

# Flow Reserve in Patients with Myocardial Infarction

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Miniaturised sensors can nowadays be mounted on angioplasty guide wires to assess pressure, flow velocity, and temperature. The excellent mechanical properties of these sensor-tipped wires revived the interest in the physiological approach of coronary artery disease. Fractional flow reserve (FFR) and coronary flow reserve (CFR) are two indices used to assess the severity of an epicardial stenosis detected at angiography.

This review focuses on the use of FFR and CFR in the setting of myocardial infarction. This article is not intended to be an exhaustive review of the various concepts related to myocardial flow reserve, for which readers are referred elsewhere<sup>1</sup>.

## Definitions

FFR represents the ratio of normal to maximal myocardial blood flow. Stated in another way, FFR is the ratio of maximal myocardial flow in the presence of the stenosis to maximal myocardial flow in the absence of

the stenosis<sup>2,3</sup>. FFR measurement requires the use of a pressure monitoring guide wire and is calculated as the ratio of distal coronary pressure to aortic pressure obtained simultaneously during maximal hyperemia.

CFR represents the ratio of hyperemic to resting blood flow. In the catheterization laboratory, CFR can be measured from coronary blood flow velocity (Doppler wire)<sup>4</sup> or, more recently, by applying the principle of thermodilution<sup>5</sup>.

The definition and some key characteristics of FFR and CFR are summarized in table 1 and illustrated in figure 1.

## FFR and CFR in patients with remote infarction

With respect to FFR and CFR the presence of a prior myocardial infarction (MI) in the distribution area of the stenosis under study induces two major changes: (1) the mass of viable myocardium is smaller and (2) infarct related resistive vessel dysfunction might blunt maximal hyperemic response (figure 2).

Uren et al. indeed demonstrated that basal and hyperemic myocardial flows per gram or perfusable tissue are lower in infarcted regions than in regions remote from the infarction up to 6 months after MI<sup>6</sup>. In addition, Claeys et al. observed that for similar degrees of stenosis, coronary flow velocity reserve is lower in regions with, than in regions without prior MI

both before and after angioplasty<sup>7</sup>. The mechanisms responsible for a reduced basal flow remain speculative and include the decreased oxygen consumption in the residual viable myocardium, inappropriate constriction of both the epicardial and resistance vessels distal to the site of the coronary thrombosis, “stunning” of the resistance vessels, and partial obliteration of the microvasculature.

## Ischemic threshold of FFR and CFR after prior MI

In patients with normal left ventricular function a well-defined cut-off value of FFR has been shown to accurately distinguish stenoses capable (FFR < 0.75) of inducing myocardial ischemia from those that are not (FFR ≥ 0.75)<sup>9-15</sup>. The corresponding cut-off value for CFR varies in the literature from 1.6<sup>16</sup> to 2.5<sup>17</sup>. This large gray zone renders CFR-based decision-making difficult. Due to the infarction-induced changes in myocardial mass and in microvascular reactivity it is questionable whether the established ischemic threshold for FFR and CFR are valid for clinical decision making in patients with prior MI.

To the best of our knowledge, this was never investigated for CFR. To determine whether the FFR value of 0.75 may apply to patients with prior MI, we studied 57 patients who sustained a MI at least 6 days earlier<sup>18</sup>. FFR measurements were compared to

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**Table 1:** Characteristics of FFR and CFR

	FFR	CFR
<u>Theoretical definition:</u>	Fraction of normal to maximal myocardial blood flow	Ratio of hyperemic to resting flow.
<u>Partical definition (for the interventionalists):</u>	FFR tells to what extent myocardial flow will increase after removal of the epicardial resistance by PCI. e.g.: If FFR is 0.45, PCI should induce an increase in maximal flow of an additional 55% of normal maximal blood flow. If FFR is 0.85, PCI should induce an increase in maximal flow by an additional 15% of normal maximal blood flow.	CFR gives information on both the epicardial resistance and the microvascular resistance (see fig 1). It does not allow to distinguish between the two components. e.g. If CFR is 1.5 before PCI, it is impossible to predict whether it will increase to 1.8 or to 3.5 after PCI.
Normal value	1	3-6
Ischemic threshold	0.75 (-0.80)	1.8 – 2.5
Collaterals	Collateral flows is taken into account	?
Hyperemia	Only hyperemic (simultaneous) pressure measurements needed for CFR	Resting + hyperemic (not simultaneous) flow index measurements
Influence of systemic hemodynamic	Almost absent  → low variability	Large influence of changes in blood pressure, HR and contractility on resting flow  → large variability

flow maldistribution at Tc-sestamibi SPECT. Only the studies that reverted from positive before revascularization to negative after revascularization were considered truly positive or truly negative, respectively. The sensitivity, specificity, positive and negative predictive values of the 0.75 value of FFR were 87%, 100%, 89% and 94%, respectively (figure 3).

