**Editorial**

**Assessment of Structural Disease in the Coronary Microvasculature**

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Reductions in myocardial blood flow in patients free of epicardial artery obstructions have been reported in numerous conditions, including hypertrophic and dilated cardiomyopathy, hypertensive heart disease, diabetes mellitus, and syndrome X.\(^1,2\) These findings have been attributed to microvascular disease, either structural or functional. However, evidence that directly implicates microvascular impairment has been hampered by methodologic limitations.

**Coronary Flow Reserve**

Coronary flow reserve (CFR), calculated as the ratio of maximal hyperemic blood flow to basal flow, is a time-honored index used in cardiac catheterization laboratories to assess microvascular impairment or the physiological significance of epicardial stenoses. Despite early acceptance by clinical investigators, CFR has substantial shortcomings because it is greatly affected by hemodynamic conditions present at the time of measurement, including variability in heart rate, arterial pressure, and contractility.\(^1\) Perhaps as a result, the optimal cutoff values for CFR have not been established.\(^1\) Furthermore, CFR cannot pinpoint the site of abnormal resistance when disease affects both the epicardial arteries and the downstream microvessels.

The Diastolic Hyperemic Flow Versus Pressure Relation

To overcome these limitations of CFR, Mancini and colleagues\(^3\) developed a new index of coronary hemodynamics, which is the slope of the instantaneous relationship between mid- and late-diastolic hyperemic flow versus pressure (known as the Instantaneous Hyperemic Diastolic Velocity Pressure Slope, IHDVPS). The mid- to late-diastolic timing of this measurement avoids not only the effects of extracardiac flow velocity reserve on coronary blood flow but also the early diastolic discharge of the epicardial artery capacitance that alters the pressure–flow relationship.\(^3,4\)

The IHDVPS was primarily developed to assess the hemodynamic severity of coronary stenoses in epicardial arteries. In canine studies\(^5\) IHDVPS was found to be independent of heart rate, aortic pressure, preload, myocardial contractility, and basal blood flow, and it correlated well with the severity of coronary stenoses. Thus, it offered distinct advantages over the CFR measurement. Key elements of the experimental findings were replicated in clinical studies, in particular demonstrating that IHDVPS is independent of heart rate and aortic pressure.\(^4\)

Yet, with a principal focus on coronary stenoses, any coexistent microvascular impairment was viewed as a potential Achilles heel in the use of IHDVPS\(^1\) because conditions in both vascular sites may independently alter its value. The simultaneous measurement of distal pressure and flow velocity with capable guidewires now largely overcomes this problem because it facilitates the separate evaluation of microvascular resistance in the face of proximal coronary stenoses.\(^1,5\) However, despite these advances, a wide application of IHDVPS for stenosis assessment has fallen short because of its complexity coupled with the development of a far simpler approach that uses intracoronary pressures, the so-called fractional flow reserve, a measurement that is also independent of baseline loading conditions.\(^6\)

Recently, the aforementioned microvascular diseases without obstructive epicardial stenoses have come to clinical attention, and IHDVPS is once again being reevaluated as a potentially valuable research tool.\(^7\) However, the application of IHDVPS for the assessment of microvascular diseases, though theoretically sound, has been in dire need of clinical validation.

In this issue of *Circulation*, Escaned and colleagues\(^8\) have provided an elegant validation by correlating IHDVPS as well as coronary flow velocity reserve, along with 2 less commonly used coronary hemodynamic indexes against the structural appearance of the microvasculature in transplanted hearts. In 17 cardiac allograft recipients without angiographic evidence of coronary stenoses, intracoronary Doppler flow velocity and aortic pressure were recorded before and during maximal hyperemia. Quantitative microvascular morphometry was performed in endomyocardial biopsy specimens obtained during the same hospitalization. The IHDVPS correlated significantly with arteriolar obliteration (narrowing of the arteriolar lumen due to medial proliferation) and with a reduction in capillary density (capillary rarefaction). Lower (ie, more abnormal) values of IHDVPS also correlated with adverse cardiac events in long-term follow-up, although this finding was limited by the modest size of the study. By contrast, coronary flow velocity reserve did not correlate with histological microvascular changes or with adverse clinical outcomes. Thus, Escaned and colleagues\(^8\) have provided a key initial step in validating IHDVPS as a potentially useful measure of microvascular structural changes, superior to coronary flow velocity reserve. The authors are to be congratulated.

