Similarities of Ergonovine-Induced and Spontaneous Attacks of Variant Angina

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SUMMARY Ergonovine has been shown to provoke attacks of variant angina, but a question remains whether spontaneous and ergonovine-induced attacks of variant angina are similar. Seven patients with variant angina undergoing cardiac catheterization were studied during transient episodes of spontaneous and ergonovine-induced rest angina with ST-segment elevation. Clinical, electrocardiographic, left ventricular hemodynamic and coronary angiographic observations were made before and repeated after ergonovine (0.05 - 0.2 mg I.V.). The character and duration of chest pain were similar during both spontaneous and ergonovine-induced episodes. ST-segment elevation (> 1 mm) was present inferiorly in three patients, anteriorly in three patients, and both inferiorly and anteriorly in one patient during both episodes. Mean heart rate and systolic arterial pressure changed little, while left ventricular end-diastolic pressure increased significantly during spontaneous or ergonovine-induced attacks. We observed subtotal or total dynamic obstruction in the left anterior descending (three patients), right coronary arteries (three patients) and both arteries in one patient during both attacks. Thus, in selected patients ergonovine-induced attacks of variant angina were remarkably similar to spontaneous episodes.

DYNAMIC CORONARY ARTERY OBSTRUCTION has recently been demonstrated in patients with the clinical syndrome of variant angina,1-9 as originally postulated by Prinzmetal and colleagues,10 to explain transient episodes of rest angina with ST-segment elevation. We11 and others12-14 have shown that ergonovine can provoke transient episodes of rest angina with ST-segment elevation associated with dynamic coronary artery obstruction in patients with variant angina. Before this phenomenon can be accepted as clinically useful, a central question must be answered: whether spontaneous and ergonovine-induced attacks of variant angina are similar.

In this paper we present evidence that clinical, electrocardiographic, left ventricular hemodynamic and coronary angiographic changes during ergonovine-induced attacks of variant angina are remarkably similar to spontaneous episodes.

Patient Selection and Methods

Patient Selection

Over 18 months 18 patients with the clinical syndrome of variant angina defined as cyclic rest angina with ST-segment elevation were studied at cardiac catheterization. Seven of these patients were studied during spontaneous chest pain and during pain provoked by ergonovine administration. Findings from these patients are the basis of this report.

Protocol

Before study each patient signed a written informed consent after a full explanation of the risks of cardiac catheterization and ergonovine testing. Our criteria for patient selection and exclusion from ergonovine testing have been previously reported.11 After an overnight fast and without premedication patients underwent combined heart catheterization and angiography using standard techniques.15, 16 During episodes of spontaneous pain, ECGs and left ventricular pressures were recorded, followed by selective angiography. When possible both coronary arteries were studied during episodes of pain. The coronary artery supplying the region of the heart showing ST-segment elevation was injected first. If the patient remained stable with respect to blood pressure and rhythm, the catheter was repositioned in the other artery and selective coronary angiograms were repeated. After resolution of chest pain and ST-segment shifts without administering nitroglycerin, repeat coronary angiography was performed. Ergonovine maleate (Ergotrate, Eli Lilly Co) was then given intravenously in divided doses. Bolus doses of 0.05 mg of ergonovine were given at 5-minute intervals to a dose of 0.2 mg in an attempt to titrate the minimal dose of ergonovine necessary to evoke chest pain with ST-segment elevation. Patients were continuously monitored for symptomatic, electrocardiographic and left ventricular pressure changes. When chest pain and ST-segment elevation occurred, coronary angiography was again performed in the manner outlined during spontaneous angina. After angiography, sublingual nitroglycerin was given. Repeat coronary angiography was performed after nitroglycerin had completely relieved chest pain.

A standardized 12-lead ECG was recorded during a pain-free interval, and when possible during spontaneous and ergonovine-induced pain. Significant ST-segment elevation was defined as an upsloping shift \( \geq 1 \) mm compared with a pain-free interval.

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Coronary artery diameters were measured in millimeters with calipers, from an end-diastolic frame in the same projection, using the catheter diameter as a reference. Measurements of the coronary artery lumen diameter at the site of maximal obstruction were compared with the lumen diameter proximal to the obstruction. The percentage narrowing was calculated as follows:

\[
\text{Percentage lumen narrowing} = \left(\frac{\text{proximal vessel (mm)} - \text{obstructed vessel (mm)}}{\text{proximal vessel (mm)}}\right) \times 100
\]

Coronary lumen narrowing (percentage) during spontaneous or ergonovine-induced angina was compared with measurements made during a pain-free interval.

