



How Different is Invasive Coronary Physiology in the Left Anterior Descending Artery?

REVIEW

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ABSTRACT

Given the large amount of myocardium supplied by the left anterior descending (LAD) artery, it understandably receives additional scrutiny during coronary angiography. However, these same features make the interpretation of pressure wire physiology more nuanced to avoid overtreatment. This review provides case examples to underpin an extensive literature review supporting the argument that a “positive” fractional flow reserve (FFR) in the LAD needs to be approached with caution. A large hyperemic gradient, or low FFR, can arise from either a severe and focal lesion in conjunction with low flow or diffuse disease coupled with intact or normal flow. Separating these two scenarios, and the wide continuum between them, ultimately requires upstream assessment of absolute myocardial perfusion, although a pressure wire pullback can help identify diffuse patterns unsuitable for revascularization.

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INTRODUCTION

Percutaneous coronary intervention (PCI) of a stable lesion in the left anterior descending (LAD) coronary artery launched the field of interventional cardiology on September 16, 1977.¹ As we approach this 50th anniversary, we return to the LAD and explore its hemodynamic physiology. After the left main coronary artery, the LAD supplies the largest amount of distal myocardium and therefore understandably undergoes more scrutiny and treatment than other vessels. However, this review summarizes the evidence that our common tool of invasive pressure measurement can mislead us into overtreatment, especially in the LAD.

LEARNING FROM A FAILURE

To start with a concrete example, consider the case shown in [Figure 1](#). A 62-year-old woman presented with 2 weeks of new angina and exertional dyspnea. Her internist ordered a treadmill stress test with single photon emission computed tomography (SPECT) imaging, which was abnormal for limiting symptoms after 7:21 minutes, > 1 mm of new ST-segment depression, and hypotension (blood pressure fell from 158/94 mm Hg at baseline to 97/60 mm Hg during exercise). Immediate hospitalization revealed negative cardiac enzymes (28 and 32 pg/mL with a high sensitivity

troponin assay), a severe lesion in the proximal right coronary artery (RCA), and an intermediate proximal LAD lesion.

Because the SPECT images did not show a stress-induced defect in the anterior, septal, or apical regions, the operator chose to assess the LAD using a pressure wire. In the mid portion of the LAD, the resting Pd/Pa equaled 0.78 (absolute gradient of 19 mm Hg) and during an intravenous infusion of adenosine fell to a fractional flow reserve (FFR) of 0.56 (absolute gradient 35 mm Hg). Given proximal disease in two major vessels, plus angiographic plaque in the mid left circumflex (LCx) artery, the patient underwent total arterial coronary artery bypass grafting (CABG) with an uneventful recovery.

Approximately 3 weeks after discharge, her symptoms of angina and dyspnea returned. Advanced quantitative imaging with cardiac positron emission tomography (PET) demonstrated essentially normal perfusion² in the LAD distribution—almost 3 mL/min/g—but a mixture of non-transmural scar plus stress-induced ischemia in the region of the RCA. Repeat invasive angiography revealed total failure of every bypass graft along with progressive RCA disease. Successful PCI of the RCA culprit improved her symptoms. The nonculprit LAD with an FFR of 0.56 was left untreated.

What can we learn from the case in [Figure 1](#)? Seemingly everything was done “correctly”—clinically important and new complaints indicating unstable angina, reproduction of

