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EDITORIAL

Coronary Artery Spasm and Flow-Limiting Coronary Stenoses: A Malevolent Duo?

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Flow-limiting coronary atherosclerotic obstructions can cause myocardial ischemia and severe angina, which impair both quality of life and clinical outcomes. On the other hand, coronary artery spasm, a functional disorder of the coronary artery, as seen typically in Prinzmetal variant angina, can cause transient coronary blood flow reductions, severe angina pectoris, life-threatening arrhythmias, and myocardial infarction (MI), in the presence or in the absence of obstructive coronary artery disease (CAD).[1] The identification of flow-limiting atherosclerotic epicardial coronary obstructions with the use of coronary physiological investigations (ie, fractional flow reserve [FFR]) has markedly influenced our approach to the management of obstructive CAD over the past years.[2] It has also generated a belief among patients and healthcare professionals alike that in addition to improving myocardial ischemia and anginal symptoms, the elimination of the flow-limiting effect of a coronary stenosis by coronary revascularization with surgical bypass or percutaneous coronary intervention also reduces the incidence of MI and improves patient clinical outcomes. Although the latter is right in high-risk patients with acute coronary syndrome and ST-segment–elevation MI, the concept is not necessarily fully applicable to patients with chronic coronary syndrome (stable angina), as shown by several meta-analyses and large randomized studies,[3–6] including the recent ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches).[6] Indeed, in ISCHEMIA,[6] the primary study end point did not differ significantly in patients with chronic coronary syndrome who were undergoing revascularization compared with conservatively treated patients with chronic coronary syndrome (16.4% and 18.2%, respectively; 95% CI, 4.7–1.0). For the major secondary end point of cardiovascular mortality or MI, the hazard ratio (HR) for the invasive versus conservative strategies was 0.90 (95% CI, 0.77–1.06; *P*=0.21). More important, there were no between-group differences in either all-cause mortality (5.6% in each arm; HR, 1.05 [95% CI, 0.83–1.32]; *P*=0.67) or cardiovascular mortality (HR, 0.87 [95% CI, 0.66–1.15]; *P*=0.33) during follow-up. Although ISCHEMIA[6] highlighted the important role of optimal medical therapy in patients with stable angina who had obstructive CAD, the study excluded patients whose anginal symptoms occurred in the absence of obstructive coronary artery stenosis and did not look into the role of invasive versus medical treatment of functional causes of angina (ie, coronary artery spasm). Functional mechanisms of myocardial ischemia, including epicardial coronary artery spasm and coronary microvascular dysfunction, play an important pathogenic role in both patients with and patients without obstructive CAD, but cardiologists have not embraced this notion universally.[7] More important, coronary artery spasm can lead to refractory angina and both acute MI and life-threatening arrhythmias,[1] and in recent years, studies have shown that the presence of coronary microvascular dysfunction is associated with impaired cardiovascular outcomes in patients with or without obstructive CAD.[8] It is therefore conceivable that not only organic coronary stenoses but different combinations of obstructive and functional

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mechanisms, often coexisting in the individual patient, are finally responsible for the many different forms of presentation of ischemic heart disease in clinical practice, and the often unpredictable clinical evolution of the disease process, in certain patients.

See Article by Hao et al.

Interestingly, although cardiologists are aware of the important role of functional mechanisms in the pathogenesis of angina pectoris, anatomical assessment of the epicardial coronary arteries with conventional coronary angiography continues to be used as the gold standard diagnostic test for angina, despite the limitations of the technique to determine the hemodynamic effects of a coronary stenosis or to evaluate vasomotor changes that may occur in the epicardial arteries or in the coronary microvasculature and can, per se, trigger angina in patients with or without obstructive CAD. Unfortunately, this diagnostic strategy, used in routine clinical practice for several decades now, has precluded a proper understanding of the incidence and relevance of coronary vasomotion abnormalities as a cause of myocardial ischemia or the true prognostic role of combined obstructive CAD and superimposed coronary spasm in patients with angina. However, the implementation of coronary physiological tests to establish the flow-limiting effects of epicardial coronary stenoses[2] and, more recently, of tests of coronary microvascular function[9] is helping physicians to understand how complex a problem angina/ischemic heart disease truly is. Interestingly, despite the established role that coronary artery spasm plays in the pathogenesis of different coronary syndromes, tests for coronary spasm are not routinely performed in patients with obstructive CAD. In this issue of the *Journal of the American Heart Association* (*JAHA*), an article by Hao et al[10] contributes to our understanding of the prognostic role of the combined assessment of flow-limiting obstructive CAD and epicardial coronary artery spasm. They observed that patients with both coronary artery spasm and flow-limiting atheromatous coronary stenoses (ie, FFR <0.80) represent a high-risk subgroup. Briefly, the study involved 236 consecutive patients with angina who underwent coronary arteriography and both acetylcholine provocation for coronary spasm and FFR measurements to establish the flow-limiting effect of obstructive coronary stenoses, with 175 patients having a positive test result for coronary spasm. Of these patients, 110 had no organic stenosis (<50% lumen diameter reduction), 36 had obstructive CAD but no flow-limiting stenoses (FFR >0.80), and 29 had significant stenoses and a reduced FFR <0.80. All patients with vasospastic angina received treatment with calcium channel blockers, and 28 of the 29 (95%) patients with reduced FFR also underwent elective percutaneous coronary intervention. During a median follow-up of almost 2 years, the incidence of major adverse cardiac events was low and similar among patients with vasospastic angina and no obstructive CAD and patients with obstructive CAD but no flow-limiting stenoses. Conversely, patients with both coronary spasm and CAD with low FFR had markedly impaired clinical outcomes, despite appropriate treatment with calcium channel blockers and percutaneous coronary intervention. The reasons for the markedly impaired clinical outcomes in these patients were not explored in the study, but the authors speculate that ρ-kinase activation may play a role and that the administration of angiotensin-converting enzyme inhibitors may have beneficial effects in addition to those of calcium channel blockers, conceivably through enhanced bradykinin concentration and inhibition of the ρ-kinase pathway.[11,12] The findings by Hao et al[10] are of potential clinical importance as they, first, highlight the safety and usefulness of performing provocative tests for coronary spasm, even in patients with obstructive CAD, and, second, showed what appears to be a synergistic effect of obstructive CAD and coronary spasm, leading to markedly impaired clinical outcomes in patients with coronary spasm and CAD with low FFR that is not beneficially affected by stenting and/or the use of calcium channel blockers. Another important finding in the study was that provocative testing for coronary spasm was safe, as previously reported by other investigators.[13–15]

