Effects of Intravenous Nesiritide on Human Coronary Vasomotor Regulation and Myocardial Oxygen Uptake

Andrew D. Michaels, MD; Andrew Klein, MD; James A. Madden, RN; Kanu Chatterjee, MB, FRCP

Background—Nesiritide, recombinant human B-type natriuretic peptide, has been shown to be efficacious in the treatment of decompensated heart failure. The effects of intravenous nesiritide on the human coronary vasculature have not been studied.

Methods and Results—Ten patients underwent right and left heart catheterization. Baseline coronary blood flow was determined using quantitative coronary angiography (QCA) and an intracoronary Doppler-tipped guidewire. Myocardial oxygen uptake was measured using a coronary sinus catheter. Patients then received an intravenous infusion of nesiritide (2 μg/kg bolus followed by 0.01 μg/kg per min infusion) for 30 minutes. Right atrial pressure decreased 52% (P=0.012), pulmonary artery mean pressure decreased 19% (P=0.03), pulmonary capillary wedge pressure decreased 46% (P=0.002), and mean arterial pressure decreased 11% (P=0.007). QCA demonstrated a 15% increase in coronary artery diameter from a baseline of 2.6±0.8 to 3.0±0.8 mm at 30 minutes (P=0.007). The coronary velocity measure of average peak velocity increased 14% from 20.8±6.4 at baseline to 23.8±7.2 cm/s at 5 minutes (P=0.015) and then returned to baseline for the remainder of the infusion. Coronary blood flow increased 35% (P=0.007), whereas coronary resistance decreased 23% at 15 and 30 minutes (P=0.036). Myocardial oxygen uptake decreased 8% during the nesiritide infusion (P=0.043).

Conclusions—Nesiritide exerts coronary vasodilator effects on both the coronary conductance and resistance arteries. Despite a decrease in coronary perfusion pressure, coronary artery blood flow is increased, coronary resistance is decreased, and myocardial oxygen uptake is decreased. (Circulation. 2003;107:2697-2701.)

Key Words: natriuretic peptides ■ vasodilation ■ hemodynamics ■ heart failure ■ blood flow

B-type natriuretic peptide (BNP) is secreted by the cardiac ventricles in response to fluid and pressure overload and is involved in maintaining homeostasis of fluid and electrolytes. Animal and human studies have demonstrated the diuretic, natriuretic, and hemodynamic effects of BNP. Nesiritide (Natrecor, Scios Inc) recombinant human BNP has been shown to have beneficial effects in patients with decompensated congestive heart failure. Animal studies have shown that BNP activates the membrane-bound guanylyl cyclase-A receptor, which results in the accumulation of intracellular cyclic GMP (cGMP) in target tissues. cGMP mediates the vascular smooth muscle relaxant effect of BNP. BNP has been shown to induce vasodilation in isolated human arterial and venous tissue preparations, in vivo human forearm studies, human pulmonary circulation, and porcine coronary conductance and resistance arteries. Furthermore, human BNP infused into the left main coronary artery or the pulmonary artery has been shown to induce epicardial artery vasodilation. The effects of intravenous nesiritide on the coronary circulation in humans have not been evaluated. In this study, we examined the coronary hemodynamic effects of intravenous nesiritide. We also studied the effects of nesiritide on myocardial oxygen uptake.

Methods

Study Design and Patient Selection
This was a prospective cohort study that enrolled patients referred for cardiac catheterization and coronary angiography at the University of California-San Francisco Adult Cardiac Catheterization Laboratory. Patients with a contraindication to receiving adenosine (ie, active bronchospasm or theophylline use) or intravenous heparin (ie, platelet count <100 000 or active or recent bleeding disorder), those with a systolic blood pressure <95 mm Hg or heart rate <50 beats per minute, and those receiving vasopressors were excluded. Patients with native coronary arteries with >40% diameter stenosis or angiographic evidence of thrombus were excluded from the study. Calcium channel blockers and nitrates were withheld at least 24 hours before the study. All patients gave written informed consent before the procedure, and the protocol was approved by the UCSF Committee on Human Research. The number of patients enrolled was prospectively preset at 10.