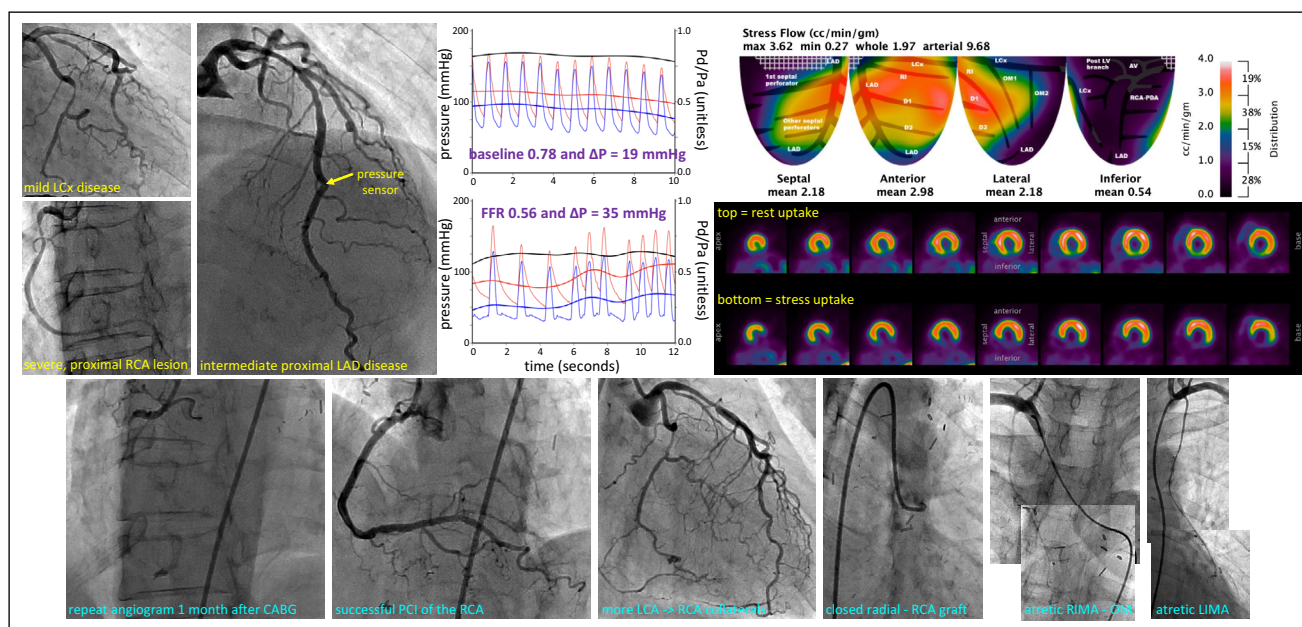


Figure 1 Rapid graft failure due to competitive flow. While the severe RCA lesion limits flow and explains her unstable angina, the intermediate and long proximal lesion in the LAD artery does not limit flow but instead produces a sizable pressure gradient and low FFR because of normal myocardial perfusion. See the main text for a full description of the case. RCA: right coronary artery; LAD: left anterior descending; FFR: fractional flow reserve; LCx: left circumflex; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; LCA: left coronary artery; RIMA-OM: right internal mammary artery-obtuse marginals; LIMA: left internal mammary artery

symptoms on the treadmill, objective ST-segment changes during stress, an angiographically significant culprit RCA lesion, and a physiologically significant nonculprit LAD lesion by both rest and stress pressure assessment—and yet the CABG failed within 1 month and only PCI of the RCA was necessary. We will return to this case at the end of the review after assembling the necessary tools and evidence to understand it correctly.

This review brings together several well-established physiologic principles and empirical data from the literature to make the following argument as summarized in the conceptual montage of [Figure 2](#). First, pressure gradients along a coronary artery depend on the absolute amount of flow.³ Second, the absolute amount of mass varies among coronary arteries, being largest on average for the LAD.⁴ Third, myocardial perfusion—flow (mL/min) indexed to mass (g) for composite units of mL/min/g—does not differ among the coronary arteries under normal conditions.⁵ Consequently, even in normal arteries the LAD has a systematically lower FFR due to its greater absolute flow.⁶ In clinical practice this lower FFR value in the LAD leads to an inappropriate skew in revascularization procedures beyond what is necessary to improve myocardial perfusion. However, by focusing on focal lesions and avoiding diffuse disease, the imbalance can largely be restored.

