SIGNIFICANCE OF CORONARY ARTERY TONE ASSESSED BY CORONARY RESPONSES TO ERGONOVINE AND NITRATE

AKIRA HOSHIO, M.D., HIROYUKI MIYAKODA, M.D., MASAHARU FUKUKI, M.D.
JUNICHI YAMASAKI, M.D., HIROSHI KOTAKE, M.D.
AND HIROTO MASHIBA, M.D., FACC

The coronary artery response to ergonovine (EM) and nitrate of the proximal, middle and distal segments of the three major coronary artery branches and the main trunk was quantified in 67 patients without coronary spasm and in 69 patients with coronary spasm without significant organic stenosis. The changes in control diameter and diameter after EM administration compared to diameter after nitrate were used as the index of coronary artery tone. EM increased coronary artery tone regardless of the occurrence of coronary spasm (p<0.01). In all segments, basal coronary artery tone was greater in patients with spasm than in patients without spasm (p<0.01) in a way similar to the coronary responses to EM (p<0.01). In patients with spasm, both coronary artery tone after EM and basal coronary tone were greater in the spastic segments than in the nonspastic segments (p<0.01), which were greater than those in patients without spasm (p<0.01). Our data suggest that patients with spasm may have increased basal tone, and that coronary artery spasm may be based on increased coronary tone. Clinically, evaluation of the basal tone and response to EM in the entire coronary artery tree may be useful for predicting the presence of coronary artery spasm.

The causes of coronary artery spasm are still unknown, but the ergonovine (EM) provocative test is highly sensitive and specific for the detection of coronary spasm. However, it has some risks. If the presence of coronary spasm could be identified before or without the provocative test, its diagnosis would be safer.

Our previous study indicated that increased coronary artery tone of both the spastic and nonspastic segments was observed in patients with vasospastic angina, and might predict the occurrence of coronary spasm. However, in the study, the vasospastic angina group consisted only of patients with typical vasospastic angina, while patients with strongly suspected vasospastic angina and negative EM tests were excluded from the group.

The purpose of the present study was to quantify coronary artery responses to EM and nitrate in 136 consecutive patients without significant coronary artery stenosis, who were subjected to the EM provocative test.

METHODS

Patient selection: From March 1981 through April 1986, we surveyed 136 consecutive patients who were subjected to the EM provocative test during coronary angiography. One hundred and twenty pa-
tients had normal coronary arteries and 16 patients had minor fixed lesions with < 40% diameter reduction. Patients with myocardial infarction, hypertrophic cardiomyopathy or valvular disease were excluded. The patients were separated into two groups according to the results of the EM provocative test.

Group A consisted of 67 patients (41 men and 26 women, mean age 50 ± 9 years) who didn’t have coronary spasm during the EM provocative test. Two patients had typical rest angina, 8 arrhythmias or minor electrocardiographic abnormalities, and the remainder atypical chest pain.

Group B consisted of 69 patients (43 men and 26 women, mean age 55 ± 8 years) who had coronary spasm during the EM provocative test. 63 patients had rest angina and the remaining 6 had suspected clinical rest angina.

Catheterization procedure: Informed consent was obtained from each patient. Our procedure has been reported in detail previously. Briefly, coronary angiography was performed using the Sones technique. Pharmacologic therapy was withheld for at least 24h before cardiac catheterization. After coronary angiography was performed without premedication as a control, EM (0.05 to 0.20 mg) was administered into the ascending aorta. Coronary angiography was performed immediately if typical chest pain or ECG changes indicating myocardial ischemia occurred. In the absence of these symptoms after EM administration, coronary angiography was performed 4 min later. Additional EM (0.05 to 0.20 mg) was administered to patients who did not develop coronary spasm or chest pain after the initial dose of EM. After EM administration both coronary arteries were visualized, and either 0.33 mg nitroglycerin or 5 mg isosorbide dinitrate, which produces a maximal coronary vasodilation, was administered as a bolus injection into the ascending aorta. Coronary angiography was repeated 2–4 min after nitrate administration.

