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The Physiologic Evaluation of Stenosis by Transthoracic Doppler: A Bit of Theory, a Lot of Practice

Jonathan R. Lindner, MD, FASE

Division of Cardiovascular Medicine and Department of Biomedical Engineering, Oregon Health & Science University, Portland, Oregon

CFR IN CLINICAL PRACTICE

Myocardial ischemia is the metabolic derangement that results when myocardial blood flow is insufficient to meet demand. Epicardial coronary artery disease that is moderate to severe, but not flow-limiting at rest, often produces a situation where ischemia occurs only when further increases in flow cannot meet increases in myocardial oxygen demand beyond resting conditions. The “unmasking” of this inadequacy of flow reserve in the clinical setting generally relies on exercise stress or inotropic drugs such as dobutamine that increase myocardial oxygen demand, or on the drugs that directly dilate the coronary resistance arterioles. These “stressors” are generally used in conjunction with methods that non-invasively image myocardial function (wall motion, strain) or regional perfusion.

Abnormal flow reserve caused by epicardial stenosis or by conditions that alter microvascular function can also be detected invasively by measurement of coronary “flow” reserve (CFR). This measurement has traditionally been made at the time of angiography with a steerable intracoronary Doppler flow wire and intracoronary administration of a vasodilator such as adenosine. The word *flow* is in quotations because conventionally only coronary flow velocity is measured and coronary arterial diameter is not. Because of improvements in ultrasound technology and the advent of ultrasound contrast agents that augment spectral Doppler signals, it has become possible to detect epicardial flow responses in coronary artery disease non-invasively with transthoracic echocardiography.^{1–3} This approach has been shown to be possible not only for the left anterior descending (LAD) vessel, which is easily identified in the anterior interventricular sulcus, but also for the right and left circumflex arteries.⁴ It is also worth noting that while the use of epicardial Doppler to measure CFR is relatively new, CFR was the first method applied to evaluate the physiologic significance of stenosis by Gould *et al* in 1974.⁵

There are several common clinical scenarios that justify the evaluation of epicardial CFR, either invasively or non-invasively. The physiologic significance of a stenosis can be in question when intermediate-severity disease is discovered in patients referred for angiography without preceding stress imaging. CFR has also been used to assess “incidental” disease that is found in vessels other than those of primary concern in patients undergoing catheterization due to acute coronary syndrome or positive stress imaging. In these settings, rapid assessment of CFR can be used to make a decision on coronary intervention while the patient is still in the angiography suite. Assessment of CFR may also be useful when, despite high clinical suspicion for a significant obstructive disease, non-invasive imaging is equivocal or is negative. There are recognized limitations in detecting

Reprint requests: Jonathan R. Lindner, MD, FASE, Cardiovascular Division UHN-62, Oregon Health & Science University, 3181 W Sam Jackson Park Rd., Portland, OR 97239 (lindnerj@ohsu.edu).

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mild to moderate ischemia by using non-invasive imaging of either wall thickening response or regional uptake of radionuclide imaging probes. In other words, there is non-linearity, or a “leveling off” of the relation between flow reserve and either wall motion during inotropic stress or uptake of ^{99m}Tc and ^{201}Tl imaging probes.^{6,7} As a result, only small differences that are difficult to discern may be present between normal myocardial regions and abnormal regions supplied by vessels with moderate stenosis. Finally, measurement of CFR may be of value in identifying individuals with multivessel disease in whom relative uptake of radionuclide tracers may not show regional heterogeneity, although data are scarce regarding this application.

COMPETING TECHNIQUES FOR MEASURING CFR

In the study by Meimoun *et al*⁸ in this issue of *JASE*, transthoracic Doppler echocardiography was used to test the physiologic impact of intermediate severity stenosis in the LAD in patients referred for diagnostic angiography. The vast majority of these patients had one of the clinical scenarios described above where evaluation of the physiologic significance in the angiography suite may be helpful. Non-invasive CFR measurement by transthoracic Doppler during hyperemia produced by intravenous adenosine was compared to fractional flow reserve (FFR) after intracoronary bolus administration of adenosine. The latter is a technique also commonly employed in the angiography suite to evaluate the significance of coronary stenosis.^{9,10} The physiologic measurements made for each approach are shown schematically in Figure 1. For CFR (*top panel*), the spectral pulsed-wave Doppler flow velocity in the LAD is recorded at rest (*dark gray waveform*) and during peak hyperemia (*light gray waveform*) produced by intravenous adenosine infusion. CFR is calculated simply as the ratio of the peak diastolic flow velocity during adenosine to that at rest. For FFR (*bottom panel*), measurements are made only during hyperemia, usually produced by intracoronary adenosine. FFR is calculated as the ratio of mean coronary pressure distal to stenosis to that measured in the aorta. The derivation of FFR was intended to provide an estimate of the ratio of flow during maximal hyperemia to that which can be achieved, in theory, in the absence of stenosis, and assumes that microvascular resistance during hyperemia is not different in these two circumstances.^{9,11}

One is tempted to criticize Meimoun *et al*'s study design since FFR is used as a comparator rather than quantifying microvascular blood flow with positron emission tomography or myocardial contrast echocardiography. However, the authors clearly state that the purpose of the study was to evaluate concordance for two different practical approaches that can be used to evaluate the physiologic significance of stenosis in the catheterization lab. It is also worth noting that small studies comparing CFR to myocardial perfusion have already been performed.¹² The current study was appropriately designed to exclude infarction which may affect one measurement more than the other, and to perform FFR and CFR at approximately the same vascular segment. Although the study was somewhat limited by the small number of patients with physiologically significant disease (n=13 with FFR <0.8), the authors found a good agreement between CFR and FFR.