DISPROPORTIONATE PCI OF THE LAD

We might expect that PCI of each major epicardial vessel (LAD, LCx, and RCA) will scale in rough proportion to the amount of distal myocardium. (Note that we exclude the

left main from this analysis given the general preference for CABG over PCI,⁷ and also do not include bypass graft PCI given its low frequency and heterogenous anatomy.) Using cardiac computed tomography (CT), investigators pooled 948 patient scans and applied an automated segmentation algorithm to quantify the percentage of the left ventricle (LV) supplied by the key epicardial arteries.⁴ The LV relative mass subtended by the LAD equaled 43%, compared to 29% for the LCx and 26% for the RCA (note that median values do not sum to 100% exactly). As summarized in [Table 1](#) and reviewed next, these percentages closely match the relative frequency of PCI in trials that base their selection on typical clinical and angiographic criteria.

For example, a massive individual patient data (IPD) meta-analysis from the Coronary Stent Trialists' Collaboration provides a contemporary view of modern PCI.⁸ Over 25,000 subjects from 20 randomized trials received PCI to an LAD target vessel in 41%, an LCx in 25%, and the RCA in 33% (after removing left main target vessels). Similarly, another massive IPD meta-analysis from the Single Versus Dual Antiplatelet Therapy Collaboration compiled over 25,000 subjects from six randomized trials.⁹ The target vessel for PCI was the LAD in 47%, LCx in 23%, and RCA in 30% (again after removing left main and bypass grafts).

As a final group of typical PCI targets, consider nonculprit disease noted at the time of acute ST-segment elevation myocardial infarction (STEMI). The optimal treatment of these so-called bystander lesions has been the topic of several randomized controlled trials.¹⁰⁻¹⁵ Compiling the epicardial vessel of these stenoses leads to over 12,000 subjects as summarized in [Table 1](#). The target vessel for

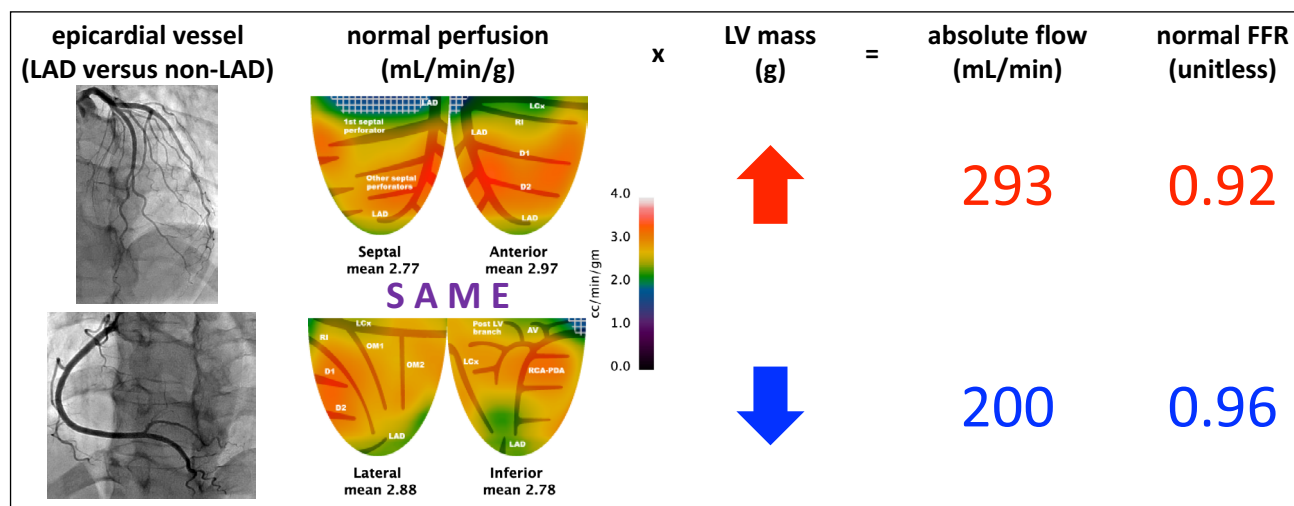


Figure 2 Conceptual roadmap. Examples represent a montage from various clinical cases and absolute values are taken from published literature. No difference in absolute perfusion (mL/min/g) exists between the LAD and non-LAD territories.⁵ However, the LAD supplies more mass,⁴ leading to greater absolute flow (mL/min). Consequently, the FFR in a normal vessel is lower for the LAD than non-LAD.⁶ LAD: left anterior descending; LV: left ventricle; FFR: fractional flow reserve

