Effects of Ergonovine in Patients with and without Coronary Artery Disease

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SUMMARY Recently, ergonovine has been suggested to evoke coronary artery spasm in patients with variant angina. The purpose of our investigation was to study clinical, hemodynamic, electrocardiographic (ECG), and coronary angiographic effects of ergonovine in 60 selected patients undergoing angiography. The patients were equally divided, 30 with coronary artery disease (CAD), lesions ≥50%, and 30 with minimal (<50%) or no CAD. Ergonovine (0.05 to 0.4 mg i.v. bolus) was given while each patient was monitored for symptoms and changes in ECG, heart rate, QTc intervals, blood pressure, and coronary diameter. After ergonovine, 18 patients developed chest pain, eight of whom had associated ST-segment shifts (≥1 mm). Heart rate and QTc showed no significant change. Systolic blood pressure increased from 133 mm Hg (mean) to 147 mm Hg (P < 0.01). The mean diameter of 164 coronary arteries examined decreased 18% (P < 0.001) after ergonovine. Five patients with documented variant angina all developed typical chest pain and ST-segment shifts following ergonovine. Spasm of the anterior descending evoked with ergonovine was similar in location and magnitude to spasm occurring during spontaneous pain (two patients). Thus, the ergonovine test appears sensitive in confirming the presence of variant angina. No serious problems requiring therapy other than nitroglycerin arose following ergonovine. Nonetheless, we do not recommend its use outside the cardiac catheterization laboratory. Prolonged chest pain and myocardial infarction following ergonovine are possible complications in patients with severe CAD and/or variant angina.

Ergonovine Maleate, an ergot alkaloid, is a direct acting smooth muscle constrictor. Almost 30 years ago, ergonovine was introduced by Stein as a provocative test in patients with suspected coronary artery disease. Several reports by Stein implied the ergonovine test may be clinically useful and safe, but interest waned. Renewed interest in the potential coronary actions of this agent developed following a recent preliminary report by Heupler and co-workers suggesting that ergonovine may provoke attacks of “variant” angina. Additionally, new evidence by Maseri and Weiner now supports coronary arterial spasm as an important pathophysiologic mechanism in patients with variant angina and possibly in the production of myocardial ischemia in other patients. These reports stimulated us to examine the effects of ergonovine in patients with chest pain, since a provocative test to identify patients with coronary spasm would be clinically useful. The purpose of this study was to evaluate clinical, electrocardiographic, and coronary angiographic responses to ergonovine maleate in patients with and without angiographic evidence of coronary artery disease.

Methods

Studies were conducted in 60 patients (56 males and 4 females) with a mean age of 52 years (range 28–67) referred for cardiac catheterization studies to further evaluate a chest pain syndrome. Patients with recent myocardial infarction (less than 3 months), left main coronary obstruction (greater than 50%), aortic stenosis, or prior coronary revascularization were specifically excluded. No studies were performed in amenorrheic, premenopausal females.

Each patient was studied after an overnight fast during which all cardiac drugs were temporarily discontinued. A written informed consent was obtained from each patient, specifically in regard to the use of ergonovine, and a detailed explanation of its known complications including stroke and myocardial infarction. Following multilead electrocardiographic recording and pressure monitoring, selective coronary angiography was performed in each patient. In patients who had electrocardiographic evidence of heart block during an acute attack of variant angina, the method was altered to include the addition of a temporary pacing catheter in the right heart.

Ergonovine maleate (Ergotrate, Lilly) 0.05 to 0.4 mg was given intravenously (rapid bolus injection) as heart rate (HR), systemic arterial blood pressure (BP), and electrocardiograms were continuously monitored for 10–15 min. Repeat coronary angiography was performed (33 patients) between 5 and 10 min after ergonovine injection, or during chest pain and/or ST-segment shifts when these responses occurred. Since only one set of coronary angiograms were obtained following ergonovine, it is apparent that our methods would not identify variation in the degree and location of coronary artery spasm during an attack of variant angina.