Study Procedures
Right and left heart catheterization and quantitative coronary angiography (QCA) was performed using 6F diagnostic coronary catheters. A 6F catheter was inserted into the mid coronary sinus for blood gas monitoring. After full heparinization, a 0.014-inch Doppler-tipped FloWire (Jomed, Rancho Cordo, Calif) was advanced to the mid coronary artery. Coronary flow reserve (CFR) was measured after
administration of intracoronary adenosine (18 μg for the right and 24 μg for the left coronary artery). Nesiritide (Natrecor, Scios Inc; 2 μg/kg IV bolus followed by 0.01 μg/kg per min) was infused via a peripheral IV for 30 minutes. Intracoronary Doppler flow was recorded from the same position throughout the 30-minute infusion. Repeat QCA was performed at 15 and 30 minutes. Repeat coronary sinus blood gas sampling and right heart catheterization were performed at 30 minutes.

Quantitative Coronary Angiography
QCA was performed at baseline, 15 minutes, and 30 minutes, acquired and analyzed digitally using a real-time digital image acquisition and analysis system (General Electric Advantx system with Camtronics Medical Systems digital processing). Analysis was performed offline following the procedures using the Camtronics ARTREK QCA algorithm. QCA analysis determined the diameter and cross-sectional area of the mid coronary artery 5 mm distal to the tip of the FloWire in the sample volume site.

Intracoronary Doppler Velocity Protocol
The Doppler guidewire FloWire system has a miniature Doppler ultrasound crystal that transmits signals at a carrier frequency of 15 MHz and received pulsed-wave ultrasound signals, sampled at a distance of 5 mm from the guidewire tip. The Doppler signals are analyzed by a FloMap instrument (Jomed) in which dedicated digital signal-processing chips perform the fast Fourier transformation required for the spectral display. The spectrum and the ECG are simultaneously displayed on the monitor. Also displayed were quantitative measurements of average peak velocity (APV) and diastolic to systolic velocity ratio (DSVR). The monitor display was continuously recorded on a high-quality super-VHS (S-VHS, Fuji) videotape for subsequent offline analysis.

Calculations of Systemic Hemodynamics, Coronary Blood Flow Hemodynamics, and Myocardial Oxygen Consumption
Stroke volume index (SVI, mL/m²) equals CI×HR, where CI is cardiac index and HR is heart rate. The thermodilution technique for measuring cardiac index was used for SVI calculations. Stroke work index (SWI, g/m²) equals SVI×(MSP−PCWP)/(0.0136), where MSP is mean systolic blood pressure and PCWP is mean pulmonary capillary wedge pressure. Systemic vascular resistance (SVR, dynes·s/cm⁵) equals (MAP−RAP/CO)/(80), where MAP is mean arterial pressure, RAP is right atrial pressure, and CO is cardiac output. Pulmonary vascular resistance (PVR, Wood units) equals (PAM−PCWP)/CO, where PAM is pulmonary artery mean pressure.

Coronary blood flow (mL/min) in the epicardial artery studied was calculated as π(D⁴/4)(APV/2)(0.6). Coronary resistance (mm Hg·min/mL) equals (MAP−RAP)/CBF.

All patients received 2 L/min of nasal cannula oxygen throughout the study period. Measured oxygen content was obtained from the directly measured data using the following formula: oxygen content (vol %) = oxygen saturation/100×hemoglobin content (g/dL)×1.34 (mL/g) + 0.0031 partial pressure of oxygen (mm Hg). Myocardial oxygen uptake (mL O₂/L) equals arterial oxygen content (mL O₂/L)−coronary sinus oxygen content (mL O₂/L).

Statistical Analysis
Data are presented as mean values and standard deviations for continuous variables. Differences between baseline and nesiritide treatment values were assessed using a paired 2-tailed Student’s t test for paired observations or ANOVA where appropriate. P<0.05 was considered significant.

Results
Patient Population
Ten patients were enrolled. Seven were men, and the mean age was 58±12 years (range, 43 to 80 years). Five patients had coronary artery disease with at least one coronary artery with ≥75% diameter stenosis. There was no significant difference in age among the patients without coronary artery disease (56.8±7.9 years) compared with those with coronary disease (58.6±15.4 years). Two patients had diabetes mellitus, and 2 had nonischemic cardiomyopathy. Four patients had a LVEF ≤35%, and the mean LVEF was 48±20% (range, 20% to 70%). Cardiac medication use included angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (70%), β-blockers (60%), calcium channel blockers (30%), nitrates (20%), and statins (60%).