AUTHOR	VESSELS	ACRONYM	GROUP	MEAN FFR	LAD	LCx	RCA
Stalikas ^{*4}	948		CT mass		43%	29%	26%
Piccolo ^{†8}	29695				41%	25%	33%
Valgimigli ^{‡9}	29696				47%	23%	30%
Pooled	59391		Typical PCI		44%	24%	32%
Biscaglia ¹⁰	1899	FIRE			31%	36%	33%
Stähli ^{†11}	991	MULTISTARS AMI			39%	35%	26%
Mehta ¹²	5342	COMPLETE			40%	36%	24%
Böhm ^{†13}	1966	FULL REVASC		0.76 [‡]	42%	34%	24%
Lee ¹⁴	752	FRAME-AMI		0.79 [‡]	44%	29%	27%
Puymirat ^{†15}	1479	FLOWER-MI		0.79 [‡]	45%	31%	24%
Pooled	12429		Nonculprit during acute MI		40%	35%	26%
Collison ¹⁶	260	TARGET	Severe lesions	0.59	58%	17%	26%
Xaplanteris ^{§17}	888	FAME 2	FFR ≤ 0.80	0.60	64%	NR	NR
Al-Lamee ¹⁸	200	ORBITA	Severe lesions	0.69	71%	13%	16%
Collet ¹⁹	1043	PPG	FFR ≤ 0.80	0.68	73%	12%	16%
Sonck ²⁰	123	P3	FFR ≤ 0.80	0.66	76%	11%	13%
Shin ²¹	341		FFR ≤ 0.80	0.68	77%	7%	16%
Pooled**	1964		Physiology trials		72%	12%	17%

Table 1 Epicardial target vessels for revascularization. CT: computed tomography, FFR: fractional flow reserve, LAD: left anterior descending, LCx: left circumflex, MI: myocardial infarction, NR: not reported, PCI: percutaneous coronary intervention, RCA: right coronary artery

* Median values for mass do not exactly sum to 100%

† Percentages exclude left main and bypass graft target vessels

‡ FFR measured in lesions randomized to a physiologic strategy, including deferred lesions

§ Only reported percentage of proximal or mid LAD lesions

** Excluding the FAME 2 trial as its target vessel reporting was incomplete

PCI (in the angiographic arm of these trials) was the LAD in 40%, LCx in 35%, and RCA in 26%. This distribution of “significant” nonculprit lesions largely matches the relative amounts of myocardial mass as well as PCI in the two IPD meta-analyses—generally 40% LAD, 30% LCx, and 30% RCA.

However, the situation in PCI trials guided by FFR appears markedly different.¹⁶⁻²¹ Consider the PPG Global Registry¹⁹ as an exemplar of the physiology-based trials summarized in Table 1. This prospective and observational study enrolled almost 1,000 subjects from 25 centers over 4 continents. It asked operators to recruit stable lesions suitable for PCI but demanded that FFR ≤ 0.80, thereby ensuring a 100% cohort of FFR-positive vessels. As a result of this physiologic inclusion criterion, the target vessel for PCI shifted markedly to the LAD in 73%, LCx in 12%, and RCA in 16%.

When compiling all the physiology PCI trials for a total of almost 2,000 vessels, the LAD accounts for just over 70% of their targets. Compare that high percentage to about 40% based on myocardial mass or typical clinical criteria. This massive shift towards PCI of the LAD—or, conversely, a proportional shift away from PCI of the LCx or RCA—poses a dilemma. Do typical angiographic and clinical criteria produce overtreatment of the LCx or RCA? Or does an FFR-guided strategy trigger revascularization in too many LAD vessels?