Before and after ergonovine, HR and corrected QT intervals (QTc) were measured and averaged over at least 10 consecutive beats, and systolic BP was recorded from the aorta or brachial artery. The ST segment shifts were analyzed by measuring average ST segment shift from the PR segment. Significant shifts ≥1.0 mm from the control measurements were tabulated.

Coronary artery diameters were measured at readily identifiable branch points from appropriately selected projected cine frames. The following branch points were used: the left main before its bifurcation; the anterior descending before the first septal perforator; the circumflex before the obtuse marginal branch; the right before the acute marginal branch.
and the obtuse marginal branch just after its take-off. In any
given patient, these selective angiograms were obtained in
the same projection at the same tube to tabletop and cardiac
apex to tabletop distances before and after ergonovine.

Cine films were analyzed on the same projector (Tagarno,
Model #3500). Matched end-diastolic frames were com-
pared and measurements of the coronary artery diameter
made with calipers. With this technique, we have found that
reproducible measurements can be made to ±0.5 mm. If
coronary artery spasm occurred at areas other than the
measured branch points, no attempt was made to quantitate
the narrowing. Subtotal or totally occluded vessels could not
be accurately quantitated.

The patients were questioned regarding the presence of
symptoms following ergonovine. When present, they were
carefully recorded in detail. These findings along with electro-
cardiographic (ST segments, QTc, and dysrhythmias), hemody-
namic (HR and BP), and coronary artery diameter changes
occurring after ergonovine were tabulated in patients with
coronary artery disease (CAD) and with minimal or no CAD.
The double product was calculated as HR × systolic BP. Mean values for HR, QTc, systolic BP,
double product and coronary artery diameter were cal-
culated, and the statistical significance of the pre- to post-
ergonovine comparisons were analyzed using Student's t-
test for paired data.

Results

Clinical and Electrocardiographic Responses

The clinical and ECG responses to ergonovine in patients
with CAD (defined as ≥50% obstruction of at least one ma-
jor vessel) are compared with patients demonstrating
minimal (<50%) or no CAD in table 1. Eighteen patients
(30%) developed chest pain typical of their usual daily
complaints following ergonovine: 12 (40%) with CAD and six
(20%) with minimal or no CAD. Three of the former and
two of the latter patients had clinical features of variant
angina (defined as cyclic rest pain with transient ST-segment
elevation) prior to the study. Brief salvos of supraven-
tricular tachycardia occurred in two subjects (one with
CAD and one with minimal CAD). Transient ventricular
dysrhythmias occurred in eight (13%) individuals (three of
whom had variant angina). One patient with variant angina
developed transient complete A-V block with a slow idio-
ventricular rhythm during pain after ergonovine. Myo-
cardial infarction, cardiac arrest, or dysrhythmias requiring
therapy did not occur. In every case, sublingual nitrogly-
cerin, usually with repeated doses, (0.4 to 1.6 mg) relieved
the chest pain within 5 to 10 min. Other noncardiac symp-
toms including nausea, vomiting, breathlessness, flushing,
and headache occurred in 16 (27%) patients.

Significant ST-segment shifts following ergonovine oc-
curred in eight (13%) patients during chest pain. The clinical
features of this subgroup are summarized in tables 2, 3.
Their responses following ergonovine are given in table 3.
Five patients (cases 1–5) with variant angina documented
prior to study (three with CAD and two with minimal or no
CAD) developed ST shifts (elevation in four and depression
in one, case 2), during pain. Three other CAD patients, one
with typical exertional angina (case 6) and two with rest pain
(cases 7, 8), developed ST shifts, all three with ST-segment
elevation. While two of these three patients had symptoms
suggesting a variant angina syndrome, (cases 7, 8) ST eleva-
tion during pain had not been observed prior to this study,
despite repeated observations. In all patients developing ST
shifts the dosage was 0.2 mg or less and the response
developed within five minutes (table 3). The ST segment
change usually preceded the chest pain by less than one
minute and returned to baseline just before complete relief
of pain. In each case the ST segment shifts returned to base-
line and chest pain was relieved within 5 to 10 min following
administration of sublingual nitroglycerin. QTc intervals
did not change significantly following ergonovine. ST-segment
elevation was most prominent in lead V4 in four patients, but
also occurred in lead V2, V5 and aV1 (one patient each). ST-
segment depression was most marked in one patient with
changes in lead V4. The occurrence of ST-segment shifts
(marked elevation or depression) in association with chest
pain following ergonovine identified all of the patients

