Measurement of Coronary Flow Reserve in the Catheterization Laboratory

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11.1 Introduction

The coronary flow reserve (CFR) [1] is a well-validated physiological index that allows the identification of blood flow impairment in the coronary territory under investigation [1, 2]. This index summarizes flow impairment originating from focal epicardial, diffuse epicardial, and microcirculatory disease and therefore allows one to identify the overall available vasodilator capacity in the vasculature under investigation. The principle of CFR has been extensively applied to both invasive and noninvasive diagnostic techniques, including intracoronary Doppler- and thermodilution-derived flow [3–7], transthoracic echocardiography, positron emission tomography, and magnetic resonance imaging. All of these investigations have documented CFR to be a robust risk stratification tool [8–11]. Nonetheless, several limitations, including its sensitivity toward hemodynamic conditions, practical ambiguities associated with its assessment, and ambiguities related to its interpretation, have been important limitations toward its application in clinical practice. However, besides the well-documented prognostic information that can be derived from CFR, novel insights into its combined interpretation with fractional flow reserve (FFR), the contemporary physiological standard for functional stenosis assessment, have led to a renewed interest in this physiological index [9, 12, 13]. As such, ongoing developments on a technical level, as well as the development of novel concepts based on CFR theory, underscore the relevance of CFR in daily clinical practice.

This chapter will discuss the invasive assessment of CFR in the catheterization laboratory, starting from the physical aspects of currently available armamentarium to measure coronary flow invasively, toward clinical data, its application in daily clinical practice, and future outlooks regarding novel CFR-based concepts.

11.2 Invasive Assessment of Coronary Flow in the Cardiac Catheterization Laboratory

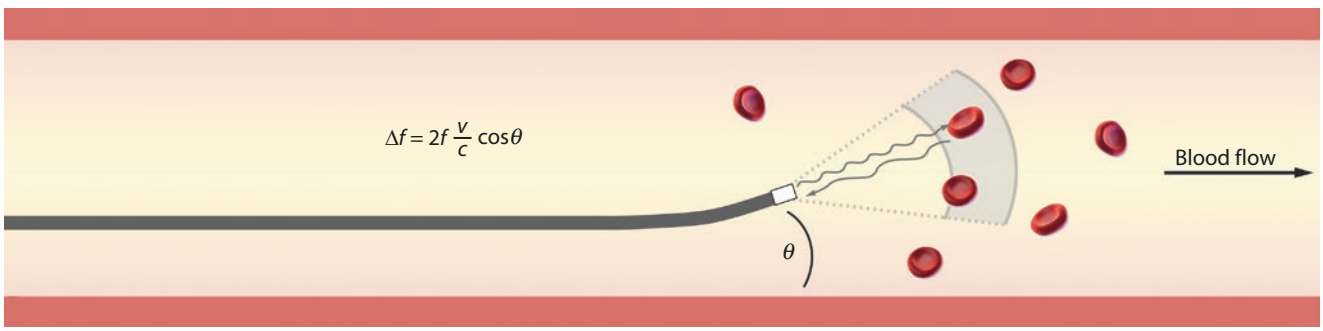
The ad hoc calculation of coronary flow reserve in the catheterization laboratory requires the invasive assessment of coronary flow. For this purpose, three modalities are currently available that will be reviewed in detail below.

11.2.1 Doppler Flow Velocity

Physical Principles

First described by Christian Andreas Doppler in 1842, the Doppler effect has found distinct practical expression cardiovascular medicine within ultrasound-based assessment of blood flow velocity. The principle described by Doppler is the apparent change in the frequency or wavelength of a wave when there is relative motion between the source of the wave and an observer. The observed frequency is higher (compared to the actual emitted frequency) when the source of the wave is moving toward the observer, and it is lower when the source of the wave is moving away from the observer. This apparent change in the pitch (or frequency) of sound is called Doppler effect or Doppler shift (Fig. 11.1) and can be used to determine the velocity of an object.

The currently available intracoronary Doppler flow velocity system (ComboMap, Volcano Corp., San Diego, CA) utilizes a piezoelectric crystal at the tip of a 0.014″ guide wire (ComboWire or FloWire, Volcano Corp., San Diego, CA), which serves as both the transmitter and receiver of a pulsed ultrasound signal and has a relatively large sample volume about 5 mm distal to the tip (Fig. 11.2a, b). The signal is emitted by the crystal in short bursts and is "echoed" by blood cells within the sample volume, which are moving away from



f = transmitter frequency
Δf= frequency Doppler shift
v = velocity of blood cells within sample volume
c = speed of sound in blood
θ = angle between ultrasound beam and direction of blood flow

Fig. 11.1 Intravascular velocity measurement by Doppler ultrasound. The ultrasound signal emitted by the Doppler crystal (*in white*) is reflected by red blood cells moving away from the transducer. The reflected sound waves, which have a lower frequency than the emitted waves, are received by the Doppler crystal. The console converts the received signal to velocity information expressed in cm/s

the transducer (Fig. 11.1). These echoes therefore return at the receiver at a lower frequency, and it is this Doppler shift that is detected by the instrumentation. When the Doppler beam is parallel to the bloodstream and given a constant transmitter frequency and a constant speed of sound in blood, this Doppler shift is directly proportional to the velocity of the blood cells within the sample volume (Fig. 11.1). When the Doppler beam is not parallel to the bloodstream, flow velocity may be underestimated. Nonetheless, such inaccuracy is limited to 6% when at a 20-degree angle, and it is therefore an accepted assumption that the ultrasound beam is relatively parallel to the main direction of the bloodstream.

The spectrum of frequencies received by the transmitter from the sample volume at any given moment represents a range of velocities at which the blood cells within the sample volume travel. The instrumentation then provides an overview of the frequency components of the Doppler signal converted to velocity, their relative intensity, and their variation in time. Flow velocity is extracted from these data by detecting the instantaneous peak velocity, which represents the maximum velocity within the sample volume (Fig. 11.2c). The average of instantaneous peak velocity over one or multiple heartbeats is termed average peak velocity and is the common parameter described in investigations using intracoronary Doppler flow velocity.