Before addressing that question in the next section, it is important to note that PCI of the LAD (or left main) remains a multivariable predictor of worse outcomes in the first year after stent implantation. In a large, pooled analysis of over 25,000 patients from 19 randomized trials,²² PCI in the LAD or left main significantly increased the risk of target lesion failure (rate ratio 1.20, *P*-value .0006)

during the first year. However, during the subsequent 4 years, both LAD and non-LAD stents performed similarly (rate ratio 1.10, P -value .48). Overall this cohort had 42% LAD as the target vessel (when excluding the left main), reflecting typical angiographic and clinical criteria. Therefore moving towards a massive dominance of LAD targets like 70%, as obtained using an FFR criterion, warrants caution at the outset given the excess risk of stent failure in this vessel.

FOCAL VERSUS DIFFUSE DISEASE

Figure 3 contrasts two clinical cases of physiologic evaluation in the LAD. One patient presented at age 51 after his internist performed a coronary calcium score and found it to be > 400 Agatston units. He exercised vigorously without symptoms and was well treated for his dyslipidemia, achieving a low-density lipoprotein (LDL) level of 37 mg/dL with statin and ezetimibe. After an abnormal SPECT scan, the patient requested a cardiac PET test with flow quantification, identifying a subtotal ramus branch that was ultimately treated medically given its modest caliber, ostial extension, and lack of symptoms. Diffuse and mild-to-moderate angiographic atherosclerosis of the LAD prompted invasive pressure wire assessment. At baseline the rest Pd/Pa was 0.90 (absolute gradient of 8 mm Hg),

falling to an FFR of 0.58 (absolute gradient 28 mm Hg) during intravenous adenosine.

During pullback assessment, however, the tracing did not show any focal jumps, but instead a diffuse pattern of pressure loss. The pressure pullback gradient (PPG)—a unitless index between 0 (completely diffuse) and 1 (purely focal) derived automatically from the pullback curve—equaled 0.47, consistent with marked diffuse disease.²³ This LAD was treated medically given its high stress perfusion of almost 3 mL/min/g, and the patient has had no symptoms or events during roughly 3 years of follow-up.

In contrast, the other patient was a 63-year-old man with new-onset and severe chest pain with exertion but without medical history and not taking any medications. He underwent a cardiac PET scan with flow quantification that demonstrated a severe and large stress-induced defect in $> 50\%$ of the LV including 20% LV with myocardial steal (coronary flow reserve < 1). Invasive angiography confirmed a severe proximal LAD lesion with FFR 0.50 distally but an exquisitely focal pressure jump when moving the wire across the stenosis. Imaging-guided PCI with a drug-eluting stent dilated to 4.5 mm completely eliminated his angina and normalized LAD perfusion on repeat PET imaging (average of the anterior and septal quadrants rose from 0.78 to 2.16 mL/min/g, a 2.8-fold increase). He remains symptom free almost 3 years after his procedure.