### Table 1. Clinical and ECG Responses Following Ergonovine

<table>
<thead>
<tr>
<th>Coronary arteriography</th>
<th>Normal</th>
<th>CAD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>6</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Supraventricular</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Premature ventricular</td>
<td>2</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>contractions</td>
<td>6</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>ST-segment shift</td>
<td>19</td>
<td>33</td>
<td>52</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Sum of the 5 responses more than totals due to multiple criteria for some patients.

### Table 2. Summary of Clinical Findings in Patients with ST-Segment Shifts Following Ergonovine

<table>
<thead>
<tr>
<th>Case #/Age (yr)/Sex</th>
<th>Angina</th>
<th>ECG</th>
<th>ST shift with spontaneous pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Rest</td>
<td>Duration of symptoms (mos)</td>
<td>on Exertion</td>
<td>with syncope</td>
</tr>
<tr>
<td>1/53/M</td>
<td>+</td>
<td>360</td>
<td>0</td>
</tr>
<tr>
<td>2/53/F</td>
<td>+</td>
<td>42</td>
<td>0</td>
</tr>
<tr>
<td>3/61/M</td>
<td>+</td>
<td>2</td>
<td>+</td>
</tr>
<tr>
<td>4/45/M</td>
<td>+</td>
<td>21</td>
<td>+</td>
</tr>
<tr>
<td>5/60/M</td>
<td>+</td>
<td>18</td>
<td>+</td>
</tr>
<tr>
<td>6/62/M</td>
<td>0</td>
<td>42</td>
<td>+</td>
</tr>
<tr>
<td>7/51/M</td>
<td>+</td>
<td>84</td>
<td>0</td>
</tr>
<tr>
<td>8/45/M</td>
<td>+</td>
<td>6</td>
<td>+</td>
</tr>
</tbody>
</table>

Abbreviations: F = female; III = lead III; M = male; MCL1 = bipolar V1 lead; mos = months; MI = myocardial infarction; positive stress test = ≥ 1.0 mm of horizontal ST segment depression; yr = years.
studied whose clinical presentation was variant angina (cases 1–5). In two of the three other patients with this combination of responses, variant angina was suspected but not documented previously.

Heart rate and blood pressure findings occurring after ergonovine are shown in figure 1. Heart rate was not significantly influenced by ergonovine (mean 73 beats/min before versus 74 beats/min after). Arterial systolic BP after ergonovine increased from a mean of 133 to 147 mm Hg, an 11% increase ($P < 0.01$). Nine patients developed a systolic BP rise >30 mm Hg. Six of these had a history of hypertension. In one other patient (case 1, table 2) a 30 mm Hg decrease in systolic BP occurred during complete heart block with chest pain. The double product increased from a mean of 9,709 to 10,878 mm Hg/min ($P < 0.01$).

### Angiographic Studies

The influence of ergonovine on coronary artery diameter in 33 patients (164 arteries) is shown in figure 2. Mean projected coronary diameter decreased from 6.7 to 5.5 mm, an 18% decrease ($P < 0.001$). An illustrative example of the typical changes in coronary diameter before and after ergonovine is shown in figure 3. In six patients (cases 1–3, 5, 7, and 8, tables 2 and 3) with ST-segment shifts (four with documented variant angina and two without) restudied with coronary angiography during ergonovine pain, coronary diameter decreased 24% (mean) compared to 15% in the group without ST changes. While the differences between these patient subgroups were not statistically significant when compared to the measured proximal branch points, each of the six patients with ST shifts developed either total or subtotal obliteration of at least one long segment of a major coronary artery. The coronary angiographic responses are summarized in detail in table 3. This type of angiographic response was not found in any of the patients without ST-segment shifts. Figures 4 and 5 show illustrative examples of the coronary angiographic findings before and after ergonovine in two variant angina patients (cases 1 and 3, table 2).

