



Physiological Lesion Assessment in STEMI and Other Acute Coronary Syndromes

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15.1 Introduction

Although coronary artery disease (CAD), the most common cause of morbidity and mortality in the USA, is identified principally by coronary angiography, the relationship between the degrees of angiographic narrowing (% stenosis) is poorly correlated to its functional response (e.g., stress testing or intracoronary physiology). Over the past two decades, the use of in-lab coronary physiology has demonstrated that angiography alone is not accurate in determining ischemia for intermediate lesions. Compared with angiographically guided percutaneous coronary intervention (PCI), physiology-guided PCI is associated with improved clinical outcomes and cost-effectiveness. The most commonly used invasive physiologic indices include fractional flow reserve (FFR), coronary flow reserve (CFR), and instantaneous wave-free ratio (iFR). Understanding applied coronary physiology and the tools for measuring it in the cath lab is paramount to best clinical decision-making in interventional cardiology.

While FFR has been well validated in patients with chronic stable coronary artery disease, in ACS, physiological assessment of the culprit coronary artery is not performed because reduced flow to the myocardial bed can lead to false negatives. However, FFR can be measured in the non-culprit vessels because theoretically it is presumed that flow is not reduced to myocardial regions remote for the culprit

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infarct vessel territory. This chapter will be to review the different methods of invasive physiological assessment of coronary stenoses and their outcomes with a focus on their practical applications in patients with ST-elevation myocardial infarction (STEMI) and other ACS.

15.2 ACS and FFR Case

A 58-year-old man presented with 1 day of intermittent chest pain. His medical history was significant for hypertension and hyperlipidemia. The ECG showed anterior T wave inversions and his troponin was 4. Urgent cardiac catheterization revealed a 95% stenosis in the proximal left circumflex (LCX) artery and a 60% stenosis in the proximal left anterior descending (LAD) artery (Figs. 15.1 and 15.2). The presumed culprit vessel, the left circumflex artery, was stented (Fig. 15.3). Turning to the LAD, should we proceed to stent, defer and treat medically, or measure FFR and treat based on the ischemic potential of the lesion? Based on the evidence (see below), FFR of the non-infarct LAD artery is not only reasonable but favored to reduce operator uncertainty and shorten the current and future hospitalizations. As the lesion was fairly remote from the injured lateral wall myocardial zone, FFR should be valid (especially if positive). FFR of the proximal LAD lesion was 0.78 (Fig. 15.4) and stented (Fig. 15.5) in the same procedure. The patient was discharged uneventfully.

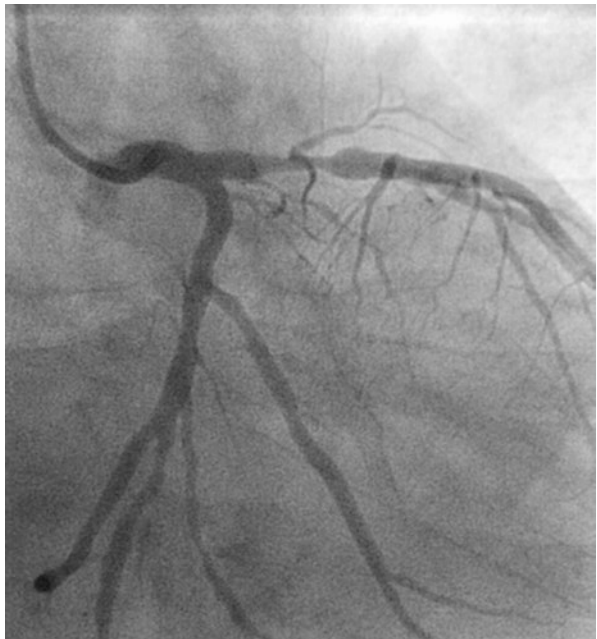


Fig. 15.1 Cineangiogram from ACS and FFR case (LAO cranial and RAO projections) showing 95% circumflex and 60% LAD lesions

Fig. 15.2 Cineangiogram from ACS and FFR case (LAO Caudal) showing 95% circumflex and 60% LAD lesions