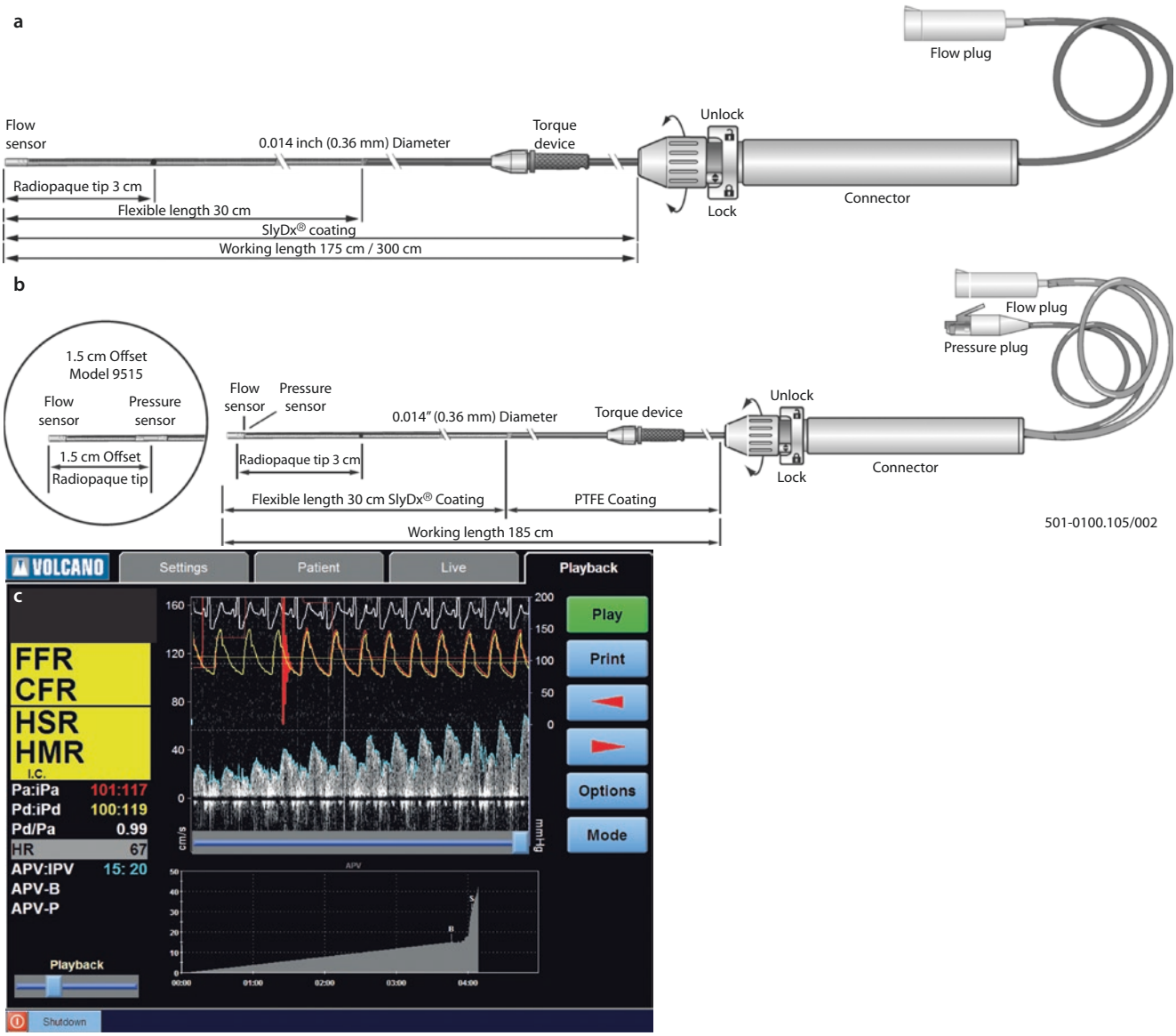


Fig. 11.2 Doppler flow velocity instrumentation. **a** FloWire (Volcano-Philips). A 0.014″ guide wire with a Doppler crystal at the tip. **b** ComboWire (Volcano-Philips). A 0.014″ guide wire equipped with both a Doppler crystal at the tip and a pressure sensor either just distal or at 1.5 cm distal to the Doppler crystal. **c** ComboMap console display. Instrumentation displays temporal changes in coronary flow velocity (Doppler signal in *white*). The instantaneous peak velocity (the maximum velocity in the sample volume) is represented by the blue line on top of the Doppler signal. The console additionally displays ECG (*top white line*), aortic pressure (*red line*), and (in case of the ComboWire) distal coronary pressure (*yellow line*)

Practical Aspects and Limitations

An advantage of Doppler flow velocity as a coronary flow parameter is that it is intrinsically normalized for the magnitude of perfused myocardial mass. This is due to the fact that nature normalizes coronary artery wall stress, which means that vessel diameter is directly related to the myocardial mass in its arterial distribution: the larger the perfused myocardial mass, the larger the supplying coronary artery [14, 15]. Where absolute flow (in mL/min) decreases with each branching of the coronary tree, the accommodating decrease in arterial diameter means that flow velocity is intrinsically corrected. This facilitates the interpretation of Doppler flow velocity values, since, despite its expression in cm/s, it is an accurate reflection of absolute flow per unit of perfused myocardial tissue.

As is illustrated by the description of the Doppler ultrasound technique above, the most important practical aspects of intracoronary Doppler flow velocity measurements are related to wire positioning to ensure optimal quality of the acquired signal and to ensure that these Doppler signals are representative of true blood flow velocity. Hence, operators are to be familiar with Doppler technology and should aim to manipulate wire position until a stable signal is obtained that is representative of the maximal cross-sectional velocity (Fig. 11.3). This aim is interfered by the natural tortuous vessel anatomy and cardiac motion, which can both degrade velocity signals. When inadequate signal quality is encountered despite wire position manipulation or when prolonged periods of stable velocity profiles are required, such as in extended research protocols, flipping of the wire tip can improve signal quality and ensures stable signals for prolonged recording times (Fig. 11.4). Nonetheless, the Doppler flow measurements remain technically difficult with the currently available measurement system, which leads to acquisition of Doppler signals of insufficient quality in up to 10–15 % of cases.