In addition, in patients with residual flow maldistribution, FFR was significantly lower and LVEF significantly higher than in patients without residual reversible flow maldistribution, even though stenosis severity was similar in both groups (figure 4).

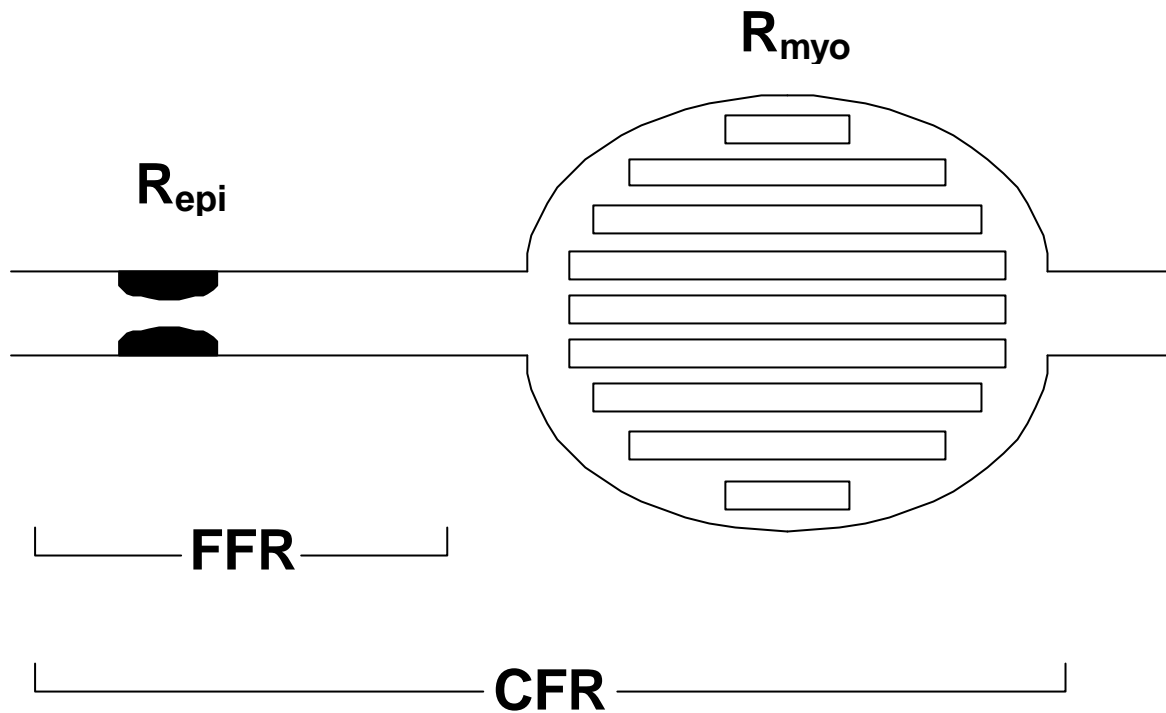
Taken together, these data illustrate the inter-relationship between stenosis severity, epicardial blood supply, myocardial mass, and ischemic threshold: the smaller the infarcted area (and thus the better preserved the LVEF and the larger the reversible perfusion defect), the lower the FFR for a given degree of stenosis. Because after

MI, the mass of viable tissue decreases in the perfusion territory supplied by a stenosis, adenosine-induced hyperemic flow and transstenotic gradient will be smaller, and thus, FFR will be larger, even though the stenosis remained unchanged. This implies that at unchanged stenosis severity, FFR will be larger after, than before MI, illustrating the fact that 2 identical stenoses may have a different FFR, depending on their distribution area. Therefore, in case of prior MI, FFR does not underestimate stenosis severity. In contrast, FFR still represents the fraction of maximal flow to the remaining viable myocardium, which is preserved despite the presence of the stenosis. In fact, it is the angiogram that tends to overestimate the functional severity after prior MI. Conversely, within the partially infarcted area, the perfusion pressure associated with flow maldistribution or ischemia of the remaining viable myocardial tissue is unlikely to change. This

explains why the same cutoff value of FFR was found in patients with a prior MI and in patients with normal LV function. In summary, these data indicate that the 0.75 threshold-value of FFR also applies in patients after MI. Above the FFR value of 0.8, the SPECT imaging was uniformly negative for reversible myocardial ischemia.