Right Heart Hemodynamics
Mean right atrial pressure decreased 52% from 6.4±3.2 mm Hg at baseline to 3.1±1.8 mm Hg after 30 minutes of nesiritide (P=0.012). Pulmonary artery systolic pressure decreased 18% from

Figure 1. Representative intracoronary Doppler flow tracings at baseline (A) and 5 minutes after beginning intravenous nesiritide (B).
26.1±6.3 to 21.5±4.4 mm Hg (P=0.008), mean pulmonary artery pressure decreased 19% from 16.7±5.3 to 13.6±3.5 mm Hg (P=0.033), and mean pulmonary capillary wedge pressure decreased 46% from 10.7±4.8 to 5.8±3.3 mm Hg during the nesiritide infusion (P=0.002). Heart rate and cardiac output calculated by both thermodilution and Fick methods were unchanged. PVR increased 25% from 1.6±0.4 at baseline to 2.0±0.3 Wood units at 30 minutes (P=0.008).

**Systemic Hemodynamics**
Mean arterial pressure decreased 11% from 90±14 mm Hg at baseline to 80±8 mm Hg at 30 minutes (P=0.007). Decreases in SVR by 6% from 1777±443 at baseline to 1664±346 dynes·s/cm² at 30 minutes (P=0.22) and of stroke volume index from 33.1 mL/m² at baseline to 31.2 mL/m² at 30 minutes (P=0.27) were statistically and clinically insignificant. Stroke work index decreased from 50.9 g/m² at baseline to 40.9 g/m² at 30 minutes (P=0.016).

**Coronary Hemodynamics**
The left circumflex artery was studied in 5 patients, the left anterior descending artery in 4 patients, and the right coronary artery in 1 patient. The coronary flow reserve in response to intracoronary adenosine was 2.6±0.8. The intracoronary average peak velocity (APV) determined with the FloWire increased 14% from 20.8±6.4 cm/s at baseline to 23.8±7.2 cm/s at 5 minutes (P=0.015), then returned to baseline at 15 and 30 minutes (Figures 1 and 2). Baseline mean coronary artery diameter increased 15% from 2.6±0.8 mm at baseline to 3.0±0.8 mm at 15 minutes and 3.0±0.9 mm at 30 minutes (P=0.007 compared with baseline; Figure 3). CBF increased 35% from 37±25 mL/min at baseline to 50±32 at 15 minutes (P=0.031) and 49±35 at 30 minutes (P=0.073; Figure 4). Coronary resistance decreased 23% from 4.4±5.0 mm Hg·min/mL at baseline to 3.4±4.7 at 15 minutes (P=0.019) and 3.3±3.7 at 30 minutes (P=0.046; Figure 5).

The coronary hemodynamic effects of nesiritide for the 5 patients without coronary artery disease were compared with the 5 patients with at least 1 coronary artery with ≥75% diameter stenosis. Patients without coronary artery disease had nonsignificant trends toward a higher coronary flow reserve in response to intracoronary adenosine, a greater increase in coronary diameter with nesiritide, and a greater increase in coronary blood flow with nesiritide (Table). Both groups tended to have a comparable reduction in coronary resistance with nesiritide.

**Myocardial Oxygen Uptake**
Coronary sinus sampling was performed in 9 patients. Coronary sinus oxygen content increased from 6.3±1.7 vol % at baseline to 7.3±2.1 vol % at 30 minutes (P=0.047). Arterial oxygen content was 19.3±2.2 vol % at both baseline and 30 minutes. Myocardial oxygen uptake decreased 8% from 13.0±1.7 mL O₂/L at baseline to 12.0±1.5 mL O₂/L at 30 minutes (P=0.043; Figure 6). Both patients with and without coronary artery disease had a reduction in myocardial oxygen uptake during the nesiritide infusion (Table).

**Discussion**
We demonstrated that intravenous administration of nesiritide exerts vasodilatory effects on the coronary conductance and resistance arteries. The dose of nesiritide used in this study was the clinically used starting dose for patients with decompensated heart failure. The magnitudes of coronary epicardial vasodilation and augmentation in coronary blood flow in response to
Coronary Hemodynamics for Patients Based on the Presence of Significant Coronary Artery Disease in Other Coronary Arteries

