CHAPTER 5

Physiological Assessment of Coronary Lesions

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Introduction

The treatment of symptomatic coronary artery disease (CAD) depends on the hemodynamic impairment of flow, a physiologic parameter that is not captured with coronary angiography alone. The miniaturization of sensor-guidewires capable of crossing coronary stenoses provided a rationale for physiological assessment of coronary lesions to guide coronary revascularization. Multiple clinical trials have demonstrated the superiority of using invasive physiologic assessment to guide decision-making in intermediate vessel stenosis over angiography alone. [1,2] Current guidelines give a class IA recommendation for use invasive physiological assessment to guide revascularization of angiographically intermediate lesions in patients with stable angina. [3,4] Coronary physiology measurement has therefore become routine practice in every cardiac catherization lab with expanding techniques and indications. This chapter will cover the basic physiologic principles of coronary blood flow, technical aspects of coronary physiology measurements, and the expanding clinical data supporting the use of coronary physiology measurement in every day practice.

Understanding Coronary Blood Flow

Myocardial blood flow provides oxygen *supply* in an effort to meet the myocardial oxygen demand (MVO2) and prevent ischemia or infarction. The main determinants of myocardial oxygen demand and supply are highlighted in **Table 1**.

In a healthy coronary and capillary circuit, blood flows from the aorta though an epicardial conduit, then precapillary arterioles and the microvascular capillary bed in a highly regulated process (**Figure 1**).

The resistance (pressure/flow) across the circuit is the sum of the resistances within the circuit: the epicardial coronaries ($R_{epicardial}$), the precapillary arterioles ($R_{arteriolar}$), and the microvascular capillary bed ($R_{capillary}$).

$$R = R_{epicardial} + R_{arteriolar} + R_{capillary}$$

In the absence of coronary stenosis or severe vasospasm, $R_{epicardial}$ is minimal. On the contrary, precapillary arterioles ($R_{arteriolar}$) are resistive vessels and primary regulators of coronary blood flow to the microcirculation. Capillaries have pre-capillary sphincters that regulate flow depending on the oxygen demand. $R_{capillary}$ *is* increased in conditions such as hypertrophic cardiomyopathy, diabetes, or myocardial infarction.

Ultimately, blood flow to the myocardial depends on two factors:

(1) the coronary artery driving pressure from the aorta

(2) the resistance R of the serial components of the circulation bed

R is regulated by a variety of mechanisms including myocardial metabolism, endothelial function, myogenic, neural, and extra-vascular compressive forces. Several of those are also altered in disease states and with pharmacological therapies.

Collateral circulation that develops secondary to chronic ischemia and surgical bypass grafts constitute two exceptions to this serial capillary circulation and must be factored in any physiologic assessment of coronary stenosis.

Angiographic Measurements of Coronary Blood Flow

The simplest method to measure coronary blood flow is Thrombolysis in Myocardial Infarction (TIMI) Flow Grades which evaluates the flow of contrast material through the coronary tree: grade 0 (no perfusion) perfusion, grade 1 (penetration without perfusion), grade 2 (partial perfusion), and grade 3: (complete perfusion). [5] The TIMI Frame Count is a more quantitative version that uses the number of cine frames from the injection of contrast to a set distal landmark to measure coronary flow. [6] The TIMI Blush Score is another angiographic measure of perfusion at the capillary level. Myocardial blush grading is obtained by extending the length of angiographic runs to visualize the venous phase of contrast passage. The extent of blush is quantified as 0 indicating no myocardial blush, 1 indicating minimal, 2 indicating moderate, or 3 indicating normal myocardial blush. [7]

Sensor-Tipped Guidewire Technique to Evaluate Coronary Physiology

Sensor-tipped guidewires provide the opportunity to accurately measure coronary flow before and after pharmacologic and mechanical interventions, to evaluate the functional significance of stenoses and to assess the health of the microvascular bed and collateral circulation. **Figure 2** shows a schematic depicting the use sensor-tipped guidewires for the assessment of coronary artery lesions. The sensing tips include pressure sensors that enable measurement of pressure gradients across a stenosis, Doppler ultrasound that determine flow velocity of blood, and thermistors that measure blood flow through thermodilution flow technique.

The sensor-tipped guidewire technique is used to measure coronary flow reserve (CFR), fractional flow reserve (FFR), or instantaneous wave-free ratio (iFR). **Table 2** defines each of those physiological measurements, which are discussed in detail in the following section.

Coronary Flow Reserve (CFR)

Reactive hyperemia is the ability of the distal coronary bed to vasodilate and provide increased flow to the myocardium. This occurs naturally with exercise or following a transient coronary occlusion. Coronary flow reserve (CFR) is the ratio of maximal hyperemic flow to baseline coronary flow.

$CFR = Q_{hyperemia} / Q_{baseline}$

where Q = velocity if the cross-sectional area is unchanged during hyperemia[8]

The general approach to sensor-guidewire use for measurement of coronary flow reserve (CFR), fractional flow reserve (FFR), or instantaneous wave-free ratio (iFR) for the purpose of physiologic evaluation coronary stenosis is similar across modalities and is detailed in **Table 3**. The type of wire, calibration, and need for coronary hyperemia differ depending on the measurement. CFR sensors measure either Doppler flow velocity formula above or use thermodilution blood flow technique.