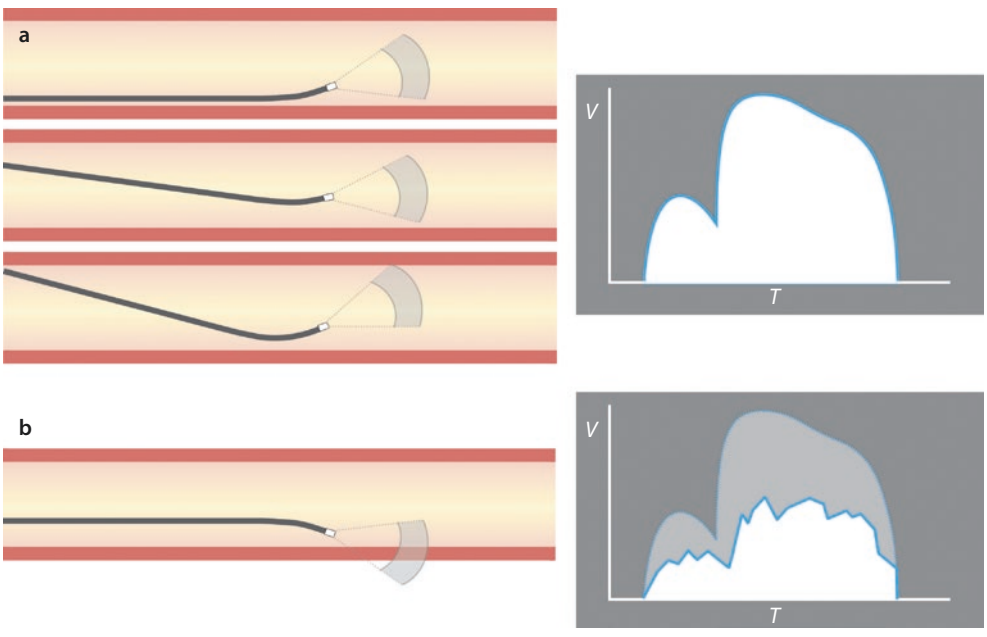


Fig. 11.3 Wire positioning and Doppler flow velocity signal quality. Signal quality is determined by the location of the sample volume. Optimal signals are obtained when the sample volume is positioned midstream **a**. When the sample volume is directed toward the vessel wall, the Doppler signal is degraded **b**

11.2.2 Coronary Thermodilution-Derived Mean Transit Time

Physical Principles

The indicator-dilution principle, first introduced by Stewart in 1897 for the measurement of cardiac output, has been validated for the invasive assessment of coronary flow as well. In short, the indicator-dilution theory dictates that injection of

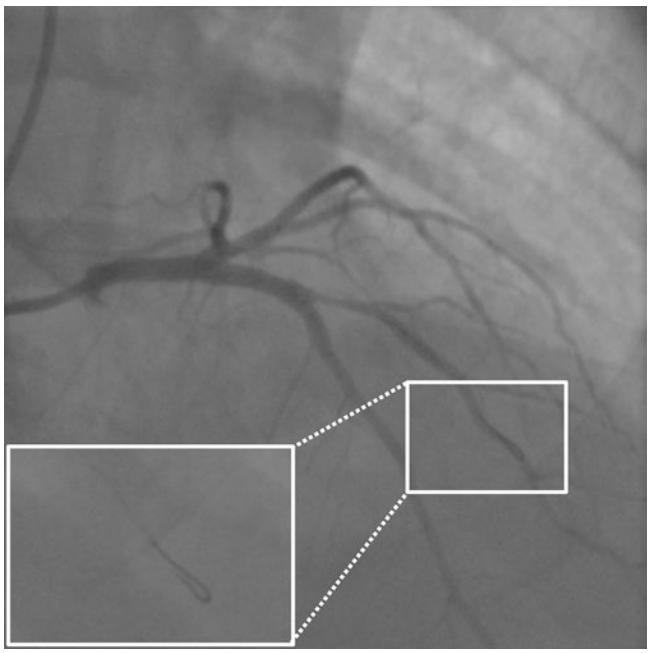


Fig. 11.4 Flipping of the wire tip. When suboptimal signal quality is encountered despite wire manipulation, flipping of the wire tip may be performed. The Doppler signal is the obtained in a retrograde fashion, and such retrograde wire position frequently allows to obtain stable Doppler signals of higher quality (Adapted from van Lavieren et al. with permission [16])

a known amount of indicator into the bloodstream and measurement of the indicator concentration over time distal to the injection site allow quantification of coronary blood flow. This theory can be applied to the coronary circulation by exploiting the temperature sensitivity of sensor-equipped coronary guide wires [6, 7]. In this application, the shaft of the coronary guide wire serves as the proximal thermistor, allowing the identification of the start of the indicator injection. The temperature-sensitive sensor at the distal end of the guide wire then serves as the distal thermistor. While keeping the distance between the proximal and distal thermistor constant throughout the measurements, the volume of blood between the two remains equal. As such, the change in temperature over time can be registered and allows calculation of the mean transit time of the indicator from the proximal to the distal thermistor (Fig. 11.5a, b). Since greater magnitudes of coronary flow cause greater and more rapid dilution of the injected indicator, mean transit time of the

