vessel under investigation remains constant while measurements are made. It also assumes that the velocity profile across the vessel is not grossly distorted by luminal disease and is, in general, a parabolic configuration so that a correction factor of 0.5 can be used to calculate mean velocity from peak velocity. Furthermore, the Doppler catheter or guidewire, to reflect the true flow velocity, must lie within an angle of less than 30° to the flow stream for the cosine of the angle to be within 15% of the assumed value (41).

Problems in Coronary Flow Velocity Signal Acquisition

Occasionally, it may be difficult to find the maximal distal flow velocity signals and conclude falsely that a significant flow reduction is being caused by a particular stenosis. Therefore, the Doppler velocity signal should be examined during several different tip orientations to identify the maximal and most intense velocity spectra. In tortuous segments, stable distal signals can usually be obtained, but more guidewire manipulation may be needed to record a satisfactory Doppler envelope. In some patients, guidewire manipulation may not be successful due to tortuosity or lesion complexity. In these instances, the Doppler wire may be placed distally through a small-diameter catheter (Tracker, Target Therapeutics, Boston Scientific Co., Quincy MA), positioned over a standard angioplasty guidewire. Both translesional pressure and flow velocity can then be measured.

An elevated distal flow velocity may falsely normalize the proximal-to-distal flow velocity ratio. In a region with diffuse distal disease, flow velocity acceleration may occur secondary to distal luminal narrowing. In patients with serial lesions or diffuse distal disease, the proximal-to-distal flow ratio should not be used. In these cases, confirmation of lesion significance with coronary vasodilatory reserve and translesional pressure gradients may be needed.

Guide catheter obstruction to inflow at the ostium of the coronary artery may interfere with interpretation of both
pressure and distal velocity signals. For this reason, intermediate lesions can be assessed at the time of diagnostic catheterization with small (6F) diagnostic or guiding catheters, or with the catheter disengaged from the coronary ostium.

**Intracoronary Pressure-Derived Blood Flow Measurements**

Historically, Andreas Grünzig used coronary-pressure gradients to judge lesion severity and angioplasty success as the technique began in 1977 (42). Grünzig showed that reductions in mean pressure gradient correlated well with reduction in lesion stenoses (Fig. 18.15). Impeded flow by the balloon catheter, however, frequently led to overestimation of translesional gradients, and angiography subsequently evolved as the gold standard of procedural success. Miniature fiber-optic and electronic pressure guidewires have overcome these limitations and renewed interest in the initial concept. Theoretical models of flow–pressure relationships in the coronary circulation were initially described by Gould and Kirkeeide (43) and later refined by Pijls et al. (44). In the basal state, pressure gradients are determined primarily by coronary autoregulation of vascular resistance. Myocardial resistance responds to changes in hemodynamics, myocardial oxygen demand, and coronary vasomotion, followed by alterations in pressure and flow. In the absence of coronary stenoses, pressure is constant throughout a vascular bed and the ratio of distal to proximal pressure equals 1. Theoretically, coronary flow can be predicted by coronary pressure if coronary resistance remains constant. This condition occurs during maximum vasodilation when all coronary resistances are close to minimal. Under these circumstances, coronary pressure measurements are also able to quantify collateral flow and their contribution to maximal coronary blood flow.

**FIG. 18.15.**


**Pressure Guidewire System**

Pressure measurements can be easily incorporated in routine cardiac catheterization using pressure guidewire systems. The most commonly used pressure-monitoring guidewire is a 0.014-inch guidewire equipped with a high-fidelity, electronic, miniaturized pressure sensor (PressureWire, Radi Medical Systems, Uppsala, Sweden), located 3 cm proximal to the flexible tip. The sensor is a piezoresistive pressure sensor coupled in a Wheatstone bridge. The linear working range of the sensor is -30 to 300 mm Hg and the bandwidth is 0 to 1,000 Hz. The wire is connected to a small interface that allows display of the pressure signal on standard monitors and calibration outside the patient's body. Baseline pressure drift is less than 5 mm Hg/hour according to the manufacturer. The wire is advanced to the tip of the guiding catheter where it is verified that the pressure recorded by the guidewire sensor and the guiding catheter are equal. The wire is then advanced into the coronary artery and positioned distal to the stenosis with continuous monitoring and simultaneous display of phasic pressure tracings. In very tortuous anatomy, the pressure wire may not cross a specific lesion. A regular guidewire with optimal steerability and torqueability may be used to pass the lesion, and the pressure guidewire then can be advanced using an infusion catheter or multifunctional probing catheter. The fractional flow reserve of the coronary artery and its dependent myocardium is then calculated as the mean distal pressure (from the pressure guidewire), divided by the mean proximal pressure (from the catheter tip) at hyperemia (peak effect of intravenous adenosine at a rate of 140 µg/kg/min (45), or subselective intracoronary injections as outlined earlier). During balloon inflation, coronary wedge pressure can be recorded and the following calculations of myocardial and coronary fractional flow reserve (\(\text{FFR}_{\text{myo}}\) and \(\text{FFR}_{\text{cor}}\)) are performed:

\[
\begin{align*}
\text{FFR}_{\text{myo}} &= \frac{(P_d - P_v)}{(P_a - P_v)} \\
\text{FFR}_{\text{cor}} &= \frac{(P_d - P_w)}{(P_a - P_w)}
\end{align*}
\]
where $P_d$ represents mean pressure distal to a stenosis, $P_a$ represents mean aortic pressure, $P_v$ represents mean central venous pressure at maximal hyperemia, and $P_w$ represents distal coronary wedge pressure. Frequently, $P_v$ is estimated as 5 mm Hg, which simplifies the determination of $\text{FFR}_{\text{myo}}$. At the end of the case the guidewire is withdrawn to the ostium and pressure tracings are superimposed again to exclude drift.

**Myocardial, Coronary, and Collateral Fractional Flow Reserves**

Myocardial fractional flow reserve reflects antegrade and collateral contribution to maximal myocardial flow. In contrast, coronary fractional flow reserve measures only antegrade flow. The difference between myocardial and coronary fractional flow reserve represents the collateral contribution to hyperemic myocardial perfusion and allows the assessment of collateral flow. In the absence of antegrade flow ($\text{FFR}_{\text{cor}} = 0$), the collateral contribution averaged 30% of the expected value for hyperemic myocardial perfusion in patients with coronary disease (46).

**Practical Uses of Flow Velocity and Pressure Gradients in the Assessment of Stenosis Severity**

Coronary angiography cannot delineate the functional severity of many epicardial stenoses. Intracoronary velocity and pressure, measured with sensor-tipped angioplasty guidewires during cardiac catheterization, provide immediate data discriminating the physiologic significance of coronary stenoses. Functional analysis provides objective criteria for refining the selection of cases for revascularization, and prospective clinical data have confirmed the safety of deferring intervention on lesions with normal physiologic assessment (47). The following physiologic indexes complement both diagnostic and therapeutic aspects of coronary catheterization: (a) Coronary vasodilatory reserve ($\text{CVR}$), the ratio of hyperemic to basal mean velocity, represents the summed result of flow through the coronary artery and myocardial microvasculature (49). A CVR within the normal range identifies both a normal coronary conduit and microvascular response, excluding a coronary lesion from being flow-limiting. To identify coexistent microvascular disease, relative coronary vasodilator reserve ($r\text{CVR}$, computed as the ratio of coronary vasodilator reserve in the target to coronary vasodilator reserve in a normal reference zone, $\text{CVR}_{\text{target}} / \text{CVR}_{\text{reference}}$) has been proposed (37). $r\text{CVR}$ has a normal range of 0.8 to 1.0 (37) and appears to be a more lesion-specific index than absolute coronary flow reserve ($\text{aCVR}$). (b) Another approach to assessing coronary blood flow uses the hyperemic poststenotic pressure in the computation of the fractional flow reserve of the myocardium ($\text{FFR}_{\text{myo}}$) (50). $\text{FFR}_{\text{myo}}$ represents the maximal blood flow to the myocardium across the stenosis compared with the theoretical normal maximal flow in the same vessel without the stenosis. A $\text{FFR}_{\text{myo}}$ between 1.0 and 0.75 is considered normal (51).

