Coronary Microvasculature
Small Vessels With Large Impact

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hemodynamic measurements in vivo during heart catheterization are increasingly used to drive clinical decision making in the cardiac catheterization laboratory. Coronary flow velocity reserve (CFVR), also referred to as coronary flow reserve, was introduced in the 1970s and was one of the first hemodynamic measurements which could be applied clinically to help evaluate these lesions. Moreover, the development of hemodynamic measurements which could be applied clinically to be readily obtained. CFVR is defined as the ratio of steady-state hyperemic average peak velocity to resting average peak velocity for the artery of interest (target vessel). The concept is based on observations that increased oxygen demand is met under physiological conditions through a 4 to 5 fold increase in myocardial blood flow caused by autoregulation, and that the degree of epicardial or microvascular resistance can be determined by the ratio of hyperemic to resting blood flow. Although invasively measured CFVR is considered the gold standard, CFVR can also be measured by noninvasive imaging modalities, such as positron emission tomography, single-photon emission computerized tomography, transthoracic Doppler or myocardial contrast echocardiography, or cardiac MRI.

It is important to emphasize that CFVR reflects the combined epicardial and microvascular resistance to coronary blood flow. Although overlap between normal and abnormal measurements does exist, a CFVR<2.0 has reasonable predictive accuracy to identify hemodynamically significant stenoses in the absence of microvascular dysfunction. CFVR is, however, susceptible to fluctuating hemodynamic parameters, as well as changes in ventricular loading conditions, and varies in situations of increased basal blood flow such as fever, tachycardia, hypoxia, anemia, and ventricular hypertrophy. In addition, reliably obtaining reproducible Doppler envelopes can be highly variable, limiting the accuracy of CFVR measurements. Other epicardial-specific indices have emerged that include hyperemic stenosis resistance (HSR) index, which requires pressure and velocity measurements, and fractional flow reserve (FFR). Given the focus of interventional cardiologists on epicardial disease management, CFVR has largely been replaced by FFR for physiological interrogation in the cardiac catheterization laboratory.

Conversely, in angiographically normal coronary arteries diminished CFVR reflects microvascular dysfunction as seen in conditions such as diabetes mellitus, ischemic or hypertensive heart disease, and heart failure with preserved or reduced ejection fraction. Attempts to address the limitations of CFVR have led to the development of relative CFVR, which is derived from the ratio of the target vessel CFVR to an adjacent reference vessel CFVR (refCFVR) that has minimal epicardial disease. Although relative CFVR has been used to improve assessment of lesion severity in the target vessel, little is known about the prognostic value of refCFVR, an indicator of the underlying degree of microvascular dysfunction.

In this issue of Circulation: Cardiovascular Interventions, van de Hoef et al found an increase in mortality among patients with abnormal refCFVR. They followed up on 178 patients with stable coronary artery disease who had undergone physiological evaluation of their coronary lesions, including CFVR, FFR, HSR, and basal and hyperemic microvascular resistance. Patients included had angiography which showed ≥1 vessel with an intermediate lesion requiring physiological evaluation, with 36% undergoing percutaneous coronary intervention of their target vessel. Patients were stratified according to refCFVR: those with refCFVR≤2.7 were deemed to have abnormal flow, whereas those with refCFVR>2.7 were considered to have normal coronary blood flow. There were fewer patients in the abnormal group (n=77) than in the normal group (n=101), and there were slightly more men than women in both groups. The 2 cohorts had overall similar baseline characteristics and medications; however, those with refCFVR≤2.7 were older, had less hyperlipidemia, and had lower target vessel CFVR (1.9±0.6 versus 2.4±0.8). Because FFR and HSR values were similar, diminished CFVR might have reflected microvascular dysfunction in the target bed. Interestingly, comparison between patients with abnormal versus normal blood flow showed that the decreased value of refCFVR seemed to be driven mostly by higher baseline average peak velocity (16±5 versus 21±7; P<0.001) and microvascular resistance (P<0.001), as opposed to any substantial difference in hyperemic velocity (52±18 versus 48±16; P=0.23) or hyperemic microvascular resistance (P=0.35). In terms of outcomes, patients with refCFVR≤2.7 had higher all-cause mortality (39.6% versus 16.7%; P<0.001) and cardiac mortality (31.6% versus 7.7%; P<0.001) at 11.6 years compared with those with refCFVR>2.7. After multivariable adjustment, patients with refCFVR≤2.7 had significant hazard ratios of 2.24 for all-cause mortality and 3.32 for cardiac-related mortality.