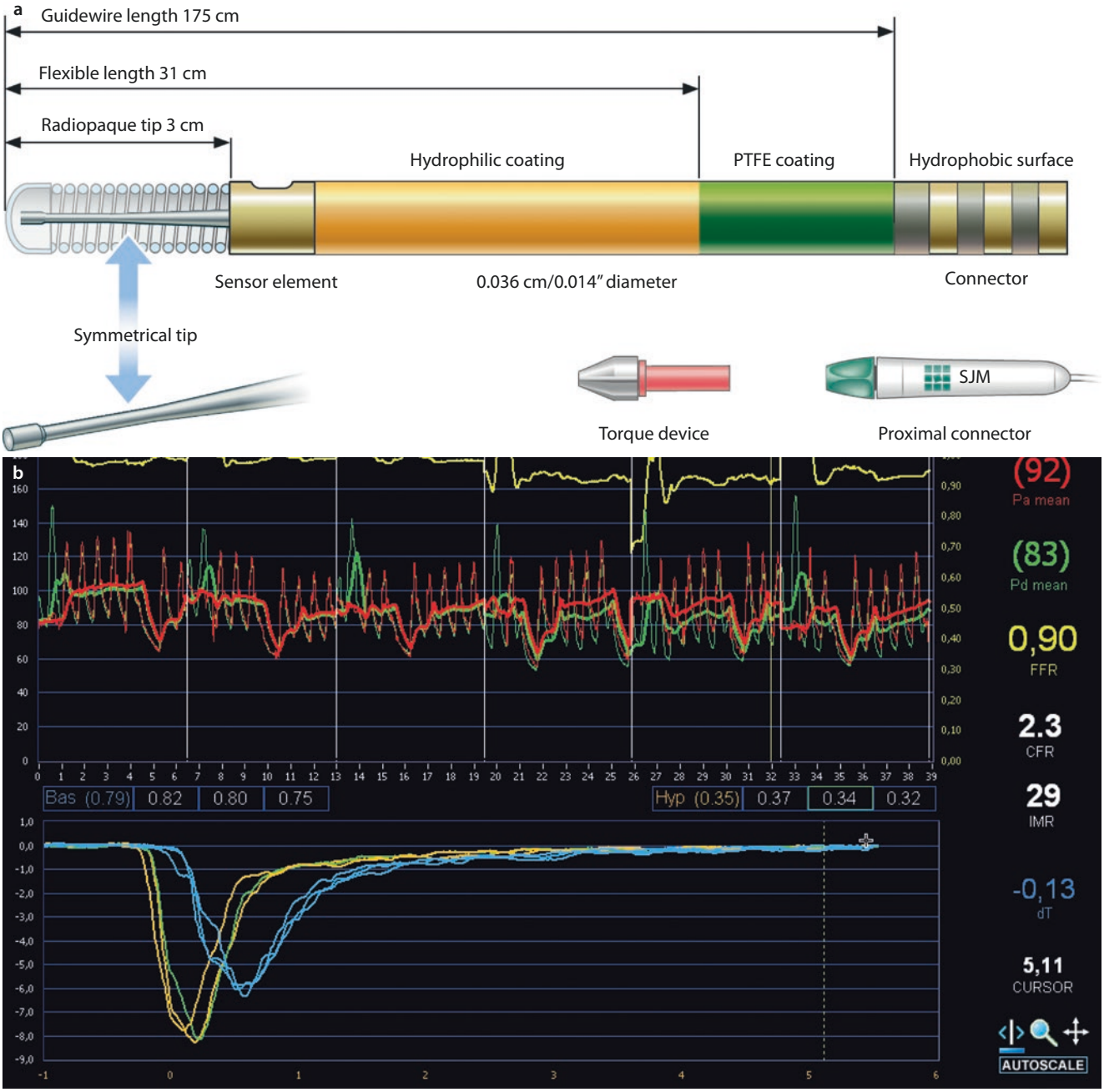


Fig. 11.5 Coronary thermodilution instrumentation. **a** PressureWire (St Jude Medical). A 0.014″ guide wire equipped with a temperature-sensitive pressure sensor, which allows the assessment of both intracoronary pressure and coronary thermodilution curves. **b** RadiAnalyzer (St Jude Medical) console display. Instrumentation displays the thermodilution curves in performed in triplicate in resting (*blue curves*) and hyperemic (*yellow curves*) conditions. The mean transit time is calculated from these curves and is shown to decrease from resting to hyperemic conditions (Bas (0.79) to Hyp (0.35)). The console additionally displays the ECG (*top yellow line*), as well as aortic pressure (*red line*) and distal coronary pressure (*green line*) (Courtesy of Dr. J. Escaned, Hospital Clinico San Carlos, Madrid, Spain)

indicator will decrease with increasing blood flow. Since the amount of indicator injected is known and equal across measurements, mean transit time provides a measure of coronary blood flow defined as the inverse of mean transit time.

Practical Aspects and Limitations

The contemporary application of coronary thermodilution in the catheterization laboratory requires the bolus injection of 3 cc of room-temperature saline as the indicator, which should be rapid and brisk. Since the timing of the injection during the cardiac cycle may influence the thermodilution curve, the latter is performed in triplicate, and the average mean transit time of these three injections is used for calculations. This is likely only clinically relevant when there is marked bradycardia, and it has been documented that ECG-controlled injection is generally not superior to manual injection of saline as the indicator [7].

Since saline boluses themselves cause significant transient reactive hyperemia [17], even in doses of 3 cc [18], it is important that sufficient time is allowed between repeated saline injections, especially during resting conditions. Otherwise, the repeated assessment of mean transit time is performed during a period of reactive hyperemia, which leads to overestimation of resting flow and therefore underestimation of CFR.

It is recommended that the distal thermistor, thus the guide wire sensor, be placed at least 6 cm distal from the injection site of the indicator, thus the catheter tip, to allow adequate mixing of blood and saline [7]. Neglecting this requisite leads to a larger variability in measurements and weaker correlation of the obtained mean transit time with absolute flow and therefore diminishes the accuracy of the measurements. This may not generally be a practical issue but should be considered while performing these measurements in clinical practice as coronary anatomy may not allow adherence to these guidelines and may therefore not allow accurate thermodilution flow measurements. Moreover, since the use of mean transit time as a surrogate for flow requires that the volume between the thermistors remains equal, catheter and wire position should remain the same throughout the measurements both during resting and hyperemic conditions for accurate flow measurements of flow and accurate calculation of CFR.

The measurement of coronary thermodilution-derived mean transit time during coronary hyperemia necessitates the induction of a hyperemic plateau long enough to perform the bolus injection and preferably long enough to perform these in triplicate. As such, thermodilution measurements cannot be performed with intracoronary adenosine administration, but requires the use of either intravenous adenosine administration, the administration of regadenoson, or the use of papaverine for the induction of a hyperemic plateau phase. In practice, the use of intravenously administered adenosine is customary for thermodilution measurements. The important consequences of this limitation will be discussed separately below.

Similar to Doppler flow velocity measurements, the assessment of adequate thermodilution curves is challenging, and sets of thermodilution curves of insufficient quality are also reported to occur in 10–15 % of cases, which mainly originate from cases where the distal thermistor cannot be placed distally enough to ensure a 6-cm distance between the two thermistors, leading to unacceptable variability in the repeated measurement of mean transit time to ensure accurate assessment of flow [6, 7].

11.2.3 Coronary Thermodilution-Derived Absolute Flow Measurement

The indicator-dilution theory also allows the assessment of absolute flow by coronary thermodilution, but this is much more complex and practically challenging. Nonetheless, using the same indicator-dilution theory, and the same 0.014-in. temperature-sensitive sensor-equipped coronary guide wire, the use of continuous infusion of room-temperature saline through a 2.8-F infusion catheter allows the measurement of absolute volumetric flow in mL/min directly in the catheterization laboratory [19, 20].

Practical Aspects and Limitations

Besides the intrinsic limitations of absolute flow values for their interpretation and application in clinical practice [20], the requisite of continuous saline infusion for the assessment of absolute flow means that this technology does not allow to measure coronary flow reserve, since resting flow cannot be accurately assessed. Moreover, the setup and measurement process is much more complicated than for regular thermodilution or Doppler flow velocity measurements and therefore takes 10–15 min to complete [20]. Nonetheless, technical advancements may make absolute flow measurements less cumbersome in the catheterization laboratory and may lead to novel insights into their applicability and value in clinical practice.

