LETTERS TO THE EDITOR

Angina Caused by Reduced Vasodilator Reserve of the Small Coronary Arteries. I: Spasm of Resistance Vessel Concept

The spasm of resistance vessel concept (1) avers that inappropriate arteriolar constriction induces symptoms in ischemic heart disease, and two studies in the June issue of JACC (2,3) appear to provide information in favor of the hypothesis.

Study of Cannon et al.

Cannon and colleagues (2) demonstrated inappropriate arteriolar constriction in patients with atypical chest pain and significant coronary artery disease. These cases, which may represent a distinct syndrome, offer a number of lines of evidence.

First, Cannon et al. demonstrated for the first time that "vasoconstrictor stimuli acting at the arteriolar level can actually cause myocardial ischemia by overriding the powerful autoregulatory mechanisms that are 'designed' to prevent ischemia," and the ability to override vasodilation has been a basic premise of the spasm of resistance vessel concept. When the concept was first proposed in 1973, it was unquestioned conventional wisdom that resistance vessels were invariably widely dilated in ischemic heart disease because of the physiologic vasodilating reactive hyperemic response to ischemia, and symptoms were thought to occur only when the dilatory or cardiac reserve was exhausted. While usually not clearly verbalized, it seemed to be understood that spasm of resistance vessels could not occur, as this spasm would itself induce ischemia and this ischemia would activate reactive hyperemia and reverse spasm.

Second, Cannon's group demonstrated vasoconstriction of resistance vessels in the absence of spasm of epicardial arteries, and this occurrence is another basic tenet of the concept. As the hypothesis considers spasm in epicardial arteries to be concomitant with or reflex to primary spasm in mural arteries, it follows that mild primary spasm of resistance vessels might not be accompanied by significant changes in epicardial arteries.

Third, evidence was presented that ergonovine can act on resistance vessels, and as ergonovine potentiates preexisting tendencies for spasm, this has important implications for the concept. It is suggested that serious consideration be given to the possibility that all ergonovine-induced angina is due to spasm of resistance vessels and not to primary spasm of epicardial arteries, and that spasm evident in epicardial arteries is reflex. If this is so, a major step has been taken toward localizing spasm to resistance vessels in ischemic heart disease.

Fourth, nearly a quarter of the patients had histories of previous myocardial infarction, and the association of vasoconstriction of resistance vessels with myocardial infarction is of critical importance to the concept. The hypothesis states that myocardial infarction is due to spasm of resistance vessels, and Cannon et al. provided direct evidence that at least some patients with infarction have coronary arteriolar constriction. This evidence supports the information that factors associated with infarction, such as cold exposure and smoking, cause vasoconstriction of resistance vessels, and it is known that ischemic heart disease is linked with disorders involving vasoconstriction of resistance vessels, such as hypertension, scleroderma (4), migraine (5) and Raynaud's disease (5).

Fifth, it was suggested that vasoconstriction of resistance vessels could involve relatively smaller regions of myocardium, and the concept used the term microlesions (6) to describe these smaller areas of involvement.

The authors did not use the word "spasm" in relation to inappropriate arteriolar constriction, and it is noted that although reduced flow occasionally was demonstrated, the dominant finding in their study was reduced vasodilator reserve during pacing. However, assuming that the vasoconstriction found in the laboratory was responsible for the chest pain (and infarction) these patients experienced, it seems reasonable to designate vasoconstriction associated with clinical symptoms as spasm.

The spasm of resistance vessel concept does provide a frame of reference by which to evaluate Cannon and colleagues' study. The concept assumes that spasm of resistance vessels induces symptoms in all of the various types of ischemic heart disease, and cases of atypical chest pain are assigned a place within the complex spectrum of ischemic heart disease. The special clinical features reflect the nature of the spasm of resistance vessels in these individuals; the absence of reflex spasm and ST changes suggests the spasm of resistance vessels to be mild and limited, but its potential is reflected by the occurrence of infarction in some of these cases.

Although not explicitly stated, it appears that Cannon et al. regard their cases as a separate group with an implied separate pathogenetic mechanism. They did not discuss vasoconstriction of resistance vessels in context of the infarctions previously sustained by some of these patients, suggesting that they assume infarction to be due to primary occlusion of epicardial arteries, as by thromboses or spasm of these arteries, or both. Also, their discussion of Prinzmetal's angina seems to imply that they regard vasoconstriction of resistance vessels as separate from spasm of epicardial arteries. It may be that ischemic heart disease represents a heterologous group of disorders, but conversely, these disorders may represent a single pathogenetic entity which has a spectrum of findings.