Fig. 15.3 Cineangiogram frame after circumflex stenting



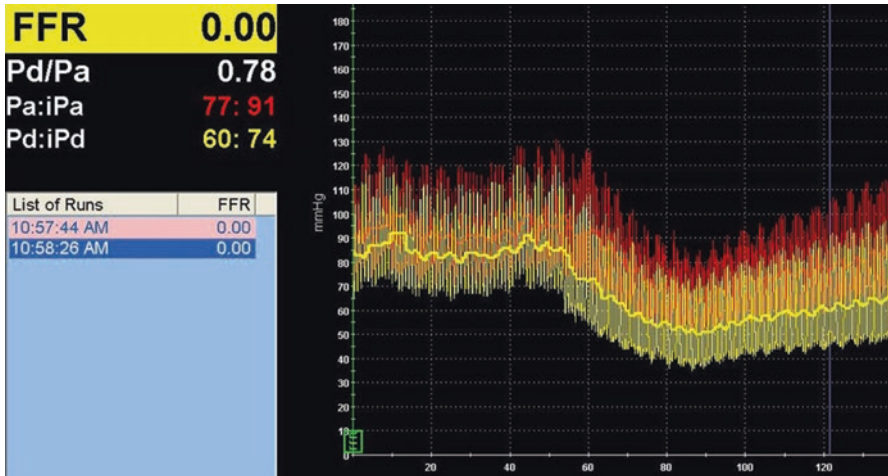


Fig. 15.4 LAD FFR (Pd/Pa) is 0.78

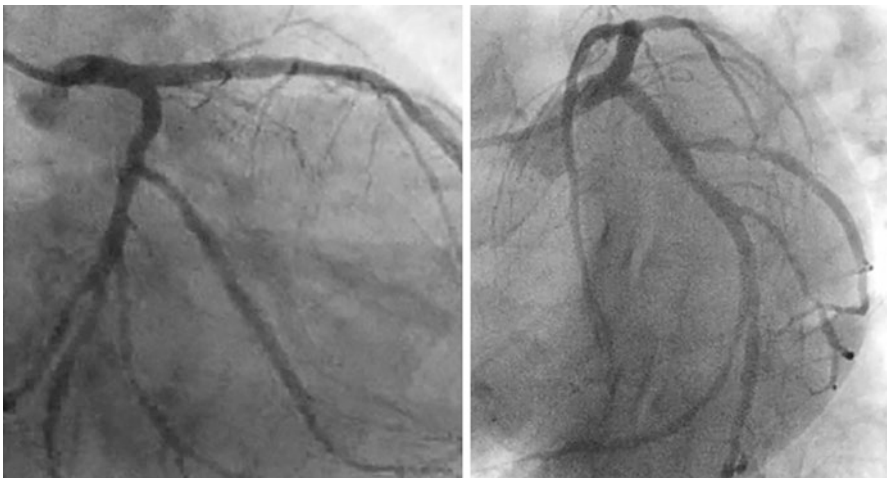


Fig. 15.5 Cineangiogram frame after LAD stenting

15.3 Fractional Flow Reserve Foundations

FFR is the ratio of the mean coronary pressure distal (Pd) to a stenosis to the mean aortic pressure (Pa) at maximal hyperemia when myocardial resistance is at its presumed absolute minimum. This condition permits pressure and flow to be linearly related, and thus the ratio represents the fraction of normal coronary blood flow across a stenosis with a normal value being 1 (i.e., Pd = Pa). FFR requires the

induction of maximal hyperemia, most commonly with an intravenous infusion or intracoronary bolus of adenosine. Initial validation studies in stable angina patients have shown that an FFR <0.75, a reduction in coronary perfusion pressure by 25% of normal, was indicative of ischemia on stress testing. Additional investigations comparing FFR to different types of stress tests found that nearly all were negative when FFR > 0.80 and positive with FFR < 0.75, thereby establishing a gray zone of uncertainty. Clinical trials opted to use the upper end of the gray zone, 0.80 as the clinical threshold for outcome decision-making. This threshold is endorsed by the American College of Cardiology (ACC), American Heart Association (AHA), Society for Cardiovascular Angiography and Interventions (SCAI), and European Society of Cardiology (ESC) in their guidelines for PCI.

The outcomes of patients within the gray zone of 0.75–0.80 have been studied by Adjedj J et al. [1] who found that among 238 patients with gray-zone FFR, revascularization was associated with a significantly reduced risk of major adverse cardiovascular events (MACE) compared with medical therapy alone (Fig. 15.6) [1, 2]. On the other hand, the risk of MACE was not significantly different between deferred and revascularized lesions for FFR ≥0.76 (including the gray zone) in the large, prospective, multicenter Interventional Cardiology Research Incooperation Society Fractional Flow Reserve (IRIS-FFR) registry [3]. For patients with an FFR between 0.75 and 0.8, the decision to revascularize requires the operators’ synthesis of findings based on the clinical context of the patient.

