Multiple Causes for Ischemia Without Obstructive Coronary Artery Disease
Not a Short List

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Among angina patients undergoing coronary angiography to further evaluate suspected ischemic heart disease, normal or nonobstructive coronary artery disease (CAD) is found in 30% of men and 40% to 60% of women and appears to be increasing. It is becoming very clear that such patients do not have benign outcomes as documented in larger and larger prospective cohorts. Also important are accumulating data indicating that patient-reported outcomes and societal implications rival those observed with obstructive CAD.

After several hundred years of focus on obstructive stenosis, numerous reports have described coronary physiological evaluations documenting that mechanisms other than flow-limiting CAD are present among such patients with symptoms or signs of ischemia. Some of these such as endothelial or vascular smooth muscle dysfunction and spasm are associated with heightened risk for adverse outcomes. However, almost all of the reports are directed at only one or another mechanism (most often endothelial or vascular smooth muscle dysfunction), and very limited information is available about the possible coexistence of several such coronary mechanisms in the same patient. In addition, the frequency of such patients without a coronary explanation for ischemia after multiple tests is unknown, again because most publications have focused on only 1 or 2 possible mechanisms.

Multiple Mechanisms for Angina in the Absence of Obstructive CAD

To this end, the work by Lee et al in this issue of Circulation contributes important new information by testing for multiple different mechanisms in a prospective cohort with symptoms suggesting ischemic heart disease without apparent flow-limiting obstruction on angiography. Their comprehensive invasive assessment included fractional flow reserve (FFR) to evaluate epicardial obstructive disease that was not apparent from the angiogram, endothelial function testing with acetylcholine, index of microvascular resistance with adenosine, and myocardial bridge evaluation by intravascular ultrasound (IVUS). Concealed diffuse obstructive disease defined by an abnormal FFR was the least frequent (≈5% of cases) finding, whereas endothelial dysfunction, microvascular dysfunction, or myocardial bridges were detected in about three quarters of these patients. Importantly, several of these processes often were operative in combination as coronary artery–based explanations for angina. The authors conclude that, at the time of coronary angiography, a comprehensive assessment can be performed safely and very often will provide important diagnostic information that may affect treatment and outcomes.

There are some points that the clinician should understand best use this information. The conclusion that a coronary cause for angina can be identified in about three fourths of such patients is likely an underestimate. The definition chosen for epicardial endothelial dysfunction was very restrictive. Considering that normal coronary endothelium releases nitric oxide in response to low-dose acetylcholine resulting in vasodilation, the definition chosen for endothelial dysfunction (>20% decrease in diameter) will include only patients with severe endothelial dysfunction. Endothelial dysfunction is frequently present in patients with cardiovascular risk factors. A less restrictive definition such as any detectable constriction beyond the threshold of the qualitative analysis method occurred in 106 of these patients (76%) and would have resulted in many more patients categorized as having evidence of endothelial dysfunction. This conclusion is also consistent with the authors’ finding of endothelial thickening (eg, plaque) in all patients with IVUS of the left anterior descending artery. The IVUS findings better characterize the cohort by identifying those with endothelial abnormalities in whom progression may be preventable by medical treatment (eg, statins). Additionally, microvascular endothelial dysfunction is among the earliest abnormalities detected in experimental and patient studies; however, this was not evaluated.

What About Coronary Artery Spasm?

It is puzzling that no patients had coronary artery spasm when tested with 100 μg acetylcholine. Epicardial coronary spasm is very well documented to occur in ≈5% of unselected angina cases without (and with) obstructive CAD. This information is critically important because spasm can be managed effectively when known to be present. There is considerable recent interest in microvascular coronary spasm, which would have also been expected to occur with acetylcholine provocation. However, data on angina and 12-lead ECG recordings were not available with acetylcholine, so information is lacking on the frequency of microvascular spasm.
The Role of Coronary Atherosclerosis
It was very important that these investigators provided IVUS evidence of coronary atherosclerosis in all patients tested, confirming our findings from the Women’s Ischemia Syndrome Evaluation (WISE) IVUS substudy. This information could provide direction for future management (eg, statin to prevent atherosclerosis progression). Importantly, it also raises the question of whether atherosclerosis or its preceding risk conditions could be linked to these other mechanisms. Certainly, this would be true for endothelial dysfunction and for microvascular dysfunction. This notion would broaden our traditional concepts of atherosclerotic CAD to include dysfunction of the smaller coronary vessels and microcirculation.

To this end, discordance between epicardial coronary function (by FFR) and microvascular function (by coronary flow velocity reserve [CFVR]) has generated recent interest. Finding a normal FFR, indicating no obstructive epicardial stenosis, but reduced CFVR, indicating predominant microvascular disease, is associated with a particularly unfavorable prognosis. In contrast, preserved microvascular function (normal CFVR) in the presence of flow-limiting epicardial stenosis (abnormal FFR) has been associated with a long-term clinical outcome comparable to concordant normal FFR and CFVR.