Study of Goldhaber et al.

Goldhaber and colleagues (3) offer further evidence that the cold pressor test might incite vasoconstriction in ischemic heart disease, and this is in keeping with the concept. The vascular autoregulatory response to cold is vasoconstriction, and the concept attributes vasoconstrictive forces in ischemic heart disease to inappropriate activation of vascular autoregulatory mechanisms.

It is of interest that the discussion of Goldhaber et al. concerning spasm or vasoconstriction did not clearly differentiate between involvement of small and large coronary arteries. Although apparently describing vasoconstriction of resistance vessels, the size of spastic vessels was not defined, and the spasm was discussed in context of Prinzmetal's angina, which is attributed to spasm of epicardial arteries. Also, the noncommittal terms used, such as "coronary vasoconstriction" and "coronary vasculature," might imply involvement of both resistance vessels and epicardial arteries.

Considering conventional attitudes, it seems important to iden-
Primary and Reflex Spasm

The spasm of resistance vessel concept, which attempts to relate spasm to the pathophysiology of the coronary vasculature, also accepts vasoconstriction of both small and large coronary arteries. As symptoms are attributed to spasm of resistance vessels, this spasm is described as primary, and changes in epicardial arteries are listed as reflex. That vasoconstriction of mural, and not epicardial arteries induces clinical symptoms is suggested by the physiologic role of these arteries. Resistance vessels are designed to modulate flow by active vasomotion, and spasm is considered to represent an exaggerated vasoconstrictive activity of these small arteries. The function of epicardial arteries is to transport blood, and as they contribute only 5% to the resistance of the coronary vascular tree, it seems unlikely that their contribution to the constriction of the coronary arterial tree would be a major factor in flow reduction. This, however, does not imply that severe spasm of resistance vessels cannot be accompanied by severe narrowing or spastic closure of epicardial arteries, but such spasm would be most in the face of prominent spasm of resistance vessels. As evidence that spasm isolated in epicardial arteries probably does not cause symptoms. Direct catheter-induced spasm, which may be severe, almost never is described as inducing chest pain (1).

The concept has received little attention, probably because its views differ markedly from the conventional. However, some of the positions might now seem less radical, and there probably is more positive evidence available about the hypothesis (1) than is appreciated. The concept, if valid, should have a very major impact on ischemic heart disease, and it is suggested that its premises should be considered.

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Angina Caused by Reduced Vasodilator Reserve of the Small Coronary Arteries. II: Role of Coronary Microcirculation

Cannon et al. corroboratingly demonstrated the possible role of small coronary artery vasoactivity in the genesis of myocardial ischemia. But, unlike the concept of inappropriate vasoconstriction or spasm in the nonobstructed epicardial coronary vessels, inappropriate subepicardial vasoreactivity causing myocardial ischemia postulated by the authors is based solely on hemodynamic evidence. One must ask then, what is the status of the small coronary arterioles in these patients and if arteriolar vasoconstriction causing ischemia occurs in nonoccluded or partly occluded coronary vessels. The authors failed to address these important questions. During the last decade, a significant body of information related to the role of coronary small vessel disease in causing angina has been accumulated. Myocardial biopsy and especially autopsy studies have shown that the small coronary arteries are the site of clinically significant disease more often than is generally realized. Progressive occlusion of many small vessels may cause impaired effective perfusion pressure (1). Small vessel resistance caused by small vessel disease remains the most important and controversial factor in regulating regional myocardial perfusion (2,3). Small variations in the luminal diameter of these vessels may cause profound alterations in myocardial blood flow (4).

The authors have included in their group three diabetic patients treated with insulin. In such patients, subepicardial coronary involvement may cause angina (5). Furthermore, of 10 patients with angina and normal arteriograms, Dwyer et al. (6) found 6 patients who had either abnormal glucose tolerance test or a family history of diabetes mellitus. The authors suggested that small coronary arteries may account for the clinical manifestations. The question arises whether subclinical diabetes was present in some of the patients of Cannon et al.

Underlying but unrecognized cardiomyopathy may increase wall tension during diastole and thereby interfere with coronary flow in some patients with overt and subclinical diabetes. Functional derangements in the microcirculation of diabetic patients as a result of small vessel involvement might represent one of the basic causes of myocardial impairment and conduct disturbances (7-12).

By offering original hemodynamic information, Cannon et al.