In terms of pharmacologic agents to induce maximal coronary hyperemia, adenosine is the most commonly used agent because of its overall safety. It can be given as an intravenous drip that allows measurement over a longer time interval which is sometimes necessary for tandem lesions. Alternatively, it can be given as an intracoronary bolus, which has the advantage of fewer side effect to the patient and shorter duration. A recent study compared FFR measurements in 114 patients using intracoronary and intravenous adenosine and found a very high correlation in measurements (r=0.99, p<0.001), but intracoronary bolus required less time and was associated with lower discomfort to the patient.[9] Intracoronary papaverine is another agent that could induce hyperemia, but it has fallen out of practice due to risk of QT prolongation and ventricular tachycardia. Intravenous dobutamine is an alternative to adenosine but its use is limited by tachycardia and hypertension (**Table 4**).[9,10]

A normal CFR ranges usually between 2 and 5, but this varies tremendously depending on the patient and coronary health. CFR is reduced with physiologically significant coronary stenosis. A CFR<2 is considered abnormal and has been associated with ischemia on stress testing. [11] The flow at maximal

hyperemia (numerator) will start declining at a diameter stenosis of approximately 60% but the resting blood flow (denominator) does not decline until coronary stenoses reach a severity of approximately 80% (**Figure 3**).[12]

In the absence of epicardial stenosis, a low CFR indicates microvascular disease and/or endothelial dysfunction. Alternative factors that may be responsible for low CFR include abnormal vascular reactivity, abnormal myocardial metabolism, abnormal sensitivity to vasoactive substances, coronary vasospasm, myocardial infarction, hypertrophy, vasculitis, hypertension, or diabetes.[13] The relationship between diameter narrowing and CFR in a particular individual is unpredictable because of the multifactorial drivers of CFR and the variable morphological characteristics of atherosclerotic lesions.[14] Together, these limitations limit the clinical utility of CFR in evaluating the physiology of coronary stenosis.[15]

Fractional Flow Reserve (FFR)

FFR is a pressure-derived ratio that estimates the proportion of coronary flow that crosses a stenotic artery by computing the pressure distal to a coronary stenosis divided by the aortic pressure. This pressure-derived ratio is used to describe flow in the epicardial coronary ($FFR_{coronary}$), in the myocardium ($FFR_{myocardium}$) and in the collateral circulation ($FFR_{collateral}$) and is calculated using the following formulas:

$$FFR_{coronary} = (P_{distal} - P_{right.atrium}) / (P_{aortic} - P_{right.atrium})$$

$$FFR_{myocardial} = (P_{distal} - P_{coronary.wedge}) / (P_{aortic} - P_{coronary.wedge})$$

$$FFR_{collateral} = FFR_{coronary} - FFR_{myocardial}$$

The right atrial pressure $P_{right.atrium}$ is often negligible yielding the modified formula:

$$FFR = P_{distal} / P_{aortic}$$

FFR is measured using the step-wise approach in **Table 2**. Baseline recording shows P_{distal} /P_{aortic} (Pd/Pa) followed by induction of maximal coronary hyperemia during which FFR is measured (**Figure 4**). As noted in **Figure 4**, the Pd/Pa decreases after adenosine infusion in the presence of significant coronary obstruction. Coronary autoregulation compensates for moderate epicardial stenosis by increasing vasodilation of the microcirculation, thereby maintaining resting flow to match myocardial demand. While distal pressure (Pd) falls, the resting flow remains unchanged until stenoses reach a severe of approximately 80% (**Figure 5**).[16,17] Inducing maximal coronary hyperemia with adenosine impairs the auto-regulation and makes coronary flow dependent on the driving pressure, which in turn allows for the use of the pressure gradient across a stenotic lesion to evaluate its physiologic severity. An FFR value of 1 is considered normal and indicates no impairment of flow in the coronary. The non-ischemic threshold of FFR is > (0.75-0.8) based on clinical trials that showed improved clinical outcomes using this threshold for FFR-guided revascularization compared to angiographically-guided revascularization.[16]

In the case of serial lesions, a pull-back technique can be performed to evaluate the drop in Pd/Pa across each of the lesions. In this technique, the wire is first passed beyond the distal lesion and the FFR is recorded, and in this case, it represents the summed hemodynamic effect of both proximal and distal lesions. If the summed FFR is >0.8 then none of the lesions need to be treated. If the summed FFR is <0.8, the wire is pulled back such that the sensor is between the proximal and distal lesions and another recording is measured. The gradient between the two measurements represents the hemodynamic effect of the distal lesion. Further pullback is then performed to measure the gradient across the proximal lesion. The lesion with the highest gradient is treated first, then the FFR is repeated for the remaining untreated lesions and it is treated if FFR <0.8. Unlike CFR, FFR is specific for epicardial stenosis and independent of hemodynamic alterations and microvascular disease. It is highly reproducible and possesses high spatial resolution. FFR carries the advantage of accounting for all

sources of myocardial blood flow to a territory, including collateral circulation and coronary bypass grafts.[8]

Several possible artifacts and pitfalls may limit accurate measurement of FFR. Awareness of the possible reasons and step-wise troubleshooting can help avoid artifacts and potential pitfalls (**Table 5**).[18]

The initial human studies of FFR aimed at establishing cut-off values of FFR to detect inducible ischemia on stress testing. The cutoff value ranged between 0.76 and 0.8 and the diagnostic accuracy of FFR compared to the different stress test modalities was ~80%.[16] In interpreting an FFR measurement in a patient with suspected coronary ischemia, it is important to remember that there is no true gold standard for ischemia and that the FFR threshold values were obtained from comparison to noninvasive tests in multiple studies with small sample sizes in the 1990s.[16]

The DEFER study in 2001 was the first study to determine the impact of FFR use on clinical outcomes. The randomized clinical trial showed that in patients with stable CAD and intermediate lesions, deferred revascularization in lesions with FFR >0.75 was safe and associated with comparable event-free survival (**Table 6**).[19] The FAME study in 2009 showed that FFR-guided revascularization in patients with multivessel CAD undergoing PCI reduced the rate of death, nonfatal MI and repeat revascularization at 1 year compared to angiography-guided revascularization (13.2% vs. 18.3%, relative risk 0.72, p=0.02).[20] Of note, the FAME study used an FFR cut-off of 0.8 and had larger sample size (1005 patients) compared to DEFER (325 patients). The FAME-2 study in 2012 showed that in patients with multivessel disease on optimal medical therapy (OMT) and in which PCI is being considered, FFR-guided PCI reduced the need for urgent revascularization compared to OMT alone (4.7% vs. 12.3%, hazard ratio 0.13, p <0.001).[21] Collectively, these 3 studies highlighted the superiority of FFR-guided revascularization over angiography alone in stable ischemic heart disease and intermediate stenosis in the absence of stress testing.