**Flow Velocity and Coronary Vasodilator Reserve**

Translesional flow velocity can be used for assessment of coronary lesion significance, subject to two assumptions: first, that changes in flow velocity accurately reflect changes in volumetric blood flow, requiring that the cross-sectional area of a vessel remain constant; second, that epicardial artery cross-sectional area diminishes in proportion to volumetric flow as the parent gives off daughter branches (Fig. 18.16), so that flow velocity is maintained nearly constant from proximal to distal locations in segments 2.5 mm in diameter. A ratio of proximal-to-distal flow velocity approaching 1 is present in normal arteries (39). Significant epicardial lesions produce increased resistance and divert blood flow to branches proximal to the lesion, reducing flow velocity in the poststenotic region (Fig. 18.17A). Initial studies (39), (52) demonstrated that a decrease in poststenotic flow velocity, such that the ratio of proximal-to-distal velocity integral was more than 1.7, was related to translesional pressure loss resulting in gradients of more than 30 mm Hg in branching arterial systems (52) (Fig. 18.17B). However, flow velocity measured in normal and abnormal vessels proximal to a stenosis demonstrated significant overlap in flow velocity parameters, thus limiting the predictive accuracy of proximal values.

**FIG. 18.16.**
Diagram of branching coronary artery illustrating three major principles: (a) that volumetric flow is proportional to velocity and cross-sectional area; (b) that coronary arteries normally taper; and (c) that blood flow is distributed through the branches across the myocardium as the vessel traverses the myocardium. Because coronary vessels normally taper, cross-sectional area is reduced and volumetric flow is reduced. Thus the relative relationship between proximal and distal velocities approaches 1. (With permission from Kern MJ, Aguirre FV, Bach RG, Caracciolo EA, Donohue TJ. Translesional pressure-flow velocity assessment in patients: part I. Cathet Cardiovasc Diagn 1994;31:49.)

FIG. 18.17.


A:B: Left: Percent diameter stenosis by quantitative coronary angiography versus translesional pressure gradient; right: ratio of proximal-to-distal peak velocity integral versus gradient. Patients in this study with proximal-to-distal velocity ratios of less than 1.7 had translesional pressure gradients of less than 30 mm Hg, with two exceptions (dark boxes) in which flow velocity was measured in the proximal right coronary artery. This ratio is sensitive but not specific for translesional pressure gradients and may not be applicable in ostial lesions, diffuse distal disease, or serial lesions for assessment of pressure gradients. However, it is one of three indices used to assess intermediate lesion severity. (With permission from Donohue TJ, Kern MJ, Aguirre FV, et al. Assessing the hemodynamic significance of coronary artery stenoses: analysis of translesional pressure-flow velocity relations in patients. J Am Coll Cardiol 1993;22:449.)

Coronary Blood Flow Velocity During Angioplasty

Characterization of severe coronary stenosis during angioplasty is associated with three major alterations of the intracoronary flow velocity in the poststenotic region. These alterations are as follows: (a) A decrease in mean velocity [usually less than 20 cm/sec-for lesions in branching artery systems, a mean proximal-to-distal flow velocity integral ratio of more than 1.7 (52) is generally associated with translesional gradients greater than 30 mm Hg]; (b) An impaired phasic pattern of coronary flow (53),(54) with diastolic to systolic velocity ratio of less than 1.5; and (c) Impaired poststenotic coronary hyperemia flow reserve (less than 2.0 × basal values) (52).

Phasic Coronary Flow and the Diastolic/Systolic Velocity Ratio

Early experimental animal studies demonstrated a reduction in the normal diastolic predominant phasic flow pattern distal to experimentally induced critical stenoses (55). Intraoperative studies in patients confirmed a reduction of diastolic flow velocity and unchanged systolic flow velocity during graft occlusion (54). Using Doppler guidewire techniques during angioplasty, stenotic arteries were demonstrated to have a reduced diastolic flow velocity with relatively preserved systolic flow velocity (53) (Figs. 18.18, 18.19, 18.20). The systolic predominant pattern was seen in more than 50% of abnormal arteries and none of the normal arteries (39),(53). Normalization of the diastolic to systolic velocity ratio after successful angioplasty was confirmed by Segal et al. and other investigators (53),(56).

FIG. 18.18.

Comparison of normal hyperemic flow velocity response to flow velocity response distal to a severe stenosis. Top: Normal flow velocity at rest and during intracoronary adenosine hyperemia demonstrates a 2.5-fold increase in flow velocity. Note increase in systolic and diastolic flow velocity components. SPVi = systolic peak velocity index; DSVR = diastolic/systolic velocity ratio. Mean velocity in the normal artery increases from 28 to 60, for a coronary vasodilatory reserve of 2.3. Bottom: In the abnormal velocity response, proximal velocity is elevated, indicating that
a jet velocity has been acquired at the site of the lesion. Peak velocity is 120 cm/sec, mean velocity is 60 cm/sec. In
the poststenotic region (distal) flow velocity demonstrates loss of phasic pattern with a low diastolic/systolic velocity
ratio of 1.4, mean velocity of 15 cm/sec, and no hyperemic response.