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on executing this cleverly designed study. A few minor limitations and future challenges are nonetheless worth noting.

Although the Doppler flow velocity was measured in the middle segment of the left anterior descending coronary artery, the corresponding pressure was assessed upstream in the left main artery ostium through a guiding catheter. As transplantation patients frequently demonstrate occult, diffuse epicardial coronary disease, pressures cannot be assumed to be uniform along the length of this conduit artery.9 Fearon and colleagues8 found fractional flow reserve reduced to <0.8 (evidence of potentially significant obstructive disease) in 15% of cardiac transplant patients even when coronary angiogram suggested that no obstructive disease was present. Thus, for microvascular assessment in transplantation patients, both arterial pressure and flow velocity used to calculate IHDVPS should ideally be derived from the same distal coronary artery location.

A particularly convincing case for the clinical significance of the reported microvascular changes may have been made by concomitant findings of any topographically associated myocardial fibrosis. If arterial obliteration or capillary rarefaction resulted in chronic ischemia, one might have observed patchy or even diffuse fibrosis in the surrounding areas, particularly because specimens are derived from the endocardial region prone to ischemia. Although fibrosis was not evaluated with specific stains, the myocardium shown in Figures 2 and 3 of the article by Escaned and colleagues8 appears relatively well preserved and free of apparent scarring. Long-term studies will be needed to correlate the presence of microvascular disease with development of myocardial fibrosis.

For research or clinical use, the range of normal values for the IHDVPS measurement will need to be defined. Although the study discussed here has drawn attention to structural microvascular impairment in cardiac allografts, ironically, prior investigations relied on a similar population of cardiac transplant recipients to establish a range of normal values for IHDVPS.7 Furthermore, to be generally applicable, the IHDVPS assessment will need to become more refined. Although pressures are simple to record, adequate Doppler flow velocity signal is not easy to obtain, and its analysis can be difficult; of note, 4 of 21 (19%) study participants recruited by Escaned and colleagues8 had inadequate data for interpretation.

Microvasculopathy After Cardiac Transplantation

After cardiac transplantation, endomyocardial biopsies have been used primarily to detect evidence of acute myocardial rejection, with a focus on postcapillary venules as the site where inflammatory and immune cells transmigrate into the allograft myocardium.10 However, long-term survival after heart transplantation is limited by arterial vasculopathy.11 Progressive narrowing of epicardial arteries due to myointimal growth and the thickening of the media in small arterioles leads to diffuse obstruction of the coronary tree. Hiemann and colleagues11 analyzed 9713 endomyocardial biopsy specimens and readily identified arterioles 10–20 μm in diameter. Evidence of obstructive microvasculopathy in these small vessels within the first posttransplant year, present in 43% of 873 patients, was associated with poor cardiac survival, independently of epicardial artery involvement. Thus, the clinical scenario of cardiac transplantation with regularly scheduled, routine endomyocardial biopsies may become a fertile ground for testing whether aggressive treatment of microvasculopathy diagnosed in endomyocardial biopsy specimens can reverse the ominous clinical course in these patients.12 Additional insights may potentially be gained by combining histological information derived from endomyocardial biopsy specimens, which of necessity provides information from only a few focal endocardial sites along with a more global assessment of microvascular structural disease provided by the newly validated physiological assessment, the IHDVPS.

