

Editorial Comment

Acetylcholine and Coronary Artery Spasm: Important Insight or Squeeze Play?*

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For over 100 years, ergot alkaloids have been known to be powerful vasoconstrictor agents, even capable of causing gangrene (1). In the late 1940s, intravenous administration of ergotamine to patients with "organic heart disease" was found to cause electrocardiographic (ECG) changes and chest pain, believed to represent a direct vasoconstrictor effect of ergotamine on the coronary arteries. Stein and Weinstein (2) reported the responses of 30 patients, 15 of whom had a clinical diagnosis of coronary artery disease, to ergonovine, 0.5 to 0.6 mg in incremental doses. In 6 of these 15 patients, prior exercise testing had failed to produce ST segment depression. In all 15, ergonovine administration resulted in ST segment depression or chest pain, or both. Chest pain was relieved by nitroglycerin, and repeat administration of ergonovine after nitroglycerin produced no or less prominent ECG changes in 10 patients. No chest pain or ECG changes were induced in 15 "controls." Thus, ergonovine administration appeared to show promise as a diagnostic agent for coronary artery disease.

Ergonovine for provocation of coronary spasm. In 1959 Prinzmetal described 32 patients, with angina primarily at rest, whose ECG showed striking ST segment elevation during episodes of pain (3). He hypothesized that these findings represented severe, transient coronary artery vasconstriction, superimposed on atherosclerotic plaque. "Prinzmetal's" or "variant" angina gained credibility with the angiographic demonstration of spontaneous episodes of coronary artery spasm in patients with rest pain primarily associated with ST segment elevation (4-6). However, such events were rarely seen during arteriography, in part because of the common practice of premedication with nitrates to avoid catheter-induced spasm of the coronary (especially right) artery. In 1975, Heupler et al. (7) reported the use of ergonovine maleate to provoke coronary artery spasm during arteriography in patients with known or suspected Prinzmetal's angina. Shortly afterward, in two large series of patients who received ergonovine intravenously (8,9), the majority of patients with rest angina associated with ST segment changes (most commonly ST segment elevation) had coronary spasm of the "culprit vessel," in association with ST segment changes similar to those noted during spontaneous attacks of angina and precipitation of the patient's characteristic chest pain. Conversely, ergonovine caused minimal, diffuse epicardial coronary narrowing without ECG changes or chest pain in the majority of patients who had no ST segment changes during angina or who had an atypical chest pain syndrome. Even after reports of other pharmacologic agents or techniques (methylene blue, cold pressor test, hyperventilation, epinephrine, histamine, exercise, for example), ergonovine has remained the reference standard for provocation of epicardial coronary artery spasm in patients with Prinzmetal's angina (10).

However, ergonovine has its down side. When it is administered intravenously, more than one third of patients experience nausea (and sometimes protracted retching) and headache, and a substantial minority become markedly hypertensive. Further, if spasm is provoked, all the consequences of spontaneous spasm may be noted in the laboratory, including a marked decline in blood pressure and cardiac output, heart block, ventricular tachycardia and fibrillation and death (11-13). The intracoronary administration of smaller doses of ergonovine (6 to 50 µg in cumulative doses) may avoid the untoward effects of this agent given intravenously, but experience with this approach is small (14).

The present study on intracoronary acetylcholine. In this issue of the Journal, Okumura and colleagues (15) report that intracoronary injection of acetylcholine in 70 patients with a clinical diagnosis of Prinzmetal's angina precipitated severe coronary constriction with chest pain or ECG changes (usually ST segment elevation), or both, in 63. Conversely, acetylcholine produced lesser degrees of vasoconstriction without chest pain or ECG changes in all but 1 of 93 patients believed on clinical grounds not to have Prinzmetal's angina. Thus, the sensitivity (90%) and specificity (99%) of acetylcholine for induction of coronary spasm in patients with Prinzmetal's angina rivals large published series of ergonovine testing (8,9,13). Further, the duration of acetylcholine-induced spasm was relatively brief even without nitroglycerin, reflecting the short half-life of acetylcholine and, with the exception of bradycardia (especially after acetylcholine administration in the right coronary artery), no complications were encountered. Thus, the investigators propose intracoronary acetylcholine as a safe and reliable provoca-

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tive test for coronary spasm in patients with features of Prinzmetal's angina but without ECGs obtained during episodes of chest pain.

