Exercise-Induced Coronary Artery Spasm

A Regional Coronary Blood Flow Study

Stefano DE SERVI, M.D., Diego ARDISSINO, M.D.,
Antonio MUSSINI, M.D., Luigi ANGOLI, M.D., Ezio BRAMUCCI, M.D.,
Colomba FALCONE, M.D., and Giuseppe SPECCHIA, M.D.

SUMMARY

Regional myocardial blood flow during exercise was determined using the thermodilution technique in 2 patients suffering from both spontaneous and exertional chest pain.

In both cases we observed that effort-related anginal attacks were due to coronary spasm with sudden reduction of regional left ventricular blood flow. In 1 patient the exercise-induced ST-segment elevation in the anterior leads was accompanied by a reduction of flow in the great cardiac vein. In the second patient the exercise-induced ST-segment depression in the lateral leads was accompanied by a reduction of coronary flow in the area supplied by the circumflex artery. In 1 patient, nifedipine was effective in prolonging exercise tolerance by preventing the occurrence of coronary spasm and by increasing blood supply to the ischemic region during exercise.

Additional Indexing Words:
Coronary blood flow    Coronary vasospasm    Exercise testing

RECENT studies have suggested that coronary vasospasm may cause angina at rest associated with transient electrocardiographic changes.1–3) Angiographic studies have demonstrated that coronary spasm may also occur during exercise, causing chest pain and myocardial ischemia.4–7)

In this paper, we report on 2 patients with vasospastic angina at rest who also complained of effort-related chest pain. In these patients, we measured coronary sinus and great cardiac vein flow during exercise using the thermodilution technique. In both cases, a fall in coronary blood flow was observed in the area supplied by the same artery which was likely to be af-
fected by coronary spasm, coincident with the exercise-induced electrocardiographic changes. In 1 patient, nifedipine increased exercise tolerance and prevented a decrease in regional blood flow during exercise.

**METHODS**

We studied 2 patients with a history of spontaneous and exercise-induced chest pain who had had no previous myocardial infarction. The clinical, electrocardiographic and angiographic data are briefly presented in the Case Report Section. In both patients, multistage supine bicycle exercise testing was performed with an initial workload of 25 watts and subsequent increments of 25 watts every 3 min. The exercise was stopped when angina or an ST-segment elevation of 2 mm occurred.

Standard 12 lead electrocardiograms were recorded before and at 1 min intervals during exercise testing. Electrocardiographic leads V₄, V₅ and V₆ were monitored on an oscilloscope. Blood pressure was measured using a cuff sphygmomanometer at rest and at the end of each loading stage. The product of heart rate and systolic blood pressure was calculated and used as an index of myocardial oxygen consumption. All therapy, including antianginal drugs, was discontinued 12 hours before the study. Neither patient was taking beta blocking agents or digitalis.

Both patients underwent coronary arteriography using Sones' technique after premedication with 10 mg of diazepam. A left ventriculogram was performed at a 30° right anterior oblique projection before the coronary arteriograms. When spontaneous ischemic episodes occurred during the procedure, selective coronary injections were repeated. Significant coronary disease was considered to be present when an arteriographic narrowing greater than 50% of one or more arteries was documented.

Coronary spasm was considered to be present when the coronary segment was reduced in caliber or completely obstructed in comparison with the initial angiographic appearance.

In both patients, we measured regional myocardial blood flow using the thermodilution technique under basal conditions and during exercise. A multithermistor catheter was introduced into the coronary sinus under fluoroscopic guidance. The distal external thermistor was advanced to the great cardiac vein, while the proximal external thermistor was positioned in the sinus between the ostium and the left marginal vein. In both patients, the venous phase of the coronary angiogram was used in positioning the thermodilution catheter. The position was checked frequently throughout the procedure. Normal saline solution at room temperature was intervals in-
jected at a rate of 50 ml/min during basal conditions at 3 min during exercise and at the time of peak exercise.

**Blood flow for CS and GCV were computed from the following formulas**

\[
\text{CSF} = V_1 \times \frac{(T_B - T_1)}{(T_B - T_{MCS})} - 1 \times 1.08
\]

\[
\text{GCVF} = V_1 \times \frac{(T_B - T_1)}{(T_B - T_{MGCV})} - 1 \times 1.08
\]

where \( V_1 \) is the volume flow of indicator per minute, 1.08 is the constant of the normal saline solution, and \( T_B, T_1, T_{MCS} \) and \( T_{MGCV} \) are the respective temperatures of the blood, the indicator, and a mixture of blood and indicator in the coronary sinus and the great cardiac vein. An arterial catheter was inserted percutaneously into the left brachial artery and the systolic arterial pressure thus obtained was used for the calculation of heart rate-systolic blood pressure product. In 1 patient (Case 2), the exercise test and the regional myocardial blood flow measurements were repeated after sublingual administration of 20 mg of nifedipine. Informed consent was obtained from each patient before the studies. The procedure did not give rise to any complications.

