CASE REPORTS

Action of Intracoronary Nitroglycerin in Refractory Coronary Artery Spasm

CARL J. PEpine, M.D., ROBERT L. FELDMAN, M.D., AND C. RICHARD CONTI, M.D.

SUMMARY Coronary artery spasm usually responds to sublingual nitroglycerin. This report describes four patients with variant angina and one patient with rest angina who had coronary spasm that was refractory to sublingual or i.v. nitroglycerin. In four patients, spasm occurred spontaneously and in one patient after 0.05 mg of ergonovine. In each case, 25–100 µg of intracoronary nitroglycerin promptly (30–45 seconds) resulted in reopacification of the vessel involved in spasm and resolution of evidence for ischemia. Thus, intracoronary nitroglycerin can reverse coronary artery spasm that does not respond to systemic nitroglycerin administration.

PATIENTS with coronary artery spasm usually respond to sublingual nitroglycerin (NTG), but occasionally, sublingual NTG is not completely effective in controlling manifestations of acute ischemia. Intravenous NTG may be more effective than sublingual NTG in promptly controlling coronary spasm and ischemia-related findings. Intracoronary NTG should provide an even higher concentration of NTG at the site of coronary arterial dilation. This route of administration, however, has had only limited use. Intracoronary NTG reverses obstruction in some patients with acute myocardial infarction and refractory ergonovine-induced spasm. Clearly, the role of intracoronary NTG in coronary spasm needs further study.

We report five patients with coronary artery spasm unresponsive to sublingual or i.v. NTG. In four of five cases, spasm occurred spontaneously. In all five cases, evidence for myocardial ischemia promptly resolved and reopacification of the vessel involved in spasm occurred after intracoronary NTG.

Methods

Patients

Five patients were evaluated to further define the basis for chest pain. All developed coronary spasm during catheterization that was unresponsive to sublingual or i.v. NTG.

Catheterization Studies

Without premedication, cardiac catheterization was performed with a #8 Sones catheter using techniques described elsewhere. Narrowings reported represent diameter reduction. No patient took calcium antagonists at the time of study. Sublingual NTG was given after crushing 0.4-mg tablets (Lilly). Companion tablets were found active in other patients. For intracoronary use, fresh NTG solution (Marion Laboratories) in saline (50 µg/ml) was made daily and handled in glass and stainless steel needles to minimize sorption.

Case Reports

Patient 1

A 56-year-old man was resuscitated after an episode of rest pain associated with ventricular fibrillation. He had no permanent sequelae, normal left ventricular (LV) function and coronary artery disease involving four vessels (table 1). Fifteen minutes after angiography, he had angina and ST elevation. The left coronary artery (LCA) was unchanged, but the right coronary artery (RCA) was totally occluded at the previously observed narrowing. Sublingual NTG given over 20 minutes did not influence symptoms, ST changes, or the RCA angiogram as systolic pressure decreased from 120 to 80 mm Hg. NTG, 25 µg, injected into the RCA, resulted in prompt reopacification of the entire vessel, as ST elevation and angina cleared and systolic pressure increased to 110 mm Hg. This sequence of events occurred six times at 20–30-minute intervals and could not be prevented or reversed by injecting NTG either intravenously or into the LCA and saline into the RCA. Symptoms persisted until NTG was again given into the RCA. When intraaortic balloon counterpulsation was established, episodes did not recur. After 24 hours, he had only minimal, nonspecific ST changes and no symptoms or CK-MB elevation as topical and i.v. NTG were continued. When counterpulsation was transiently stopped, symptoms and ST elevation occurred within 5 minutes. Bypass grafts were constructed to the obtuse marginal branch, diagonal branch and RCA. He is asymptomatic without ST shifts and has three patent grafts and normal LV wall motion.

Patient 2

A 44-year-old man had had episodes of rest angina, inferior ST elevation and premature ventricular complexes relieved by NTG for 2 years. He showed no evidence of myocardial necrosis and was taking pro-
pranolol. LV pressure was 136/17 mm Hg, with minimal inferior hypokinesis. He had RCA and circumflex (LCx) narrowings (table 1). After 0.05 mg of i.v. ergonovine,\textsuperscript{18} angina, ST- and T-wave changes and total RCA occlusion occurred. Sublingual NTG did not change his clinical or RCA findings after 8 minutes, but systolic pressure decreased from 136 to 90 mm Hg. One hundred micrograms of NTG injected into the RCA promptly reversed the occlusion, chest pain and ST changes. NTG paste was continued, but 48 hours later, episodes of pain and ST elevation recurred. Bypass grafts were constructed to the RCA and LCx. His postoperative course was unremarkable, and he is asymptomatic.