**FIG. 18.19.**


B: Left: Angiograms before and after angioplasty. Right: Poststenotic flow velocity in the posterior descending artery in the location of the white arrow, demonstrating poor phasic flow and reduced mean velocity before angioplasty and increased mean velocity and normalized distal coronary flow after coronary angioplasty. Flow velocity measurements reflect the region in which velocity data are acquired.

**FIG. 18.20.**

A: Angiogram of a left anterior descending (LAD) stenosis. (LAO, left anterior oblique projection; RAO, right anterior oblique projection.) Coronary angiography revealed a 60% diameter narrowing in the proximal left anterior descending coronary artery in this young man 6 days after an anterior myocardial infarction. In-laboratory assessment of the stenosis was performed before and after angioplasty. Basal and hyperemic flow velocity data were obtained 1 cm proximal to the stenosis. The Doppler guidewire was advanced across the stenosis. Distal (more than ten artery diameters or 2 cm) basal and hyperemic flow responses were obtained. Intracoronary adenosine (12 to 18 μg) was administered through the guide catheter to evaluate poststenotic coronary reserve.

B: Analysis of the flow velocity data revealed normal mean proximal velocity (32 cm/sec), with a normal phasic pattern and coronary flow reserve (2.5 × basal) (Fig. 18.20B, top and bottom left). Poststenotic flow velocity, however, was abnormal (reduced mean velocity 17 cm/sec), with a proximal tp distal velocity ratio of 32:17 = 1.9 (Fig. 18.20B, top right). In addition, the ratio of phasic diastolic to systolic velocity was abnormally low (1.3 in the distal vessel; a normal left coronary ratio is more than 1.5). Distal coronary flow reserve was also impaired (1.42 × basal flow) (Fig. 18.20B, bottom right). These findings were associated with a basal translesional pressure gradient of 40 mm Hg (increasing to 48 mm Hg during maximal hyperemia) (Fig. 18.20C, bottom left).

C: Coronary angioplasty was successfully performed. The stenosis was reduced (less than 30% diameter narrowing) with normalization of the distal phasic flow velocity pattern (diastolic to systolic ratio of 1.6), augmentation of basal mean velocity (33 cm/sec), and increase in distal flow reserve (1.96) (Fig. 18.20C, top panels). The velocity data corresponded to a postangioplasty translesional pressure gradient of 8 mm Hg (20 mm Hg during maximal hyperemia) (Fig. 18.20C, bottom right). (With permission from Kern MJ, Flynn MS, Caracciolo EA, Bach RG, Donohue TJ, Aguirre FV. Use of translesional coronary flow velocity for interventional decisions in a patient with multiple intermediately severe coronary stenoses. *Cathet Cardiovasc Diagn* 1993;29:148.)

**Poststenotic Coronary Hyperemia**

As previously discussed, coronary flow reserve has been shown to correlate with the physiologic severity of a coronary stenosis in experimental animal studies. Subselective coronary flow reserve measurements have been employed in patients with variable results in a number of studies to aid in determining the functional significance of a given coronary stenosis. Unlike animal studies that are performed in nonbranching segments of coronary arteries, in patients, proximally measured coronary flow reserves are contaminated by branch vessels between the Doppler crystal and the lesion in question. The usefulness of distally measured (poststenotic) coronary flow reserve measurements in predicting Tc-99m sestamibi perfusion imaging during pharmacologic stress has been demonstrated (57). Coronary flow reserves equal to or less than 2.0 had a strong correlation with the presence of a reversible perfusion deficit (57).
The Doppler Endpoints Balloon Angioplasty Trial Europe (DEBATE) study (58) found that a combined procedural end point (angiographic residual diameter stenosis of 35% or less and coronary flow reserve of less than 2.5) was associated with a favorable clinical outcome at 6 months. In a subgroup of patients with both poor anatomic and functional results, further therapy (i.e., with stenting) could be contemplated in view of the highly predictable outcome of these patients. Two ongoing trials, DEBATE II and Doppler Endpoint Stenting International Investigation (DESTINI) (59), will give further insight if coronary vasodilator reserve aids in the development of lesion-specific interventional strategies.