Instantaneous Wave-Free Ratio (iFR)

iFR provides a reliable method to evaluate physiologic severity of coronary stenosis at rest without the need of inducing coronary hyperemia. It is distinct from Pd/Pa which is biased by myocardial contraction and relaxation. Throughout the cardiac cycle, wave intensity analytics in the coronary (**Figure 6**) demonstrates a brief wave-free period in diastole that has higher coronary flow than the rest of the cycle during which coronary flow and pressure proportionally decline and microvascular resistance is stable and lower than the rest of the cardiac cycle. Those fundamental aspects of the wave-free segment make assessment of the pressure gradient during the wave-free period a reliable estimate of the hemodynamic significance of a coronary stenosis. iFR basically provides an estimate of the physiological impact of the stenosis on the distal coronary bed without the need for induced hyperemia.

iFR has been shown to be a robust measure with high diagnostic accuracy that is similar to FFR. An iFR <0.89 is considered consistent with ischemia-inducing coronary lesion(s). Two recent large patient outcomes trials supported the adoption of iFR in clinical practice (**Table 6**). The DEFINE-FLAIR and iFR SWEDEHEART trials both showed that iFR-guided revascularization was noninferior to FFR-guided revascularization of intermediate stenosis and as such is a safer approach to guide revascularization of intermediate stenosis in stable ischemic heart disease using a single cutoff of 0.89.[22,23] DEFINE-FLAIR was a prospective multicenter double-blinded trial that randomized patients with intermediate coronary stenosis in 1:1 ratio either iFR-guided or FFR-guided PCI and included both patients with stable angina as well as acute coronary syndrome. The primary outcome was MACE at one year, which was similar between the two groups. The number of patients with adverse procedural symptoms, a secondary outcome, was lower in the iFR compared to the FFR group (3.1% vs. 30.8%) and procedural time was shorter (40.5 mins vs. 45 mins).[23] The iFR SWEDEHEART trial had a similar design

except that it was open label, and the results were similar with iFR being noninferior to FFR and procedural symptoms such as chest discomfort being lower in the former.[22]

FFR is discrepant to iFR measurement in ~14% as a result of differences in hyperemic coronary flow velocity.[24] In those cases of disagreement, when Doppler-derived coronary flow was measured and used as gold standard for determining physiologic severity, iFR classification was more closely related to hyperemic coronary flow velocity.[24] Clinically, many operators resort to intravascular imaging to further define lesion severity in such cases. Future patient outcome trials will be needed to better understand those discordance cases.

Clinical Applications of Physiological Assessment of Coronary Lesions

The most recent ACC/AHA/SCAI guidelines state that it is reasonable to use FFR or CFR to evaluate intermediate coronary stenosis (30% to 70%) in patients with angina or as an alternative to noninvasive stress testing (Class IIA) and that FFR/CFR may be considered to evaluate PCI success or in patients with angina without apparent culprit (Class IIB).[25] The more recent European Society of Cardiology guidelines in 2013 recommended the use of FFR to guide revascularization in severe stable angina (Class IA).[26]

The initial implementation strategy for iFR prior to 2017 involved a hybrid approach where for iFR<0.86 was considered a threshold for physiologically significant and for iFR between 0.86 and 0.93, FFR was performed for confirmation. This hybrid approach was evaluated in 577 stenoses and resulted in high classification agreement with FFR-only approach.[27] This served as a practical way to avoid using adenosine in ~60% of patients at a time when outcomes data for iFR were still lacking and the need for adenosine limited adoption of coronary physiology measurement despite guideline recommendations. However, in current practice and following the results of DEFINE-FLAIR and iFR SWEDEHEART, it is now reasonable to use iFR cutoff of 0.89 to guide revascularization of moderate coronary stenosis (40-80%).[16]

Considerations in the use of FFR and iFR

Multivessel CAD

Multivessel CAD is increasingly more common and invasive physiological assessment of coronary lesions is particularly important in these cases since the accuracy of non-invasive stress testing may be limited due to balanced ischemia.[18] iFR/FFR can accurately localize areas of ischemia in this setting. Early evidence from observational studies showed that FFR is useful to guide revascularization of lesions of intermediate stenosis in patient with stable angina and multivessel CAD.[28,29] In a cohort of 107 patients with stable angina and multivessel CAD, 14% of the intermediate lesions without perfusion defect on SPECT had FFR<0.75, and the 1-year event rate (death, MI, and revascularization) was higher when revascularization was deferred despite low FFR<0.75 compared to the patients with FFR>0.75 (27% vs. 9%, p<0.041).[29] In the FAME trial, FFR-guided PCI in patients with multivessel CAD not only showed improvement in the primary outcome of MACE at one year (13.2% vs. 18.4%) compared to angiography alone, but also resulted in fewer PCIs, less contrast use, lower procedure cost, and shorter hospital stay.[20] An important aspect of using iFR/FFR is the ability to downgrade physiologically insignificant lesions. In the 509 patients who were randomized to FFR-guided PCI in the FAME trial, 37% (513/1387) of lesions were downgraded based on FFR≥0.8.[20] Consequently, a proportion of patients with three-vessel disease that would otherwise need CABG were downgraded to single or dual vessel disease for which PCI is appropriate. The FAME3 trial is a prospective randomized noninferiority trial to compare FFR-guided PCI to CABG in patients with multivessel disease. It is currently enrolling and is expected to be completed in 2021.