<table>
<thead>
<tr>
<th>Hemodynamic Variable</th>
<th>No CAD (n=5)</th>
<th>CAD (n=5)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary flow reserve, mL/min</td>
<td>3.1±0.7</td>
<td>2.2±0.7</td>
<td>0.09</td>
</tr>
<tr>
<td>APV, cm/s</td>
<td>19.2±6.1</td>
<td>22.4±6.9</td>
<td>0.46</td>
</tr>
<tr>
<td>Coronary diameter, mm</td>
<td>2.3±0.8</td>
<td>2.8±0.7</td>
<td>0.38</td>
</tr>
<tr>
<td>CBF, mL/min</td>
<td>30±24</td>
<td>45±26</td>
<td>0.35</td>
</tr>
<tr>
<td>Coronary resistance, mm Hg/min/mL</td>
<td>6.2±6.6</td>
<td>2.7±2.2</td>
<td>0.31</td>
</tr>
<tr>
<td>Percent change from baseline to 15 minutes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APV</td>
<td>−10±14</td>
<td>+5±22</td>
<td>0.23</td>
</tr>
<tr>
<td>Coronary diameter</td>
<td>+35±27</td>
<td>+7±4</td>
<td>0.08</td>
</tr>
<tr>
<td>CBF</td>
<td>+72±92</td>
<td>+20±31</td>
<td>0.29</td>
</tr>
<tr>
<td>Coronary resistance</td>
<td>−30±25</td>
<td>−22±12</td>
<td>0.55</td>
</tr>
<tr>
<td>Percent change from baseline to 30 minutes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APV</td>
<td>−14±16</td>
<td>+4±18</td>
<td>0.15</td>
</tr>
<tr>
<td>Coronary diameter</td>
<td>+28±16</td>
<td>+10±14</td>
<td>0.10</td>
</tr>
<tr>
<td>CBF</td>
<td>+42±40</td>
<td>+28±43</td>
<td>0.60</td>
</tr>
<tr>
<td>Coronary resistance</td>
<td>−30±25</td>
<td>−22±12</td>
<td>0.55</td>
</tr>
<tr>
<td>Myocardial oxygen uptake</td>
<td>−4.7±11.9</td>
<td>−10.4±7.0</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Nesiritide were consistent with prior studies of intracoronary infusion in pigs and humans. The vasodilatory properties of nesiritide are believed to act via the second messenger cGMP on vascular smooth muscle cells. The GC-A receptor, a biological receptor for BNP, is part of a receptor class of proteins termed particulate guanylyl cyclases. It is a membrane-bound protein with guanylyl cyclase activity. Binding of BNP to the extracellular domain of the GC-A receptor activates the intracellular guanylyl cyclase domain, resulting in the catalysis of cGMP from GTP.

In this study, we observed a differential vasodilatory response to nesiritide in conductance and resistance arteries. The conductance epicardial coronary arteries dilated with a 15% increase in coronary diameter at 15 and 30 minutes (Figure 3). There was a consistent increase in coronary velocity peaking at 5 minutes after initiation of nesiritide, followed by a gradual decline back to baseline velocities (Figures 1 and 2). It is possible that the transient augmentation of coronary velocity was attributable to the nesiritide intravenous bolus. Alternatively, in this cohort of patients where we studied unobstructed coronary arteries, coronary autoregulation may explain the return to coronary velocity baseline several minutes after the initial peak in velocity observed at 5 minutes. Because the coronary perfusion pressure did decrease during the nesiritide infusion, the absence of a decline in coronary velocity indicates vasodilation of the resistance arteries with a decrease in coronary resistance. An increase in coronary sinus oxygen content also suggests primary coronary vasodilation.

Previous studies have shown that nesiritide had a more pronounced vasodilatory effect when coronary arteries were preconstricted with endothelin. This accentuated response was felt to be attributable to optimal receptor presentation of the transmembrane receptor or participation of an allosteric binding site of the ligand ATP, which has been shown to increase guanylyl cyclase activity of natriuretic peptides. Of the 10 patients enrolled in our study, 1 patient with history of coronary vasospasm and a positive ergonovine provocation test had the most pronounced vasodilatory response to nesiritide. This patient had a 77% increase in coronary diameter, a 5% increase in average peak velocity, and a 231% increase in coronary blood flow at 15 minutes. Kato et al found that an intravenous BNP infusion suppressed hyperventilation-induced coronary artery vasospasm. Although BNP has not been studied in patients with acute myocardial infarction, atrial natriuretic peptide has been shown to prevent left ventricular remodeling better than nitroglycerin in patients after first anterior myocardial infarction.

These observations regarding the effects of BNP on preconstricted epicardial coronary arteries, the effects of BNP on suppressing hyperventilation-induced angina, and our observation in this patient with coronary vasospasm may be of importance in patients with coronary vasospasm, such as in variant coronary angina and acute coronary syndromes.