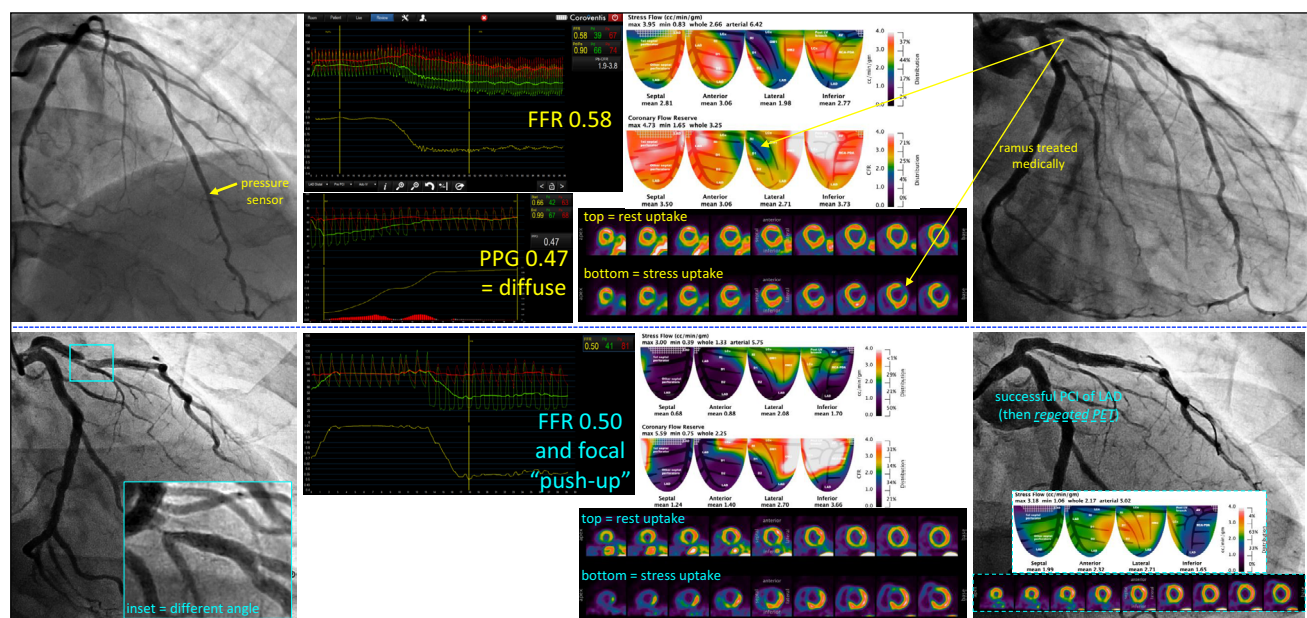


Figure 3 Two cases with large pressure gradients from different mechanisms. The upper patient has mild-to-moderate angiographic disease plus normal myocardial perfusion, leading to an FFR of 0.58 with diffuse PPG indicating medical treatment. The lower patient has a severe lesion with reduced myocardial perfusion, leading to an FFR of 0.50 with focal pressure gradient when advancing the wire (“push-up”) that was successfully treated by stent placement. See the main text for a full description of each case. FFR: fractional flow reserve; PPG: pressure pullback gradient; PCI: percutaneous coronary intervention; LAD: left anterior descending; PET: positron emission tomography

Important physiologic distinctions exist between these two LAD target vessels despite their superficial similarity of an FFR < 0.60. Invasively the pullback pattern for the first case was diffuse, unlike the extremely focal jump seen in the second case. Noninvasively the stress perfusion for the first case was normal (anterior and septal average 2.95 mL/min/g), unlike the extremely reduced stress perfusion for the second case (average 0.78 mL/min/g). The key takeaway is that a large hyperemic pressure gradient (equivalent to a low FFR) can arise via distinct mechanisms: diffuse disease combined with high perfusion (first case), an extremely focal lesion with low perfusion (second case), or an admixture of the two.

Conceptually the first case involves only viscous or friction effects, whereby $\Delta P \propto Q$ (pressure gradient is proportional to flow), but the second case involves separation or expansion loss for which $\Delta P \propto Q^2$ (pressure gradient is proportional to the square of flow). In general, the pressure gradient of a vessel will have both components ($\Delta P = v*Q + s*Q^2$, where the constants v and s depend on the geometry of the vessel and stenosis, rheologic properties of blood, and specifics of the flow profile),³ but [Figure 3](#) provides bookend examples along this spectrum.

[Table 2](#) summarizes these concepts of diffuse versus focal disease based on pullback characteristics in several of the physiology PCI trials from [Table 1](#). While the exact definitions of focal and diffuse disease varied among the studies, as detailed in a footnote to the table,^{19,21,24-26} several striking similarities emerge. First, diffuse disease is almost the exclusive domain of the LAD, reaching 88% of all target vessels. In contrast, focusing on physiologically focal disease reduces the proportion of LAD vessels to 57%, an intermediate stop between the 40% LAD from traditional PCI based on the angiogram and the nearly 90% LAD when restricted to physiologically diffuse disease. Second, diffuse disease tends to have a higher initial FFR than focal disease, approximately 0.72 compared with 0.63. This difference matches the pressure loss versus flow relationship, since ΔP increases much more quickly with Q^2 (separation loss from an orifice) compared with Q (friction forces from diffuse disease). Third, the final FFR after PCI reaches a higher value for focal disease versus diffuse disease, roughly 0.89 versus 0.85, indicating an expected larger “FFR gain” because PCI provides focal treatment.

