Coronary Artery Spasm During Exercise in Patients with Variant Angina

DAVID D. WATERS, M.D., BERNARD R. CHAITMAN, M.D., GEORGES DUPRAS, M.D., PIERRE THÉRoux, M.D., AND HENRY F. MIZGALA, M.D.

SUMMARY Seven patients with typical variant angina without coronary stenoses >50% developed angina and ST-segment elevation during treadmill exercise testing. In all cases the ST-segment elevation occurred in the same leads during exercise testing as during spontaneous attacks at rest. Five of the patients had developed spontaneous coronary spasm during coronary arteriography, in each case in the artery corresponding to the site of ST-segment elevation. In five patients, thallium was injected during the exercise test during which angina and ST-segment elevation occurred. In each case, a large perfusion defect not present at rest was found in the zone corresponding to the site of ST-segment elevation.

These findings suggest that coronary artery spasm may occur during exercise in patients with variant angina.

THE TERM VARIANT ANGINA was introduced by Prinzmetal et al.1 in 1959 to describe a syndrome characterized by angina at rest associated with ST-segment elevation. Although a severe, proximal coronary artery stenosis was present in some of their patients, subsequent studies have demonstrated that normal coronary arteriograms may also be found.2 Temporary increased tonus was postulated by Prinzmetal et al. as the cause of the syndrome, and coronary artery spasm during pain and ST-segment elevation has subsequently been documented at coronary arteriography.3,5 Therefore, coronary artery spasm is generally accepted as the mechanism responsible for variant angina at rest.6 In contrast, exertional angina, either in patients with classic angina or variant angina, has been attributed to a fixed, atherosclerotic coronary stenosis. However, exertional angina is not a common feature of the variant angina syndrome.7 This report presents evidence suggesting that angina during exertion can be caused by coronary artery spasm in some patients with variant angina.

Methods

Patient Population

For the purposes of this study, variant angina was defined as angina at rest associated with transient ST-segment elevation. Over a recent 40-month period, 33 patients with variant angina were evaluated at the Montreal Heart Institute. At coronary arteriography, 20 of these patients had one or more fixed coronary stenoses ≥70% and 13 had normal coronary arteries or stenoses <70% of the arterial luminal diameter. These 13 patients all underwent treadmill exercise testing using 15 electrocardiographic leads according to the protocol outlined below. Seven of these 13 patients developed ST-segment elevation during exercise and form the basis of this report. In table 1, their clinical, electrocardiographic, and coronary angiographic characteristics are compared with the six patients in whom exercise did not elicit ST-segment elevation. Although the patients with exercise-induced ST-segment elevation are younger, have slightly less severe fixed coronary stenoses and slightly more spontaneous coronary spasm during angiography, no important differences can be detected between the two groups. Several of the patients described symptoms compatible with exertional angina; however, no difference could be detected between the two groups with respect to this parameter and pain at rest predominated in all cases. No patient had had a previously documented myocardial infarction or coincident valvular or other type of heart disease.

The 20 patients with variant angina and fixed coronary stenoses ≥70% could not all be rigorously evaluated by the same exercise test protocol applied to the group of patients without severe fixed lesions. Several had severe coronary lesions with frequent angina at rest and, in others, propranolol or calcium antagonists could not be safely discontinued. Therefore, eight of these 20 patients did not undergo exercise testing. Of the remaining 12, two had ST-segment elevation during exercise, four had ST-segment depression and six had no ST-segment changes. These 20 patients are not included in this study because their data are incomplete.

Exercise Testing

All exercise tests were performed using a standard Bruce protocol8 modified by a 3-minute warm-up period at 1.7 mph with a 5% grade. All patients were fasting and had not smoked or received nitrates for at least 2 hours before the test. None were being treated with cardiac medication except patients AL and LR during their second exercise test, as enumerated in table 2. The ECG was monitored continuously. Cuff blood pressure measurements and 15 electrocardiographic leads (I, II, III, aVR, aVL, aVF, V1-6, V6, V5, V4, V3, V2, V1, and V5).