Left Main Stenosis

FFR can accurately identify physiologic significance of left main (LM) coronary artery lesions.[30,31] However, maximal coronary perfusion of the entire myocardial territory is essential for accurate FFR measurement of the LM stenosis. The LM supplies the LAD and LCx territories, and sometimes the RCA through collaterals if the RCA is severely stenosed or occluded. In the absence of LAD or LCx stenosis, the LM FFR will accurately reflect the physiological relevance of the LM stenosis, but in the presence of a tandem lesion distal to the left main, hyperemic flow across the left main stenosis is decreased, resulting in an overestimation of the FFR measurement. Furthermore, more severe stenoses and larger size of the myocardial territory supplied by the downstream lesion will result in greater overestimation of FFR. While there is no data to guide the use of FFR in left main stenosis in the presence of downstream stenosis, we suggest a pull-back technique using the least diseased branch. If there is significant downstream stenosis and a borderline left main FFR (0.8-0.85), consideration of intravascular ultrasound or optical coherence tomography may help guide revascularization decisions.

Data on iFR use to evaluate left main stenosis is limited. In one small study of 52 patients with left main intermediate stenosis using iFR cutoff value of 0.9 and FFR cutoff of 0.8, there was 83% concordance in measurements. Of the 9 discordant measurements, five were iFR-positive and FFR-negative, and four were iFR-negative and FFR-positive.[32] More studies are needed to better understand the discordance.

Saphenous Vein Graft Stenosis

In the case of CABG, there are three potential competing sources of blood flow: native coronary artery, bypass graft, and collateral circulation. FFR represents the sum of all sources of blood flow and as such a value of <0.8 would still indicate ischemia within the tested coronary distribution. In patients destined for CABG, invasive coronary physiology assessment may help determine the likelihood that bypass grafts of intermediate lesions would remain patent. Within a small study of 164 patients

undergoing CABG with at least one intermediate stenosis on angiography, FFR performed at the time of pre-operative coronary angiography predicted graft patency at 1-year follow-up with bypass graft failure seen in 8.9% vs. 21.4% of functionally significant and non-significant lesions, respectively.[33]

Serial lesions and diffuse atherosclerosis

In the case of serial stenoses, flow in a single coronary lesion is impacted by a second proximal or distal lesion. FFR distal to the distal-most lesion represents the summed effect of both (or more) lesions. Evaluation of the physiologic significance of each individual lesion is best performed using the pull-back technique:

FFR is assessed distal to the distal most lesion which represents the summed effect of all lesions within the vessel. If it is >0.8, then none of the lesions are hemodynamically significant. If it is <0.8, then proceed with the pull back.

During adenosine continuous intravenous infusion, pull back while monitoring Pd/Pa will identify the lesion causing the most significant obstruction to flow. This lesion should be treated first. After revascularization of the most severe lesion, FFR assessment of the remaining lesion(s) should be performed.

In the case of diffuse atherosclerosis without a clear lesion, FFR is reduced distally and recovers gradually on pull-back without an abrupt transition point.

While FFR measurement depends on hyperemic flow, a process that is impacted by the presence of a downstream stenoses, iFR is measured during resting coronary flow and is not affected by a downstream stenosis. As such, iFR pullback technique is very useful in evaluating the severity of serial stenoses.[16] While manual pullback is routinely performed, a novel motorized system capable generating a virtual plot of iFR for each millimeter of vessel may ultimately aid in guiding revascularization of tandem or diffuse lesions.[34]

Acute Coronary Syndrome

The use of FFR or iFR is limited in the infarct-related artery. Intramyocardial hemorrhage and microvascular obstruction can limit hyperemia and impact resistance to flow along the course of the vessel. Furthermore, the severity of thrombotic lesions may be dynamic due to the presence of thrombus. However, invasive physiologic evaluation of stenosis within the non-infarct artery may be helpful. The DANAMI-3-PRIMULTI, and COMPARE ACUTE trials tested the clinical value of FFR in guiding full revascularization versus culprit only revascularization in patients presenting with STEMI. The studies found that FFR-guided non-culprit revascularization, either staged during the same hospitalization or at the time of STEMI revascularization, reduced the composite primary endpoint which included all-cause mortality, nonfatal MI, and revascularization at median of 27 months and 12 months respectively.[35,36] It is notable that neither study included an angiography-only comparator arm, and as such, the utility of physiologic assessment of the non-culprit artery during ACS over angiography alone cannot be fully determined. Pooled analysis from DEFINE-FLAIR and SWEDEHEART comparing performance of FFR and iFR in 440 patients with ACS suggested that iFR may be superior prognostic tool for deferring revascularization of non-culprit lesions in ACS.[16] In this pooled analysis, ACS patients deferred using FFR had worse outcomes compared to those deferred with stable angina (HR 0.52, p<0.05), but those deferred using iFR had similar outcomes regardless of clinical presentation (HR 0.74, p=0.37.[16]