**FFR and CFR in acute MI**

During the acute phase of a myocardial infarction the need for assessing lesion severity is exceptional. The microcirculatory resistance changes very rapidly and depends on a lot of interrelated factors. After mechanical revascularization, evaluation of stent deployment should therefore account for several factors which might influence myocardial blood flow: LV diastolic pressure, residual capillary obstruction by thrombus or edema, the loss of myocardial mass, the “stunning” of the resistive vessels, the administration of Iib/IIIa receptor-blockers, etc. In general, since microvascular function is prone to improve rapidly after the acute phase, it should be kept in mind that FFR tends to be overestimated and CFR underestimated when measured in the acute setting than a few days later. Therefore both FFR and CFR obtained in the setting of an acute MI should be interpreted with great caution. Nevertheless, the observation of a high CFR immediately after revascularization of the culprit lesion might be predictive of an improvement in regional wall motion. Suryapranata et al. found a significant correlation between CFR as assessed by contrast densitometry immediately after angioplasty and regional myocardial function<sup>19</sup>. More recently, Akasaka et al. identified a typical pattern of coronary flow velocity during the acute phase of an anterior MI that is associated with the recovery of contractile function at one month (systolic



**Figure 1:** For clinical decision making FFR and CFR provide the interventionalist with different, - and therefore highly complementary - , information: CFR tells to what extent the total (epicardial and microvascular) resistance is abnormal. Changes in both microvascular and/or epicardial resistance will influence the value of CFR, and it is not possible to predict on the basis of CFR what will be the improvement in maximal myocardial flow after successful PCI. The value of pressure-derived FFR is also influenced by the status of the microvasculature (in case of abnormal microvascular function FFR will tend to be higher and vice versa) but, from a practical point of view, FFR exactly tells which increase in maximal myocardial blood flow can be expected from a PCI procedure.

In contrast in case of normal epicardial resistance (no stenosis) FFR will be equal (or very close) to one, while an abnormal CFR value would indicate microvascular dysfunction. Therefore it can be stated that, for practical purpose , FFR is stenosis specific, while CFR is not. FFR is useful in case of epicardial stenosis, while CFR is especially useful when there is no stenosis (or to complement FFR).

flow velocity larger than 0,6 m/s and diastolic deceleration time > 600 ms<sup>20</sup>. Conversely, a low FFR value immediately upon recanalization indicates a persistent epicardial resistance even though the angiogram is satisfactory.

#### FFR, CFR and Viability

Hibernating myocardium is defined as chronic, reversible left ventricular dysfunction due to CAD<sup>21</sup>. Its corollary, myocardial viability, usually designates the capability of contracting in the presence of adequate blood flow<sup>22</sup>. The concept of responsiveness to inotropic stimulation is inherent to these definitions. Viable myocardium does not necessarily imply the presence of ischemia, but tissue has to be viable to become ischemic.

Several animal and human studies have shown that hibernating myocardium was characterized by a mismatch between flow and function: a dyssynergy in the presence of a normal (or near normal) myocardial flow. Explaining the apparent paradox between severe contractile dysfunction in the presence of a normal flow, it was shown in animals<sup>23</sup> and more recently in humans<sup>24</sup> that hibernating myocardium is the consequence of repetitive post ischemic stunning rather than to a persistent decrease in flow with consequent metabolic adaptation. Therefore, patients with hibernating (and thus viable) myocardium have a normal (or near normal) flow at rest but a reduced flow reserve so that any stress results in ischemia. On recovery, myocardial stunning is

manifested and repeated episodes result in hibernating myocardium. Lee et al showed that dyssynergic myocardial segments with a contractile reserve had a lower flow reserve than normal segments but a significantly higher flow reserve than dyssynergic segments without contractile reserve<sup>25</sup>. Animal experiments even suggested that microvascular reserve (as assessed by myocardial contrast echocardiography) was superior to contractile reserve for defining the extent of viable myocardium within the infarct bed.<sup>26</sup> The relationship between hibernating myocardium, coronary flow and coronary flow reserve can be summarized as follows: (a) resting flow is normal, (b) flow reserve is reduced, (c) the higher flow reserve (but within the abnormal

range), the higher the likelihood and the extent of viability.