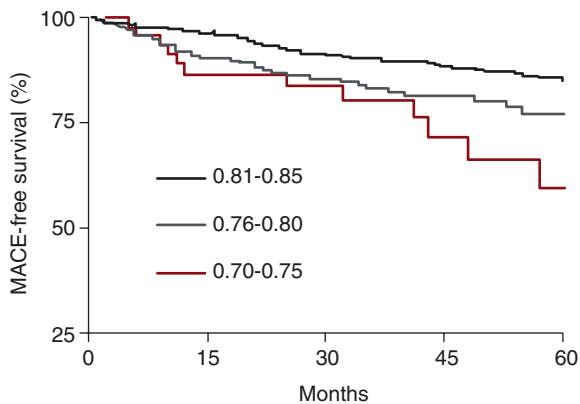


Fig. 15.6 MACE-free survival (%) in patients of the medical therapy group stratified by FFR strata (log-rank, 15; $P < 0.001$). FFR fractional flow reserve, MACE major adverse cardiovascular event. Source: Adjedj J, et al. *Circulation*. 2016;133:502–508 [1]

691	335	149
266	113	46
53	24	8

15.4 Fundamentals of Fractional Flow Reserve in STEMI and Other ACS

The utility of FFR to guide revascularization of intermediate lesions in patients with chronic stable multivessel coronary artery disease has been validated in several landmark clinical trials including the Fractional Flow Reserve to Determine the Appropriateness of Angioplasty in Moderate Coronary Stenosis (DEFER), FFR Versus Angiography for Multivessel Evaluation (FAME 1), and FFR-Guided Percutaneous Coronary Intervention Plus Medical Treatment Versus Medical Treatment Alone in Patients with Stable Coronary Artery Disease (FAME 2) trials [4–6]. The utility of FFR in acute coronary syndrome (ACS) has been controversial.

During a STEMI, the degree of damage to the infarct-related or culprit myocardial bed in the first hours of the injury makes the accuracy of FFR in the culprit artery highly questionable when >0.80 . Since microcirculatory injury reduces flow, a low flow across a stenosis can produce a high FFR. Depending on the severity of the infarct, flow may recover in the days following the infarct, and hence the prior negative FFR may become positive, i.e., <0.80 . To recap, a sub-hyperemic response to adenosine would result in an underestimation of stenosis severity so that an FFR >0.80 at the time of STEMI may initially be considered nonsignificant, but it may decrease several days later as the injured myocardial bed recovers and flow increases to the area. In other words, it may create a false negative. However, an FFR of <0.80 is truly functionally significant (Fig. 15.7).

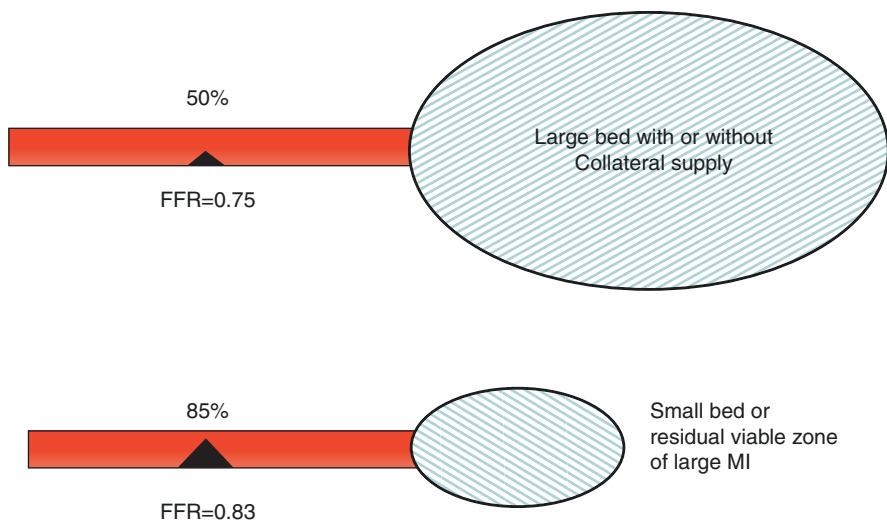


Fig. 15.7 STEMI and FFR cartoon on influence of myocardial bed size. The upper image shows a 50% stenosis supplying a large myocardial bed. Because flow to the bed is large, the FFR is 0.75. After a myocardial infarction of this bed, the injured myocardium has lower flow, and despite a more severe stenosis of 85%, the FFR is now higher 0.83