WHY THE NEED FOR COMPARISON?

The justification for this study extends beyond the simple desire to compare non-invasive CFR to FFR, the method of choice for evaluating stenosis physiology in the catheterization laboratory. The authors point out in the Discussion that this is a comparison of two techniques that rely on measuring either flow velocity or pressure gradient. This is where things become complex and interesting. In theory, there several reasons why FFR could underestimate the severity of disease compared to CFR.

Reason #1

CFR can be reduced not only by lower hyperemic flow, but also by higher resting flow (ie, a higher denominator in the CFR equation). This is not as much of an issue for FFR where measurements are made only during hyperemia. Reasons for higher resting flow in the population studied include: (a) hypertension (present in 54% by history); (b) anxiety which is common at the time of angiographic procedures; (c) heart failure; and (d) compensatory hyperkinesis in the remote territory in those with acute coronary syndrome in another territory.

Reason #2

Hypotension with adenosine could preferentially reduce CFR. During adenosine-mediated vasodilation, hyperemic flow is largely determined by the coronary perfusion pressure.¹³ Drug-mediated hypotension lowers the coronary perfusion pressure thereby reducing hyperemic flow and CFR. For FFR, lower hyperemic flow caused by hypotension would be expected to reduce the transstenotic gradient and, in theory, artificially raise the FFR. In the study by Meimoun, *et al*,⁸ this issue is relevant because of the higher likelihood for hypotension with intravenous adenosine used during CFR rather than the intracoronary route of adenosine administration used for FFR. Blood pressures during hyperemia were not reported but would have been useful.

Reason #3

Abnormal microvascular function from either abnormal nitric oxide bioavailability or other disorders of the distal resistance microvessels associated with diabetes, hyperlipidemia, smoking, etc., could have a disproportionate affect on CFR. In other words, the peak hyperemic flow during adenosine is influenced by both the stenosis resistance and microvascular resistance. CFR cannot distinguish between the two and can be abnormal due to only the latter. Effects of microvascular dysfunction on FFR are expected to be quite different since, for any degree of coronary stenosis, lower hyperemic flow would lead to a lower pressure gradient and a more normal FFR. To address these issues, it has been proposed that the coronary velocity-pressure gradient relation be measured to quantify stenosis severity.¹⁴ In essence, this measurement provides an index of stenosis resistance and could potentially be able to differentiate the contribution of epicardial disease to abnormal CFR.

Despite the potential problems outlined above, Meimoun *et al*.⁸ found that the two techniques agreed reasonably well in their ability to differentiate normal from abnormal response according to thresholds defined a priori. There were only two patients in whom the tests were discordant because of an abnormal CFR but a normal FFR. This finding does not necessarily imply that the three issues outlined above are unimportant. An FFR of 0.75 has also been previously used to define abnormal response.¹⁵ If this definition was used, there would be three additional discordant cases where FFR was normal and CFR was abnormal. Moreover, there is an interesting curvilinear relation between CFR and FFR in the study. If one examines this relationship, it can be appreciated that patients with borderline CFR of 2.0–2.5 have FFR values that are no different than those with much higher CFR (3.0–4.5).

CONCLUSIONS

The study by Meimoun *et al* is important because it provides the first evidence, and some measure of comfort, that CFR obtained by non-invasive transthoracic Doppler provides similar information as that provided by FFR, the technique that is considered state-of-the-art in the cardiac catheterization laboratory for physiologic significance of stenosis. It is important to recognize, however, that these results were obtained from a select population

without prior infarction in the LAD territory, without severe hypertension, and with a relatively low prevalence of diabetes. Hence, when considering the population at large, it is still important to recognize the physiologic underpinnings for these measurements and why they may be influenced by more than the degree of coronary artery stenosis alone.

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Abbreviations

CFR	Coronary “flow” reserve
FFR	Fractional flow reserve
LAD	Left anterior descending

Figure 1.

Schematic illustrating methods that were used to measure CFR and FFR during adenosine administration. Stenosis in these diagrams is depicted as the *dark red region* that narrows the vessel lumen. *Ado*, adenosine; *PDV*, peak diastolic velocity; *I.C.*, intracoronary; P_{ao} , mean aortic pressure; P_{distal} , mean coronary pressure beyond the stenosis. Derivation of how trans-stenotic pressure gradient during hyperemia reflects FFR can be found in Pijls NHJ, et al.⁹