Coronary Hyperemic Dose Responses of Intracoronary Sodium Nitroprusside

Walter A. Parham, MD; Andre Bouhasin, MD; Jeffrey P. Ciaramita, MD; Souheil Khoukaz, MD; Steven C. Herrmann, MD; Morton J. Kern, MD

Background—Sodium nitroprusside is one of several agents considered effective for treating the no-reflow phenomenon during acute coronary interventions. However, the coronary hyperemic dose responses and systemic hemodynamic effects of intracoronary nitroprusside have yet to be determined in humans. The purpose of this study was to compare the hyperemic and hemodynamic responses of intracoronary nitroprusside to intracoronary adenosine in patients during cardiac catheterization with angiographically normal anterior descending arteries.

Methods and Results—In 21 patients, coronary blood flow velocity (0.014-inch Doppler flow wire), heart rate, and blood pressure were measured in unobstructed left anterior descending coronary arteries at rest, after intracoronary adenosine (30- to 50-μg boluses), and after 3 serial doses (0.3-, 0.6-, and 0.9-μg/kg boluses) of intracoronary nitroprusside. Coronary reserve was calculated as hyperemia/basal coronary flow velocity. In an additional 9 patients with intermediate stenoses (53±7%), 14 fractional flow reserve (FFR) measurements (using 0.014-inch pressure wire) were performed with both intracoronary adenosine and nitroprusside (0.6 μg/kg). Intracoronary nitroprusside produced equivalent coronary hyperemia with a longer duration (≈25%) compared with intracoronary adenosine. Intracoronary nitroprusside (0.9 μg/kg) decreased systolic blood pressure by <20%, with minimal change in heart rate, whereas intracoronary adenosine had no effect on these parameters. FFR measurements with intracoronary nitroprusside were identical to those obtained with intracoronary adenosine (r=0.97).

Conclusions—Compared with adenosine, intracoronary nitroprusside produces an equivalent but more prolonged coronary hyperemic response in normal coronary arteries. Intracoronary nitroprusside, in doses commonly used for the treatment of the no-reflow phenomenon, can produce sustained coronary hyperemia without detrimental systemic hemodynamics. On the basis of FFR measurements compared with adenosine, sodium nitroprusside also appears to be a suitable hyperemic stimulus for coronary physiological measurements. (Circulation. 2004;109:1236-1243.)

Key Words: blood flow ▪ hemodynamics ▪ circulation

The no-reflow phenomenon complicates ~0.6% of percutaneous coronary interventions (PCI), the treatment of which relies, in part, on inducing coronary hyperemia.1–3 The most common intracoronary agents used to induce hyperemia include adenosine, diltiazem, verapamil, papaverine, nitroglycerin, epinephrine, nicardipine, and sodium nitroprusside.4–10 The coronary hyperemic and systemic hemodynamic effects vary among and between these pharmacological agents. Intracoronary (IC) nitroprusside (NTP) has recently gained favor for the treatment of the no-reflow phenomenon complicating PCI.11 To date, however, no systematic studies have been performed defining the specific coronary and systemic hemodynamic responses induced by IC NTP in patients undergoing cardiac catheterization.

The purpose of the present investigation was to examine the dose-related responses of IC NTP compared with IC adenosine in angiographically normal anterior descending arteries. We tested the hypothesis that IC NTP would produce similar yet sustained coronary hyperemia compared with adenosine without significant adverse systemic hemodynamic effects. These data would define the dose-related coronary responses of IC NTP and its potential as an additional agent for use during physiological assessment of coronary stenosis, in which there is a requirement for a sustained coronary hyperemia.

Methods

Patient Population
Twenty-one patients undergoing diagnostic cardiac catheterization for chest pain syndromes were enrolled in the research study to compare the coronary and systemic hemodynamic changes induced by IC adenosine and IC NTP. An additional 9 patients were enrolled to compare fractional flow reserve (FFR) determinations made with each agent. The patients were included if they had at least 2 angiographically normal coronary arteries and stable chest pain...
syndromes. The patients were excluded if they had a left ventricular ejection fraction <35%, renal failure, significant valvular heart disease, unstable angina, recent myocardial infarction (within 4 days), or had congestive heart failure. The institutional review board approved the study.

Catheterization Procedures
After diagnostic catheterization and coronary angiography performed by the standard Judkins percutaneous femoral technique, 21 patients were given a 40- to 60-U/kg intravenous bolus of heparin. A 6F guiding catheter was positioned in the left coronary artery. A 0.014-inch Doppler flow wire (Jomed Inc) was then positioned in the mid left anterior descending (LAD) coronary artery to measure coronary flow velocity, as previously described.13 Heart rate, blood pressure, and coronary flow velocity were measured at baseline and after an intracoronary bolus (30 to 50 µg) of adenosine. These measurements were performed in duplicate. After returning to a new baseline, IC NTP was then administered in 3 serial doses of 0.3, 0.6, and 0.9 µg/kg, with a return to baseline between each dose. Continuous recordings of flow velocity, systemic blood pressure, and heart rate were obtained (Figure 1).