Analysis of coronary angiograms: The 35 mm coronary angiograms were reviewed on a Vanguard projector. The coronary artery diameters were measured in the proximal, middle and distal segments of the three major coronary artery branches, the left main trunk (LMT) and the spastic segments induced by EM. Specific locations measured in each coronary artery have been described in detail elsewhere. Coronary arteries that were inadequately opacified and segments that were overlapped by other structures were not analyzed. To minimize pincushion distortion, measurements were made near the center of the angiograms. Serial measurements were taken at end-diastole in the 30 right anterior oblique projection of the left coronary artery and the 60 left anterior oblique projection of the right coronary artery (RCA). The coronary artery diameters (in millimeters) were calculated with reference to the catheter diameter. The reproducibility of calculated actual diameters was good, with an intraobserver correlation of r = 0.93 and an interobserver correlation of r = 0.93 for 111 coronary artery segments. The percent coronary narrowing before and after EM was used to quantify the degree of coronary artery tone. The percent change in coronary artery diameter was calculated as follows:

\[
\text{Percent coronary narrowing before EM} = \frac{\text{Diameter after nitrate} - \text{Control diameter}}{\text{Diameter after nitrate}} \times 100 (\%)
\]

\[
\text{Percent coronary narrowing after EM} = \frac{\text{Diameter after nitrate} - \text{Diameter after EM}}{\text{Diameter after nitrate}} \times 100 (\%)
\]

A coronary narrowing of more than 50% was considered to represent coronary spasm.

Statistics: All grouped data were reported as mean values ± standard deviation. The t test was used to compare the values in the two groups, and multiple comparisons of the groups were performed by one-way analysis of variance with the Scheffé’s test. A probability (p) value of less than 0.05 was considered to be statistically significant.

RESULTS

In Group A, the mean dose of EM was 0.25 mg, and no patient had transient S-T segment elevation or/and depression during the EM provocative test.


<table>
<thead>
<tr>
<th></th>
<th>Proximal</th>
<th></th>
<th>Middle</th>
<th></th>
<th>Distal</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td><strong>Group A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>18±12</td>
<td>26±11*</td>
<td>16±12</td>
<td>26±11*</td>
<td>18±11</td>
<td>29±11*</td>
</tr>
<tr>
<td>LAD</td>
<td>13±11</td>
<td>21±12*</td>
<td>16±11</td>
<td>24±11*</td>
<td>15±13</td>
<td>24±11*</td>
</tr>
<tr>
<td>LCX</td>
<td>14±12</td>
<td>23±11*</td>
<td>16±14</td>
<td>27±11*</td>
<td>19±12</td>
<td>27±14*</td>
</tr>
<tr>
<td><strong>Group B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>24±13</td>
<td>45±21*</td>
<td>28±16</td>
<td>47±18*</td>
<td>29±13</td>
<td>45±20*</td>
</tr>
<tr>
<td>LAD</td>
<td>21±13</td>
<td>37±20*</td>
<td>26±12</td>
<td>39±16*</td>
<td>27±13</td>
<td>35±13*</td>
</tr>
<tr>
<td>LCX</td>
<td>26±13</td>
<td>38±17*</td>
<td>29±12</td>
<td>42±17*</td>
<td>25±14</td>
<td>41±17*</td>
</tr>
</tbody>
</table>

*; p<0.01 vs. before ergonovine administration; †; p<0.05
Values are mean values ± standard deviation
LAD=left anterior descending artery; LCX=left circumflex artery; RCA=right coronary artery

In Group B, the mean dose of EM was 0.20 mg, and this was less than that in Group A (p<0.01). Coronary artery spasm was observed in RCA in 45 patients, in LMT in 11, in the left anterior descending artery (LAD) in 26, in the left circumflex artery (LCX) in 33. Ten patients (14%) had transient S-T segment elevation with chest pain and spasm during the EM test.

**Relationship of coronary narrowings of the proximal, middle and distal segments (Table I)**

**Before EM:** In Group A, the percent coronary narrowings of the proximal, middle and distal segments in RCA and LAD were similar (p=NS), but in LCX, the value of the proximal segment was less than that of the distal segment (p<0.05). In Group B, the values of the proximal, middle and distal segments in RCA and LCX were similar (p=NS), but in LAD, the value of the proximal segment was less than that of the distal segment (p<0.05).

**After EM:** In both groups, the percent coronary narrowings of the proximal, middle and distal segments were similar (p=NS) in each coronary artery (RCA, LAD and LCX).