Despite the potentially major clinical implications of the findings by Hao et al,[10] their work is not without limitations. Indeed, the study is nonrandomized and retrospective in nature, and it involved a relatively small number of patients who were assigned to different clinical subgroups, thus reducing the power of the study further. Moreover, patients with coronary spasm patients who had obstructive CAD had a higher prevalence of major risk factors (ie, diabetes mellitus and dyslipidemia), which could have affected clinical outcomes. Another limitation, also identified by the authors, is that in this single-center study, the decision to proceed to acetylcholine provocation testing and selecting the treatment strategy were left to the discretion of the treating cardiologists, potentially resulting in selection bias. Despite these limitations, which have to be considered carefully when trying to establish the clinical relevance of the reported findings and the need for further research to be performed to confirm or disprove the findings of Hao et al, their study has merit. Their findings not only are hypothesis generating but offer at least a preliminary answer to the frequently asked clinical question as to whether patients with recurrent coronary artery spasm, with or without CAD, may benefit from percutaneous coronary intervention/

stenting at the spastic site. The study clearly suggests that revascularization does not have the desired therapeutic effect and may be even harmful in these patients. Clinicians now eagerly await the results of large, randomized, placebo-controlled studies that can help to both provide further insight into the mechanisms leading to serious cardiovascular events when coronary spasm and obstructive stenoses coexist in a given patient and help identify effective treatments for patients with angina caused by the combined actions of flow-limiting obstructive CAD and vasospastic angina.

ARTICLE INFORMATION

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Disclosures

None.

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Supplemental Material

Table S1. Comparison of clinical characteristics of LVNC patients with and without LA dilatation (left atrial volume index >34 ml/m2).

Variables	**LA dilatation present (N=160)**	**LA dilatation absent (N=160)**	**p-value**
Age (years)	56 (44-65)	39 (28-51)	<0.001
Female sex	64 (40%)	84 (79%)	0.025
Hypertension	64 (40%)	34 (21%)	<0.001
Diabetes mellitus	23 (14%)	16 (10%)	0.23
Smoking	55 (34%)	44 (28%)	0.18
Stroke/TIA	13 (8%)	4 (3%)	0.02
Coronary artery disease	35 (22%)	11 (7%)	<0.001
Congestive heart failure	63 (39%)	31 (19%)	<0.001
Left Ventricular Ejection fraction (%)	36 (23-51)	53 (40-60)	<0.001
Left ventricular ejection fraction <50%	114 (71%)	68 (43%)	<0.001
Atrial fibrillation/flutter	55 (34%)	18 (11%)	<0.001
Any cardiovascular implantable device	29 (18%)	25 (16%)	0.55
Asymptomatic at presentation	33 (21%)	52 (33%)	0.017
Echocardiographic variables			
Left ventricular end diastolic diameter	59 (53-65)	51 (48-57)	<0.001
Left ventricular end systolic diameter	48 (38-56)	36 (32-43)	<0.001
Right ventricular systolic pressure (mmHg)	34 (28-49)	26 (24-31)	<0.001

Any RV enlargement	54 (34%)	27 (17%)	<0.001
Any RV dysfunction	58 (37%)	28 (18%)	<0.001
Moderate or greater mitral regurgitation	34 (22%)	7 (5%)	<0.001
Increased LV wall thickness (LV mass index >95 gm/m^2: women; >115 gm/m^2: men)	105 (66%)	53 (33%)	<0.001
Minimum systolic compacta thickness (mm)	6 (5-7)	6 (5-6)	0.015
Maximum systolic noncompacta thickness (mm)	19 (17-22)	17 (14-20)	<0.001
Maximum end systolic NC:C ratio (Jenni criteria)	2.8 (2.5-3.4)	2.8 (2.4-3.2)	0.45
Minimum end diastolic X:Y ratio (Chin criteria, per 0.1 unit increase in the ratio)	0.26 (0.22-0.29)	0.26 (0.22-0.30)	0.27
Number of segments involved	2 (1-3)	1 (1-3)	0.03
Isolated apical noncompaction	71 (44%)	84 (53%)	0.14
Delayed gadolinium enhancement on MRI	11 (24%)	6 (10%)	0.048

Supplemental Video Legends:

Video S1. Left ventricular noncompaction patient with mid-basal noncompaction extent. NC:C and X:Y ratios met for segments extending beyond the apical segment. Best viewed with Windows Media Player.

Video S2. Left ventricular noncompaction patient with isolated apical noncompaction extent. NC:C and X:Y ratios met for only the apical segment. Best viewed with Windows Media Player.