In the case of the non-culprit ACS artery, the flow to the myocardium supplied by non-infarct-related arteries should not be as affected as the culprit artery. The microcirculation should be normal, and FFR should accurately reflect the functional significance of a lesion in a non-culprit artery. All studies investigating the utility of FFR in STEMI or other ACS have assessed the non-culprit arteries. There are several studies that have found the microcirculation of the remote region can be abnormal [7], and the closer the non-culprit vessel is to the STEMI territory, the higher the potential for a false negative (due to impaired border zone microcirculatory function and less inducible hyperemia).

15.5 Fractional Flow Reserve and STEMI Revascularization Guidance

Traditionally, treating only the culprit vessel during STEMI has been considered superior to treating all lesions supported in part by several meta-analyses, and non-randomized registry studies showed that treating all vessels at the same time as the STEMI culprit was associated with more adverse events. Even the 2015 update of the 2013 ACC/AHA/SCAI STEMI guidelines gave a class III (do not do) recommendation to intervening on a non-infarct-related artery at the time of primary PCI in patients who are hemodynamically stable [8].

However, several recent studies have shown FFR is accurate in ACS, including the Fractional Flow Reserve Versus Angiography in Guiding Management to Optimize Outcomes in Non-ST-Elevation Myocardial Infarction Cardiac Magnetic Resonance (FAMOUS NSTEMI CMR) substudy that showed an excellent accuracy of FFR <0.80 for predicting perfusion defects on cardiac magnetic resonance [9]. Furthermore, multiple trials including the Preventive Angioplasty in Acute Myocardial Infarction (PRAMI), Complete Versus Lesion-Only Primary PCI Trial (CvLPRIT), and Third Danish Study of Optimal Acute Treatment of Patients With STEMI: Primary PCI in Multivessel Disease (DANAMI3-PRIMULTI) have shown that revascularizing non-culprit arteries in a STEMI, either at the time of primary PCI or later in a staged manner, reduce risk of MACE by a relative 44–65% compared with culprit-only PCI (Fig. 15.8) [10–12].

The PRAMI trial looked at 435 patients with acute STEMI and multivessel coronary artery disease. Patients were randomized to receive immediate preventive PCI in non-infarct arteries with stenosis >50% or no further PCI procedures. Recruitment was stopped early due to a highly significant between-group difference in the incidence of primary outcome favoring preventive PCI. Preventive PCI reduced the combined rate of cardiac death, nonfatal MI, or refractory angina by 65%, an absolute risk reduction of 14% over 23 months. Of note, revascularization was not included as a primary outcome. In this study, the severity of disease in non-infarct arteries was determined by angiographic assessment alone [10]. The effect of using FFR to determine the significance of disease in non-infarct arteries in STEMI patients was subsequently studied in DANAMI3-PRIMULTI and COMPARE-ACUTE trials.