Coronary angiographic observations were also made during spontaneous chest pain in cases 1 and 3 before ergonovine. Both patients had variant angina. Four matched frames from the cine angiograms of their coronary arteries are shown in figures 4 and 5. Each patient developed ST shifts during chest pain. With a spontaneous episode of pain, marked left anterior descending spasm was noted. After pain resolved without nitroglycerin, the angiograms were repeated and coronary size was restored to pre-angina levels. Ergonovine then evoked pain, again associated with anterior descending spasm. Following nitroglycerin, pain resolved and the anterior descending diameter returned to control. Thus, we observed a close similarity between spontaneous and ergonovine evoked chest pain with ST shifts and anterior descending spasm in two variant angina patients.

### Discussion

In 1948 Master et al. suggested using ergotamine as a provocative test in the evaluation of patients with suspected
coronary artery disease. Although ergonovine is structurally similar to ergotamine, it has considerably less vasoconstrictor potency. In 1949 Stein proposed that ergonovine may be clinically useful in the diagnosis of patients with suspected coronary artery disease.

The cardiovascular effects of ergonovine relate to its actions on vascular smooth muscle and the central nervous system. Ergonovine is thought to act directly on vascular smooth muscle to increase arterial pressure and decrease venous compliance. Unlike ergotamine, ergonovine has no alpha-adrenergic blocking properties. Instead, ergonovine stimulates alpha-adrenergic receptors, an action that is blocked with alpha-blocking agents. The effects of ergonovine on the central nervous system include blocking of the baroreceptor response preventing the reflex bradycardia response to increases in arterial pressure. Ergonovine also acts centrally, stimulating nausea, dizziness, and other side effects. The exact mechanism whereby ergonovine evokes chest pain and/or ST segment shifts has not been demonstrated.

In 1963 Stein found that 81% of 500 patients who had clinical evidence of coronary artery disease developed one or more of the following: (1) chest pain; (2) ST segment shifts ≥0.75 mm (limb leads) or ≥1.5 mm (V_{4,5}) or ST elevation; (3) T wave alteration; (4) premature ventricular contractions; or the (5) appearance of an inverted "U" wave. Chest pain occurred rarely in normal women in previous studies using this agent. Stein postulated that ergonovine caused coronary arterial constriction reducing coronary blood flow and producing ischemic chest pain and electrocardiographic changes. Animal studies supported Stein's clinical observations and proposed mechanism of ergonovine action. Interestingly, Stein reported two cases of transient ST-segment elevation following ergonovine almost ten years before Prinzmetal's first report of variant angina.

Using Stein's criteria we were unable to separate patients with proven CAD from those with minimal or no CAD. Thirteen (43%) patients with significant CAD and nine (30%) patients with minimal (<50%) or normal coronary arteries developed a "positive" Stein test. Furthermore, in 27 of 30 patients with significant CAD who underwent stress testing reaching a submaximal (85%) heart rate, 21 (78%) patients developed an ischemic response (≥1 mm ST segment shift). The high rate of positive stress tests supports the severe multivessel CAD found in these patients. Two variant angina patients, both with mitral valve prolapse, had positive stress tests. Thus, the ergonovine test was less useful in detection of myocardial ischemia in patients with proven CAD than the standard treadmill exercise test.

It is possible that a larger dose of ergonovine might produce a higher incidence of myocardial ischemia. Our average dose was 0.26 mg (0.05 to 0.4) compared to Stein's average dose of 0.4 mg (0.2 to 0.6).