11.3 Coronary Flow Reserve: Definition and Characteristics

11.3.1 Definition of Coronary Flow Reserve

The concept of coronary flow reserve relates to the ability of the coronary circulation to increase blood flow in response to alterations in oxygen demand. As such, coronary flow reserve is defined as the ratio of maximal flow during vasodilated conditions, termed hyperemic coronary flow, to flow during conditions of coronary autoregulation, termed resting or baseline coronary flow.

11.4 Coronary Flow Reserve: What's Normal and What's Not?

In healthy subjects, coronary flow is expected to increase more than 4.5-fold upon pharmacological induction of coronary hyperemia [21]. In contrast, in patients without

epicardial stenosis but known risk factor for cardiovascular disease, CFR was documented to amount to approximately 2.8 [3]. When assessed in vessels without epicardial coronary stenoses, CFR values below this threshold have consistently been associated with impaired clinical outcomes, including hard clinical end points such as myocardial infarction and death [10, 11, 22, 23]. CFR has additionally been investigated thoroughly in the setting of epicardial stenosis, where it is now generally accepted that a CFR of less than 2.0 should be considered a clinically relevant impairment of the vasodilator capacity of the coronary vasculature under investigation [24, 25]. In more detail, these data have documented a range of optimal cut points of invasively measured CFR for noninvasively assessed myocardial ischemia that lies from 1.7 to 2.1. In other words, a CFR below 1.7 should definitely be considered to reflect an impaired vasodilator capacity in the vasculature under investigation. A CFR in the range of 1.7–2.1 lies within the CFR range that is associated with myocardial ischemia and should also be considered clinically relevant, as it may clinically be associated with signs and symptoms of myocardial ischemia. A CFR between 2.1 and 2.8 lies above the CFR threshold that has been associated with myocardial ischemia and should be considered sufficient to prevent myocardial ischemia even though it is decreased compared with nonobstructed coronary arteries. Finally, as noted above, a CFR of 2.8 or higher can generally be considered normal for a patient population with risk factors for coronary artery disease.

These considerations borne in mind, the application of physiology techniques in both research and clinical practice is frequently dichotomous in nature. As such, the 2.0 CFR cutoff has become customary in the evaluation of adverse events in patients at risk for cardiovascular disease [26, 27]. This cutoff value is the most widely validated and allows robust risk stratification in patients at risk for cardiovascular events. Nonetheless, available data support that the spectrum of CFR values represents a risk continuum, where risk for adverse events becomes higher with decreasing CFR values: a risk stratification value that is likely not optimally reflected by a dichotomous interpretation.

11.4.1 Limitations of Coronary Flow Reserve

Despite the unequivocal prognostic information provided by CFR, several practical and intrinsic physiological limitations of this index need to be considered.

First and foremost, the assessment of coronary flow reserve requires the direct measurements of a surrogate of coronary flow in the catheterization laboratory, which is more challenging than, for example, pressure measurements. This is illustrated by the fact that flow data of insufficient quality for accurate calculations occurs in 10–15 % of cases for both Doppler- and thermodilution-derived flow, whereas insufficient data quality for pressure recordings occurs seldom. Obviously, operator experience with the specific armamentarium is crucial in this aspect, and, furthermore, technical advances are ongoing that may improve feasibility of flow measurements in the catheterization laboratory.

Second, CFR intrinsically provides insight into the overall impairment in coronary flow in the vasculature under investigation, regardless of its origin in the epicardial coronary artery, due to either focal stenosis or diffuse atherosclerosis, or in the microcirculation. Although such comprehensive assessment of flow impairment has distinct advantages and bears important prognostic information, CFR is intrinsically unable to differentiate between these domains to determine the dominant origin of blood flow impairment. Hence, solitary assessment of CFR does not allow identification of optimal treatment strategies in ischemic heart disease.

Third, CFR as an index of hyperemic to resting flow is sensitive toward alterations induced in either of these conditions [28]. Moreover, since flow during vasodilated conditions is determined by coronary perfusion pressure, changes in perfusion pressure also affect CFR. Figure 11.6 shows the effect of alterations in coronary hemodynamics on CFR on the basis of the pressure-flow relationships during resting and vasodilated conditions (e.g., during adenosine-induced coronary hyperemia). First, CFR is affected by changes in coronary perfusion pressure, which may occur secondary to the administration of vasodilators to induce hyperemia but may also occur in settings of elevated venous pressure (Fig. 11.6b). At lower perfusion pressure, autoregulated (rest) flow remains equivalent, while flow in vasodilated conditions may be significantly reduced due to the reduction in perfusion pressure, leading to a decrease in CFR. Second, CFR may be affected by alterations in resting flow. Elevated resting flows result in a decrease in CFR as shown in Fig. 11.6c and may occur in a variety of settings, which are shown in Table 11.1. Third, an increase in zero-flow pressure causes a rightward shift of the pressure-flow relationship and yields a decrease in CFR as shown in Fig. 11.6d. Such rightward shift may occur in various clinical settings, as shown in Table 11.3. Fourth, CFR may also decrease due to an increase in resistance to coronary flow in the vasodilated vessels. This increase in resistance leads to a decrease in coronary flow at maximal vasodilation as shown in Fig. 11.6e. Factors associated with a decrease in hyperemic coronary flow are noted in Table 11.3. Finally, the abovementioned factors may occur in combination, increasing the effect of both pathophysiological and physiological alterations in coronary hemodynamics on CFR. As can be derived from Tables 11.1–11.3, factors associated with a decrease in CFR represent both physiological and pathophysiological alterations in coronary hemodynamics. While it is the latter that likely drives the association of CFR with impaired clinical outcomes, one should be aware of the confounding effect of physiological adaptations on CFR to ensure its accurate interpretation.

These limitations accounted for, CFR has still been rigorously documented to provide robust prognostic information and risk stratification in a distinct number of populations and patient subsets, illustrating the clinical potential of this physiological index.