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Comparison During Exercise

1. TABLE

<table>
<thead>
<tr>
<th>Response to exercise</th>
<th>ST</th>
<th>No ST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>44.7 (33-58)</td>
<td>53.3 (38-69)</td>
</tr>
<tr>
<td>Duration of symptoms (months)</td>
<td>9.9 (1-36)</td>
<td>6.2 (1-24)</td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>6/1</td>
<td>6/0</td>
</tr>
<tr>
<td>Normal ECG at rest</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Site of ST at rest</td>
<td>Anterior</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Inferior</td>
<td>2</td>
</tr>
<tr>
<td>Normal ventriculography</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Coronary arteriography</td>
<td>Entirely normal arteries</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>One stenosis ≤50%</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>One stenosis &gt;50% - &lt;70%</td>
<td>0</td>
</tr>
<tr>
<td>Spontaneous spasm</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

All differences between groups not statistically significant. Abbreviation: ST = ST-segment elevation.

CC5, CM5, and CL) were recorded at 1-minute intervals during exercise and for 5 minutes after exercise, as previously described. Exercise was stopped when exhaustion, severe dyspnea, or progressive angina developed. Horizontal ST-segment depression of 1 mm or more or ST-segment elevation of 3 mm or more was considered significant if the resting ST segment was isoelectric.

All patients had two or more exercise tests and radioisotopic studies were performed in conjunction with at least one of them. One minute before the end of exercise, 2 mCi of thallium-201 were injected into an intravenous catheter which had been installed before the test. Within 30 minutes of this injection a gamma camera recorded left anterior oblique, lateral, and anteroposterior views which were subsequently compared with the patient’s resting thallium-201 scan.

Coronary Arteriography

Selective coronary arteriography was performed via a percutaneous femoral approach using preformed catheters, as previously described. Angulated views of each vessel were routinely filmed. Particular care was taken to avoid catheter-induced coronary artery spasm. No attempts were made to induce coronary spasm by administering ergonovine. Nitroglycerin was not given before the initial injections; however, when a lesion was noted, the vessel was filmed again in several views after administration of nitroglycerin. All angiographic documents were interpreted independently by an experienced cardiovascular radiologist. The left ventricular angiogram was filmed in the 30° right anterior oblique view before the arteriogram. Visual inspection and calculated ejection fractions (area length method) of all ventriculograms were normal.

Results

The clinical data for each patient are listed in table 2. The age range of the patients at the time of study was 32–58 years. Six of the seven were male. Spontaneous coronary artery spasm occurred in five of the patients during coronary arteriography. In each case the affected artery supplied an area corresponding to the site of ST-segment elevation during other

