The Angiographic Effect of Ergonovine and Nifedipine in Coronary Artery Spasm

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SUMMARY In a patient with variant angina, we have shown that the calcium-channel blocker nifedipine inhibits both spontaneous and ergonovine-induced coronary artery spasm. It had no effect, however, on the dose-related diffuse vasoconstriction caused by ergonovine, suggesting two distinct responses of coronary arteries to ergonovine provocation. Nifedipine did not cause epicardial coronary artery dilatation, as did nitroglycerin, supporting the rationale of using both therapies together to treat coronary artery spasm.

ERGONOVINE-INDUCED SPASM has been correlated with spontaneous coronary artery spasm in patients with variant angina.1, 2 Ergonovine produces two types of coronary artery vasoconstriction, focal and diffuse.3, 4 We report a patient with spontaneous coronary artery spasm that could also be provoked with ergonovine. By repeated coronary angiography we demonstrated that nifedipine, a new calcium-channel blocking agent, inhibited ergonovine-induced focal spasm, but not the more diffuse dose-related vasoconstriction. Nitroglycerin was effective in reversing spontaneous spasm, ergonovine-induced focal spasm and ergonovine-induced diffuse vasoconstriction.

Methods

Selective coronary arteriography and left ventriculography were performed via the percutaneous femoral approach. The coronary arterial diameters were measured by two independent observers from 35-mm cineangiograms. To allow accurate comparisons of the changes in vessel diameter, measurements of the left circumflex artery were made only in the 30° left anterior oblique projection, in diastole, either at a fixed distance from the origin of the vessel or at readily identifiable branch points. The relative changes in vessel diameter are reported using the diameter of the normal segment (see text) as the baseline.

Case Report

A 36-year-old white fireman came to the University of Chicago emergency room after experiencing a 30-minute episode of severe substernal chest pain and diaphoresis after a bowel movement. The patient experienced a similar episode at rest 3 days before but was otherwise healthy and had no history of medical problems. His physical examination was normal. He was admitted to the coronary care unit, and a myocardial infarction was ruled out after 72 hours of observation with unchanged ECGs and normal CPK determinations. On the sixth hospital day, while on the cardiology ward, the patient experienced chest pain at rest and an ECG taken at that time showed T-wave inversions in leads V1-V6. The pain was promptly relieved with 0.3 mg of nitroglycerin. The next day, after an emotional conversation with his mother, he experienced severe chest pain, and an ECG taken at that time showed massive acute-ST-segment elevation in leads II, III and aVF. During the ECG recording the patient had a 3-second run of ventricular flutter, which spontaneously converted to sinus rhythm (fig. 1). He was returned to the CCU, where his ECG normalized within 30 minutes. A myocardial infarction was again ruled out and variant angina was diagnosed.

Cardiac catheterization performed 48 hours later showed a normal left ventricle with a baseline left ventricular end-diastolic pressure (LVEDP) of 19 mm Hg and a post–premature ventricular complex ejection fraction of 71%. He had a dominant left coronary artery system, and both left and right coronary arteries were free of any significant narrowings. The left main coronary artery was very short, allowing selective catheterization of the left anterior descending and left circumflex arteries. The left circumflex trunk was a large vessel with a relatively dilated segment shortly after its origin, followed by a mildly narrowed segment. Distally the coronary artery appeared to be normal (fig. 2A). The dilated segment was 21% larger and the narrowed midsegment 14% narrower than the normal distal segment. During the course of the left coronary injections he had a spontaneous spasm of the mid-left circumflex trunk, causing a 78% diameter reduction (fig. 2B). The patient remained asymptomatic and showed no ECG changes. After administration of 0.4 mg of nitroglycerin sublingually, vasodilation of the entire coronary tree was documented, with an increase in diameter in all three aforementioned segments of the left circumflex artery from baseline (fig. 2C). Persistence of a 15% narrowing in the mid-left circumflex trunk suggests a lesion at that site.

The patient was then treated with long-acting nitrates (isosorbide dinitrate 5 mg four times daily and phenoxybenzamine 10 mg every 12 hours). A repeat coronary angiogram after 1 week of therapy without any episodes of chest pain showed the circumflex
trunk to be as seen before, with a dilated proximal segment and a mildly narrowed midsegment. After provocation with 0.05 mg of ergonovine maleate, the midsegment had a 70% diameter narrowing. The patient had no symptoms or ECG changes. No other areas of spasm were noted in the left circumflex or left anterior descending arteries. These changes were again reversed with 0.4 mg of sublingual nitroglycerin. We concluded that the drug regimen might not be effective in preventing the recurrence of his symptoms.

Figure 1. (A) Rhythm strip taken during an episode of spontaneous chest pain showing massive ST-segment elevation and ventricular flutter. (B) Twelve-lead ECG taken in the coronary care unit a short time afterwards showing return of ST-segment elevation to baseline.