In an additional 9 patients with intermediately severe coronary narrowings, 14 FFR measurements were made with a 0.014-inch pressure wire (Radi Medical Inc). FFR was calculated as distal coronary/aortic pressure at the nadir of distal pressure after hyperemia.13 Intracoronary adenosine was administered in the standard bolus fashion to calculate the FFR, followed by a repeat FFR determination with a single 0.6-µg/kg IC NTP bolus.

Coronary Angiographic Method
Coronary arteriography was performed and analyzed by means of a quantitative angiographic method (Philips DCI-DCA) for diameter of the reference vessel 5 mm distal to the site of the Doppler guide wire. In 5 patients, angiography of an unobstructed LAD was performed at rest and again 30 to 60 seconds after 0.6-µg/kg bolus NTP. Volumetric flow was computed as cross-sectional area times average peak velocity. Coronary stenosis was assessed both visually and by quantitative coronary angiography by 2 independent reviewers. The interobserver and intraobserver variabilities of quantitative angiography in our laboratory were 5% and 10%, respectively.

Coronary Flow Reserve and Resistance and FFR Calculations
Coronary flow reserve was calculated as peak hyperemic average peak velocity divided by basal average peak velocity. Coronary resistance was calculated by using the estimated volumetric flow and aortic pressure in 10 patients without LAD obstruction. Fractional flow reserve was calculated as the ratio of distal coronary pressure divided by aortic guiding pressure obtained at minimal distal pressure, which was assumed to be maximal hyperemia for each of the 2 agents studied.

Statistical Analysis
A statistical analysis was made using Student’s paired and unpaired t tests. ANOVA was used for multiple comparisons. Probability values of <0.05 were considered statistically significant. Data are presented as mean±SD.

Results
The clinical characteristics of the 21 patients with flow responses and 9 patients with FFR data are shown in Table 1. There were more men than women; 33% had diabetes, 53% had hypertension, and 80% had 2 or more risk factors for coronary artery disease.

Systemic Hemodynamics
Intracoronary adenosine did not change heart rate or systolic blood pressure (Table 2). For the 0.3-, 0.6-, and 0.9-µg/kg doses, IC NTP decreased systolic blood pressure 15%, 18%, and 20%, respectively (P<0.003 compared with adenosine), and diastolic blood pressure 0%, 12%, and 16%, respectively (P<0.001 compared with adenosine) (Figure 2). Heart rate increased 4 bpm with IC NTP (P<0.0002) (Table 2). The time to maximal systemic blood pressure change was similar for the 3 dosages (Figure 3). However, the time to return to baseline blood pressure was longer for the 0.6- and 0.9-µg/kg NTP dosages (53±25 seconds for 0.6 µg and 49±29 seconds for 0.9 µg IC NTP, both P<0.05) (Figure 3 and Table 2).

Coronary Hyperemia, Resistance, and Reserve
Increases in average peak velocity (APV) and coronary flow reserve were similar between IC adenosine and NTP. Maximal APV was equivalent to adenosine with all 3 doses of NTP (Figures 4 and 5). The time to peak APV was similar between adenosine and NTP (Figure 6). Compared with adenosine, IC NTP produced a more sustained hyperemic response (Figure 6). For the 3 doses of IC NTP the time to return to baseline from peak coronary hyperemia was 49±14, 56±23, and 64±23 seconds (all P<0.05 versus adenosine, Table 2). NTP did not dilate the coronary artery, as assessed by quantitative coronary angiography. Peak coronary resistance was similarly affected by adenosine and NTP (Table 2).

FFR and NTP
To test the equivalency of IC NTP compared with adenosine-induced coronary hyperemia for intermediate coronary lesion assessment, 14 FFR measurements were made, using both medications. Hemodynamic data, including heart rate, systolic blood pressure, diastolic blood pressure, mean aortic pressure, and mean distal coronary pressure, were obtained at baseline and peak hyperemia (Table 3). IC NTP increased heart rate 3 bpm over baseline, with a 17% and 24% fall in systolic and diastolic pressure, respectively (P<0.05), whereas adenosine modestly reduced diastolic pressure (P<0.003). When compared with adenosine, IC NTP significantly decreased systolic and diastolic pressures (P<0.01). Despite the differences in the hemodynamic effects of these
agents, there were no differences in FFR calculations, with an excellent correlation coefficient achieved ($r = 0.97$, Figure 7).