2. TABLE

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Coronary arteriogram</th>
<th>Spasm during arteriography</th>
<th>Test #</th>
<th>Exercise test results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Site</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ΔST</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rest</td>
</tr>
<tr>
<td>MS 42 F</td>
<td>Normal</td>
<td>LAD</td>
<td>1</td>
<td>( V_{5,6},CC_5 )</td>
<td>4 mm</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3</td>
<td>( V_{6,5},CM_5 )</td>
<td>2 mm</td>
<td>116</td>
<td>550</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2</td>
<td>( V_{5,6},CC_5,CM_5 )</td>
<td>3 mm</td>
<td>146</td>
<td>510</td>
</tr>
<tr>
<td>BL 38 M</td>
<td>RCA - 40%</td>
<td>RCA</td>
<td>1</td>
<td>( 2,3,F,CL )</td>
<td>3 mm</td>
<td>165</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
<td>( 2,3,F,CL )</td>
<td>3 mm</td>
<td>167</td>
<td>660</td>
</tr>
<tr>
<td>AL 58 M</td>
<td>Normal</td>
<td>no</td>
<td>1</td>
<td>( 2,3,F,V_{5,6},CC_5,CM_4,CL )</td>
<td>5 mm</td>
<td>136</td>
</tr>
<tr>
<td></td>
<td>2*</td>
<td></td>
<td></td>
<td></td>
<td>—</td>
<td>142</td>
</tr>
<tr>
<td>BM 49 M</td>
<td>RCA - 40%</td>
<td>no</td>
<td>1</td>
<td>( V_{5,6} )</td>
<td>6 mm</td>
<td>158</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
<td>( V_{5,6},CC_5,CM_5 )</td>
<td>2 mm</td>
<td>176</td>
<td>755</td>
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<tr>
<td>RM 47 M</td>
<td>LAD - 50%</td>
<td>LAD</td>
<td>1</td>
<td>( 1,L,V_{5,6},CC_5 )</td>
<td>8 mm</td>
<td>165</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
<td>( 1,L,V_{5,6},CC_5 )</td>
<td>8 mm</td>
<td>169</td>
<td>645</td>
</tr>
<tr>
<td>BD 32 M</td>
<td>LAD - 40%</td>
<td>LAD</td>
<td>1</td>
<td>( 1,L,V_{5,6},CC_5 )</td>
<td>7 mm</td>
<td>170</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
<td>( 1,L,V_{5,6},CC_5 )</td>
<td>5 mm</td>
<td>169</td>
<td>660</td>
</tr>
<tr>
<td>LR 42 M</td>
<td>RCA - 30%</td>
<td>RCA</td>
<td>2</td>
<td>( 2,3,F,CL )</td>
<td>10 mm</td>
<td>125</td>
</tr>
<tr>
<td></td>
<td>2*</td>
<td></td>
<td></td>
<td>( V_{5,6},CC_5,CM_5 )</td>
<td>2 mm</td>
<td>145</td>
</tr>
</tbody>
</table>

*Exercise test done while patient treated with perhexiline maleate.

Abbreviations: RCA = right coronary artery; LAD = left anterior descending coronary artery; Site ΔST = ECG leads with significant ST-segment abnormalities during exercise; ↑ = elevation; ↓ = depression; Max ΔST = maximum ST-segment elevation or depression during exercise.
episodes. After the administration of nitroglycerin, a
fixed stenosis of 30–50% persisted in four of the five
patients at the site where spasm had been identified. In
addition, one other patient without spasm had a
single, fixed 40% stenosis.

The data from patient MS are shown in figures 1–3.
During coronary arteriography a diffuse narrowing of
the mid left anterior descending coronary artery was
noted (fig. 1A); this lesion disappeared after adminis-
tration of nitroglycerin (fig. 1B). ST-segment eleva-
tion developed during exercise testing (fig. 2) in the
antero leads and the corresponding thallium scan
(fig. 3) revealed a large anteroseptal perfusion defect
not present on the control scan.

**Figure 1.** A) Left coronary artery injection filmed at 30° left anterior oblique with cranial angulation during spontaneous episode of variant angina. A diffuse narrowing of the mid left anterior descending coronary artery is visible. B) Left coronary artery injection after administration of sublingual nitroglycerin. The previously noted left anterior descending coronary artery lesion has disappeared.

**Figure 2.** Fifteen ECG leads are shown at rest and just before the end of treadmill exercise testing, during angina. At rest, the T wave is negative in leads D1, 2, aV1, V3, cc, and cm5; no ST-segment elevation is present. With angina, ST-segment elevation develops in leads V1–5, cc, and cm5; the QRS duration and R wave voltage increase slightly. The maximal heart rate was 146 beats/min and the treadmill duration time 510 sec. The ST segment returned to normal and the angina disappeared within 5 minutes.
Exercise Test Results

Angina and ST-segment elevation developed during exercise testing in all seven patients. The maximum amount of ST-segment elevation varied 3–10 mm (table 2). ST-segment elevation occurred during a subsequent exercise test in four of the seven patients, including the one patient who had three tests, two with ST-segment elevation and one with ST-segment depression. A second test in the remaining three patients revealed ST-segment depression in two and no ST-segment changes in the third; however, at the time of their second exercise test, two of these patients (AL and LR) were receiving perhexiline maleate, a calcium antagonist used to treat variant angina.