Since the final FFR determines prognosis and the change or delta FFR associates with the improvement in

AUTHOR	VESSELS	ACRONYM	GROUP	MEAN FFR	FINAL FFR	LAD
	948		CT mass			43%
Pooled	59391		Typical PCI			44%
Pooled	12429		Nonculprit during acute MI			40%
Collet ²⁴	52	TARGET		0.64	0.83	87%
Rajkumar ²⁵	81	ORBITA		0.78	0.89	84%
Collet ¹⁹	528	PPG		0.72	0.84	90%
Mizukami ²⁶	77	P3		0.70	0.86	90%
Shin ²¹	55			0.71	0.83	82%
Pooled	793		Diffuse* disease	0.72	0.85	88%
Collet ²⁴	51	TARGET		0.59	0.89	39%
Rajkumar ²⁵	83	ORBITA		0.60	0.90	63%
Collet ¹⁹	515	PPG		0.63	0.89	55%
Mizukami ²⁶	39	P3		0.58	0.91	46%
Shin ²¹	150			0.69	0.87	71%
Pooled	838		Focal* disease	0.63	0.89	57%

Table 2 Epicardial target vessels for revascularization with focal versus diffuse disease. CT: computed tomography, FFR: fractional flow reserve, LAD: left anterior descending, MI: myocardial infarction, PCI: percutaneous coronary intervention

* Criteria for diffuse versus focal disease as follows: TARGET: focal indicated a pressure pullback gradient of 0.66 or greater; ORBITA: focal indicated a 0.03 or greater drop in iFR over 15 mm during pullback; PPG: focal indicated a pressure pullback gradient of 0.62 or greater; and P3: focal indicated a pullback pressure gradient greater than 0.73

symptoms,²⁷ PCI for focal disease offers greater clinical advantages both for outcomes and quality of life. Whether CABG provides any meaningful advantage for the patient when applied to diffuse disease remains an unanswered question,²⁸ especially given the high rate of internal mammary artery failure for this disease pattern.²⁹

CONCEPTUAL CHALLENGES TO FFR IN ISOLATION

While the extreme examples in [Figure 3](#) might be obvious angiographically and clinically, the diverse mixture of focal and diffuse disease in daily practice clouds the naïve application of FFR. The issue becomes especially marked in the LAD given its larger mass, which produces greater pressure loss even in normal vessels. In a study of 25 patients with normal coronary arteries,⁶ the LAD compared with non-LAD vessels had higher absolute flow during hyperemia (mean 293 versus 200 mL/min) and resulting lower FFR (mean 0.92 versus 0.96). Indeed, 5% of normal LAD target vessels in that study had an FFR of 0.88 or lower, and the top 5% only reached an FFR of 0.94 or greater. These results have theoretical and practical implications for interpreting FFR since its framework assumes a value of 1.0 in a completely normal vessel.³⁰ If the reference denominator for FFR is no longer 1.0 but instead may be 0.90 for the LAD, then a measured value of 0.80 does not mean that peak flow has fallen by 20%; instead, 0.8/0.9 implies an 11% reduction.

Although tempting to advocate for routine pressure wire pullbacks to distinguish focal from diffuse disease (in addition to checking for drift that might introduce bias into the measured value), this solution does not address the fundamental physiologic issue that FFR will be systematically lower in the LAD due to its increased mass. Upstream measurement of absolute perfusion using tools like cardiac PET or magnetic resonance imaging (CMR) can avoid misleading FFR assessment in LAD vessels with intact or even completely normal perfusion that will simply generate large gradients like the example in [Figure 3](#).