Practically, in a patient with an

epicardial stenosis and a dyssynergy at left ventricular angiogram, it is reasonable to state

that: (a) a high coronary flow reserve and or a high FFR suggest the absence of reversible ischemia

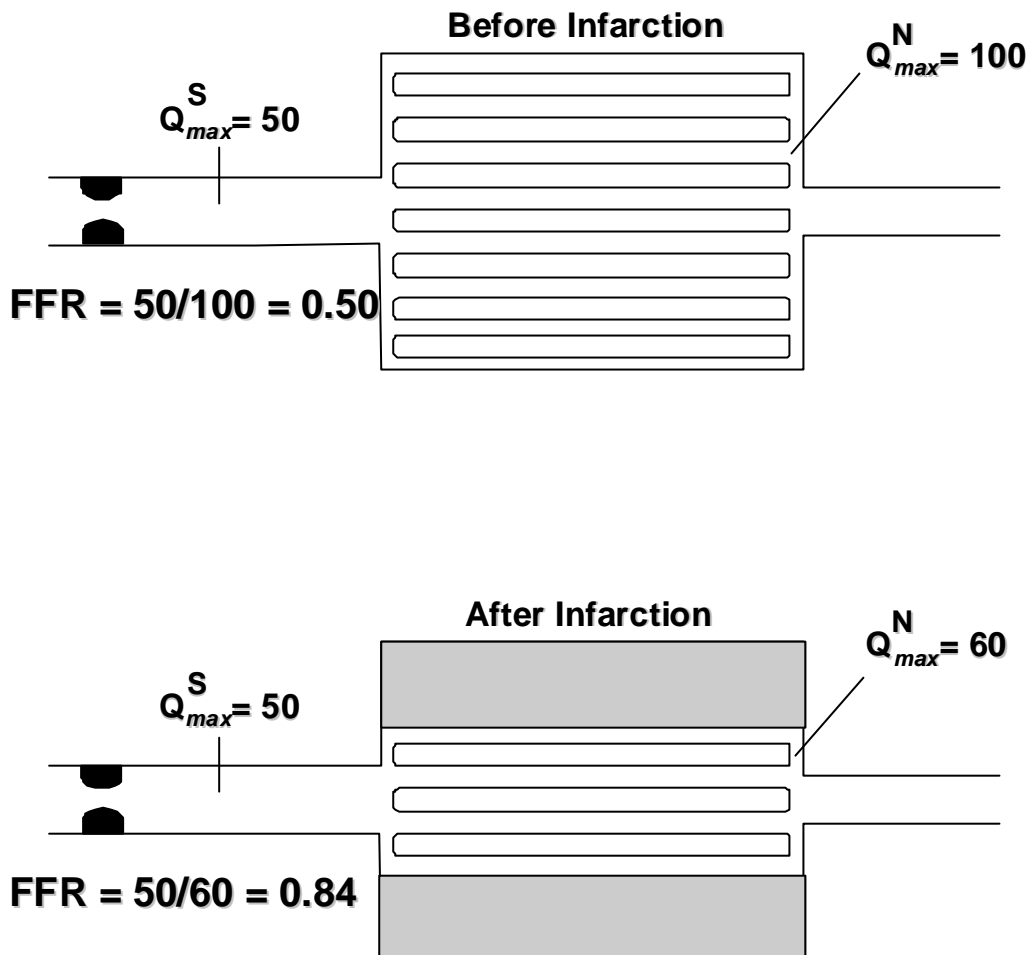
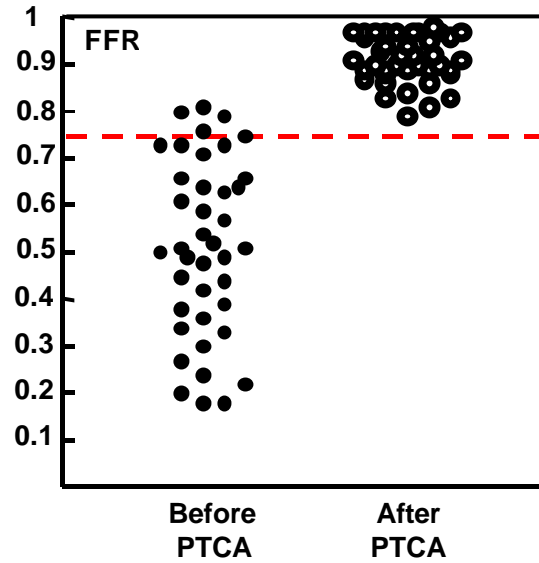