Given the small number of patients in this study, any firm conclusions regarding differences among patients either with or without coronary artery disease in the coronary hemodynamic effects of nesiritide cannot be made. Patients without coronary artery disease tended to have a higher coronary flow reserve in response to intracoronary adenosine, a greater increase in coronary diameter with nesiritide, and a greater increase in coronary blood flow with nesiritide (Table). Both groups tended to have a comparable reduction in coronary resistance with nesiritide. These findings are consistent with prior studies that have shown patients with coronary artery disease have an impaired coronary flow reserve and attenuation of endothelium-dependent vasodilatory response even in coronary arteries without hemodynamically significant disease.

We also demonstrated that myocardial oxygen uptake decreased after 30 minutes of nesiritide infusion. Systemic arterial pressure, pulmonary capillary wedge pressure, and stroke work index significantly decreased with nesiritide administration, with no change in heart rate or cardiac output. These hemodynamic changes are in contrast to what is observed with other available inotropic medications used in heart failure. The positive inotropic agent dobutamine is commonly used for management of decompensated heart failure. In contrast to nesiritide, dobutamine increases the 2 major determinants of myocardial oxygen demand, inotropic state and heart rate. Dobutamine increases both coronary blood flow and myocardial oxygen consumption and decreases coronary vascular resistance. Milrinone has been shown to decrease coronary vascular resistance with no significant change in either coronary blood flow or
myocardial oxygen consumption. The coronary hemodynamic effects of nesiritide have a more favorable profile compared with inotropic agents such as dobutamine or milrinone. Nesiritide acts as a vasodilator that decreases impedance in both the peripheral and coronary beds. Left ventricular filling pressures decrease, coronary artery blood flow increases, coronary artery resistance decreases, whereas myocardial oxygen uptake decreases during nesiritide infusion.

PVR increased by 25% during the nesiritide infusion. This finding likely is explained by the equation used for this calculation rather than a hemodynamic vasoconstrictor effect on the pulmonary vasculature. First, the patients studied did not have clinical evidence of heart failure. Only 1 of the 10 patients studied had a mean pulmonary artery pressure >20 mm Hg. In this population, nesiritide reduced the PCWP to a greater extent than the PAM and had no significant change in CO, resulting in an increase in PVR.

Because left ventricular work decreased while coronary sinus oxygen content increased, it is very unlikely that any increase in coronary blood flow during nesiritide treatment is attributable to the development of coronary ischemia or coronary autoregulation. It appears that nesiritide exerts a direct vasodilatory effect on both the conductance and resistance coronary arteries.

Study Limitations

This study was performed in patients without uncomplicated heart failure. Because coronary arteries with significant epicardial disease were excluded, the hemodynamic coronary effects of nesiritide in those arteries with significant coronary artery disease require additional study. The hemodynamic effects of nesiritide in patients with pulmonary hypertension require additional study.

This study did not address directly the clinical implications of nesiritide-induced favorable changes in coronary hemodynamics. We monitored changes in coronary artery velocity continuously with the Doppler-tipped guidewire, whereas we measured changes in coronary artery diameter at 15 and 30 minutes only. It is possible that there were more rapid changes in coronary diameter that we were not able to detect with coronary angiography performed at predetermined time points. The limitations of QCA analyses and the Doppler-tipped guidewire measurements have been described previously.

Conclusions

Nesiritide acts as a direct vasodilator that decreases impedance in the coronary conductance and resistance arteries as well as the peripheral arterial circulation. Left ventricular filling pressures decrease, coronary artery blood flow increases, coronary artery resistance decreases, and myocardial oxygen uptake decreases during nesiritide infusion. These findings confirm the favorable effects of nesiritide on coronary hemodynamics and myocardial metabolism.

Acknowledgments

This study was supported by a research grant from Scios Inc (Sunnyvale, Calif). Dr. Michaels has salary support for this research from the GlaxoSmithKline Development Partners’ Junior Faculty Award. We wish to acknowledge the following contributions: the patients who participated in this study; the staff in the UCSF Cardiac Catheterization Laboratory for their superb technical assistance; and Millie Gottwald, PharmD, and Frederic Heerinkx of Scios Inc for technical support.

References

Effects of Intravenous Nesiritide on Human Coronary Vasomotor Regulation and Myocardial Oxygen Uptake
Andrew D. Michaels, Andrew Klein, James A. Madden and Kanu Chatterjee

Circulation. 2003;107:2697-2701; originally published online May 12, 2003;
doi: 10.1161/01.CIR.0000070547.88378.EA

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/107/21/2697