These recent observations support a critical role for coronary flow evaluation in the investigation of the functional severity of coronary pathology. They further emphasize the importance of identifying pathology associated with discordance between coronary pressure– and flow–derived measures to provide optimal discrimination between coronary pathologies with and without adverse outcome implications. Said another way, these concepts will remain obscure to operators when the focus is limited to angiographic stenosis severity and only coronary pressure (eg, FFR) is assessed. Coronary microvascular dysfunction is increasingly being recognized. It has been estimated that discordance between CFVR and FFR occurs in ≈30% to 40% of coronary stenoses evaluated and originates from involvement of the coronary microvasculature (as reflected by abnormal CFVR). Importantly, the risk for major adverse cardiac events associated with FFR/CFVR discordance appears to be attributable mostly to cases in which CFVR is abnormal. This information emphasizes the requirement for coronary flow assessment, in addition to pressure, for optimal risk stratification in patients with stable CAD.

What About Myocardial Bridges?
This study is confounded by a large number of patients (70) with myocardial bridges, but almost two-thirds of these patients had other coexisting coronary abnormalities. There is no question that a bridge may cause transient ischemia in isolated cases. However, given the very high prevalence of bridges observed in unselected coronary angiograms, the failure of several series to show adverse outcome implications over long-term follow-up, and the lack of more general acceptance of the signs used here to define functionally important bridges, such emphasis may not be appropriate. Unless there is supporting evidence (eg, proximal left anterior descending artery bridge associated with an anteroseptal perfusion defect), most would not have concern for functionally important bridging. Perhaps important is the fact that bridges have been linked to more established mechanisms for ischemia, as also documented by these data (Figure 2A in the article by Lee et al), with 32 of the 70 bridge patients also having severe endothelial dysfunction.

Concept of Multiple Mechanisms for Angina in the Same Patient
Among the patients with a coronary abnormality identified, about half (58 of 107) had >1 abnormality, supporting the notion that multiple mechanisms are common, even when testing is limited to only 4 possible mechanisms. As we have discussed elsewhere, there are many additional coronary and noncoronary mechanisms beyond epicardial coronary stenosis that have the potential to contribute to angina and ischemia. The possible mechanisms for ischemia include those associated with the coronary macrovasculature and microvasculature: endothelial or vascular smooth muscle dysfunction, hypercoagulable states, microembolism, inflammatory disorders (lupus, polyarteritis, etc), dissection, and so on. Relative to the microcirculation, microparticle occlusion, inflammation, and rarefication are important. Another mechanism is increased capacitance vessel stiffening. Additional mechanisms are disorders of the cardiomyocytes (transcellular, intracellular, and mitochondrial) and the adventitia and others (central nervous system, bone marrow–derived cells, etc).

Relationship Between Angina and Coronary Functional Abnormalities
The lack of information linking the detected coronary abnormalities and patient’s symptoms or ischemia is also worthy of comment. Although endothelial dysfunction alone may not be responsible for angina in some of these cases, when combined with another coronary abnormality, the probability for an additional effect would very likely increase. In this regard, it was not possible for these authors to link findings on coronary testing with the patient’s symptoms or even noninvasive testing results for ischemia. Relative to the former, all patients were sedated during coronary angiography, 12-lead ECG and symptom recordings during acetylcholine testing were not provided, and only the left anterior descending artery was assessed. Relative to the latter and in defense of these authors, failure to identify strong associations with noninvasive stress testing results is not unexpected because these tests were designed to detect major differences in regional perfusion or wall motion. Furthermore, they were validated against identification of significant epicardial obstructive stenosis by the angiogram. We and others have published similar findings. We found that using cardiac magnetic resonance myocardial perfusion reserve by quantifying the gadolinium time-activity upslope provided superior resolution to permit evaluation of perfusion across the myocardial wall, which was significantly correlated with coronary flow reserve derived from CFVR measured invasively. Such patients were found to have a relative failure of subendocardial perfusion to increase with adenosine that correlated with CFVR. These findings could also explain the absence of major changes in
LV wall motion and the inability to detect major perfusion defects by other methods, which have been optimized to identify epicardial obstructive disease.

**Message for Interventionalists**
The “less than very good” outcomes of these patients with angina and no obstructive CAD, described recently by many groups, must be recognized so that a near-normal or “normal” angiogram does not drive diagnostic and therapeutic complacency. Importantly, given the impaired prognosis for such patients, the search for cause(s) of ischemic symptoms and signs (even troponin elevation as with non–ST-segment-elevation myocardial infarction) must be much more comprehensive than simply a 10-minute diagnostic angiogram performed as part of usual care. Additional testing must be considered to exclude some of the processes noted here (coronary spasm, angiographically nonevident plaques and diffuse narrowing, endothelial dysfunction, microvascular dysfunction, etc). In the absence of any indication of an epicardial coronary cause of ischemic symptoms and signs, further evaluation is required to identify other potential cardiac or noncardiac causes to direct appropriate short-term and long-term therapy.

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None.

**References**


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