Severe Aortic Valve Stenosis

Coronary artery disease is common (34-75%) in patients with severe aortic stenosis (AS) and portends poorer prognosis in patients being considered for aortic valve replacement (AVR).[37] In the era of transcatheter aortic valve replacement (TAVR), invasive assessment if often needed to guide percutaneous coronary revascularization. However, invasive physiologic assessment of coronary stenoses may be less accurate in the setting of severe AS. CFR is reduced in AS,[38] and hyperemia is also

impaired due to left ventricular hypertrophy which increases the resistance of the microcirculation.[39] Additionally circulating vasoconstrictors such as α-adrenoceptor agonists, vasopressin and angiotensin are increased in AS and may impair hyperemic response to adenosine.[40] Furthermore, adenosine infusion in patients with severe AS can be unsafe and result in severe hypotension. When required, intracoronary adenosine may be safer than continuous intravenous infusion. Although multiple factors influence FFR measurement in severe AS, one study in 59 patients looking at FFR measurement in 133 coronary lesions before and after TAVR found that actual FFR changes after removal of aortic stenosis were minor and only changed the indication to treat the coronary stenosis in 8 of the 133 (6%) lesions.[41] There are no prospective clinical trials investigating the value of coronary physiology measurement in intermediate coronary lesions in patients with severe aortic stenosis. A recent study underwent comprehensive evaluation of coronary physiology in 28 patients with severe AS and CAD pre- and post TAVR.[42] Whole-cycle hyperemic flow decreased post TAVR and was driven by systolic hyperemic flow. This resulted in a decrease in FFR measurements after TAVR.[42] On the contrary, the flow during the wave-free period of diastole as well as iFR measurements did not change after TAVR.[42] These findings suggested that iFR measurement may more accurately reflect coronary stenosis severity in patients with severe AS.

Future Prospects

Physiological assessment of coronary lesions has evolved from CFR to FFR to iFR. It is most valuable in guiding revascularization of lesions of moderate severity in the setting of stable angina; however, expanding indications and novel technologic advances continue to be made. Specific areas in need of further investigation include the use of iFR to guide surgical coronary revascularization, revascularization of non-culprit artery in ACS, and revascularization decisions prior to AVR. In addition, new algorithms are allowing virtual PCI planning by using iFR to predict which stenting strategy provides

the optimal physiologic outcome.[34] Another frontier that we will likely see developing is noninvasive

physiological assessment of coronary stenosis with CT-derived fractional flow reserve (FFRCT), which has

been shown to have high diagnostic accuracy when compared to invasive FFR.[43,44] Similar approaches

are being applied within the catheterization lab to derive FFR from contrast flow during invasive

coronary angiography. Initial experience with this technology has demonstrated high sensitivity,

specificity, and accuracy compared with pressure-wire derived FFR in one study of 301 patients.[45] Such

approach has a promise to eliminate the need of pressure-wire use and to portray a physiological

assessment map of the entire coronary tree.

Chapter 5: Physiological Assessment of Coronary Lesions

Tables:

Table 1: Main determinants of myocardial oxygen demand and supply

Myocardial Oxygen Demand (MVO2)	Myocardial Oxygen Supply
Heart rate	Healthy coronary and capillary circuit
Myocardial contractility	Mean arterial pressure
Myocardial wall tension	Hemoglobin concentration and function

Table 2: Definitions of coronary physiology concepts

Coronary Hyperemia	Loss of coronary arteriolar and microvascular resistance due to pharmacologic or disease states. At maximal coronary hyperemia, flow is directly proportional to the driving pressure.
Coronary Flow Reserve (CFR)	The ability of the coronary circulation to increase flow from basal level to a maximal hyperemic level

Fractional Flow Reserve (FFR)	The percentage of coronary flow expected to go distal to a coronary stenosis being assessed
Instantaneous Wave-Free Ratio (iFR)	A measure based on the wave-free portion of diastolic coronary flow that assesses the physiological impact of a coronary stenosis on the distal coronary bed

Table 3: Step-by-step technique for using sensor-tipped guidewires to evaluate for coronary stenosis

Give anticoagulation as you would with angioplasty (eg. unfractionated heparin 60-100 units/Kg)
• In the case of FFR and iFR, zero the pressure sensor to atmospheric pressure on the table prior to introducing into the body. This step is not necessary for Doppler or thermistor sensors as in the case of CFR.
• Advance the guidewire through a standard Y-connector attached to a diagnostic or guiding catheter (5F or 6F) all the way to the coronary ostium
• Give intracoronary nitroglycerin (100-200 μg) to avoid guidewire-induced vasospasm. Nitroglycerin will not affect FFR/iFR measurements (optional).
• In the case of FFR/iFR, equalize (or normalize) the sensor pressure to the guide pressure (not necessary for CFR).
• Advance the guidewire in the coronary until the sensor is >4 cm distal to the stenosis. While the sensor is at the tip of the wire in the case of CFR (Figure2), it is 3 cm proximal to the tip in the case of FFR/iFR.
• Record baseline measurements
• Induce coronary hyperemia using intracoronary or intravenous medications if indicated (i.e. for FFR and CFR, but not iFR)
• Record measurements

Table 4: Pharmacologic agents to induce coronary hyperemia

Medication	Dose	Peak Effect	Half-life	Side Effects
Adenosine IV	140 mg/Kg/min	≤1-2min	<10s	Hypotension, bradycardia, flushing, chest pressure, bronchospasm (avoid in severe COPD)
Adenosine IC	60-80 µg LCA 30-40 µg RCA	5-10s	<10s	Transient AV block if injected in RCA
Papaverine IC	15mg LCA 10mg RCA	30-60s	2min	Transient QT prolongation and T wave abnormalities, ventricular tachycardia (very rare)
Dobutamine IV	10-40 µg/Kg/min	1-2min	3-5min	Tachycardia, hypertension

Table 5: Troubleshooting FFR Measurement

Insufficient hyperemia	Check infusion, pump system, and lines.
	Infuse through central vein.
	Avoid Valsalva maneuver during infusion.
	Guiding catheter may fail to seat for intracoronary drug delivery or may obstruct flow.
Hemodynamic artifacts	Avoid damped pressure waveforms. Flush guiding catheter.
	Large guiding catheter may obstruct coronary inflow and should be disengaged.
	Guiding catheters with side holes may create ostial pseudostenosis.
	Identify pressure wire signal drift or erroneous zero.
	Poor velocity envelope requires tip manipulation to recapture signal.
Safety considerations	Guiding catheter or wire may cause vessel trauma (not different from regular angioplasty wires).
	Thrombus and vasospasm are possible.