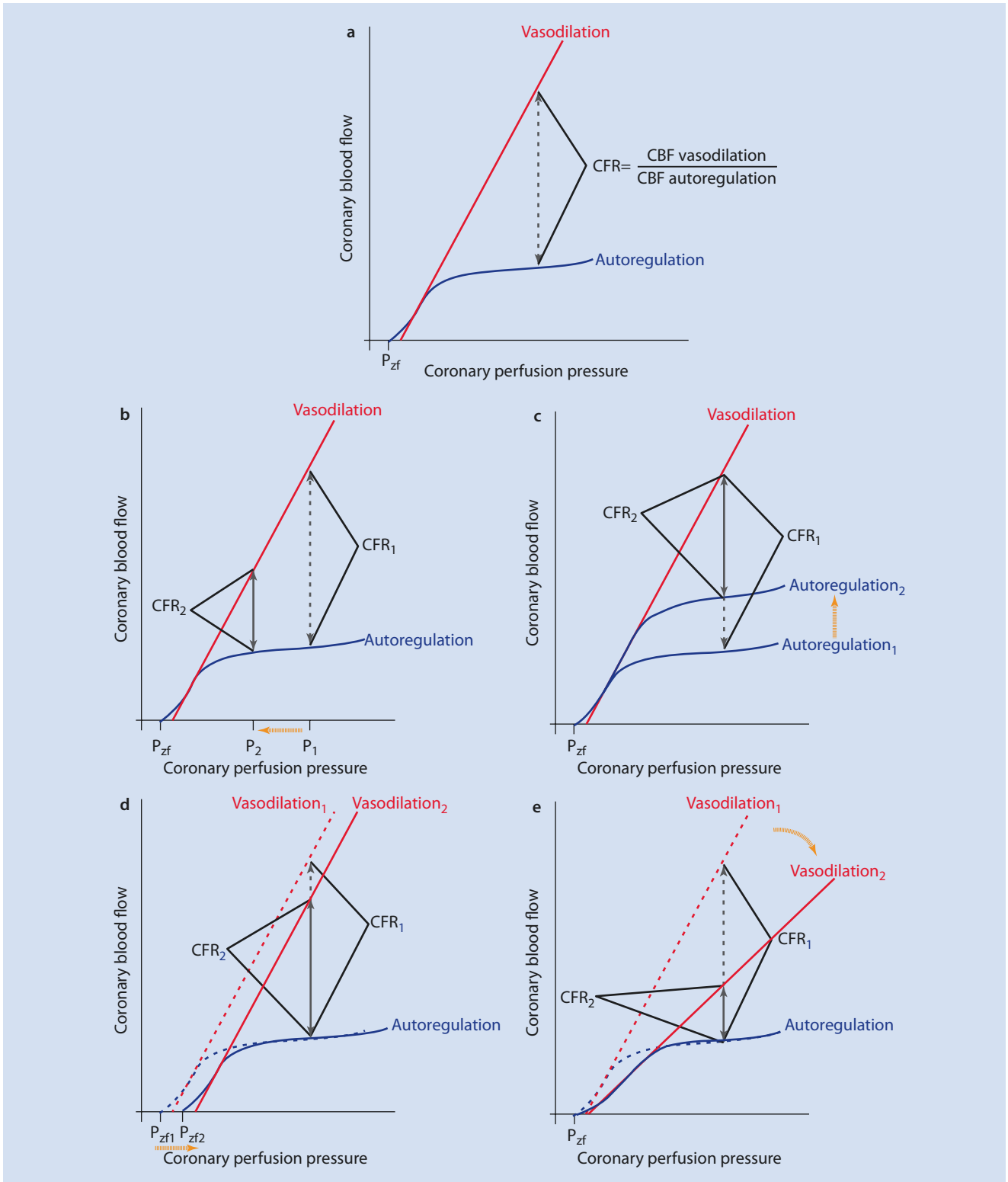


Fig. 11.6 Coronary pressure-flow relations and coronary flow reserve. **a** Normal coronary circulation and definition of CFR. P_{zf} indicates zero-flow pressure. **b** Effect of decreased perfusion pressure on CFR. Since maximal flow depends on perfusion pressure, CFR is sensitive toward changes in the latter. With a reduction in perfusion pressure, e.g., due to the intravenous administration of adenosine or regadenoson, CFR decreases from CFR_1 to CFR_2. **c** Effect of an increase in resting coronary flow on CFR. Since coronary autoregulation ensures resting flow accommodates myocardial demand, any increase in demand leads to increases in resting flow. Since CFR relates hyperemic to resting flow, increases in resting flow induce a decrease in CFR from CFR_1 to CFR_2. **d** Effect of elevated zero-flow pressure on CFR. An increase in zero-flow pressure results in a parallel rightward shift of the hyperemic pressure-flow relation from $vasodilation_1$ to $vasodilation_2$. As illustrated, this leads to a reduction in CFR from CFR_1 to CFR_2. **e** Effect of altered coronary resistance to flow on CFR. Alterations in coronary resistance to flow at vasodilation are characterized by a change in the slope of the hyperemic pressure-flow relation and are associated with a decrease in CFR as illustrated

Table 11.1 Factors associated with an increase in autoregulated flow

(Relative) increase in myocardial demand	Left shift of oxygen dissociation curve
Exercise[a]	Abnormal hemoglobins
Fever	Fetal hemoglobin
Increased inotropy[b]	Carboxyhemoglobin
Tachycardia[a,b]	Alkalosis
Thyrotoxicosis	
Ventricular hypertrophy[a,b]	
Hypoxemia	
Anemia	

[a]May additionally increase zero-flow pressure
[b]May additionally reduced maximal flow

Table 11.2 Factors associated with a rightward shift of zero-flow pressure

Increased left ventricular diastolic pressure[a]
Increased right ventricular diastolic pressure >10 mm Hg
Pericardial tamponade[a]
Increase in coronary sinus and venous pressure >10 mm Hg with normal right ventricular diastolic pressure
Beta-adrenergic blockade or alpha-adrenergic stimulation[a]
Left and right ventricular hypertrophy[a]
Tachycardia[a]
Several anesthetic agents

[a]May additionally reduce maximal flow

Table 11.3 Factors associated with a decrease in maximal flow

Small vessel disease	*Abnormal cardiac function*
Hypertension	Ventricular hypertrophy[a,b]
Hypertrophic cardiomyopathy[a,b]	Tachycardia[a,b]
Diabetes mellitus	Decrease in aortic pressure
Cigarette smoking	Increased left ventricular diastolic pressure[a]
Aortic stenosis	Pericardial tamponade[a]
Systemic lupus erythematosus	Substantial increase in myocardial contractility[b]
Large vessel disease	*Increased blood viscosity*
Atherosclerosis	Polycythemia
Thrombosis	Macroglobulinemia

[a]May additionally increase zero-flow pressure
[b]May also increase autoregulated flow