**Case Report**

**Case 1**

A 55-year-old man was admitted to our hospital with a 2-month history of spontaneous and exercise-induced anginal pain with the attacks occurring several times a day. Physical examination on admission was normal. The

<table>
<thead>
<tr>
<th></th>
<th>GCVF ml/min</th>
<th>CSF ml/min</th>
<th>(CSF-GCVF) ml/min</th>
<th>DP mmHg x beats/min 10²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>38</td>
<td>85</td>
<td>47</td>
<td>79</td>
</tr>
<tr>
<td>50 w x 3'</td>
<td>105</td>
<td>175</td>
<td>70</td>
<td>177</td>
</tr>
<tr>
<td>75 w x 3'</td>
<td>84</td>
<td>194</td>
<td>110</td>
<td>204</td>
</tr>
<tr>
<td>Case 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>62</td>
<td>98</td>
<td>36</td>
<td>107</td>
</tr>
<tr>
<td>25 w x 3'</td>
<td>111</td>
<td>119</td>
<td>8</td>
<td>175</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>82</td>
<td>133</td>
<td>51</td>
<td>111</td>
</tr>
<tr>
<td>75 w x 3'</td>
<td>134</td>
<td>228</td>
<td>94</td>
<td>291</td>
</tr>
</tbody>
</table>

GCVF = great cardiac vein flow; CSF = coronary sinus flow; (CSF-GCVF) = difference between coronary sinus and great cardiac vein flow; DP = heart rate-systolic blood pressure product.
blood pressure was 150/90 mmHg and the pulse 66/min regular. The electrocardiogram at rest was normal. Spontaneous episodes of chest pain were associated with ST-segment elevation in leads V1-V3 and ST-segment depression in leads II, III, aVF and V4-V6. The exercise test induced anginal pain and the same electrocardiographic abnormalities observed during spontaneous attacks. The left ventriculogram revealed no ventricular contraction disorders. Selective coronary arteriography demonstrated an isolated 90% stenosis of the proximal portion of the left anterior descending artery. The right coronary artery was normal. The exercise test performed during regional myocardial blood flow measurements showed the same electrocardiographic changes as the previous test.

Both GCVF and CSF increased during exercise before the appearance of ST-segment elevation. When ST-segment elevation developed, CSF continued to increase while GCVF abruptly decreased (Table I, Fig. 1).
Fig. 2. Left panel: control left coronary angiograms showed 75% stenosis of the circumflex branch. Right panel: when spontaneous chest pain occurred, the circumflex artery was completely occluded by coronary spasm (arrow).

Case 2

A 57-year-old man had a 5-year history of chest pain at rest and during normal physical activity with waxing and waning periods. In the last 3 months, the attacks had increased in frequency, occurring several times a day. Physical examination on admission proved normal. The blood pressure was 150/95 and the pulse rate was 60/min regular. The electrocardiogram at rest was normal. The exercise test induced pain with ST-segment depression in leads V4–V6. The left ventriculogram revealed normal myocardial contraction. Selective coronary arteriography demonstrated a 75% stenosis of the small left circumflex artery at a site proximal to the origin of the obtuse marginal branch and also two 50% stenoses of the mid and distal portions of the left anterior descending artery.

The preponderant right coronary artery showed mild irregularities in its caliber. During an episode of chest pain associated with ST-segment depression in leads V4–V6, coronary arteriography revealed a coronary spasm resulting in the complete occlusion of the obtuse marginal branch (Fig. 2). The electrocardiographic abnormalities and coronary spasm both subsided spontaneously. The exercise test performed during regional myocardial blood flow measurements induced chest pain associated with the same electrocardiographic changes observed during the spontaneous attack.

During exercise, both GCVF and CSF increased, but the difference between CSF and GCVF (CSF–GCVF) decreased (Table I, Fig. 3). The effects
Fig. 3. Case 2—During exercise chest pain associated with ST-segment depression occurred at a low workload. Great cardiac vein flow (GC-VF) increased during exercise, but the difference between coronary sinus and great cardiac vein flow (CSF-GCVF) decreased. After nifedipine such a decrease did not occur any longer and the patient tolerated a higher workload, obtaining a greater value of heart rate-systolic pressure product (DP).

of nifedipine administered sublingually were observed 20 min later. Myocardial blood flow at rest, prior to exercising, was consistently greater as compared with control conditions.

