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Editorial

Fixed lesions or coronary spasm? The choice is clear…

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In the Western Hemisphere, the majority of patients afflicted by coronary artery disease present with effort-related angina or acute coronary syndromes. These are the result of an atherosclerotic plaque producing a fixed narrowing of a major epicardial artery or the rupture of such a plaque and rapid accumulation of thrombus. While we always entertain the possibility of "exotic" diagnoses, such as coronary spasm, a fixed coronary stenosis is almost always identified. In contrast, among patients in East Asia, coronary vasomotion abnormalities and their clinical presentation – variant angina – appear to be more common. The initial description of variant angina was credited to Myron Prinzmetal MD in 1959 [1–4], although previous descriptions of this condition were noted as early as the 1930s. This syndrome, later associated with Syndrome X, consists of essentially normal or minimally diseased epicardial arteries in patients presenting with typical angina pectoris at rest, relieved with nitroglycerin. There was great enthusiasm in evaluating such patients with provocative invasive testing (predominantly ergonovine), but its side effects (severe ischemia and myocardial infarction) tempered the use of this aggressive approach, leading to empiric medical therapy with vasodilators. For few decades now, the majority of the interest in this syndrome has resided in the East Asia, where the condition seems to be more prevalent [5], and most of the relevant literature comes from Japan and South Korea.

Another (potentially safer) way of provoking and diagnosing coronary spasm besides ergonovine is by infusing acetylcholine (ACH) in coronary arteries and measure the change in vessel diameter. ACH causes endothelium-dependent vasodilation via activation of muscarinic receptors in the vessel wall. In patients with abnormal endothelial function – usually because of atherosclerosis – ACH may cause no response, or even paradoxical vasoconstriction. These changes can be appreciated with quantitative coronary angiography. Besides lack of production of sufficient nitric oxide for vasodilatation, other mechanisms have been proposed to explain coronary spasm, such as smooth muscle cell hyperactivity and autonomic imbalance, favoring parasympathetic stimulation [6]. Other infrequently used agents for provocation of coronary spasm are neuropeptide Y [7] and dopamine [8].

Despite being traditionally assumed to carry a favorable prognosis [9], coronary spasm remains important because it can result in cardiac arrest, myocardial infarction and death [10,11].

It is not surprising then that Lee and colleagues from Seoul, South Korea provide us, in this issue of *Atherosclerosis,* with the largest and best account of the types and clinical significance of coronary artery spasm (CAS) from a dedicated registry at their University. Over 10 years, nearly 6000 patients were enrolled after presenting with typical chest pain at rest and no significant ($\geq$50%) fixed stenosis on coronary angiography. After excluding patients with previous ergonovine stimulation, those with right coronary artery spasm (much more often seen after intubation of the artery with a catheter) and those with previous revascularization procedures, they report on 4644 subjects who underwent ACH testing with escalating doses (every 5 minutes) for evaluation of left coronary artery spasm, after withholding all vasoactive medications for 48 hours.

They distinguished between 4 types of response to ACH: normal response (vasodilation without chest pain, ECG changes), microvascular spasm (chest pain with <75% coronary vasoconstriction and relief with nitroglycerin), epicardial spasm (chest pain with $\geq$75% vasoconstriction and/or ischemic ECG changes) and inconclusive response (vasoconstriction and/or ECG changes without chest pain). All angiographic determinations of vasomotion were made by the investigators, without blinding. All patients were treated with nitroglycerin after any type of vasomotion abnormality was detected.

Roughly one third of patients had normal response, one third had microvascular spasm, less than 15% had epicardial spasm and one fifth had inconclusive results. Patients with epicardial spasm or inconclusive results were more likely to have fixed mild coronary lesions, to be smokers and to consume alcohol than the other two types. When epicardial spasm was provoked (N = 647), there was approximately 80% stenosis compared to baseline, reversed with nitroglycerine. The majority of these episodes were diffuse in nature, covering nearly two thirds of the involved artery. Spasm was noted in the left anterior descending artery in 57% of patients and in both arteries in nearly 40%.

The most important aspect of this report is the prognosis of patients with CAS. The investigators found that over 5 years, the incidence of recurrent chest pain necessitating repeat coronary angiography was only 7.9% and was approximately twice more common among those with abnormal ACH response, regardless of type pf abnormality, than in those with normal response

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(8.2%–10.9% *vs.* 5.4%, $p = 0.009$). Moreover, this endpoint was ~4 times more common among those with an atherosclerotic substrate (a fixed mild stenosis) than in those without it, suggesting that a component of abnormal vasomotion is more likely to induce a clinically relevant CAS at the site of an existing lesion. The more serious adverse events (death, myocardial infarction, stroke or revascularization) were extremely rare – only 1.6% - and did not differ significantly between those with normal or abnormal ACH response. All-cause mortality and cardiac mortality was 0.1%–0.6% and 0.1%–0.2%, respectively in the four groups. There were very rare and easily managed complications as a result of the ACH test.

The lessons gleaned from this very large registry – one unlikely to be duplicated – can be interpreted in two diametrically opposed ways. One can argue that we should all do ACH testing in many patients with rest symptoms in whom a "smoking gun" or a culprit lesion is not found. The side effects are minimal and the information acquired during the test may assist in assuaging concerns for our patients and in reassuring them that they are at low risk for future cardiac events. To the contrary, one can read the manuscript from Lee et al. and conclude there is no role for ACH testing at all, since prognosis is not different in patients with normal *vs.* abnormal left coronary vasomotion and the therapies that were prescribed in response to the results of the test did not materially affect outcome. If one considers the event rate noted in the patients with normal vasomotion as 'the control group", we can compare it with outcomes in patients with simple coronary artery disease undergoing percutaneous coronary intervention. As an example, in the Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System (EES) - SPIRIT III - trial, patients (all from the Western Hemisphere) randomized to EES had a 3-year rate of cardiovascular death, target vessel myocardial infarction or ischemia-driven target lesion revascularization of 9.2%, more than 5-fold higher than in this registry, despite a significantly shorter follow-up [12].

In summary, I congratulate the Korean investigators for providing such abundant information on a topic that continues to defy simple therapeutic paradigms. It is reassuring that, in the context of appropriate medical therapy, the prognosis of patients with vasomotion abnormalities in the left coronary artery is similar to that of patients not demonstrating them while undergoing evaluation with ACH infusion. The absolute rate of major cardiac events is probably very similar to the normal population. On the other hand, the rate of recurrent symptoms is not trivial and the quality of life may be hampered by this condition. Should one prefer a fixed lesion, easily corrected with a coronary stent or a "pulsating artery" causing evanescent symptoms? The obvious answer is neither. But spasm may be preferable.

Conflict of interest

The author declared he does not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Sorin J. Brener
New York Methodist Hospital, 506 6th Street, KP-2, Brooklyn, NY 11215, USA
E-mail address: sjb9005@nyp.org.

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