Figure 2. (A) Angiogram of the left circumflex artery in the left anterior oblique projection showing the dilated (D), spastic (S), and normal (N) segments. (B) Spontaneous spasm of the middle segment (arrow). (C) Vasodilatory response to nitroglycerin.
After approval from the Clinical Investigations Committee and with informed consent of the patient, we initiated therapy with nifedipine. To assess the efficacy of nifedipine in preventing ergonovine-induced spasm, the dose of ergonovine required to produce symptoms was determined with the patient off medications. During electrocardiographic monitoring in the CCU, the patient was given 0.05 mg of ergonovine, followed by 0.1 mg of ergonovine 5 minutes later, which caused chest pain and ST-segment elevation in lead III. A thallium scintigram performed at that time revealed a defect in the inferoposterior wall (fig. 3A). His symptoms were readily reversed with nitroglycerin.

The patient was then started on nifedipine 70 mg/day, given as 20 mg at bedtime and in the morning, and 10 mg three times during the day, along with nitrates, 5 mg every 4 hours while awake, and nitropaste, 1 inch at bedtime. A repeat challenge of ergonovine, 0.05 mg, 0.1 mg and 0.2 mg given at 5-minute intervals, failed to cause symptoms or ECG changes. A thallium scintigram done at that time showed no defects (fig. 3B). The patient was then discharged on nifedipine and nitrate therapy.

Because coronary artery spasm was previously associated with a lethal arrhythmia, and because of the infrequent occurrence of spasm associated with symptoms in this patient, we readmitted the patient after 3 weeks to see if spasm could be provoked during angiography on what appeared to be effective medical therapy. The left ventricle again appeared normal. The resting LVEDP was elevated at 28 mm Hg and the sinus beat ejection fraction was 64%. The initial appearance of his coronary arteries was as before, with the dominant left circumflex trunk showing a proximal dilated segment, a mildly narrowed midsegment, and a distal normal-appearing vessel (fig. 4A). Ergonovine was administered in doses of 0.05 mg, 0.05 mg, 0.05 mg, 0.1 mg and 0.2 mg at 5-minute intervals. The entire coronary tree showed diffuse vasoconstriction of 23% in response to the increasing doses of ergonovine (fig. 4B). Focal narrowing was not seen in the circumflex trunk. The patient remained symptom-free and had no ECG changes. Sublingual nitroglycerin was then given, resulting in diffuse vasodilatation (fig. 4C). Because neither total occlusion of a vessel, nor angina, nor ECG changes were provoked with 0.45 mg ergonovine — a dose three

![Figure 3](image)

**Figure 3.** Thallium scintigram done during ergonovine challenge. (A) With patient off medications, 0.15 mg of ergonovine causes a defect in the inferoposterior wall. (B) With the patient on nifedipine therapy, 0.25 mg ergonovine fails to produce a defect.

![Figure 4](image)

**Figure 4.** Angiogram of the left circumflex artery in the left anterior oblique projection with the patient on nifedipine and isosorbide dinitrate. (A) Before ergonovine challenge and (B) after 0.25 mg after ergonovine showing diffuse vasoconstriction. Increasing the ergonovine to 0.45 mg produced no further significant changes. (C) Sublingual nitroglycerin, 0.8 mg, produced diffuse dilatation.
times larger than the dose that created his symptoms while off medications — we concluded that a combined therapy of nifedipine and nitrates would be protective, and the patient was discharged on chronic therapy. Since discharge, the patient has had no anginal attacks for 35 weeks.

Discussion

The mechanism by which ergonovine provokes focal vascular spasm is not understood. Ergonovine has been shown to have diffuse vasoconstrictive properties on vascular smooth muscle in general. Angiographic studies have demonstrated dose-related vasoconstriction in normal coronary arteries, which has been established as the criterion for determining a negative response to ergonovine challenge. The coronary artery spasm that develops from ergonovine differs from the normal response in that the degree of vascular narrowing is much greater, the spasm is segmental and it frequently occurs after very small doses of ergonovine. Nifedipine is effective in preventing ergonovine-induced spasm and in reducing the frequency of spontaneous coronary spasm.

This study demonstrates several features about the coronary artery response to ergonovine and nifedipine. Although calcium blockers are considered coronary vasodilators, nifedipine did not appear to dilate the epicardial coronary arteries as did nitroglycerin. It was, however, effective as a "spasm inhibitor," by preventing ergonovine-provoked and spontaneous segmental spasm. Diffuse, dose-related coronary vasoconstriction from ergonovine appeared unaffected by calcium-channel blockade, so some other mechanism, distinct from that which produces focal spasm, presumably causes this normal drug effect. The observation that nitroglycerin was effective in causing vasodilatation in the presence of nifedipine supports the rationale of using both calcium-channel blockers and nitrates in the chronic therapy of variant angina.

Acknowledgment

We thank Dr. David D. Waters for providing us with a copy of his protocol on provocative ergonovine testing and calcium antagonists, which aided us in performing this study, and Dr. Bruce Greenspan for his technical assistance.

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_Circulation._ 1980;62:1127-1130
doi: 10.1161/01.CIR.62.5.1127

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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