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Several limitations of this study should be pointed out. First, it seems that the 178 study patients were recruited during a 9-year period, raising the possibility of selection bias in patient enrollment. Second, the decision to perform percutaneous coronary intervention was ischemia guided but left at the discretion of the operators. It would be important to prospectively (or at least indicate) the criteria on which revascularization was performed. Admittedly, every modality for ischemia assessment has inherent limitations. Was this ischemia guidance based on noninvasive imaging, FFR, or HSR? What threshold was used on the noninvasive data, FFR, and HSR to determine an ischemic defect? Because these target vessels had greater atherosclerotic burden than the reference vessels, adverse outcomes may have been driven by these unvascularized epicardial lesions rather than relate to the refCFVR. Third, outcomes were based on a population registry with confirmation by hospital records, and death was considered cardiac unless there was unequivocal noncardiac cause. Given the limited sample size and event rates, more clarity of the cause of death and the inclusion of patients who may have had relevant nonfatal events would be important. Fourth, other potentially relevant prognostic variables, such as changes in medication or lifestyle, were not provided. Finally, there may be methodological issues related to the data collection, including administration of low doses of intracoronary adenosine, nonperformance of FFR in reference vessel, and lack of data on epicardial plaque quantification or characterization by intravascular ultrasound or optimal coherence tomography.

Nevertheless, this study represents a detailed and comprehensive evaluation performed by a group of experienced researchers and makes an important contribution to our understanding of the prognostic value of microvascular disease in patients with stable coronary artery disease. Their findings are consistent with previous studies which associated unvascularized target vessel CFVR<2.0 with higher risk of revascularization at 1 year\(^1\) and CFVR≤2.0 in angiographically normal or near-normal coronary arteries with higher risk of death or nonfatal myocardial infarction at 4 years.\(^1\) Another recent investigation using the National Heart, Lung, and Blood Institute–sponsored Women’s Ischemia Syndrome Evaluation data set of 189 women with suspected myocardial ischemia found that CFVR<2.32 was associated with increased risk of major cardiovascular adverse effects after 5.4 years, regardless of whether obstructive epicardial disease was visualized on angiography.\(^1\) Taken together, these reports support the notion that coronary microvascular dysfunction carries adverse prognostic risk.

Another finding in this study is the observation that the diminished refCFVR results from elevated baseline velocity and not reduced hyperemic velocity. These findings are in keeping with previous reports on higher baseline velocities resulting in diminished flow reserve.\(^13\)–\(^15\) The authors of the present study shed new light on the potential mechanism of microvascular dysfunction by demonstrating that baseline and not hyperemic myocardial resistance is elevated in this cohort, leading them to hypothesize that it is related to impaired basal coronary autoregulation as opposed to reduced vasodilator reserve. This seems like a reasonable hypothesis.

What is known is that microvascular dysfunction is likely a conglomeration of concurrent structural and functional abnormalities which affect scattered areas in the myocardium.\(^16\) This impairment of the microvasculature may be caused by microembolization and subsequent release of bioactive factors, adverse vessel remodeling, or autoregulatory dysfunction.\(^17\) In turn, it could lead to further development of epicardial disease through decreased blood flow, alterations in wall shear stress, and increased oxidative stress.\(^18\) Microvascular dysfunction has already been associated with higher serum levels of high sensitivity C-reactive protein, increased plaque burden, and higher frequency of thin-cap fibroatheromas.\(^19\) In addition, the endothelium plays a critical role in modulating vascular response to injury and repair. Patients with nitric oxide–dependent endothelial dysfunction have also been shown to have poor outcomes.\(^20\)

The prognostic overlap between acetylcholine assessed vasodilatory response (endothelial function) and adenosine-induced hyperemia has not been well studied and warrants further investigation. Such refining of risk assessment in patients presenting to the catheterization laboratory can guide the aggressiveness of antiatherosclerotic and antiangiinal therapies. The aforementioned complexity of the coronary endothelial and microvascular response, systemic inflammation, oxidative stress, and the potential cross talk between epicardial and microvascular beds argues for an integrated approach in evaluating patients with coronary artery disease. Undoubtedly, there is a growing role for intravascular physiology and imaging in advancing our understanding of the pathophysiology of patients with coronary atherosclerosis.

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References


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