Despite the limitations, ergonovine injection seems to have a dramatic effect in our patients presenting with the clinical syndrome of variant angina. If we use the criteria of ≥1 mm ST segment shift following ergonovine, we were able to identify all five of the patients studied with previously documented variant angina (cases 1–5, table 2). Three additional patients (cases 6–8, table 2) with severe CAD also had ST-segment responses (two of three presented with recurrent episodes of rest pain, but did not have documented ST-segment elevation with pain). All three patients had high grade proximal coronary narrowings. Two of these (cases 7 and 8) had repeat coronary arteriography during ergo-
Figure 4. Representative cine frames (LAO projection) from case #1, table 2. The patient had a spontaneous episode of chest pain with ST elevation at the beginning of the study. Selective left coronary artery angiography demonstrated areas of both diffuse and focal spasm in the left coronary artery system (left upper panel). After chest discomfort subsided, also spontaneously, the arteriogram in the right upper panel was obtained demonstrating restoration of lumen size. Following ergonovine, chest pain accompanied by ST elevation occurred again and the arteriogram in the left lower panel was obtained. Note the areas of marked focal and diffuse spasm similar to the findings observed during spontaneous pain. Following nitroglycerin, chest pain and ST elevation were relieved and the arteriogram in the right lower panel was filmed. ERG = ergonovine, TNG = nitroglycerin.

Figure 5. Representative cine frames (RAO) selected from case #3, table 2. The angiographic frame (upper left panel) was obtained during an episode of spontaneous pain with ST elevation. When pain subsided the upper right frame was obtained, and following ergonovine, evoked pain with ST elevation, the lower left frame was obtained. Following nitroglycerin the right lower panel was filmed. Note the marked similarity between the coronary artery appearance during spontaneous pain compared to ergonovine evoked pain. ERG = ergonovine, TNG = nitroglycerin.
novine-induced pain which demonstrated transient narrowing of the anterior descending coronary artery. It is possible that two of these cases represent examples of variant angina which had not been clinically documented prior to cardiac catheterization, but was induced by ergonovine.

Ergonovine induced chest pain in a total of 18 patients (30% of the entire group), but the incidence was doubled in patients with proven CAD. It is possible that chest pain in our patients is related to transient myocardial ischemia both with and without ST-segment shifts. If this is the case, the basis for ischemic chest pain without ST shift is obscure. Further studies using other techniques (i.e., myocardial lactate metabolism or isotope perfusion studies) are necessary to quantitate the presence or absence of myocardial ischemia in this group of patients.

Ergonovine caused an increase in systolic blood pressure, decrease in coronary diameter, and had a variable, but statistically insignificant effect on heart rate in our entire group of 60 patients. The rise in systolic blood pressure can be explained by the known vasoconstrictor action of ergonovine. Although a significant rise in the double product after ergonovine was observed, there was no consistent association between the double product and the development of chest pain after ergonovine. This suggests that the development of chest pain was not related to an increased myocardial oxygen demand. The decrease in coronary artery diameter may be due to a direct effect of ergonovine or a reflex change due to an increase in blood pressure. However, there was no association between coronary diameter changes after ergonovine in patients whose blood pressure increased or remained unchanged. The lack of significant decrease in heart rate following ergonovine supports the hypothesis that ergonovine blocks the baroreceptor reflex.

In respect to the use of the ergonovine test, it is questionable whether or not the test can yet be labeled as a routine in the investigation of patients with chest pain. Our results support previously reported experiences suggesting that ergonovine can be given to selected patients with coronary artery disease. The data at this time, however, do not establish the ergonovine test as being entirely safe. The clinical usefulness and safety of intravenous ergonovine in patients with various chest pain syndromes need to be established in larger clinical trials. A few reports of serious complications following ergonovine indicates the need for caution when using this drug. Reported complications have included severe hypertension, seizures, premature ventricular contractions, myocardial infarction, intracerebral hemorrhage, and death. In our group of patients, intravenous ergonovine produced no serious complications, myocardial infarction, stroke, or cardiac arrest. All patients developing ST-segment shifts were evaluated with serial measurements of CPK-MB, electrocardiograms and technetium-99m pyrophosphate myocardial scintigrams following ergonovine administration. No detectable myocardial damage was observed in these patients. Severe hypertension (systolic BP rise greater than 50 mm Hg) occurred in two (3%) patients who responded to nitroglycerin. Hypotension (systolic BP drop of 30 mm Hg with complete heart block) occurred in one patient, and was reversed with nitroglycerin.

