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Multiple Causes for Ischemia Without Obstructive CAD: Not a Short List

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Among angina patients undergoing coronary angiography to further evaluate suspected ischemic heart disease (IHD), “normal” or “non-obstructive” coronary artery disease (CAD) is found in 30% of men and 40-60% of women and appears to be increasing.¹ It is becoming very clear that such patients do not have benign outcomes as documented in larger and larger prospective cohorts.²⁻⁵ Also important are accumulating data indicating that patient-reported outcomes and societal implications rival those observed with obstructive CAD.^{6, 7}

After several-hundred years of focus on the “obstructive stenosis”, numerous reports have described coronary physiologic evaluations documenting mechanisms other than flow limiting CAD are present among such patients with symptoms/signs of ischemia. Some of these like endothelial and/or vascular smooth muscle dysfunction, spasm, etc. are associated with heightened risk for adverse outcomes. But 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 possible coexistence of several such coronary mechanisms in the same patient. Also the frequency of such patients without a coronary explanation for ischemia after multiple tests is unknown, again since most publications have focused on only one or two possible mechanisms.

Multiple mechanisms for angina in the absence of obstructive CAD

To this end, work by Lee et al⁸ in the current issue contributes important new information by testing for multiple different mechanisms in a prospective cohort with symptoms suggesting IHD 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 (Ach), index of microvascular resistance with adenosine, and myocardial bridge evaluation by intravascular ultrasound (IVUS). Concealed diffuse obstructive disease defined by abnormal FFR was the least frequent (~5% of cases) finding, while endothelial dysfunction, microvascular dysfunction, and/or myocardial bridges were detected in about three-quarters of these patients. Importantly, often several of these processes were operative in combination as coronary artery-based explanations for angina. The authors conclude that at the time of coronary angiography a comprehensive assessment

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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 in order to 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 NO in response to low-dose Ach 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 ($\sim 76\%$) of these cases and would have resulted in many more patients categorized as having evidence for endothelial dysfunction. This conclusion is also consistent with the authors finding endothelial thickening (e.g., plaque) in all cases with IVUS of the left anterior descending artery (LAD). The IVUS findings better characterize the cohort by identifying those with endothelial abnormalities where progression may be preventable by medical treatment (e.g., 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 cases had coronary artery spasm when tested with 100 μ g of Ach. Epicardial coronary spasm is very well documented to occur in $\sim 5\%$ of unselected angina cases without (as well as with) obstructive CAD. This information is critically important since spasm can be effectively managed when known to be present. There is considerable recent interest in microvascular coronary spasm, which would have also been expected to occur with Ach provocation.⁹ But data on angina and 12-lead electrocardiographic (ECG) recordings were not available with Ach 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 WISE IVUS substudy.¹⁰ This information could provide direction for future management (e.g., statin to prevent atherosclerosis progression). Importantly, it also raises the question whether atherosclerosis and/or its preceding risk conditions could be linked to these other mechanisms. Certainly this would be true for endothelial dysfunction and also 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.¹¹ In contrast, preserved microvascular function (normal CFVR) in the presence of flow-limiting epicardial stenosis (abnormal FFR), indicating non flow-limiting epicardial CAD, has been associated with a long-term clinical outcome comparable with 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 identification of 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 (e.g., FFR) is assessed. Coronary microvascular dysfunction is increasingly being recognized.¹² It has been estimated that discordance between CFVR and FFR occurs in about 30-40% of coronary stenoses evaluated¹¹ 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 mostly attributable to cases where 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 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, failure of several series to show adverse outcome implications over long-term follow-up, and 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 (e.g., proximal LAD 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 with more established mechanisms for ischemia as also documented by these data (Figure 2A in Lee et al.⁸) 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 more than one abnormality, supporting the notion that multiple mechanisms are common, even when testing is limited to only four possible mechanisms. As we have discussed elsewhere, there are many additional coronary and non-coronary mechanisms beyond epicardial coronary stenosis that have the potential to contribute to angina and ischemia.¹³ The possible mechanisms for ischemia include those associated with the coronary macro and microvasculature—endothelial and/or vascular smooth muscle dysfunction, hypercoagulable states, microembolism, inflammatory disorders (e.g., lupus, polyarteritis, etc.), dissection, and so on. Relative to the microcirculation, microparticle occlusion, inflammation, and

rarefaction 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 (CNS, 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 and/or ischemia is also worthy of comment. Although endothelial dysfunction alone may not be responsible for angina in some of these cases, in combination 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 non-invasive testing results for ischemia. Relative to the former, all patients were sedated during coronary angiography, 12-lead ECG and symptom recordings during Ach testing were not provided, and only the LAD was assessed. Relative to the latter and in defense of these authors, failure to identify strong associations with non-invasive stress testing results is not unexpected as 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. We¹⁴ and others^{15, 16} 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 CFR derived from CFVR measured invasively.¹⁴ 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 absence of major changes in LV wall motion and 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 non-evident 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 non-cardiac causes to direct appropriate short-term and long-term therapy.

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