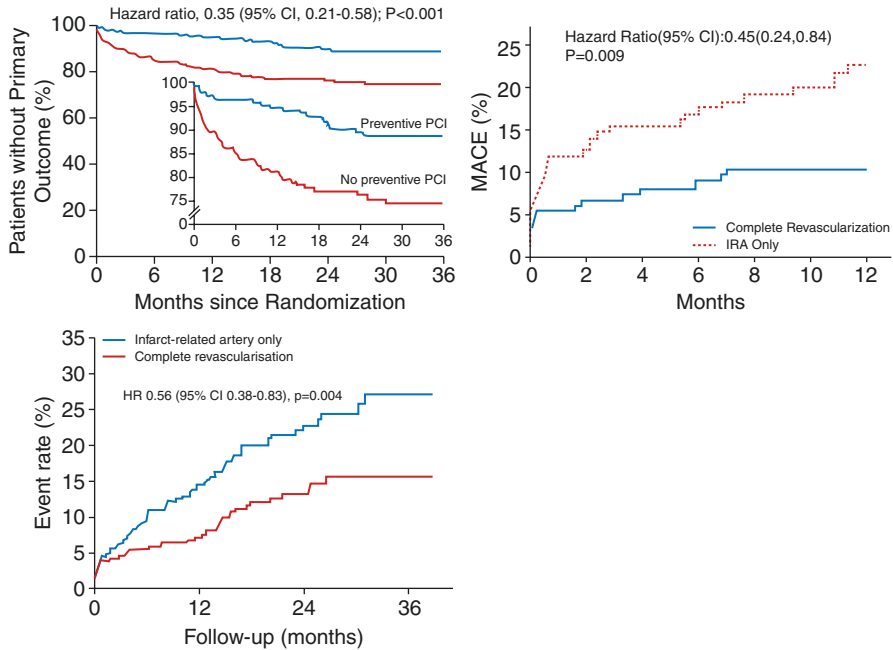
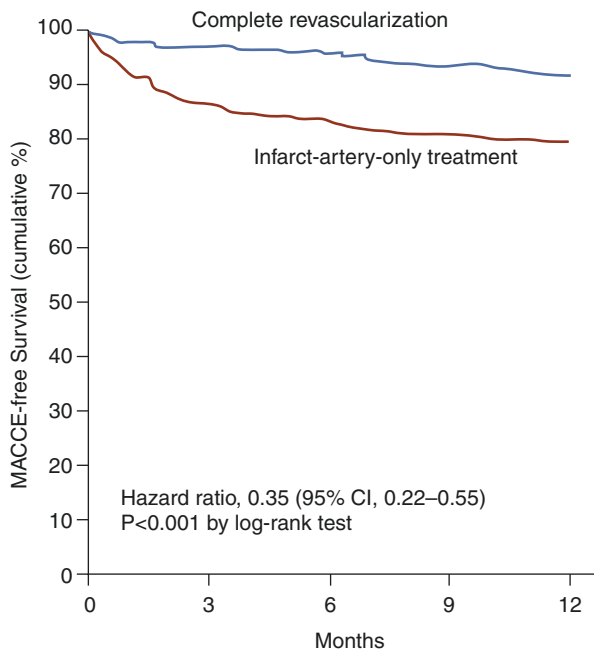


Fig. 15.8 Kaplan-Meier curves of PRAMI, CvLPRIT, and DANAMI3-PRIMULTI. Source: Wald, et al., 2013; Gershlick, et al., 2015; Engstrom, et al., 2015 [10–12]

DANAMI3-PRIMULTI was an open-label, randomized controlled trial that enrolled 627 patients with STEMI who had ≥ 1 clinically significant coronary stenosis in addition to the culprit lesion. After successful PCI to the culprit lesion, patients were randomized into no further invasive treatment or complete FFR-guided revascularization before discharge. A threshold of FFR < 0.80 was used, and FFR was performed 2 days after primary PCI to avoid the risk of invalid FFR measurements inferred from acute changes in macrovascular tone or microvascular flow obstruction. The primary endpoint of a composite of all-cause mortality, nonfatal reinfarction, and ischemia-driven revascularization of lesions in non-infarct-related arteries was significantly lower in the complete revascularization group (13%) compared with the infarct-related-only group (22%). The favorable effect was driven by significantly fewer revascularizations. A substudy of the DANAMI3-PRIMULTI trial found that the benefit of staged FFR-guided complete revascularization was observed primarily in patients with three-vessel disease and at least one non-infarct-related stenosis with a $\geq 90\%$ diameter (Fig. 15.9) [13].

In the Fractional Flow Reserve-Guided Multivessel Angioplasty in Myocardial Infarction, COMPARE-ACUTE trial, 885 patients with STEMI and multivessel disease who had undergone primary PCI of the infarct-related artery were randomized to undergo FFR-guided complete revascularization of non-infarct-related coronary arteries or no revascularization of non-infarct-related arteries. Unlike DANAMI3-PRIMULTI, FFR of the non-infarct-related artery was done in the acute STEMI

Fig. 15.9 Results from the DANAMI3-PRIMULTI study. In STEMI patients, the primary composite endpoint of all cause death, reinfarction, and ischemia-driven revascularization was lower in those who received FFR-guided complete revascularization compared to infarct-related PCI alone. The primary endpoint was further reduced in patients with at least one non-infarct-related stenosis $\geq 90\%$ compared to those with $<90\%$. *FFR* fractional flow reserve, *STEMI* ST-elevation myocardial infarction. Source: Lønberg, et al., 2017 [13]



setting, during the time of primary PCI. At 1 year those who underwent FFR-guided complete revascularization of non-infarct-related arteries had a lower risk of death (1.4 vs. 1.7%), MI (2.4 vs. 4.7%), revascularization (6.1 vs. 17.5%), and cerebrovascular events (0.0 vs. 0.7%) compared with those who were treated for the infarct-related artery only [14]. Approximately half of the non-infarct-related artery lesions that were angiographically significant were not physiologically significant by FFR (≥ 0.80).