Patient 3

A 60-year-old man had angina usually occurring at rest, but sometimes provoked by exercise and relieved by NTG. He was taking propranolol. His LV pressure was 130/17 mm Hg, the anterior descending (LAD) was 80% narrowed and the RCA totally occluded but filled distally from RCA collaterals (table 1, fig. 1A). Five minutes after angiography, severe angina, increased LV pressure (160/30 mm Hg) and peaked T waves evolved. The LAD became totally occluded, without collateral filling. Intravenous NTG decreased the pain minimally and LV pressure to 120/20 mm Hg, but total LAD occlusion persisted (fig. 1B). NTG was injected into the LCA and did not relieve symptoms, LV pressure or the total LAD occlusion. NTG, 50 \( \mu \)g, was then injected into the RCA. Within 45 seconds, the patient noted almost complete pain relief, and LV pressure was 130/15 mm Hg. The mid-distal LAD was not visualized on LCA angiography, but RCA injection filled the entire RCA from large epicardial collaterals (figs. 1C and D). Serial CK-MB determinations and ECGs were unchanged. He has improved with nifedipine.

### Table 1. Summary of Pertinent Clinical and Angiographic Findings

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Spasm</th>
<th>ECG Baseline</th>
<th>Spasm</th>
<th>ECG Coronary angiogram (% narrowing)</th>
<th>NTG given during spasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56</td>
<td>Spontaneous</td>
<td>ST-T-wave changes</td>
<td>ST\textsuperscript{1} inferiorly (at another time, VF)</td>
<td>70% LMCA</td>
<td>Sublingual 2.0 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50% LAD-DI</td>
<td>I.V. 300 ( \mu )g</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100% LCx</td>
<td>IC-RCA 25–100 ( \mu )g</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60% RCA</td>
<td>LCA 100 ( \mu )g</td>
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<tr>
<td>2</td>
<td>44</td>
<td>Ergonovine-induced</td>
<td>Normal</td>
<td>ST\textsuperscript{1} inferiorly with PVCs.</td>
<td>Minor irreg LAD</td>
<td>Sublingual 0.8 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50% LCx</td>
<td>IC-RCA 100 ( \mu )g</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>70% RCA</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>Spontaneous</td>
<td>Non-specific ST-T-wave changes</td>
<td>ST\textsuperscript{1} anteriorly with PVCs (at other times peaked T waves)</td>
<td>80% LAD</td>
<td>I.V. 200 ( \mu )g</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70% RCA</td>
<td>IC-LCA 100 ( \mu )g</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100% LAD</td>
<td>IC-RCA 50 ( \mu )g</td>
</tr>
<tr>
<td>4</td>
<td>64</td>
<td>Spontaneous</td>
<td>Non-specific ST-T-wave changes</td>
<td>ST\textsuperscript{1} anteriorly (at other times ST\textsuperscript{1})</td>
<td>Normal</td>
<td>Sublingual 0.4 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70–95% LAD</td>
<td>IC-LCA 100 ( \mu )g</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>Spontaneous</td>
<td>Non-specific ST-T-wave changes</td>
<td>SVBG-LCx widely patent</td>
<td>Native LAD and LCx 100% proximal</td>
<td>Sublingual 0.4 mg</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>SVBG-LAD widely patent</td>
<td>LAD 99% distal to SVBG</td>
</tr>
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<td></td>
<td>SVBG-LCx widely patent</td>
<td>I.C.-SVBG-LAD</td>
</tr>
</tbody>
</table>

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Abbreviations: VF = ventricular fibrillation; PVC = premature ventricular complex; LMCA = left main coronary artery; LAD = left anterior descending coronary artery; DI = diagonal artery; LCx = left circumflex coronary artery; RCA = right coronary artery; SVBG = saphenous vein bypass graft; LCA = left coronary artery; I.C. = intracoronary; I.V. = intravenous; Response = reopacification of artery with occlusion with relief of angina and ST shifts (when present).
After 100 μg of NTG were injected into the LCA, chest discomfort, ST depression and LAD narrowing resolved. He is asymptomatic with nifedipine.