After cardiac catheterization and angiographic studies we observed each of these patients with serial ECGs, CK-MB, and a technetium-99m pyrophosphate myocardial scintigram to exclude the possibility of acute myocardial infarction.

Data Analysis

Mean values and standard deviations were calculated from 10 consecutive beats for heart rate, left ventricular systolic and end-diastolic pressure. Changes occurring during spontaneous and ergonovine-induced pain were compared with measurements during pain-free intervals and analyzed by the t test for paired data. A p value < 0.05 was considered significant.

Results

Clinical Findings

Clinical findings are summarized in table 1. There were six males and one female. Their mean age was 50 years (range 41–63 years). All patients presented with well-documented variant angina as their major clinical problem. In addition to variant angina, five patients had a history of myocardial infarction.

The character of chest pain during spontaneous and ergonovine-induced attacks were similar in five patients. Two (patients 3 and 5) said the ergonovine-induced attacks were less severe than their usual attacks. The duration of spontaneous attacks averaged 3 minutes (range 2–6 minutes). Ergonovine-evoked attacks were always interrupted after 4–6 minutes with administration of nitroglycerin.

Electrocardiographic Findings

Electrocardiographic changes during spontaneous and ergonovine-induced chest pain are summarized in table 1. Only patient 5, with a history of myocardial infarction, had an abnormal ECG, showing a QS pattern in leads V<sub>1</sub>–V<sub>3</sub> with poor R-wave progression. The ECGs from patient 1 appear in figure 1, and are typical of the electrocardiographic findings in these patients. During angina maximal elevation of the ST segment was observed inferiorly (lead II) in three patients, anteriorly (leads V<sub>1</sub>, I, aV<sub>L</sub>) in three patients, and both inferiorly and anteriorly (leads II and V<sub>1</sub>) in one patient. The location of ST-segment elevation was similar during both spontaneous and ergonovine-induced attacks of chest pain in any given patient.

Three patients developed premature ventricular contractions during spontaneous and ergonovine-induced attacks. Two of these patients also developed brief salvos of ventricular tachycardia during both attacks. Patients 3 and 7 developed complete heart block during both attacks.

Hemodynamic Findings

Hemodynamic findings are summarized in table 2. Left ventricular end-diastolic pressure increased significantly during both spontaneous and ergonovine-evoked angina compared with the pain-free period.

Coronary Angiographic Findings

Coronary angiographic findings are summarized in Table 2. Four patients had significant coronary artery disease, defined as one or more major arteries with a narrowing (percentage) during spontaneous or ergonovine-induced angina was compared with measurements made during a pain-free interval.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>Chest pain</th>
<th>Previous MI</th>
<th>Location ST</th>
<th>Dysrhythmias</th>
<th>Electrocardiography</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>41/F</td>
<td>Rest +</td>
<td>0</td>
<td>0/0</td>
<td>Inf/0</td>
<td>Inf/0</td>
</tr>
<tr>
<td>2</td>
<td>63/M</td>
<td>+</td>
<td>0</td>
<td>0/0</td>
<td>Ant/PVCs</td>
<td>Ant/PVCs</td>
</tr>
<tr>
<td>3</td>
<td>54/M</td>
<td>+</td>
<td>0</td>
<td>0/0</td>
<td>Ant/PVCs</td>
<td>VT, CHB</td>
</tr>
<tr>
<td>4</td>
<td>49/M</td>
<td>+</td>
<td>+</td>
<td>0/0</td>
<td>Inf/0</td>
<td>Inf/0</td>
</tr>
<tr>
<td>5</td>
<td>50/M</td>
<td>+</td>
<td>+</td>
<td>0/0</td>
<td>Ant/0</td>
<td>Ant/0</td>
</tr>
<tr>
<td>6</td>
<td>48/M</td>
<td>+</td>
<td>+</td>
<td>Inf/0</td>
<td>Inf Lat/VT, PVCs</td>
<td>Inf Lat/VT, PVCs, VT</td>
</tr>
<tr>
<td>7</td>
<td>44/M</td>
<td>+</td>
<td>+</td>
<td>0/0</td>
<td>Inf/JR</td>
<td>Inf/CHB</td>
</tr>
</tbody>
</table>

Abbreviations: Ant = anterior precordial leads; CHB = complete heart block; CP = chest pain; F = female; M = male; Inf = inferior leads; Inf Lat = inferior lateral leads; JR = junctional rhythm; MI = myocardial infarction; PVCs = premature ventricular contractions; Spont = spontaneous; ST↑ = ST-segment elevation; VT = ventricular tachycardia.