Discussion
This study shows that maximal coronary hyperemia, equivalent to that induced by intracoronary adenosine, can be achieved with IC NTP in doses of 0.3, 0.6, and 0.9 µg/kg, with only a modest decrease in systolic pressure and without significant tachycardia. The duration of coronary hyperemia is ≈25% greater with IC NTP than adenosine. When used for coronary lesion assessment, IC NTP yields identical FFR values compared with those obtained with adenosine.

Comparison With Other Pharmacological Hyperemic Stimuli
Coronary hyperemia induced by NTP appears to be significantly more potent than that of IC calcium channel blockers. Rossen et al$^{14}$ reported that the administration of a 125- or 250-µg/kg bolus of intravenous diltiazem followed by a 5-µg/kg per minute infusion in 8 patients reduced heart rate (77±18 to 72±17 bpm, $P<0.005$) and mean arterial pressure (96±11 to 86±15 mm Hg, $P<0.005$) while decreasing coronary flow reserve from 3.9±1.2 to 3.6±1.1 ($P<0.01$).$^5$ In 10 patients treated with IC diltiazem, in dosages of 150 to 600 µg given as bolus infusions, mean arterial pressure was unchanged. The heart rate was maintained constant by atrial pacing. Coronary flow reserve was

### TABLE 1. Patient Characteristics

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<th>Age, y</th>
<th>Sex</th>
<th>Weight, kg</th>
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<th>LVEDP, mm Hg</th>
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</table>

Mean 55 ... 82 53 50 15
SD 13 ... 18 7 7 4

M indicates male; F, female; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; and LVEDP, left ventricular end-diastolic pressure.
again unchanged (3.8 ± 0.9) after IC diltiazem. Diltiazem had only a minimal effect on APV and did not influence coronary flow reserve, and the diltiazem-induced attenuation of maximal coronary dilatation probably was not a mechanism responsible for the antiischemic effects of this calcium channel blocker. Despite the limited effects on coronary blood flow, the ability to produce epicardial vasodilation and blunt coronary vasospasm without adversely altering coronary flow reserve made IC calcium channel blockers the favored agents for the treatment of the no-reflow phenomenon.15–21 Fugit et al15 examined IC nicardipine, diltiazem, and verapamil to define their effects on coronary blood flow velocity in humans. IC nicardipine (200 μg), diltiazem (1 mg), and verapamil (200 μg) were serially administered in a randomized, double-blinded fashion in minimally diseased

<table>
<thead>
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<th>TABLE 2. Systemic and Coronary Hemodynamics Data</th>
<th>ADENO 1</th>
<th>ADENO 2</th>
<th>NTP 1</th>
<th>NTP 2</th>
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<td>57±15</td>
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<td>72±15</td>
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<td>Peak hyperemia</td>
<td>75±18</td>
<td>70±12</td>
<td>73±15</td>
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ADENO 1 indicates 30 μg IC adenosine; ADENO 2, 50 μg IC adenosine; NTP 1, 0.3 μg/kg IC nitroprusside; NTP 2, 0.6 μg/kg IC nitroprusside; NTP 3, 0.9 μg/kg IC nitroprusside.

Coronary resistance, mm Hg/mL per minute; units of coronary resistance, mL·min⁻¹·mm Hg⁻¹.

*P<0.05 vs ADENO 1.
LAD and circumflex arteries in 9 patients. Epicardial coronary diameter was determined by quantitative coronary angiography, and coronary blood flow velocity was measured with a Doppler guide wire. Nicardipine increased coronary blood flow velocity with a more prolonged (20%) duration compared with diltiazem and verapamil without affecting coronary diameter. Peak coronary flow velocity was increased $123\pm 60\%$ for nicardipine, $99\pm 66\%$ for diltiazem, and $69\pm 27\%$ for verapamil. Nicardipine had a longer duration of action, with 50% of its peak effect still being present at $5\pm 2$ minutes after dosing, compared with $2.7\pm 1.3$ minutes for diltiazem and $1.8\pm 0.7$ minutes for verapamil (all $P<0.05$). The hyperemic effect at 7 minutes was 75% of maximal blood flow for nicardipine and $<15\%$ for diltiazem and verapamil. No statistically significant differences were noted between the 3 medications with regard to changes in heart rate or arterial pressure. Two patients who received diltiazem, however, had transient type 1 second-degree atrioventricular block. This study suggested that compared with diltiazem and verapamil, nicardipine offered more potent and prolonged vasodilation with less risk of serious systemic side effects. None of these agents were tested against IC adenosine or nitroprusside. In this study, both adenosine and NTP hyperemia greatly exceeded that reported with any of the above calcium channel blockers.