11.4.2 Induction of Coronary Hyperemia: Intracoronary Versus Systemic Vasodilation

For the assessment of CFR, flow values should be obtained during both resting and vasodilated conditions. Several agents are available for the induction of coronary hyperemia, such as adenosine, adenosine triphosphate (ATP), regadenoson, and papaverine, among which adenosine is the most commonly used agent in the catheterization laboratory. Whereas for Doppler flow velocity, measurements for either of these agents suffice; coronary thermodilution requires the administration of an agent that allows to create a hyperemic plateau during which the repeated bolus injections of saline can take place, such as intravenous administration of adenosine or ATP, regadenoson, or papaverine. It is important to realize that although intracoronary and intravenous adenosine administration, as well as the use of ATP, regadenoson, or papaverine, is generally considered interchangeable for the assessment of physiology techniques in clinical practice, this is not completely accurate for the assessment of maximal coronary flow at hyperemia. The administration of either of these agents is intended to induce coronary vasodilation and thereby to abolish coronary vasomotor tone. At coronary vasodilatation, coronary flow directly depends on the magnitude of the driving pressure. While intracoronary administration of adenosine does not alter systemic hemodynamics and therefore maintains equivalent driving pressure from resting to hyperemic conditions, intravenous infusion of adenosine/ATP or the use of regadenoson leads to significant decreases in aortic pressure at hyperemia of 10–15 % [29, 30]. Since maximal coronary flow at coronary hyperemia, and therefore CFR, depends on driving pressure, such a reduction in aortic pressure is associated with a proportional drop in maximal coronary flow (Fig. 11.6). Therefore, maximal flows and CFR assessed with the use of systemic vasodilation are prone to significant underestimation when these are determined using systemically administered vasodilators. It should therefore be considered to correct the obtained flow and CFR values for the accompanying drop in blood pressure by multiplying the CFR value with the ratio of resting to hyperemic mean aortic pressure, as was suggested previously [31].

11.5 Reintroduction of CFR in Clinical Practice: Combined Assessment of CFR and FFR

Although CFR is not routinely assessed in the clinical management of stable coronary artery disease, a setting where FFR is routinely applied to study the functional effect of a coronary stenosis [32], convincing data documents that the

impairment of coronary flow goes beyond the domain can be interrogated by fractional flow reserve [9, 12, 13]. As such, a strong body of evidence now supports the complementary nature of these two modalities, showing an important added diagnostic and prognostic value of CFR over FFR alone. Although FFR estimates whether a focal stenosis plays a dominant role in the impairment in myocardial perfusion [33–35], concomitant diffuse epicardial atherosclerosis or microvascular disease is not identified by this technique. The latter two conditions have been documented to be associated with a quantifiable risk for cardiovascular morbidity and mortality [8, 9] and thereby constitute an important area of interest both in clinical research and clinical practice settings. A wealth of data supports CFR as a tool to quantify the effect of both diffuse epicardial atherosclerosis and microvascular disease on myocardial perfusion, and CFR has been demonstrated to represent a robust risk stratification tool. Whether assessed invasively, as discussed in this chapter, or noninvasively, a normal CFR has repeatedly been associated with a low risk of cardiovascular events, with risk for such events increasing proportionally with decreasing CFR values. This ability of CFR to stratify risk for adverse cardiovascular events is independent of the presence of epicardial coronary artery disease and even of the presence or absence of stress-induced myocardial ischemia. Hence, CFR provides substantial incremental information over contemporary pressure-derived standards.

The combined assessment of FFR and CFR leads to challenges regarding the interpretation of the results, since disagreement occurs in over 30 % of cases (Fig. 11.7). When CFR and FFR agree, and they are both either in the normal range or in the abnormal range, interpretation of the results poses no difficulty. A stenosis yielding an abnormal FFR and normal CFR is by definition non-flow limiting, since flow can increase normally despite the atherosclerotic narrowing. Smalling et al. already documented that when coronary flow remains stable, coronary perfusion pressure may lower to FFR values below 0.5 without occurrence of myocardial ischemia [36]. Additionally, recent observational data suggests that the natural course of these non-flow-limiting stenoses is indeed associated with favorable clinical outcome [9]. Since non-flow-limiting stenoses are therefore likely not associated with myocardial ischemia and have a favorable clinical outcome, it is now debated whether these stenoses are optimally managed with percutaneous coronary intervention [37]. When FFR is normal and CFR is abnormal, two situations may (co)exist. First, this may represent the presence of dominant diffuse epicardial coronary artery disease, diminishing flow without inducing a significant pressure gradient due to the lack of flow acceleration and flow separation that dominates pressure gradients in focal disease [25, 38]. Second, this may be a representation of dominant microvascular disease, limiting the vasodilator reserve of the vasculature under investigation. Pure microvascular disease is more likely when the FFR value approaches 1.0, and these pathophysiological patterns may

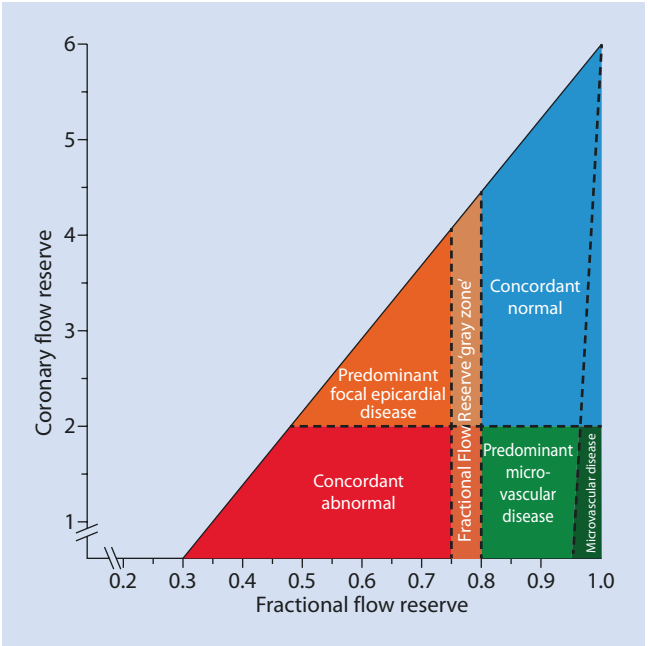


Fig. 11.7 Conceptual plot of the fractional flow reserve (FFR)-coronary flow velocity reserve (CFR) relationship. Four main quadrants can be identified by applying the clinically applicable cutoff values for FFR and CFVR, indicated by the dotted lines. Patients in the upper right blue area are characterized by concordantly normal FFR and CFVR, and patients in the red lower left area are characterized by concordantly abnormal FFR and CFVR. Patients in the upper left orange area and lower right light green area are characterized by discordant results between FFR and CFVR, where the combination of an abnormal FFR and a normal CFVR indicates predominant focal epicardial but non-flow-limiting, coronary artery disease, and the combination of a normal FFR and an abnormal CFVR indicates predominant microvascular involvement in coronary artery disease. The small dark green region in the lower right is characterized by an FFR near 1 and an abnormal CFVR, indicating sole involvement of the coronary microvasculature. The FFR gray zone indicates the equivocal 0.75–0.80 FFR range (Reproduced from van de Hoef et al. [9])

coexist leading to the individual CFR-FFR pattern in a given patient. Importantly, this FFR-CFR pattern has been associated with a distinct risk for cardiovascular events [9, 39], and it was recently hypothesized that these patients may benefit from mechanical revascularization in specific situations [16].