TABLE 1. Clinical and Electrocardiographic Summary
TABLE 2.  Hemodynamic and Angiographic* Summary

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Rest HR</th>
<th>RCA</th>
<th>LAD</th>
<th>Spont CP HR</th>
<th>RCA</th>
<th>LAD</th>
<th>Ergo CP HR</th>
<th>RCA</th>
<th>LAD</th>
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<tr>
<td>1</td>
<td>68</td>
<td>140/8</td>
<td>0</td>
<td>0</td>
<td>60</td>
<td>170/12</td>
<td>99%</td>
<td>—</td>
<td>70</td>
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<tr>
<td>2</td>
<td>66</td>
<td>130/16</td>
<td>50%</td>
<td>70%</td>
<td>66</td>
<td>125/30</td>
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<td>100%</td>
<td>67</td>
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<tr>
<td>3</td>
<td>58</td>
<td>88/10</td>
<td>30%</td>
<td>30%</td>
<td>40</td>
<td>58/—</td>
<td>50%</td>
<td>90%</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>155/12</td>
<td>0</td>
<td>70%</td>
<td>81</td>
<td>156/25</td>
<td>40%</td>
<td>99%</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>70</td>
<td>102/13</td>
<td>0</td>
<td>60%</td>
<td>68</td>
<td>97/19</td>
<td>—</td>
<td>95%</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>74</td>
<td>145/10</td>
<td>30%</td>
<td>50%</td>
<td>58</td>
<td>160/18</td>
<td>95%</td>
<td>95%</td>
<td>75</td>
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<tr>
<td>7</td>
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<td>30%</td>
<td>40</td>
<td>90/—</td>
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<td>40%</td>
<td>53</td>
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<tr>
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<td>65</td>
<td>124/12</td>
<td>50</td>
<td>22/21</td>
<td>15</td>
<td>42/8</td>
<td></td>
<td>73</td>
<td>132/24</td>
</tr>
<tr>
<td>sd</td>
<td>6</td>
<td>25/3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12</td>
</tr>
</tbody>
</table>

*Angiographic findings in percent (%) diameter reduction.

Abbreviations: CP = chest pain; Ergo = ergonovine; HR = heart rate in beats/minute; LAD = left anterior descending coronary artery; LV = left ventricular systolic and end-diastolic pressure in mm Hg; RCA = right coronary artery; Spont = spontaneous.
No patient suffered permanent ill effects as a result of a spontaneous or ergonovine-induced attack, and no patient had complications related to catheterization or angiographic procedures used in this study.

Discussion

Coronary artery spasm is thought to be responsible for rest angina in patients with transient ST-segment elevation. A reliable and safe provocative test to detect patients with variant angina, analogous to the treadmill exercise test for patients with typical exertional angina, would be clinically useful. Such a test would be helpful to evoke attacks of variant angina with dynamic coronary arterial obstruction and to evaluate therapy. The ergonovine test, first described by Stein and recently by Heupler, Clark, Schroeder and us, has shown promise as a provocative test for coronary artery spasm and variant angina. Preliminary results in over 400 patients from the English literature, who were given ergonovine since 1975 in an attempt to provoke variant angina, suggest the ergonovine test can be useful and relatively safe. However, it is important to emphasize that the test should be performed with caution. Reproduction of coronary spasm and attacks of variant angina are frequently associated with life-threatening dysrhythmias and with possible hypotension in some patients. The clinical, electrocardiographic, and coronary angiographic changes during spontaneous attacks of variant angina should be similar to changes evoked by ergonovine if the response to ergonovine is to be clinically useful as a provocative test for variant angina.

In seven selected patients we found very similar electrocardiographic, left ventricular hemodynamic, and coronary angiographic changes during ergonovine-induced and spontaneous attacks of variant angina. The character and location of the chest pain was similar during spontaneous and ergonovine-evoked attacks. The onset of symptoms was 3–5 minutes after an intravenous bolus of ergonovine, and was usually preceded by ST-segment elevation. In each patient the left ventricular region localized by the leads with ST-segment elevation were similar in both spontaneous and ergonovine-induced attacks. All patients demonstrated ST-segment elevation with a dose of ergonovine less than or equal to 0.2 mg I.V. ergonovine. Chest pain, ST-segment shifts and dysrhythmias were transient. These responses were relieved by 0.4–1.6 mg nitroglycerin, within 5–10 minutes in each patient. No permanent ill effects such as death, myocardial infarction or stroke occurred. No patients developed ventricular fibrillation or sustained ventricular tachycardia.
We have previously shown that ergonovine minimally increases systemic arterial pressure. We observed a similar trend in these patients, although the change was not statistically significant, probably because of the small sample size. Spontaneous attacks of angina with ST-segment elevation were associated with a small decline in systemic pressure, but again the change was not significant. Guazzi and colleagues and Maseri and colleagues have reported significant declines in systemic arterial pressure during spontaneous attacks of variant angina. Both spontaneous and ergonovine-induced chest pain were associated with left ventricular hemodynamic dysfunction. This was indicated by transient increases in left ventricular end-diastolic pressure while heart rate did not change significantly. These changes may be explained by transient myocardial ischemia resulting from an acute decrease in myocardial blood supply consistent with dynamic coronary artery obstruction. We feel that this alteration is probably one of the initial events leading to transient myocardial hypoxemia rather than an increase in indices of myocardial oxygen demand.