Pressure Guidewire and Fractional Flow Reserve

Myocardial fractional flow reserve (FFR\textsubscript{myo} ) is an index of the functional severity of coronary stenoses derived from coronary pressure measurements. The index represents the maximal blood flow to the myocardium in the presence of a stenosis of a supplying artery, divided by the theoretical normal maximal flow in the same distribution (Figs. 18.21, 18.22). Unique features of FFR\textsubscript{myo} are that the index is independent of changes in systemic blood pressure or heart rate and that it takes into account the contribution of collateral blood supply to maximal myocardial perfusion (60). The concept of FFR\textsubscript{myo} has been carefully validated (61) and shows a high reproducibility and a well-defined cutoff value for inducible ischemia. A FFR\textsubscript{myo} of more than 0.75 appears to be uniformly associated with the absence of exercise-inducible myocardial ischemia (51) and correlated better with dobutamine stress echocardiography than with angiographic indexes of stenosis severity (62–64). In symptomatic patients, deferral of intervention on the basis of an FFR\textsubscript{myo} of more than 0.75 is safe and is associated with a low clinical event rate (65). The value of FFR\textsubscript{myo} in the evaluation of coronary interventions such as angioplasty and stenting is currently under investigation. Similar to coronary vasodilator reserve, preliminary results suggest that FFR\textsubscript{myo} may aid in the decision process during interventional procedures and is associated with low restenosis rates (66).

FIG. 18.21.


FIG. 18.22.

Procedure for calculating myocardial flow reserve (FFR\textsubscript{myo} ) from coronary pressure measurements. After calibration (top), a translesional gradient is clearly seen when the pressure sensor crosses the stenosis (middle). At steady-state maximum hyperemia (bottom) FFR\textsubscript{myo} is calculated as indicated. (Adapted with permission from Pijls NH, Bech GJ, De Bruyne B, van Straten A. Clinical assessment of functional stenosis severity: use of coronary pressure measurements for the decision to bypass a lesion. Ann Thorac Surg 1997;63[Suppl]:S6.)

Limitations of Coronary Vasodilator Reserve and Fractional Flow Reserve

Although coronary vasodilator reserve was initially devised to quantify limitation of flow caused by an epicardial coronary stenosis, microvascular dysfunction can influence both maximal or baseline flow. Increased extravascular forces such as elevated left ventricular diastolic pressure compress the intramyocardial microvasculature and limit peak flow rates. Structural alterations of the resistance vessel wall occur in hypertension, diabetes, and hypertrophic cardiomyopathy and limit vasodilation, thereby impairing maximal flow rates. Hyperlipidemia and other metabolic disorders may also impair coronary resistance vessel dilation. While adenosine induces vasodilation in arterioles with a diameter of less than 100 µm, a substantial amount of coronary resistance lies within small arteries with a size 100 to 400 µm. A flow increase though arterioles will induce shear-stress-mediated release of nitric oxide and vasodilation in these small arteries. Impaired vasodilator reserve thus may be mediated by endothelial dysfunction in resistance vessels with a diameter between 100 and 400 µm.
All functional studies are limited by submaximal hyperemic vasodilation. Lesion assessments relying on velocity and pressure measurements are invalid if inadequate hyperemic vasodilation occurs and may underestimate lesion severity. The presence of diffuse epicardial disease in the reference vessel may also lead to a reduction in reference CVR and thus to an underestimation of target-lesion severity in using rCVR (67). Additionally, similar to the TIMI frame count observations, CVR is frequently reduced in the perfusion territory of the culprit artery after myocardial infarction (68–70).

**Conclusions**

Measurements of coronary blood flow and myocardial metabolism have given important insights into cardiac function in health and disease. While there continues to be a role for noninvasive techniques in patient screening, catheter-derived estimates of coronary flow provide similar and potentially greater precision in measurement. With the availability of guidewire-based Doppler flow velocity and pressure measurements, clinically relevant measurements of coronary flow can be estimated during interventional procedures to evaluate patient-by-patient results, as well as enhance our understanding of coronary physiology and its response to intervention. Acceptance of traditional CVR to assess stenosis severity has been hampered by variable threshold values. Pressure-derived FFR, a well-validated and accepted concept to assess lesion-specific significance, and rCVR circumvent these problems and may serve as valid and more accurate measures of stenosis severity in the clinical setting.

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