The ECG leads with ST-segment elevation during exercise corresponded in all patients to the leads where ST-segment elevation was recorded during spontaneous attacks at rest. In addition, the ECG site of ST-segment elevation corresponded to the area supplied by the artery in which coronary spasm was noted during arteriography in each of the five patients with this finding.

All patients had normal thallium scans at rest. The thallium scan during exercise was normal in the patient who had thallium injected during the test without angina or ST-segment changes. Two patients received thallium during the test where ST-segment depression was noted; one had a normal scan and the other a localized zone of hypoperfusion. In five patients, thallium was injected during exercise coincident with angina and ST-segment elevation. All five patients had large, clear-cut zones of marked hypoperfusion which were not present on the resting scan. In each case the hypoperfused zone corresponded to the ECG leads with ST-segment elevation. The hypoperfused region was always in the distribution of the artery which had demonstrated coronary spasm during arteriography.

Discussion

The normal physiological response to exercise includes an increase in coronary blood flow caused by coronary vasodilatation. The seven patients with variant angina reported in this study appear to react paradoxically, with coronary artery spasm occurring during exercise.

Could a mechanism other than coronary artery spasm explain the exercise-induced abnormalities in
these patients? ST-segment elevation provoked by exercise occurs occasionally in association with coronary artery disease, and has been attributed to either a severe fixed coronary stenosis, or more frequently, to a left ventricular akinetic or dyskinetic zone. Neither of these causes are possible in our patients, since all had normal left ventricular angiograms and none had severe, fixed coronary stenoses. In five patients, a coronary stenosis of 50% or less persisted in one artery after the administration of nitroglycerin. Although the severity of a coronary stenosis cannot always be accurately assessed by angiography, these lesions were all clearly visualized in multiple views, including angulation, and none appeared critical. Even if these lesions alone were severe enough to cause exercise-induced ischemia, ST-segment depression, not marked elevation, would be expected. In the five patients who received thallium during the exercise test with ST-segment elevation the scan demonstrated a zone of hypoperfusion not present at rest corresponding both to the electrocardiographic sites of ST-segment elevation and to the coronary artery where spasm was detected during angiography. Therefore, coronary artery spasm during exercise probably caused the angina, ST-segment elevation, and radioisotopic perfusion defects seen in these patients.

Could coronary artery spasm have occurred coincidentally during these exercise tests and not as a direct result of the exercise itself? The absence of ST-segment elevation during the second exercise test in three of the six patients with two tests supports this possibility; however, during two of these three negative tests the patients were receiving the calcium antagonist perhexiline maleate, which may inhibit coronary artery spasm. The patient with three exercise tests developed angina with ST-segment elevation twice, but at markedly different heart rates and treadmill duration times.

When tested, only two of the seven patients were averaging two or more attacks of angina per day; of the other five, four were having less than one episode per day and the other none at all. All patients had undergone continuous electrocardiographic monitoring for 7 days or more, including at least 24 hours of ambulatory Holter monitoring. Three of these seven patients exhibited rare episodes of minimal ST-segment elevation without angina, but in no patient did this occur more frequently than once per day. Therefore, the possibility that coincidence accounted for the angina or ST-segment elevation during exercise testing in these patients seems remote.