The exercise test performed after the administration of nifedipine induced chest pain and ECG signs of myocardial ischemia at a higher workload and with a far greater value of heart rate-systolic blood pressure product at peak exercise. During the test, GCVF and CSF further increased, while the decrease in the (CS–GCV) flow was no longer observed.

**DISCUSSION**

The thermodilution technique which was advanced by Ganz and coworkers\(^9\) is a useful method to measure the changes in coronary sinus blood flow that occur with exercise or drugs. Using this method, coronary hemodynamic responses to cold stimulation,\(^10\) mental stress testing\(^11\) and indomethacin\(^12\) have been reported in patients with coronary artery disease. Furthermore, changes in coronary sinus blood flow during exercise have been studied by Ferguson et al\(^13\) in patients with angina pectoris. Ganz and coworkers\(^9\) also applied an additional thermistor to the coronary sinus ther-
modilution technique and measured great cardiac vein flow. Pepine and co-workers\(^8\) confirmed the validity of the multisensor thermodilution method in assessing regional left ventricular blood flow by comparing the thermodilution measurements with simultaneous electromagnetic flowmeter recordings from anterior descending grafts in patients with occluded or partially occluded left anterior descending arteries. The thermodilution method yielded values for both absolute anterior regional blood flow and changes in anterior regional flow which compared closely to left anterior descending bypass graft flow rates measured independently. Feldman et al\(^{14}\) applied this technique to a clinical setting and measured coronary sinus and great cardiac vein flow in 6 patients with variant angina. In 4 patients with anterior ischemia, great cardiac vein flow decreased, while in the 2 patients with inferior ischemia, great cardiac vein flow was unchanged. The difference, however, between coronary sinus and great cardiac vein flow, which the authors considered an index of inferior regional blood flow, decreased during ischemia. These results supported the concept that in patients with spontaneous angina, left ventricular blood flow decreases in ischemic regions coincident with ST-T changes.

Our patients complained of spontaneous and exercise-induced angina. Coronary vasospasm was responsible for the anginal attacks at rest, as documented by coronary angiography in 1 patient and by the demonstration of transient ST-segment elevation during chest pain in the other patient.\(^{1,2,15}\) Coronary flow studies during exercise also showed that the effort-related anginal attacks were due to coronary spasm. In 1 patient, the exercise-induced ST-segment elevation in the anterior leads was accompanied by a reduction in great cardiac vein flow while coronary sinus flow remained increased.

Since the great cardiac vein drains blood from the left anterior descending artery,\(^{16}\) a sudden decrease in flow coincident with ST-segment elevation is strongly indicative of a vasospastic occlusion of this artery. In a previous paper\(^{17}\) we have shown that exercise-induced ST-segment elevation in patients without myocardial infarction or left ventricular aneurysm is caused by spasm of a major coronary artery. In the second patient in the present study, exercise-induced electrocardiographic abnormalities were accompanied by a reduction in the difference between coronary sinus and great cardiac vein flow compared with the resting values, while great cardiac vein flow increased. In this patient, the difference between coronary sinus and great cardiac vein flow probably reflected only the left circumflex flow, while the venous effluent of the right coronary artery was not sensed by coronary sinus sampling. Indeed, these veins often enter the coronary sinus at or near its ostium or drain separately into the right atrium.\(^{16,18}\) We believe that the marked decrease in the difference between coronary sinus and great cardiac vein flow at peak
exercise was secondary to coronary spasm of a small circumflex branch, resulting in complete occlusion of the obtuse marginal branch. Previous reports have shown that vasospastic occlusion of the obtuse marginal branch may be accompanied by transient ST-segment depression rather than ST-segment elevation.\textsuperscript{1,3}

After receiving nifedipine, which is a calcium channel blocking drug, our patient was able to tolerate a higher workload and the electrocardiographic changes occurred at a higher double product, an index of myocardial oxygen consumption. Great cardiac vein flow and coronary sinus flow both increased during exercise after the drug was administered and the marked reduction in the difference between coronary sinus and great cardiac vein flow was then no longer observed. Thus, nifedipine increased the patient’s exercise capacity by preventing the occurrence of coronary spasm and also by increasing the blood supply to the ischemic region during exercise.

We conclude that in selected patients with vasospastic angina, regional coronary flow studies may be useful in clarifying the pathogenetic mechanism underlying exercise-induced chest pain and related electrocardiographic abnormalities.

References

10. Mudge GH Jr, Grossman W, Mills RM Jr, Lesch M, Braunwald E: Reflex increase in