Figure 2: Schematic representation of coronary stenosis and its dependent myocardium before and after MI. FFR is defined as the ratio of myocardial blood flow in the presence of epicardial stenosis ( $Q_{max}^S$ ) to maximal myocardial blood flow in absence of the epicardial stenosis ( $Q_{max}^N$ ). In clinical practice, FFR can be calculated by the ratio of distal coronary pressure to aortic pressure during maximal hyperemia. After MI, the amount of viable myocardium distal to the stenosis is smaller than before, associated with the decrease in absolute hyperemic blood flow. Therefore, in the hypothetical case, epicardial stenosis remains unchanged, the hyperemic pressure gradient decreased and FFR increased. Thus, despite unchanged anatomic severity of stenosis, its functional severity has decreased because of smaller amount of viable tissue to be supplied.

	<b>MIBI + n = 40</b>	<b>MIBI - n = 40</b>
<b>FFR<sub>≥</sub>0.75 n = 45</b>	<b>5</b>	<b>40</b>
<b>FFR&lt;0.75 n = 35</b>	<b>35</b>	<b>0</b>

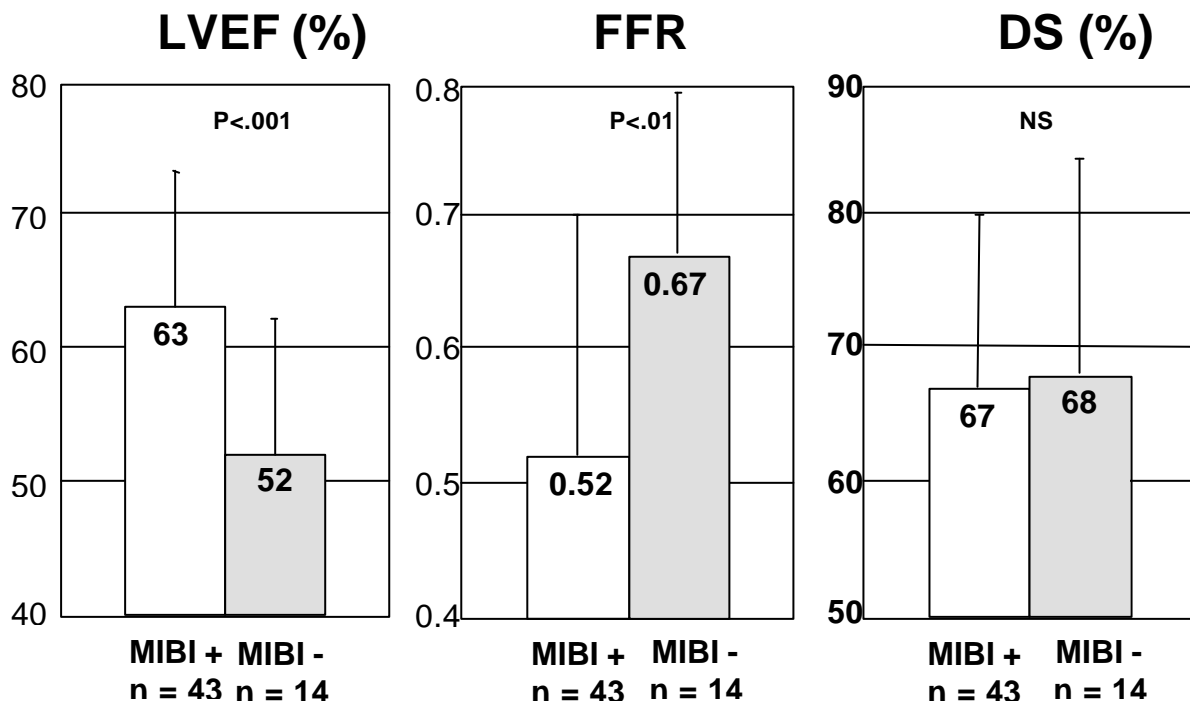
Concordance = 94%  
 $\kappa = 0.87$ ;  $P < 0.0001$