15.6 FFR in Other Acute Coronary Syndrome

FFR also plays a role in patients with non-STEMI ACS. This population may be more difficult to study than patients with STEMI because the culprit vessel is not always clear in NSTEMI or unstable angina (USA) group. The Impact of Routine Fractional Flow Reserve on Management Decision and 1-Year Clinical Outcome of Patients with Acute Coronary Syndrome (PRIME-FFR) pooled the results of the French FFR Registry (R3F) and the Portuguese Study on the Evaluation of FFR-Guided Treatment of Coronary Disease (POST-IT). A total of 1983 patients with NSTEMI or unstable angina (USA) were included in the large, international prospective study. They found that the use of FFR was associated with a high rate of reclassification of treatment. The percent of patients with ACS who were reclassified by FFR was similar to those with non-ACS (38 vs. 39%, $P = \text{NS}$). There was no significant difference in MACE (8.0 vs. 11.6%,

$p = 0.2$) or symptoms (92.3 vs. 94.8%, $p = 0.25$) in patients reclassified based on FFR compared to those who were not reclassified. Fewer patients with ACS were reclassified from revascularization to medical treatment compared with those with non-ACS ($P = 0.01$). Furthermore, deferral to medical treatment based on FFR was as safe in ACS as it was in non-ACS patients. Patients with disregarded FFR had higher rates of MACE [15].

The ideal threshold for FFR in the ACS population has been debated. The FFR threshold of 0.80, which is used to determine functional significance in the stable ischemic heart disease (SIHD) population, was applied to the ACS population in the above studies. The accuracy of this threshold for ACS patients has been challenged. Hakeem et al. found that using the standard FFR threshold of 0.80 for clinical decision-making in ACS patients was associated with a threefold increase in the risk of subsequent MI and target vessel failure compared with SIHD patients and advised caution in using FFR-derived values for clinical decision-making in patients with ACS. They found that ACS patients had a higher FFR threshold of functional significance, and those with an FFR <0.85 had significantly higher event rates than those with FFR >0.85 [16].

Lee et al. found that regardless of the FFR value (FFR = 0.8–1.0), non-culprit lesions of ACS had a more than twofold higher rate of MACE than that of SIHD. The clinical outcomes of 449 non-culprit lesions in 301 patients with ACS were compared with the outcomes of lesions in patients with SIHD. The primary outcome of MACE (a composite of cardiac death, target vessel-related MI, and ischemia-driven revascularization) was higher in the ACS population (3.8 vs. 1.6%, $HR_{adj} 2.97$, 95%

Table 15.1 Table of key trials in FFR and ACS

	PRAMI	CvLPRIT	DANAMI3-PRIMULTI	COMPARE-ACUTE	PRIME-FFR
Study design	Single-blind randomized	RCT	RCT	Prospective randomized trial	Prospective study
N	465	296	627	885	1983
Follow-up period	23 months	296 months	627	36 months	12 months
Long-term mortality	Complete revascularization better	Complete revascularization better	Complete revascularization better	Complete revascularization better	Deferral based on FFR is safe in ACS
Assessment of non-culprit lesion	Angiography	Angiography	FFR	FFR	FFR
Timing	Immediate complete revascularization	Immediate complete revascularization or staged PCI	Staged PCI	Immediate complete revascularization or staged PCI	--

Source: Wald, et al., 2013; Gershlick, et al., 2015; Engstrom, et al., 2015; Smits, et al. 2017; Van Belle, et al. 2017 [10–12, 14]

CI: 1.23–7.17, $p = 0.016$) after 2 years and was mainly driven by a higher rate of ischemia-driven revascularization [17]. Table 15.1 summarizes the key trials of FFR in STEMI and other ACS.