Our clinical experience in these 60 patients has led to the development of the following protocol for use of intravenous ergonovine. 1) Informed consent is obtained for cardiac catheterization and use of ergonovine explaining its known responses in detail. 2) A pacing catheter is placed in the right heart. 3) Left heart catheterization is performed to continuously monitor left ventricular pressure and repeat coronary arteriography. 4) Nitroprusside (50 μg/ml) is available for use in patients who fail to respond to nitroglycerin or develop severe hypertension. 5) Patients with the clinical syndrome of variant angina or with systemic hypertension receive an initial dose of 0.05 mg ergonovine. This dose may be repeated up to a maximum of 0.2 mg over a five minute period. 6) Other patients are given 0.2 mg as the initial dose.

Using this protocol, no patient has developed lasting ill effects during or after the injection of ergonovine. We strongly warn against the use of ergonovine in a setting in which proper safety precautions are not available, particularly in the presence of severe CAD. Prolonged chest pain with myocardial infarction may occur as a complication of administration of ergonovine, although this complication was not observed in any of our patients.

In summary, the effects of ergonovine on 60 patients (30 with CAD and 30 with minimal or no CAD) were similar. Following administration of ergonovine, blood pressure rose, coronary artery diameter decreased, heart rate and QTc remained unchanged. Using ST-segment shift ≥1 mm, the ergonovine test identified five of five patients with previously documented variant angina. The test appears sensitive to detect patients with variant angina. Spontaneous spasm of the left anterior descending coronary artery occurred in two variant angina patients during coronary arteriography. The arteriographic findings were similar following ergonovine. This suggests that spontaneous and ergonovine induced coronary spasms were similar. No permanent ill effects developed following ergonovine, but we warn against its use in patients with severe CAD since prolonged pain and myocardial infarction may result.

Acknowledgment

We thank Dr. Michael Ray for permission to include Case 7 and Eli Lilly and Company for supplying Ergotrate. We also thank Mrs. June Malinowski for typing the paper.

Addendum

Since the preparation of this manuscript 48 additional patients have been studied. Results in these patients were similar to those found in our first 60 patients and add further support to our conclusions.

References

“Reverse Coronary Steal”
Induced by Coronary Vasoconstriction
Following Coronary Artery Occlusion in Dogs

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MICHAEL A. DAVIS, D.S.C., AND PETER R. MAROKO, M.D.

SUMMARY The phenomenon of “coronary steal,” i.e., the shunting of blood from ischemic to normally perfused areas of myocardium, has been described as an effect of the administration of several vasodilating agents. This study was performed to ascertain whether the reverse situation can be induced, i.e., whether vasoconstriction of the vessels supplying the nonischemic zone could increase the collateral flow to the ischemic area. In 16 open chest dogs, 15 and 30 min after occlusion of the left anterior descending coronary artery, epicardial electrograms were recorded and regional myocardial blood flow (RMBF) was measured with radiolabeled microspheres. Methoxamine was infused intravenously between 17 and 30 min, the mean arterial pressure being kept constant. The results indicate that while the coronary arterial flow to the normal myocardium fell from 90.6 ± 4.3 to 77.7 ± 3.2 ml/min/100 g (P < 0.01), the collateral blood flow to the ischemic area increased from 21.4 ± 3.5 to 41.0 ± 4.2 ml/min/100 g (P < 0.01), and thereby reduced acute myocardial ischemic injury. This favorable redistribution of blood flow might be considered a “reverse coronary steal.”

“VASCULAR STEAL” may occur whenever a sudden reduction in the vascular resistance of a given area results in the shunting of blood to it through collateral channels from adjacent areas of unchanged resistance. This steal phenomenon has been observed in the subclavian,1 aortic, iliac3 mesenteric1 and coronary14–12 vascular beds. In dogs with coronary artery occlusions or patients with ischemic heart disease, coronary vasoconstrictor agents may increase the total coronary blood flow, but they may do this at the expense of reducing the collateral blood flow to the ischemic area already maximally dilated as a result of metabolic stimuli. This phenomenon has been described with carbochromen,4 diprydiamole,4, 6, 9, 10, 11 isoproterenol8 and minoxidil.12 Since drugs which cause arterial dilatation in normal myocardium also reduce the arterial flow to ischemic areas, interventions which cause arterial constric-
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