The prevalence of coronary artery spasm during exercise in patients with variant angina is not known. Exertional angina is not a usual feature of variant angina, and when it does occur it has been routinely attributed to fixed coronary stenotic lesions. However, in several isolated cases mentioned in the literature, coronary artery spasm during exercise probably accounted for the findings. Cheng et al. described four patients with variant angina and normal coronary arteriograms, one of whom had ST-segment elevation with exercise. Similarly, one patient with Prinzmetal's angina and normal coronary arteriography reported by Whiting et al. and another reported by McLaughlin et al. had ST-segment elevation immediately after exercise testing. One patient of Chahine et al. who had no significant coronary stenoses, developed coronary artery spasm during arteriography and ST-segment elevation during exercise. Finally, Betriu et al. have described a case of variant angina in a patient with a normal coronary arteriogram and left ventriculogram who exhibited marked ST-segment elevation without angina during two consecutive exercise tests. Since patients with variant angina do not routinely undergo exercise testing with multiple leads, some cases with these findings may be overlooked.

Although coronary spasm and variant angina can be provoked by ergonovine, mecholine and other interventions which alter autonomic tone, the mechanism responsible for spontaneous attacks has not been elucidated. Although this study does not define a cause-and-effect relationship between exercise and coronary spasm, we suspect that an exercise-induced increase in sympathetic tone may induce coronary spasm in susceptible patients. Further investigation is required to clarify the pathophysiology of coronary spasm in variant angina.

If exertional angina can result from coronary spasm in patients with variant angina without severe fixed stenoses, as suggested by this study, the possibility that this phenomenon might also occur in other groups of patients with coronary disease, both with and without variant angina, should be considered.

Acknowledgments

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References

9. Chaitman BR, Bourassa MG, Wagniart P, Corbara F, Ferguson RJ: Improved efficiency of treadmill exercise testing using a multiple lead ECG system and basic hemodynamic ex-
BLOOD LEVELS AFTER NITROGLYCERIN/Armstrong et al.

SUMMARY Pharmacokinetic analysis of nitroglycerin (GTN) has been hampered by the lack of a sensitive and specific method for measuring GTN in blood. Therefore, we examined the appearance of GTN in blood after administering 0.6 mg sublingually in 10 studies of normal volunteers. We used a gas-liquid chromatographic method with electron-capture detection and isosorbide dinitrate as the internal standard. GTN appeared in blood at 0.5 minutes, reached a peak of 2.3 ± 0.36 ng/ml at 2 minutes, fell to 50% of peak value at 7.5 minutes and was barely detectable at 20 minutes. These blood levels paralleled the changes in heart rate and systolic blood pressure. These data show rapid appearance and disappearance of GTN from blood after sublingual administration, a large volume of distribution, and a rapid rate of total body clearance that precludes the liver from being the sole elimination site. This method for analysis of GTN and isosorbide dinitrate should be helpful in defining the role of chronic nitrate therapy.

NITROGLYCERIN (GTN) HAS BEEN USED FOR over a century, but uncertainty exists about many aspects of its use. The lack of a sensitive and specific method for measurement of GTN in blood has precluded pharmacokinetic analysis, adding to this uncertainty. Traditionally, GTN has been used in sublingual form for the therapy of angina pectoris. There is continuing interest in the development of long-acting nitrate preparations as prophylactic therapy for angina. This interest has been stimulated by recent research on the role of nitrate therapy in acute myocardial infarction and chronic congestive cardiac failure. The overall role of long-acting nitrate therapy however, has not been established.

In 1973, Rosseel and Bogaert reported a gas-liquid chromatographic method for identifying and quantitating GTN and isosorbide dinitrate (ISDN) in plasma; they also demonstrated that GTN could be recovered from blood after sublingual administration. GTN has also been recovered from blood after sublingual administration using a modification of this method. However, in both of these reports the data were obtained from a single patient.

In this investigation we attempted to establish whether a relationship exists between the blood levels of GTN and its physiologic effects after sublingual administration.

Methods Ten studies were conducted in seven normal male volunteers (ages 24–48 years). The studies were done with the subject in the supine posture. During a 10–15-minute control period, heart rate and indirect sphygmomanometric blood pressure measurements were made to ensure stability. Eighty milliliters of blood were withdrawn through an indwelling venous


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