15.7 Coronary Flow Reserve and the Index of Microvascular Resistance

Coronary flow reserve measures flow through both the epicardial resistance conduit and the microcirculation. It represents the vasodilator capacity of the coronary vascular bed during hyperemia and is another validated index of the functional significance of a coronary stenosis. Since most resistance occurs in the microcirculation, it is a primary method to measure microvascular flow. It is well-established that the failure to achieve myocardial reperfusion in a STEMI results in myocardial hemorrhage and infarct. Despite timely reperfusion therapy with PPCI, microvascular obstruction still occurs in up to 25–50% of STEMI patients who go on to have a higher degree of MACE. Therefore, measuring microvascular function may be a useful way to risk stratify STEMI patients.

In a STEMI, the microvasculature of the myocardium supplied by the non-infarct coronary arteries, in addition to the infarct-related artery, is abnormal. Cheng et al. evaluated 18 patients with acute MI and found that the CFR in the remote region (i.e., the region supplied by the non-infarct artery) was linked to CFR in the infarcted region and correlated with infarct size and severity. Even after successful PCI, the CFR in the myocardium supplied by the infarct-related artery was lower than normal [18]. A CFR > 2.0 is generally considered normal.

The index of microvascular resistance (IMR) is a direct invasive measure of microvascular resistance. It is defined as the distal coronary pressure multiplied by the mean transit time of a 3 mL bolus of saline at room temperature during maximal coronary hyperemia. It has been less well studied compared to FFR, but it may be a useful tool in evaluating the microcirculation during primary PCI. An IMR > 40 is considered abnormal and has been found to be associated with microvascular pathology, changes in LV function and EDV, and all-cause death and heart failure [19]. In a meta-analysis of six studies, a median IMR > 40 was an independent predictor of death [20]. In some studies, the combination of a high IMR and reduced CFR enhances the detection of microvascular obstruction, but in other studies, the combination did not have any prognostic value [21, 22].

An invasive measurement of the coronary microcirculation at the end of primary PCI may be a more sensitive measure of successful reperfusion compared with standard tests such as angiography or ECG. This could help identify high-risk patients who may benefit from continued treatment such as with glycoprotein IIb/IIIa inhibitors or intracoronary thrombolysis.

15.8 Instant Wave-Free Ratio

iFR is a resting index used to assess the severity of an intracoronary stenosis. It measures the ratio of the Pd to the Pa during an isolated period of diastole (i.e., the “wave-free period”). It is an attractive alternative to FFR because it does not require hyperemia and therefore has a lower incidence of patient discomfort, side effects, and a shorter procedural time. iFR has been shown to be non-inferior compared to FFR in two large, multicenter, randomized controlled trials: the Instantaneous Wave-Free Ratio Versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome (iFR-SWEDEHEART) trial and the Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularization (DEFINE-FLAIR) trial. Both included patients with NSTEMI ACS, while DEFINE-FLAIR also included STEMI patients. The iFR-SWEDEHEART trial included 2037 patients with stable angina, unstable angina, or NSTEMI and randomly assigned them to undergo either iFR- or FFR-guided revascularization. For patients with unstable angina or NSTEMI, only non-culprit lesions were evaluated, and the culprit lesions were managed as clinically indicated. The rate of primary endpoint (composite of death from any cause, nonfatal MI, or unplanned revascularization within 12 months after the procedure) was not significantly different between the iFR and FFR groups [23].

In the DEFINE-FLAIR trial, 2492 patients with CAD were randomized to have iFR-guided or FFR-guided coronary revascularization. Patients with ACS were included but only non-culprit vessels and outside of primary intervention during acute STEMI. The primary endpoint of a composite of death from any cause, non-fatal MI, or unplanned revascularization did not differ significantly between groups. Additionally, the number of patients in the iFR group had lower rates of adverse side effects from the procedure (3.1 vs. 30.8%) and a shorter median procedural time (40.5 vs. 45.0 min) compared with the FFR group [24].

Conclusion

The physiological assessment of coronary stenoses is an integral part of the decision-making process for interventional cardiologists. Functional assessment in the STEMI and other ACS situation should consider the altered milieu of the microvasculature in an infarcted territory. While FFR is not valid in the infarct-related artery until recovery of the injured myocardium, the microcirculation in the non-infarct-related artery is not generally affected to reduce the accuracy of FFR and iFR. Future applications of translesional physiologic indices will expand the use of these methods into unique clinical scenarios to improve outcomes and prognosis.

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KMY has no conflict of interest to declare.

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