Table 6: Patient outcome trials of FFR and iFR

Trial	Year	Sample Size	FFR/iFR	Inclusion	Randomization (N)	Outcomes
DEFER [19]	2001	325 (91 FFR deferred)	>0.75	Planned PTCA without known ischemia	BMS-PCI vs. FFR-guided deferral	Rate of death, nonfatal MI and repeat revascularization at 1 year was lower in the FFR group (13.2%) compared to the angiography group (18.3%, p=0.02)
FAME [20]	2009	1005 (509 FFR-guided)	≤0.8	Multivessel CAD undergoing PCI	Angiography-guided vs. FFR-guided DES-PCI	Rate of death, nonfatal MI and repeat revascularization at 1 year was lower in the FFR group (18.3%) compared to angiography (13.2%; p=0.02)
FAME2 [21]	2012	888 (447 FFR-guided)	≤0.8	Stable CAD for whom PCI is being considered	FFR-guided DES-PCI +OMT vs. OMT alone	Stopped prematurely. Rate of death, MI, or urgent revascularization lower in FFR group (12.7% compared to OMT (4.3%, HR 0.32, p<0.001)
DEFINE-FLAIR [23]	2017	1242 (iFR) 1250 (FFR)	FFR 0.83±0.09 iFR 0.91±0.09	CAD patient with stenosis (40-70%) of questionable physiology	FFR vs. iFR	MACE at 1 year, noninferior between iFR (6.8%) and FFR (7%, P<0.001).
iFR SWEDEHEART [22]	2017	1018 (iFR) 1019 (FFR)	FFR 0.81±0.1 iFR 0.91±0.1	Stable angina or ACS with indication of physiologically guided assessment of CAD	FFR vs. iFR	Composite of death, nonfatal MI, or unplanned revascularization at 1 year noninferior

					between iFR (6.7%) and FFR (6.1%, P=0.007)

