

# This Week's Citation Classic

Maseri A, Severi S, Denes M, L'Abbate A, Chierchia S, Marzilli M, Ballestra A M, Parodi O, Biagini A & Distante A. Variant angina—one aspect of a continuous spectrum of vasospastic myocardial ischemia—pathogenetic mechanisms, estimated incidence and clinical and coronary arteriographic findings in 138 patients. *Amer. J. Cardiol.* 42:1019-35, 1978.

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Electrocardiographic and hemodynamic monitoring coupled with myocardial scintigraphy and angiography during ischemic episodes converged to prove that angina at rest with preserved effort tolerance could be caused by coronary artery spasm. The salient features of 138 such patients collected during a seven-year period were described. [The *SCI*® indicates that this article has been cited in more than 670 publications.]

## Coronary Artery Spasm

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Coronary artery spasm was thought to be the cause of recurring, spontaneous angina by attentive clinicians about a century ago. However, the idea disappeared from textbooks when educated, but unproven, hypotheses became no longer respectable: At postmortem, spasm was not seen, but atherosclerosis was nearly always the rule. In 1959, M. Prinzmetal proposed that an increased tonus around a plaque (he dared not mention the word spasm) was the cause of spontaneous angina with transmural myocardial ischemia, occurring in the absence of severe coronary stenoses at postmortem.<sup>1</sup>

During the 1970s, when occasional angiographic observations of coronary artery spasm in Prinzmetal's angina began to appear (more by chance than design), they were considered by most observers to be catheter artifacts. Our first prospective hemodynamic and angiographic study was initially rejected by a journal of whose editorial board I was a member at that time, but it was subsequently accepted for publication by *Chest*. Doubts still persisted, however, and in our next study we excluded the question of catheter artifacts by demonstrating massive defects in myocardial perfusion during painful and silent spontaneous ischemic episodes using intravenous scintigraphy. This work was promptly accepted for publication by *Circulation*.

At that time in the mid-1970s, the notion that transient ischemia could only be caused by fixed coronary obstructions and increased myocardial demand was deeply ingrained in cardiologist teaching. Our demonstration of the existence of coronary artery spasm showed that dogmatic generalizations in textbooks could not always be relied upon. In 1976, at an international meeting organized in Pisa by the Coronary Research Group (to which most of my coauthors belonged), we proposed the term "primary" angina in order to stress the possibility of the existence of other forms of transient impairment of coronary flow in patients who did not have Prinzmetal's angina. Such a possibility was considered so unlikely that it was defined "Pisa" angina by skeptical participants.<sup>2</sup>

Thereafter it became accepted that coronary artery spasm could cause infarction in association with thrombosis<sup>3</sup> and that vasomotor tone could dynamically modulate the caliber of coronary stenoses. This led not only to the widespread use of calcium antagonists and nitrates, but also to the use of the term "spasm" to describe any sort of coronary constriction. However, occlusive epicardial coronary artery spasm, as typically observed in Prinzmetal's angina, is a distinct entity, characterized by a local, postreceptor hyperreactivity of the smooth muscle to a variety of stimuli that produce only mild constriction in nonspastic segments of the coronary arteries.<sup>4</sup> A similar segmental coronary artery hyperreactivity is also frequently found in unstable angina and recent infarction, but not in patients with stable angina or old infarction.<sup>5</sup>

Therapy for spasm can now only rely on the use of drugs that reduce smooth muscle tone in the whole body. The understanding of this local hyperreactivity could therefore lead to the development of specific local antagonistic drugs. By applying the same clinical approach we used to identify the role of spasm in spontaneous angina, we have recently documented that diffuse constriction of small distal coronary vessels can cause ischemia in chronic effort angina.<sup>6</sup>

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