These findings and conclusions appear to conflict with the observations of Ludmer et al. (16). In that study, intracoronary infusions of acetylcholine over 2 min produced severe vasoconstriction at the site of left anterior descending coronary artery lesions with transient occlusion in five of eight patients and angina in four (ECG changes were not reported). All eight were reported as having a history of effort angina rather than Prinzmetal's angina. Thus, at least in patients with coronary artery disease, the specificity of acetylcholine-induced spasm associated with Prinzmetal's angina may be substantially lower than Okumura et al. (15) suggest. Further, in the study of Ludmer et al. (16), intracoronary acetylcholine caused dilation of most "normal" coronary arteries, whereas in the study of Okumura et al., the coronary arteries in almost 50% of the "control" group constricted to <50% of the control diameter (which was normal or near normal in 82% of patients in this group): only 14% of this group demonstrated vasodilation. In a previous report from the group of Okumura et al. (17), acetylcholine-induced coronary vasoconstriction in patients with Prinzmetal's angina could be blocked only by atropine, and not by phentolamine, a finding that argues against a reflex-sympathetic vasoconstrictor effect. The discrepancies in coronary artery responses may be due to differences in acetylcholine administration. Okumura et al. (15) gave up to 100 µg of acetylcholine over 20 s, whereas Ludmer et al. gave a somewhat smaller total dose of acetylcholine as a constant infusion over 2 min.

Role of endothelium-derived relaxant factor. Both groups refer to the work of Furchgott (18,19) and the observation that rings of aorta (and subsequently other arteries) denuded of endothelium constrict in response to acetylcholine, a response not seen with intact endothelium. Endothelium-derived relaxant factor promotes underlying smooth muscle relaxation and vasodilation in response to agonists that would cause smooth muscle contraction and vasoconstriction when in direct contact with smooth muscle (18,19). Thus, intracoronary acetylcholine might have identified regions of the coronary artery with atherosclerotic disease coexisting with absent or altered endothelium, leaving underlying smooth muscle vulnerable to vasoactive substances. The different vascular responses to acetylcholine noted in the studies of Okumura and Ludmer and their colleagues may relate to an apparent dose-dependent biphasic response of arteries with intact endothelium noted by Furchgott (19). At low doses, acetylcholine caused vasorelaxation. However, at higher doses (>10 -6 M), acetylcholine caused vasoconstriction, perhaps by "overwhelming" endothelium-derived relaxant factor and stimulating muscarinic receptors on underlying smooth muscle. Curiously, stimulation of the vagus nerve causes coronary artery dilatation, not constriction, with acetylcholine as the effector transmitter (20-22). Indeed, vasorelaxation in response to parasympathetic nerve stimulation appears to be independent of endothelium (22). Does this finding mean that two populations of muscarinic receptors exist, some causing smooth muscle contraction (to intravascular acetylcholine exposure) and others causing relaxation (to acetylcholine by way of neural release)?

Implications. The relevance of these observations to coronary spasm is unclear. Although the denuded endothelium hypothesis invoked by Okumura, Ludmer and colleagues is appealing, and probably explains exaggerated coronary vasomotion in patients with coronary artery disease that may be clinically relevant (that is, variable angina threshold [23]), a question remains. Why does a syndrome characterized by spontaneous severe, focal vasoconstriction occur in a relatively small subset of patients with an ischemic syndrome? One would think that with the ubiquity of coronary artery disease in developed societies, Prinzmetal's angina due to coronary artery spasm would be rampant. Yet in the United States, it appears to be an uncommon ischemic syndrome. Clearly, we have much to learn regarding the mechanisms and clinical significance of coronary artery vasomotion.

References


