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Review

Some observations on and controversies about coronary arterial spasm

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ABSTRACT

The pathogenesis, clinical features, diagnosis, and treatment of spasm of epicardial coronary arteries are reviewed briefly, especially with regard to some issues that remain controversial. For diagnosis, emphasis is placed on the need for objective observations during an attack, even if that requires an attempt at pharmacologic provocation during coronary arteriography, or during echocardiography when prior arteriography has demonstrated the absence of severe coronary stenosis.

Spasm of large, epicardial coronary arteries can cause myocardial ischemia. Before this was unequivocally demonstrated by coronary angiography with simultaneous electrocardiographic observations in the late 1960's and early 1970's [1–3], there was a great controversy among cardiology experts about whether spasm of these vessels could actually generate myocardial ischemia and manifestations thereof [4]. One learned clinician even published in a respected medical journal that a diagnosis of coronary spasm "———— is a resort of the diagnostically destitute" [5]. Coronary artery spasm (CAS) is now a well accepted part of the spectrum of ischemic heart disease. However, more than four and a half decades after its clear demonstration, there remain a number of controversies about it, some of which I will discuss in this article. This is not meant to be a comprehensive review of the topic, as there have been excellent ones published recently [6,7], nor will it attempt to address the problem of "microvascular" vasomotor abnormalities, which has been well reviewed recently, [7] but rather it will concentrate on pointing out some of the clinical aspects of spasm of large, epicardial coronary arteries that need further discussion and study.

1. Definitions

As the epicardial coronary arteries in humans contain considerable vascular smooth muscle in their walls, it is not surprising that active vasoconstriction and vasodilation are normal parts of their daily function. The degree of normal vasomotion in response, for example, to changes in autonomic tone or increased coronary flow, is modest. Angiographic studies with intravenous or intracoronary administration of potent vasoconstrictors and vasodilators, as illustrated in Fig. 1, suggest that from their most constricted to most dilated state, the lumina of normal coronary arteries can about double in size [8]. That vasodilation is uniformly seen in normal vessels with the administration of nitroglycerin indicates that there is a baseline degree of arterial smooth muscle tone maintaining the dimension of these arteries. For a normal epicardial artery, the changes in diameter produced by vasoactive agents do not produce a critical change in resistance to blood flow. Coronary arteries diseased with significant atherosclerosis have abnormal responses to a number of stimuli. For example, instead of dilating in response to increased blood flow, they will constrict, usually not to a degree that will produce ischemia [9], but when combined with a severe organic stenosis and a stress increasing myocardial oxygen demand, this modest vasoconstriction can increase the severity of the stenosis and contribute to production of myocardial ischemia [9,10]. I would not consider this "spasm".

In the past, angiographic definitions of CAS did not always insist on coexistence of signs of myocardial ischemia with an arbitrarily assigned degree of abnormal vasoconstriction (e.g., a >70% decline in luminal diameter), which is problematic for the clinician. This was a more common practice several decades ago, and today, most angiographers would insist that in order to diagnose "coronary spasm" there be objective signs of myocardial ischemia at the time the luminal constriction turns a supposedly normal lumen or a lesion insufficient to reduce resting blood flow into a critical, flow-reducing stenosis [6]. In the case of an angiographically normal lumen or a mild coronary stenosis, this

Abbreviations: CABG, coronary artery bypass graft; CAS, coronary artery spasm; ECG, electrocardiogram; e-NOS, endothelial nitric oxide synthase; LAD, left anterior descending coronary artery.

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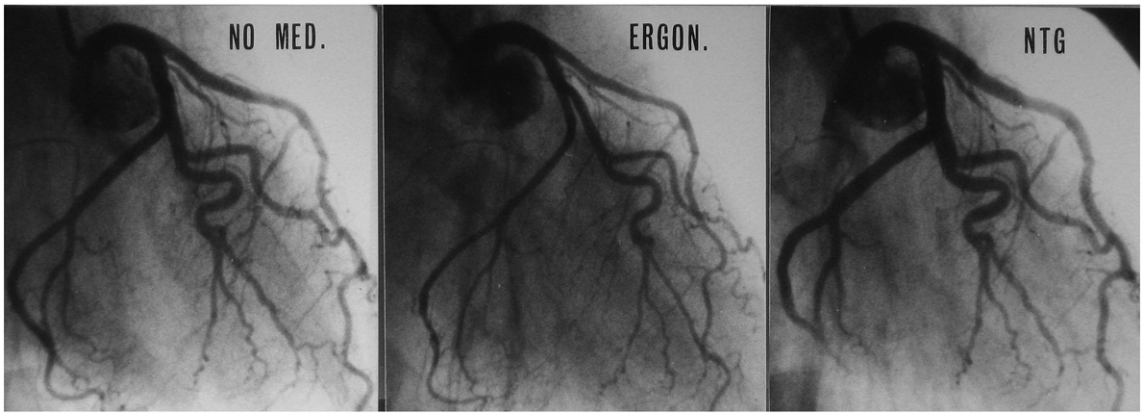

Fig. 1. Normal coronary responses to vasoactive agents. Left coronary arteriograms in right anterior oblique projection of a 60 year old woman with atypical chest pain: in baseline, symptom-free state (NO MED); following intravenous ergonovine challenge that caused no symptoms (ERGON); and 5 min following sublingual nitroglycerin (NTG). Position and geometry of imaging identical for all 3 states.

generally would require a greater degree of contraction of the vascular smooth muscle at that site than at an adjacent, supposedly normal site [11]. In other words, it would indicate a hyper-contractility of the smooth muscle at the spasm site [12,13].