**Patient 5**

A 45-year-old man, who had LAD and LCx bypass graft surgery 3 years ago for effort angina, recently noted rest pain episodes of increasing frequency. Effort tolerance was good. LV pressure was 130/6 mm Hg, with minimal anterolateral hypokinesis. The LAD and LCx were totally occluded proximally and filled by patent bypass grafts (table 1). The mid-LAD was subtotally occluded 0.5 cm distal to the bypass graft anastomosis. The occlusion persisted after sublingual NTG, 0.4 mg (fig. 2A), given for spontaneous angina. There was excellent retrograde LAD filling but poor opacification beyond the subtotal occlusion. After 100 μg of NTG were injected into the LAD bypass graft, the subtotal occlusion disappeared with good distal opacification (fig. 2B) without a change in blood pressure.

**Discussion**

Five patients with transient myocardial ischemia due to coronary spasm were unresponsive to systemic NTG administration. Each case responded to intracoronary NTG. Spasm occurred in the RCA in patients 1 and 2 and in the LAD in patients 3-5. In four patients, spasm was spontaneous and in patient 2 it occurred after ergonovine. In patients 1-3, previously patent coronary arteries, with what appeared to be physiologically important atherosclerotic narrowings, were not visualized during angina. In patient 4, spasm occurred in a vessel that appeared normal angiographically and in patient 5 in a normally appearing vessel filled by a patent vein graft. Although these occlusions persisted after systemic NTG, relatively small doses (25–100 μg) of intracoronary NTG resulted in prompt relief of findings of ischemia and visualization of the occluded artery. In patients 1 and 2, this resulted from reversal of spasm at a hemodynamically important atherosclerotic RCA obstruction. In the third case, direct LCA injection of NTG did not resolve the presumed LAD spasm. NTG was probably delivered to the low-resistance circumflex system and did not reach the LAD site of spasm. RCA injection of NTG, however, resulted in prompt
reopacification of the LAD distal to the site of spasm with resolution of angina and ischemic ECG changes. The RCA injection of NTG appeared to dilate an RCA-to-LAD collateral network. So hemodynamic conditions now favored flow to the mid-distal LAD from the RCA collaterals instead of through the series of proximal LAD narrowings. Spasm involving angiographically normal portions of the LAD reversed when NTG was injected directly into the LCA in patient 4 and through a vein graft in patient 5.

The mechanism responsible for failure to respond to systemic NTG is open to speculation. Systemic NTG could have contributed to persistent spasm. Vasodilation due to systemic NTG reduces LV wall tension, and thus, oxygen demand. Reflex changes mediated by autonomic stimulation occur secondary to pressure reduction. But parasympathetic or sympathetic stimulation may evoke coronary spasm. Systemic NTG could also increase flow in LCA branches not involved with spasm. In animals, increases in LCA flow trigger reflex cardiac sympathetic discharge. The hypothesis that NTG-induced increases in coronary flow evoke autonomic discharges that cause coronary constriction could explain other coronary constriction responses seen after sublingual NTG. Finally, blood flow reduction during spasm could simply prevent delivery of NTG to the vaso vasmor and smooth muscle at the spasm site.

Recently, in two patients with ergonovine-evoked coronary spasm unresponsive to sublingual or i.v. NTG, intracoronary NTG reversed the spasm. Our patient 2 is the third reported case with ergonovine-evoked spasm unresponsive to sublingual NTG but responsive to intracoronary NTG. Each case had spasm involving the RCA. Unlike the other two cases, our patient received only 0.05 mg of ergonovine. Ergonovine must be used with caution. We believe that this test should be limited to the catheterization laboratory, where intracoronary NTG can be given.

The findings in our patients support other claims relative to the value of intracoronary NTG in control of refractory coronary spasm, and emphasize the action of intracoronary NTG to reverse refractory spasm occurring spontaneously or evoked by ergonovine. Reversal of spasm occurred promptly after intracoronary NTG even when spasm did not respond to systemic NTG. More studies are needed to document the safety and effectiveness of intracoronary NTG.

When coronary spasm occurs during catheterization, intracoronary NTG can promptly reverse spasm without inducing hypotension.

References

Action of intracoronary nitroglycerin in refractory coronary artery spasm.
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