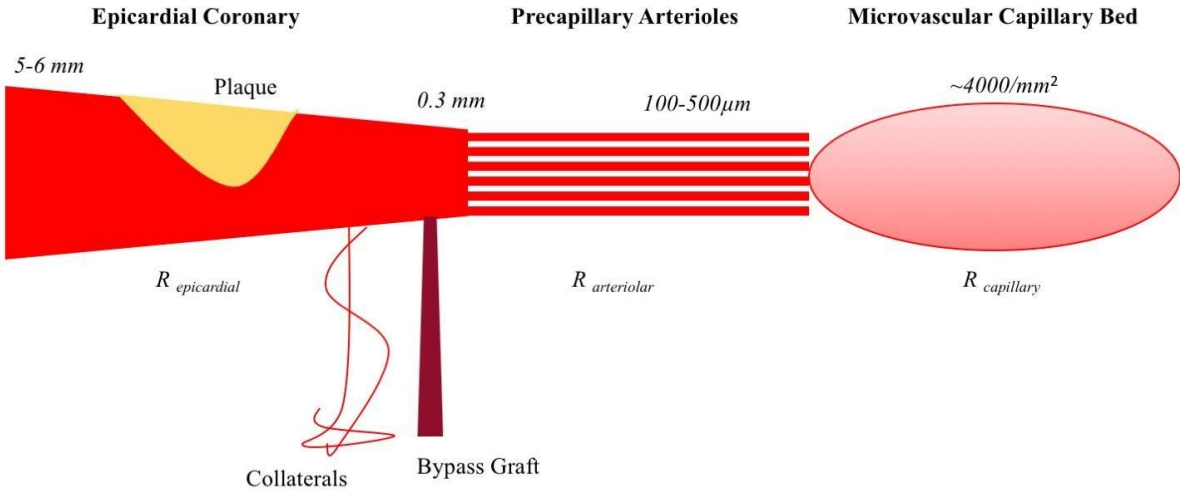**Figures**

Figure 1: Schematic of coronary circulation and regulation

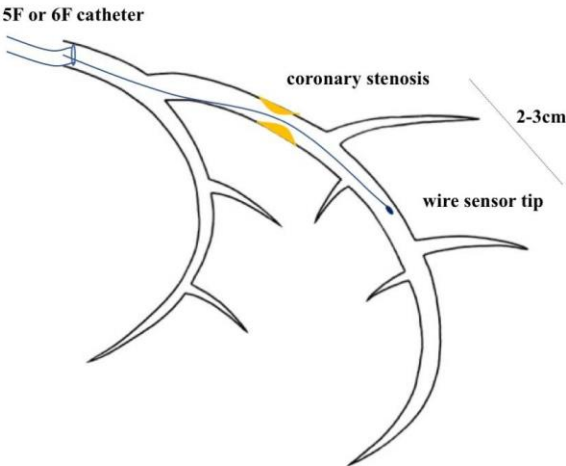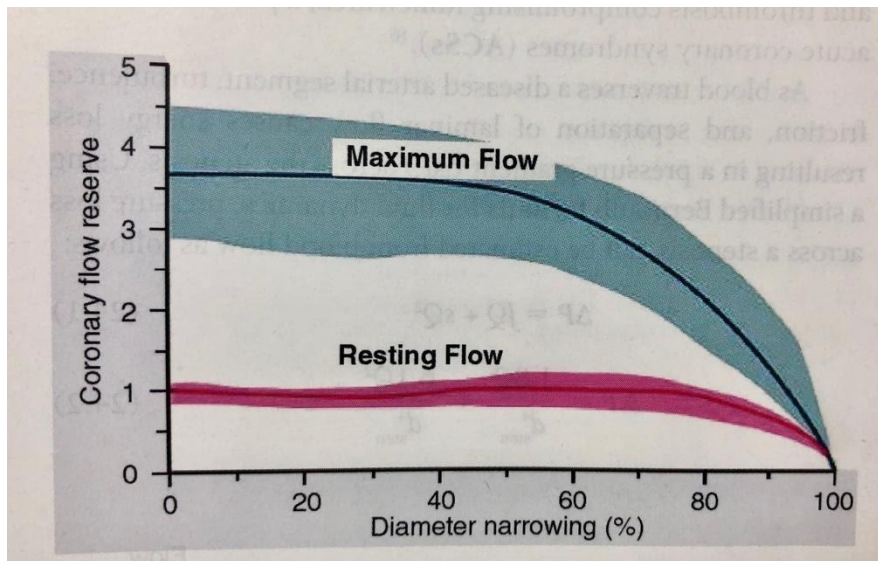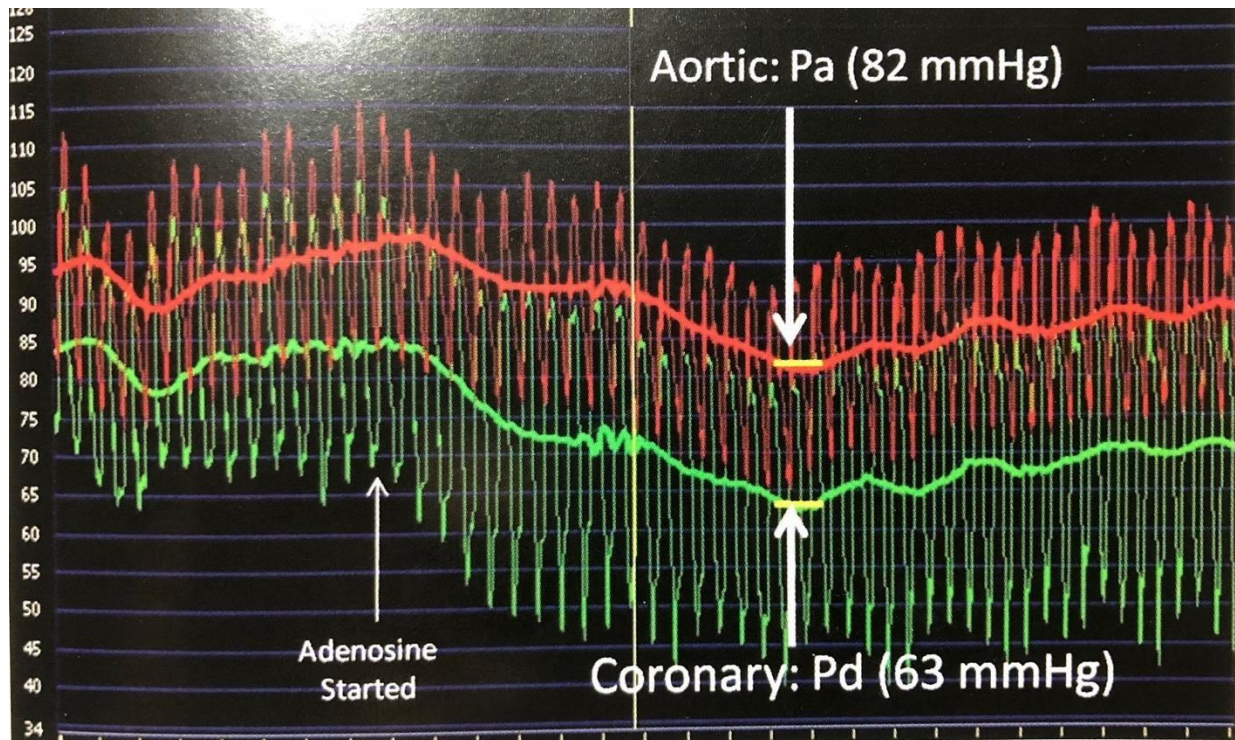Figure 2: Sensor-tipped guidewire placement

Figure 3: Coronary flow reserve expressed as a ratio of maximum to resting flow as a function of diameter narrowing