CAS can produce any of the manifestations of ischemic heart disease from myocardial ischemia without symptoms, to effort-induced angina and unstable angina with ST segment depression during attacks, to myocardial infarction or sudden death [6,7,14]. A special CAS syndrome which has received much attention and study is the Prinzmetal's variant angina, or just variant angina, described over 50 years ago by Prinzmetal et al. [15]. In this syndrome, angina typically occurs at rest, with transient ST segment elevation in ECG leads overlying the ischemic zone, which usually represents the territory supplied by a single major coronary artery. In most cases there is no critical coronary stenosis present on angiography between attacks, and exercise testing will not provoke an attack, especially if not done in the morning as the first effort of the day [6,15].

2. What is an angiographically normal coronary artery?

In my experience with cases of angina pectoris and myocardial ischemia due to CAS, the angiographic substrate on which this occurs is rarely normal: only about 4% of cases I observed had absolutely normal coronary arteries by angiography. Mild luminal irregularities and/or non-critical coronary stenoses were present in the great majority of cases [14]. A much higher incidence of "normal" coronary arteries in vasospastic angina reported from Japan seems at odds with my own findings. Genetic and environmental factors have been suggested as explanations of this difference [6]. Another possibility was revealed to me in conversations with a Japanese researcher who had published a number of seminal clinical articles about CAS. When asked what his group considered angiographically normal coronary arteries, he answered that they called normal any study with less than a 25% luminal narrowing [16]. Long-term studies have clearly shown that in cases without CAS undergoing coronary angiography, the presence of minor luminal irregularities consistent with atherosclerosis carries a significantly worse prognosis compared to cases with angiographically normal arteries [17]. Pathologic studies indicate that positive remodeling of human coronary arteries affected with atherosclerotic plaques prevents encroachment of the plaque on the vessel's lumen until it occupies about 40% of the cross sectional area of the artery's wall [18]. In most cases of vasospastic angina with angiographically normal coronary arteries, intravascular ultrasound imaging documents disease of the arterial wall at sites where spasm occurs [19].

Thus, CAS rarely occurs in normal vessels. It is rare in young persons; exceptions may be in variants of severe systemic allergic reactions, the Kuonis syndrome [20], and with non-atherosclerotic diseases of the coronary arteries [21,22].

3. What is the cause of CAS?

Atherosclerotic coronary artery disease is the anatomic substrate on which CAS is usually found. Prinzmetal et al. [23] predicted that by histologic examination, pathologists would be unable to tell the difference between coronary arteries of persons dying following attacks of variant angina and those of subjects dying with classic coronary syndromes. This prediction has proven true: histological examination of coronary sites that have demonstrated spasm during angiography has revealed fairly typical atherosclerotic lesions that are not predictably different from non-spastic lesions [24–26]. As coronary smooth muscle tone disappears soon after death, CAS is not a diagnosis that a pathologist can make by gross or microscopic post mortem examination. Studies with intracoronary ultrasound and optical coherence tomography, and with computerized tomographic coronary angiography have suggested that compared with lesions at sites where spasm is not provocable, lesions at sites where spasm is inducible have less plaque, more diffuse intimal thickening, no calcification, less lipid and necrotic core, less thin cap fibrous atheromata, thicker baseline medial width, smaller baseline luminal area, more common baseline intimal bump, and more common negative remodeling [19,27–29]. The latter four characteristics may be due in part to a greater baseline smooth muscle tone in potentially spastic segments between attacks of spasm [30,31].

Atherosclerotic disease in general impairs normal endothelial function such that large coronary arteries, which normally dilate in response to an increase in blood flow rate or infusions of low concentrations of acetylcholine, actually constrict with these stimuli [9].

Significant organic coronary stenoses are usually hyporeactive to vasoactive stimuli, probably because of stiffening of the vessel wall at points of plaque buildup and calcification [8,32]. Any hypothesis about the pathophysiology underlying CAS must explain why the hyperreactivity of the arterial smooth muscle and CAS occur in only a minority of cases afflicted with coronary atherosclerosis. It must also account for the fact that in some cases, the spasm is limited to a single coronary site, often in conjunction with an atherosclerotic lesion, whereas in other cases spasm can involve the entire epicardial course of one or multiple coronary arteries. It should also explain why some patients may have only one or a few attacks of CAS, while in others attacks fade out after a few years, and in yet others attacks continue for decades. What are the mechanisms that in many cases trigger attacks usually in late night or early morning hours, leaving subjects attack-free most of the rest of the day? And why do most attacks subside spontaneously? These are all important but poorly understood aspects of CAS.