Structural Microvascular Diseases in Nontransplantation Settings

Structural diseases involving the coronary microvasculature, outside of the aforementioned transplantation setting, have been largely neglected by clinicians because they are difficult to diagnose, have uncertain clinical relevance, and often lack a clear-cut treatment strategy. Nevertheless, structural microvascular changes have been reported in numerous diseases. For example, arteriolar obliteration due to medial thickening or perivascular fibrosis was noted in arterial hypertension13 and in hypertrophic cardiomyopathy.14 Microvascular wall thickening typically involving the intima has been reported in infiltrative heart diseases.13 Diabetic individuals exhibit both structural and functional microvascular impairment.13 Patients with aortic stenosis may experience periarteriolar fibrosis that may lead to vascular narrowing and potentially to heart failure.13 In some of these entities, as reported in hypertrophic cardiomyopathy, the degree of microvascular impairment is a strong, independent predictor of clinical deterioration and death.15 Krams and colleagues7 have compared the utility of IHDVPS and CFR to evaluate microvascular structural impairment in patients with hypertrophic cardiomyopathy with septal hypertrophy. They observed that IHDVPS revealed microvascular impairment selectively in the left anterior descending territory, which supplies the abnormal septal region, but not in the circumflex artery territory, which supplies the relatively uninvolved posterolateral wall. The CFR values did not distinguish these 2 arterial territories. Thus, IHDVPS, in contrast to CFR, correctly identified those regions that commonly display structural disturbances in the microcirculation. Application of IHDVPS should be helpful in pinpointing whether microvascular disease reported in various cardiac conditions is an epiphenomenon or whether it directly contributes to the pathogenesis of myocardial ischemia and its sequelae.

Capillary Rarefaction

From a hemodynamic standpoint, capillaries, organized into an extensive parallel network, have been largely neglected until recently because they were believed to make a minimal contribution to overall vascular resistance. Kaul and colleagues16 have proposed, on the basis of their studies using myocardial contrast echocardiography, that in a maximally vasodilated normal coronary bed (eg, with adenosine) the capillaries become the “bottleneck” to hyperemic blood flow. They estimated that capillaries account for three quarters of microvascular resistance during reactive hyperemia. A reduc-
tion in capillary density (capillary rarefaction), which accentuates this problem, has been reported in several conditions, including hypertension, diabetes mellitus, and dilated cardiomyopathy. In patients with advanced idiopathic dilated cardiomyopathy and congestive heart failure, analysis of right ventricular endomyocardial biopsy specimens revealed markedly reduced capillary density and diameter in association with a reduced CFR assessed by coronary thermodilution. Escaned and colleagues, using statistical adjustment, found independent contributions of capillary rarefaction and arteriolar obliteration to reductions in IHDVPS in cardiac allografts free of coronary stenoses. Thus, evidence is accumulating that both capillary rarefaction and arteriolar obliteration represent independent forms of structural microvascular disease with potential clinical consequences. One challenging scenario that often stumps clinicians occurs in a patient with typical anginal chest pain and objective evidence of myocardial ischemia who has a normal coronary arteriogram. Rarefaction of skin capillaries has been reported in these individuals; further studies potentially using IHDVPS are needed to determine whether cardiac capillary rarefaction accounts for these unexplained reductions in myocardial blood flow.

**IHDVPS Is Not a Test of Microvascular Function**

As already noted, IHDVPS is well suited for the assessment of structural disease in coronary arteries, arterioles, and capillaries. However, it is not a proper test of microvascular function. Microvascular tone is regulated elegantly by metabolic demand (metabolic regulation), by the need to maintain steady blood flow despite varying arterial perfusion pressure (autoregulation), and by other mechanisms. This microvascular response is orchestrated through vascular heterogeneity as arteriolar segments of different sizes respond preferentially to a sequence of specific stimuli. For example, mediators released in response to increased metabolic demand trigger dilation of the smallest arterioles, which in turn triggers myogenic dilation in slightly larger arterioles and flow-mediated dilation in still larger arterioles, forming an elegant amplification loop. However, inasmuch as IHDVPS is measured during the administration of maximal microvascular vasodilators, such as adenosine, which are intended to eliminate vascular tone and to override autoregulation and metabolic regulation, microvascular resistance under these conditions is determined essentially by structure, not function. Accordingly, a normal IHDVPS does not preclude a microvascular functional defect. Other approaches are needed to investigate coronary microvascular function. In summary, Escaned and colleagues not only have drawn attention to the potential clinical importance of microvascular diseases but, by elegantly correlating IHDVPS with microvascular histology, have now provided a validated tool for future investigations.

**Disclosures**

None.

**References**


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