In both groups, the percent coronary narrowings of all segments were significantly greater after EM than before EM administration (p<0.01). Both before and after EM administration, the percent coronary narrowings of all segments were greater in Group B than in Group A (p<0.01).

**Relationship of the percent coronary narrowings before and after EM administration (Fig. 1)**

**Before EM:** The percent coronary narrowings of RCA, LMT, LAD, LCX were 17±12%, 10±8%, 15±12% and 16±13% in Group A, and 27±14%, 14±10%, 25±13% and 27±13% in Group B, respectively. In both groups, LMT values were less than the other values (p<0.05), while RCA, LAD and LCX values were similar (p=NS). All values were greater in Group B than in Group A (p<0.01).

**After EM:** The percent coronary narrowings of RCA, LMT, LAD, LCX were 27±11%, 13±9%, 23±11% and 26±12% in Group A, and 46±20%, 20±12%, 37±16% and 40±17% in Group B, respectively. In both groups, LMT values were less than the other values (p<0.01); and RCA values were greater than LAD (p<0.01), while LAD values were similar to LCX (p=NS). In Group A, RCA value was similar to LCX (p=NS), while in Group B, RCA value was greater than LCX (p<0.05). All values were greater in Group B than in Group A (p<0.01).

In both groups, all values were greater after EM than before EM administration.
Fig. 1. The percent coronary narrowings of each coronary artery before (upper panel) and after (lower panel) ergonovine (EM) administration.
LAD = left anterior descending artery; LCX = left circumflex artery; LMT = left main trunk; NS = not significant; RCA = right coronary artery.

\( p < 0.01 \).

Correlation between the percent maximal coronary narrowing after EM and mean coronary narrowing before or after EM administration in each patient (Fig. 2)
The percent mean coronary narrowing represents the mean value of all segments.
(10 segments) measured in each patient, and the percent maximal coronary narrowing represents the value in the maximal vasoconstrictive segment induced by EM administration.

There were significant (p<0.01) correlations between the percent maximal coronary narrowing after EM and the percent mean coronary narrowings in each patient before (r=0.66) or after (r=0.82) EM administration. The greater the percent mean coronary narrowing in each patient before and after EM administration, the greater the percent maximal coronary narrowing after EM administration.

*Figure 2. Correlations between the percent maximal coronary narrowing after ergonovine (EM) administration and the percent mean coronary narrowing before (upper panel) and after (lower panel) EM administration.*
Effects of EM and nitrate on diameter of the spastic and nonspastic segments (Fig. 3)

The percent coronary narrowing before EM administration in the spastic segments (n=169), nonspastic segments (n=479) and the combined segments (n=656) in Group A was 36±11%, 21±12% and 15±12%, respectively. The percent coronary narrowing after EM administration in those segments was 62±13%, 31±12% and 24±12%, respectively. The percent coronary narrowings before and after EM administration were greater in the spastic segments than in the nonspastic segments (p<0.01), which were greater than those in Group A (p<0.01).

DISCUSSION

Dilatation of coronary arteries induced by nitrate is observed during coronary angiography, however different responses in large and small coronary arteries to nitrate have been observed by several investigators in patients during coronary angiography or in experimental models. Some investigators have reported that the effect of nitrate on the large coronary artery was greater than on the small coronary artery. In a study by Harder et al., nitroglycerin selectively blocked the action potential in large (diameter>1.0 mm) rather than small coronary arteries (diameter<0.5 mm). Other investigators have reported that nitrate has a greater effect on small coronary arteries. Feldman et al. reported that the smaller the coronary diameter before nitroglycerin, the greater the relative dilatation after nitroglycerin, the dilatation not being related to the site of coronary angiography. Simonetti et al. examining responses to isosorbide dinitrate, suggested that the reason for these different responses in arteries of varying sizes with similar anatomic structure and physiologic significance may be the higher resting tone or higher sensitivity to coronary vasodilators, or both, of small coronary arteries compared with large coronary arteries. The present study showed that the percent coronary narrowings before EM administration, namely, coronary vasodilation induced by nitrate, were not related to location (proximal, middle and distal segments) in each coronary artery, and that its LMT value was less than RCA, LAD and LCX values. However, the value of the distal segment was greater than that of the proximal segment in LCX of Group A and LAD of Group B, so if the distal segment had been measured at the site of smaller diameter, the percent coronary narrowing before EM administration might have been greater in the distal segment than in the proximal segment.