Nitrovasodilators: NTP Versus NTG
Using xenon-133 washout techniques, Mann et al studied regional myocardial blood flow in 25 patients with coronary artery disease, comparing NTP and nitroglycerin (NTG). In patients with normal coronary arteries, regional myocardial blood flow was unchanged after intravenous nitroprusside infusion but significantly decreased in patients with coronary disease with or without high-grade collateral vessels. In contrast, sublingual nitroglycerin decreased regional myocardial blood flow in normal coronary arteries but increased...
regional myocardial blood flow in patients with coronary artery disease with high-grade collaterals. Mean arterial pressure and rate-pressure product were comparable with both agents. Nitroprusside was postulated to affect resistance vessels as opposed to conductance vessels, thereby leading to redistribution of coronary blood flow away from ischemic zones by a coronary steal phenomenon and subsequently inducing myocardial ischemia, effects not seen with nitroglycerin. The effects of NTP on resistance vessels were similar to adenosine. No comparison with IC NTG was made. It was also of interest that both IV NTG and NTP affected epicardial vasodilation to a similar degree, \(^{23}\) a finding not duplicated by IC drug administration.

Feldman et al\(^{24}\) also compared coronary hemodynamic effects of NTP and NTG in 9 patients with severe LAD coronary artery occlusions that were filled by collaterals. Intravenous nitroprusside in doses averaging 44 \(\mu\)g/min (range, 19 to 76 \(\mu\)g/min) and NTG (average dose, 556 \(\mu\)g; range, 400 to 1200 \(\mu\)g/min) produced similar changes in heart rate during both control and drug periods (for NTP and NTG, 75±17 and 74±19 bpm, respectively). NTP and NTG decreased aortic pressure equivalently 10% to 15% (95±16 and 93±13 mm Hg, respectively, \(P<0.05\) compared with control values). Great cardiac vein flow as a measure of LAD flow was also unchanged after NTP (70±44 to 72±4 mL/min) and NTG (71±43 to 72±40 mL/min, \(P=NS\)), with similar changes in coronary resistance for both agents. Thus, compared with NTG, NTP produced similar degrees of systemic arterial dilation with equally beneficial but minimal coronary hemodynamic effects.

In concert with Doppler flow velocity data, IC NTP increases angiographic flow velocity. Hillegass et al\(^{11}\) examined TIMI grade flow and TIMI frame count in 19 consecutive patients undergoing PCI complicated by no- or slow-reflow who were treated with IC NTP. Patients were given 2.2±1.6 doses of 207±178 \(\mu\)g of IC NTP (median, 200 \(\mu\)g)
Mechanisms of NTP-Induced Hyperemia
Nitroprusside relaxes arterial and venous smooth muscle without effects on other types of smooth muscle or myocardial contractility. Vasodilatory actions of NTP may occur, in part through interactions with the sympathetic nervous system, but are not dependent on any specific adrenergic receptor or ganglion. Because nitroprusside directly affects vascular smooth muscle, vasodilatation of diverse vascular beds occurs to similar degrees. Therefore, regional distribution of blood flow is little affected by nitroprusside in contrast to the response of drugs acting through sympathetic blockade of either α- or β-receptors. Nitroprusside is effective at inducing hyperemia as the result of its ability to preferentially vasodilate the coronary microcirculation. It is postulated that the main mechanism of action of nitroprusside is mediated through the genesis of nitric oxide that subsequently produces direct smooth muscle vasodilatation.

Limitations
Although this study is limited by a relatively small sample size, consistent physiological responses were observed. The dose responses of IC NTP and adenosine were studied serially, and the order of administration was not randomized. Because of the rapid and complete metabolism of adenosine, there is only a remote possibility of drug interaction from a preceding bolus. All hemodynamics returned to baseline before the next drug or dose was given. Adenosine combined with NTP was not examined; thus, we cannot comment on whether this combination would have produced greater hyperemia or more hypotension than when either agent was given alone. For the FFR measurements, we tested only the intermediate dose of nitroprusside (0.6 μg/kg), the dose with maximal hyperemia, and only a modest reduction of arterial pressure. A higher dose may have produced different hemodynamic responses but without effect on maximal hyperemia, which was similar for all 3 doses. Finally, the flow data were obtained in nondiseased arteries in stable patients with chest pain syndromes. None of the study patients had the no-reflow phenomenon or were undergoing intervention of the study artery. Conclusions about the hyperemic effects of these drugs in the clinical setting of no-reflow cannot be made with certainty.

Clinical Implications
These data indicate that in the doses tested, IC NTP is a safe and effective agent for the induction of maximal coronary hyperemia. NTP hyperemia is equivalent to that of adenosine, while providing a more sustained duration of the hyperemic response with only a modest decrease in systolic pressure without tachycardia. Additionally, IC NTP appears to be a useful hyperemic stimulus for determinations of FFR in patients in whom a more prolonged hyperemia is desired.
Acknowledgments
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References
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