We observed the most striking similarities of ergonovine-induced and spontaneous attacks of chest pain in the coronary angiograms. In any patient the same artery or arteries demonstrated subtotal or total dynamic obstruction during both ergonovine-induced and spontaneous attacks. This dynamic obstruction occurred in areas of existing organic coronary artery narrowing in all but one patient whose arteries were angiographically normal during a pain-free period. The exact location and percentage narrowing of an artery varied during the ergonovine-induced and spontaneous episodes. Only one set of post-ergonovine coronary angiograms were performed, so major changes in the location and percentage narrowing for graded doses of ergonovine could not be determined.

The trigger mechanism underlying spontaneous and ergonovine-induced coronary artery spasm is unknown. Knowledge of the mechanism of action of ergonovine may partly explain the pathophysiology of coronary artery spasm. Ergonovine maleate is a naturally occurring ergot alkaloid which has properties of direct smooth muscle constriction. The drug caused mild, generalized epicardial coronary arterial vasoconstriction in our patients who did not develop chest pain or ST-segment change. However, the actions of ergonovine appear complex, involving both direct and indirect effects on the peripheral vasculature and stimulation of central nervous system vaso-regulatory centers in both animals and humans. Ergonovine has been shown in animals to be an α-adrenergic stimulating agent for vascular smooth muscle due to its synergistic action with norepinephrine. Alpha-adrenergic antagonists block its action. Pretreatment with reserpine does not block the action of ergonovine, indicating that the drug has a direct α-agonist action, and does not act by stimulating release of norepinephrine.

An important role for calcium in the mechanism of coronary arterial vasoconstriction has been suggested by the symptomatic improvement in patients with variant angina treated with a new group of calcium antagonist agents. These drugs include perilhexilene, nifedipine, verapamil and diltiazem. They appear to act on the major coronary epicardial arteries, causing vasodilatation by interrupting excitation-contraction coupling within vascular smooth muscle by preventing calcium flux across cell membranes. The role of calcium-mediated coronary vasoconstriction should be investigated further to identify the mechanism of dynamic coronary arterial obstruction.

Two additional areas related to this report should be noted. The first concerns patient selection. Each patient was selected from a group of patients at our hospital whose major clinical problem was variant angina. This problem had been present for months to years, and had become refractory to standard medical management. Five patients also gave a history of one or more episodes of angina occurring with exertion. This was clearly not their major problem, compared with the frequency and severity of attacks of variant angina. None of these patients were admitted to a coronary care unit within 6 weeks before cardiac catheterization. No patient evolved from a stable, effort-related angina syndrome to an unstable or preinfarction syndrome. It is not clear whether there are differences in the clinical, electrocardiographic, hemodynamic or coronary angiographic changes during angina in patients with unstable angina and ST-segment depression or elevation compared with patients with variant angina. Patients with rest angina reported by Maseri and colleagues have shown similar hemodynamic changes and coronary artery spasm during both ST-segment elevation and depression.

The other problem concerns a more precise quantitation of the degree and length of dynamic coronary arterial obstruction. Unlike fixed coronary lesions, during an episode of dynamic coronary artery obstruction both the proximal vessel and the site of narrowing may show lumen diameter changes. Thus, the percentage narrowing calculation may not accurately reflect the actual change in lumen diameter. A more meaningful method of analyzing such data might be to use the absolute dimensions of the lumen at the stenotic site. This measurement could then be related to an uninvolved proximal portion of the vessel or even the same site measured from the angiogram during a pain-free period used as a reference.

There are no simple methods to quantitate the diffuse coronary vasoconstriction that may occur during episodes of coronary artery spasm. The method developed by Brown and colleagues to quantitate coronary artery dimensions using computer analysis of orthogonal views appears to be a promising new approach. Better methods are needed to quantitate coronary lumen narrowsings.

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References


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