Furthermore, our data showed that the percent coronary narrowing after EM administration was greater in RCA than in LAD, and the LMT value was less than the other values. Higgins et al. reported that most instances of documented coronary spasm involved RCA, and that ST segment elevations during anginal attack had been observed mostly in the inferior leads of patients with variant angina and "normal" coronary arteries. Actually, our data showed that coronary
spasm in RCA was observed in 45 of the 69 patients (65%). Chahine et al.\textsuperscript{18} suggested that a difference in innervation may make RCA more prone to spasm than other arteries.

It is well known that EM induces coronary spasm at sites where spontaneous spasm has been observed during coronary angiography.\textsuperscript{1,2,5} In both groups, the percent coronary narrowings of all segments were significantly greater after EM than before EM administration. Consequently, EM may be a vasoconstrictor which increases coronary artery tone regardless of the occurrence of coronary spasm. This finding may account for the observation of Schmartz et al.\textsuperscript{19} that a transient increase in coronary vascular resistance and a decrease in coronary blood flow occurred in response to EM administration in patients with normal coronary arteries and atypical chest pain.

Freedman et al.\textsuperscript{20} reported that normal segments of arteries adjacent to the site of spasm and arteries without spasm in patients with positive EM tests showed no greater sensitivity to EM than arteries of control patients, and that coronary spasm resulted from the hypersensitivity of coronary arteries to vasoconstrictors, which was localized at the sites of the atherosclerotic lesions. Hill et al.\textsuperscript{21} reported that a localized segment in patients with variant angina may have increased basal tone reflected by a smaller coronary diameter in the control angiogram. In contrast to the observations of Freedman et al and Hill et al, our findings showed that the greater the percent mean coronary narrowing in each patient was before (r=0.66, p<0.01) and after (r=0.82, p<0.01) EM administration, the greater was the percent maximal coronary narrowing after EM administration. Additionally, Freedman et al.\textsuperscript{20} proposed that if a similar dose of EM had been given to patients with vasospastic angina, the small increase in sensitivity of the uninvolved segments might have been significant. The percent coronary narrowing before EM administration was significantly greater in the nonspastic segments than in patients without spasm. These findings suggest that basal tone in patients with vasospastic angina may be increased in comparison with that of control patients, and that coronary spasm may be based on an increase of coronary artery tone. In previous studies,\textsuperscript{7,22} basal coronary tone in the nonspastic segments was higher than that in patients without ischemic heart disease. According to Epstein et al.\textsuperscript{23} a mild to moderate increase in coronary artery tone, either in a “normal” artery or in one with an existing lesion, could predispose coronary artery spasm. Spontaneous coronary spasm during coronary angiography has been documented by various investigators,\textsuperscript{17,24,25} and some investigators\textsuperscript{18,26} have indicated that coronary spasm during coronary angiography may be more common than generally recognized.

MacAlpin\textsuperscript{27} suggested that coronary spasm is the result of physiologic vasomotion at the site of organic stenosis. In agreement with this hypothesis, namely geometric theory, we speculated that the change in generalized coronary tone may be part of the cause of coronary spasm. However, the increase of generalized coronary tone is abnormal beyond the limits of physiologic tone. On the other hand, as shown in Fig. 2, in the patients with dynamic total or subtotal obstruction induced by EM, the percent mean coronary narrowings before and after EM administration in each patient were of fairly varying range. Coronary responses to EM and nitrate were greater in the spastic segments than in the nonspastic segments (Fig. 3). Consequently, we speculated that the occurrence of coronary spasm required a localized disorder in addition to increased basal tone.

The EM provocative test is highly sensitive and specific for the detection of coronary artery spasm\textsuperscript{1,4} but some risks exist.\textsuperscript{4–6} It is possible that a larger dose of EM may produce a higher incidence of myocardial ischemia.\textsuperscript{3} Clinically, patients with increased basal tone should be administered a smaller dose of EM to avoid some complications due to spasm. When it is difficult to introduce the catheter into the orifice of the coronary artery and the provocative test for spasm is not recommended, such as with coronary spasm in multiple organic stenosis, evaluation of basal tone in the entire coronary artery tree may be useful for predicting the presence of coronary artery spasm before or without the provocative test.

REFERENCES