11.6 Future Perspectives

CFR likely represents the most widely studied physiological index available, since its application is not restricted to invasive cardiology. Nonetheless, the limitations described above and lack of acknowledgement of its clinical potential have led to CFR being applied mainly as a research tool. Novel insights into the complexity of ischemic heart disease have now led to a renewed research and clinical interest, which is closely followed by technical partners that are improving flow assessment armamentarium. Hence, the clinical application of CFR

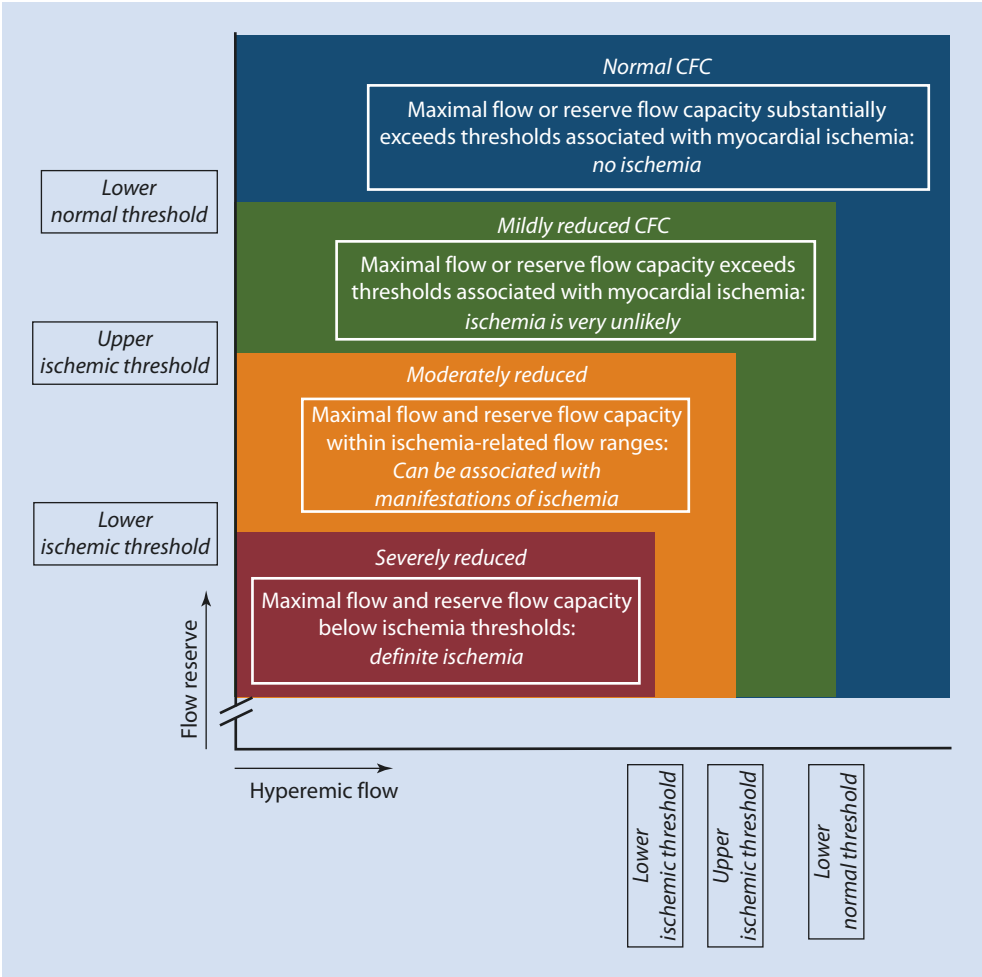


Fig. 11.8 Coronary flow capacity concept. Since coronary flow reserve (CFR) equals hyperemic to baseline flow, a two-dimensional map of CFR versus hyperemic flow comprehensively describes the invasive flow characteristics of the coronary vasculature under investigation. Within this concept, four clinically meaningful categories are defined (coded with different colors in the graph) based on well-validated invasive CFR cutoff values and the corresponding hyperemic flow values (Reproduced from van de Hoef et al. [40])

is likely to become more important in the near future and will likely become more feasible as soon as industrial partners distribute updated measurement systems.

Moreover, concepts are now being developed that overcome part of the limitations associated with the use of CFR. One of these is the concept of coronary flow capacity, which incorporates CFR and maximal hyperemic flow in a comprehensive flow map of the coronary vasculature under investigation (Fig. 11.8) [40–42]. First applied to positron emission tomography, this coronary flow capacity concept was recently introduced based on invasive Doppler flow data and was documented to improve risk stratification characteristics of CFR. This is likely due to the fact that coronary flow capacity overcomes the limitations of CFR related to variations in the resting state.

Besides the improvement in the application of CFR and development of concepts that overcome its associated limitations, measurement systems nowadays allow to measure both pressure and flow simultaneously. Such techniques allow calculation and differentiation of the resistance to coronary blood flow induced by a stenosis or epicardial segment and the microcirculation [43, 44]. Ultimately, techniques that apply CFR or coronary flow capacity may therefore allow to evaluate whether clinically significant flow abnormalities occur in the vasculature under investigation, after which these novel technologies may be applied to identify the dominant source of flow impairment and to guide treatment strategies [37].

11.7 Conclusion

CFR is a well-validated physiological index that provides extensive diagnostic and prognostic information. Its assessment in the cardiac catheterization laboratory is associated with practical ambiguities that dominantly require operator experience with the specific armamentarium. For this purpose either intracoronary Doppler flow velocity or thermodilution can be used, both having their own practical and physiological advantages and limitations. Recent acknowledgement of the clinical pertinence of CFR will support reintroduction of CFR in the daily interventional cardiology, and the accompanying conceptual and technical advances may overcome many of the intrinsic and practical ambiguities associated with its assessment in the catheterization laboratory.

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