Notably, a head-to-head randomized trial of FFR versus CMR to guide revascularization is consistent with this very effect.³¹ A CMR-informed strategy led to PCI or CABG in 36% of subjects compared to a significantly higher 45% when guided by FFR (*P*-value .005). Despite less revascularization, subjects in the CMR group had equivalent rates of angina relief (49% versus 44%, *P*-value .21) and no difference in major adverse cardiac events (hazard ratio 0.96 with *P*-value .91). While the study did not report comparative rates of revascularization by LAD versus non-LAD, the results support that notion that some abnormal

FFR values arise due to good flow, not low flow, and should therefore be treated medically. Potentially future results from the ongoing ORBITA-MOON study (clinicaltrials.gov NCT06400290) could be examined for the FFR angina threshold in this cohort of patients with multivessel disease (we should expect a lower FFR threshold in the LAD versus non-LAD).

Now that we have the knowledge and tools, let us return to the case in [Figure 1](#). The internal mammary graft to the LAD failed from competitive flow, a well-known sensitivity of this type of conduit,³² since the native perfusion was almost 3 mL/min/g. Like the first case in [Figure 3](#), this LAD is an example of a large hyperemic gradient due to mainly diffuse disease and excellent perfusion. Although the operator did not perform a pullback that likely would have confirmed this angiographic impression, a “back of the envelope” calculation supports this conclusion as follows. Assume that the vessel is 3.25 mm in diameter with an intermediate 50% diameter stenosis over 20 mm of length, all in rough agreement with the angiogram. Geometric and rheologic considerations³ led to a viscous coefficient of 3.51 mm Hg/(mL/s) and a separation coefficient of 0.77 mm Hg/(mL/s)². The PET-measured stress perfusion of 3 mL/min/g, coupled with 100 g of distal myocardium, a typical value for the LAD in women,³³ implies an absolute stress flow of 300 mL/s. At these high flow levels, the absolute pressure gradient would be 37 mm Hg, nearly exactly equal to the measured value of 35 mm Hg.

CONCLUSION

Invasive pressure measurements in the LAD need to be made and interpreted cautiously. Even normal LAD arteries have an FFR around 0.90, and overzealous pressure wire interrogation of mild stenoses or diffuse disease can uncover an abundance of “positive” vessels. Pressure wire pullbacks can eliminate a substantial proportion of LAD vessels unsuitable for PCI due to diffuse disease, but ultimately separating low flow and a severe lesion from high flow and a mild lesion can be challenging in all but the most extreme situations. Upstream measurement of absolute myocardial perfusion using cardiac PET or CMR provides an objective guide to avoid overtreatment.

KEY POINTS

- The left anterior descending (LAD) artery supplies the largest amount of myocardium, which also produces greater pressure gradients even in normal vessels.

- A “positive” fractional flow reserve (FFR), especially in the LAD, can arise due to a severe and focal lesion with low flow, diffuse disease with intact or normal flow, or any mixture of these two components.
- Distinguishing intact or normal flow ultimately needs noninvasive assessment of absolute myocardial perfusion, but a careful pressure pullback curve can identify clear diffuse disease unsuitable for revascularization.
- Without assessment of absolute perfusion or the pullback pattern of pressure loss, simplistic physiologic selection for revascularization leads to an overabundance of LAD target vessels.

COMPETING INTERESTS

NPJ and KLG report no direct relationships but, outside of the present work, receive internal funding from the Weatherhead PET Imaging Center and have patents pending on diagnostic methods for quantifying aortic stenosis and TAVI physiology and on methods to correct pressure tracings from fluid-filled catheters.

NPJ receives significant institutional research support from Neovasc/Shockwave (PET core lab for COSIRA-II, NCT05102019). KLG is the 510(k) applicant for several cardiac PET software packages approved by the FDA (K113754, K143664, K171303, K202679, K231731) but does not receive any licensing fees paid to UTHealth by Bracco Diagnostics and GE Healthcare.

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