Adapted from: Gould KL, Lipscomb K and Hamilton GW. Physiologic basis for assessing critical coronary stenosis. Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. Am J Cardiol 1974;33:87-94.
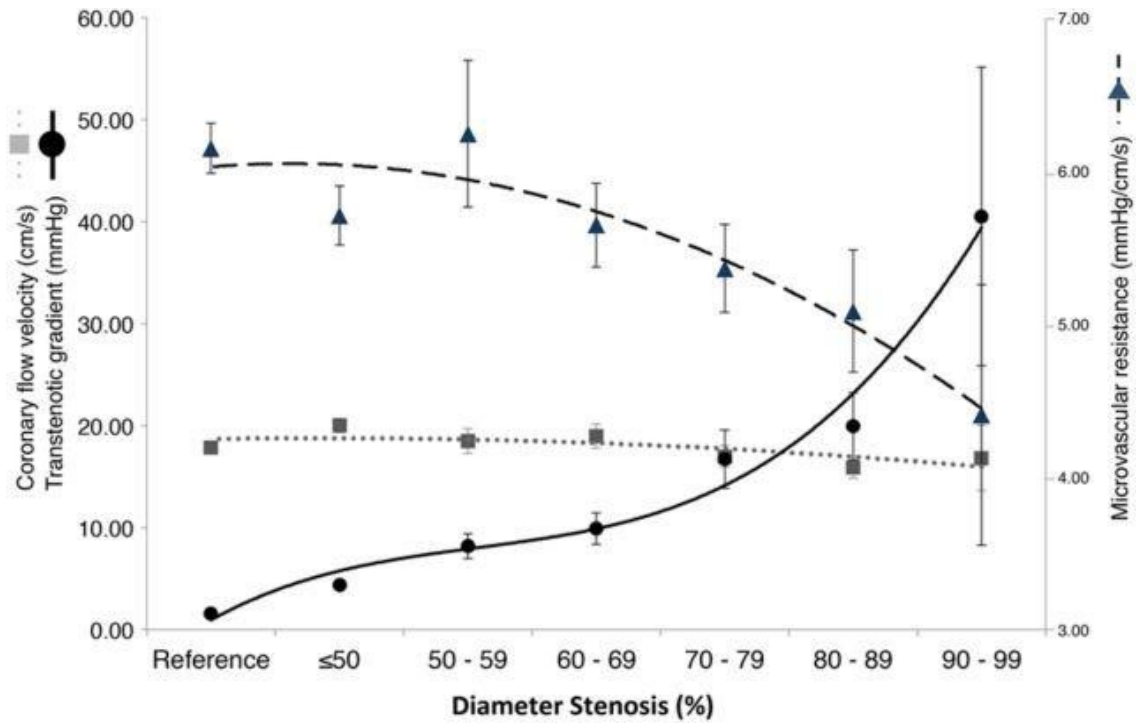
Modified by: Moscucci M. Grossman & Baim's Cardiac Catheterization, Angiography, and Intervention. 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2013.

Figure 4: FFR Measurement. Pressure tracings depict aortic Pa and distal coronary Pd pressures before and after induction of maximal coronary hyperemia with adenosine. The FFR in this case is Pd/Pa=63/82=0.77.
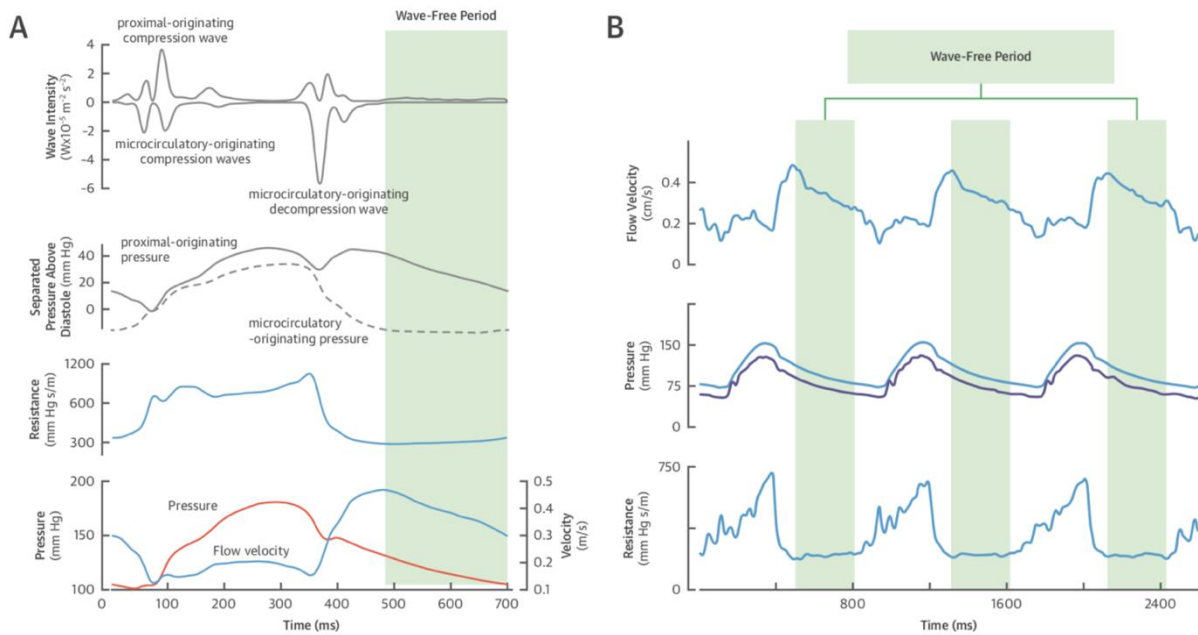

Adapted from: Moscucci M. Grossman & Baim's Cardiac Catheterization, Angiography, and Intervention. 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2013.

Figure 5: Illustration of coronary autoregulation in the face of increasing stenosis

Adapted from: Nijjer SS, de Waard GA, Sen S, et al. Coronary pressure and flow relationships in humans: phasic analysis of normal and pathological vessels and the implications for stenosis assessment: a report from the Iberian-Dutch-English (IDEAL) collaborators. Eur Heart J 2016;37:2069-80.

Figure 6: Wave intensity analytics of coronary blood flow

Adapted from: Gotberg M, Cook CM, Sen S, et al. The Evolving Future of Instantaneous Wave-Free Ratio and Fractional Flow Reserve. J Am Coll Cardiol 2017;70:1379-1402.

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