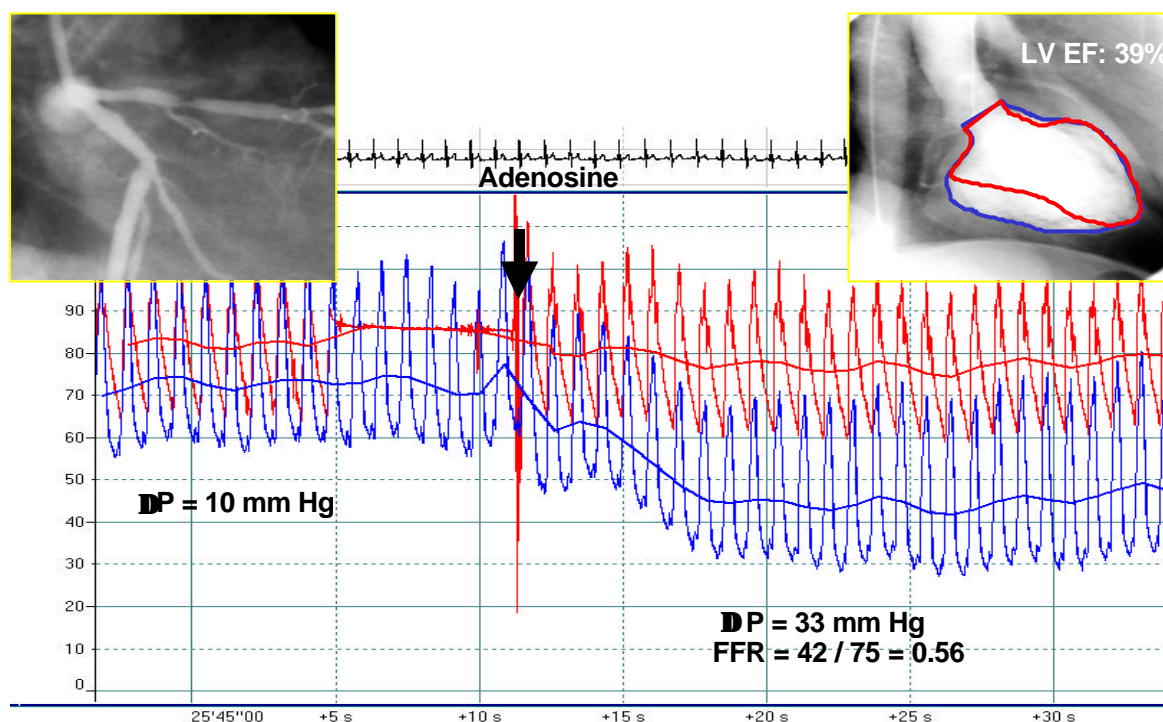
**Figure 3:**

*Right panel:* values of FFR before and after PCI in patients with truly positive and truly negative SPECT imaging studies.

*Left panel:* Concordance between FFR and SPECT imaging in patients in whom SPECT imaging was truly positive and truly negative.



**Figure 4:** Values of LVEF, FFR and diameter stenosis (DS) according to the results of SPECT imaging. At similar degree of stenosis, patients with positive SPECT imaging have better preserved LVEF and lower FFR than patients with negative SPECT imaging, suggesting a larger amount of viable tissue. This corroborates that for a same anatomic obstruction, the value of FFR depends on the mass of myocardium at risk.



**Figure 5:** Example of pressure recording in 60-year-old woman who sustained anterior MI 6 days before catheterization. Coronary angiogram showed a 64% diameter stenosis in proximal left anterior descending coronary artery. Left ventriculography shows severe anterior hypokinesia. Transstenotic pressure gradient is 9 mmHg at rest and 33 mmHg during maximal hyperemia, which corresponds to FFR of 0.56. Thus large increase in pressure gradient during hyperemia indicates maintained vasoreactivity, which, in turn, suggests the presence of myocardial viability of anterior wall.

myocardium; (b) fractional flow reserve lower than 0.75 in the presence of a large increase in pressure gradient during pharmacological vasodilation is very suggestive of the presence of the hemodynamically significant stenosis subtending viable but hibernating myocardium. This is illustrated in figure 5 but so far the relationship between CFR, FFR and myocardial viability has not yet been investigated systematically.

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