Low Dose Nesiritide and the Preservation of Renal Function in Patients With Renal Dysfunction Undergoing Cardiopulmonary-Bypass Surgery
A Double-Blind Placebo-Controlled Pilot Study

Horng H. Chen, MBBCh; Thoralf M. Sundt, MD; David J. Cook, MD; Denise M. Heublein; John C Burnett, Jr, MD

Background—Renal insufficiency is associated with increased morbidity and mortality after cardiopulmonary bypass cardiac surgery. B-type natriuretic peptide is a cardiac hormone that enhances glomerular filtration rate and inhibits aldosterone. Cystatin has been shown to be a better endogenous marker of renal function than creatinine.

Methods and Results—We performed a double-blinded placebo-controlled proof of concept pilot study in patients \( n/11005 40 \) with renal insufficiency preoperatively (defined as an estimated creatinine clearance of \( 60 \text{ mL/min} \) determined by the Cockroft-Gault formula), undergoing cardiopulmonary bypass cardiac surgery. Patients were randomized to placebo \( n/11005 20 \) or IV low dose nesiritide \( n/11005 20; 0.005 \text{ g/Kg/min} \) for 24 hours started after the induction of anesthesia and before cardiopulmonary bypass. Patients in the nesiritide group had an increase of plasma B-type natriuretic peptide and its second messenger cGMP with a decrease in plasma cystatin levels at the end of the 24-hour infusion. These changes were not observed in the placebo group. There was a significant activation of aldosterone in the placebo group at the end of the 24-hour infusion, but not in the nesiritide group. At 48 and 72 hours, there was a decrease in estimated creatinine clearance and an increase in plasma cystatin as compared with end of the 24-hour infusion in the placebo group. In contrast, renal function was preserved in the nesiritide group with no significant change in estimated creatinine clearance and a trend for plasma cystatin to increase as compared with end of the 24-hour infusion.

Conclusion—This proof of concept pilot study supports the conclusion that perioperative administration of low dose nesiritide is biologically active and decreases plasma cystatin in patients with renal insufficiency undergoing cardiopulmonary bypass cardiac surgery. Further studies are warranted to determine whether these physiological observations can be translated into improved clinical outcomes. \( (\text{Circulation. 2007;116[suppl I]:I-134–I-138.}) \)

Key Words: natriuretic peptides • cardiac surgery • renal • therapy

Mild to moderate renal insufficiency is associated with increased morbidity and mortality postcardiopulmonary bypass (CPB) cardiac surgery. Specifically, there is an increased likelihood of postoperative mechanical renal support, longer length of hospital stay and higher in hospital mortality. The incidence of worsening renal function after cardiac surgery has been reported to range from 5% to 30% with the highest incidence in patients with baseline renal insufficiency, as defined by an estimated creatinine clearance (CrCl) of \( <60 \text{ mL/min} \) preoperatively. Plasma cystatin and estimated CrCl using the Cockroft-Gault formula have been shown to be better markers for renal function as compared with plasma creatinine.

B-type natriuretic peptide (BNP) is a cardiac hormone, which is similar to atrial natriuretic peptide (ANP) but genetically distinct. BNP has natriuretic, diuretic, vasodilating, antiproliferative, lusitropic and aldosterone-inhibiting properties. Specifically, the beneficial renal actions of BNP include increases in renal blood flow and glomerular filtration rate resulting in natriuresis and diuresis. Unlike conventional diuretics which activate aldosterone, BNP inhibits aldosterone despite marked natriuresis and diuresis. Of note, the FDA has recently approved human BNP (nesiritide) for the management of acute decompensated heart failure.

Low dose IV ANP infusion has been shown to improve estimated CrCl in patients post-CPB cardiac surgery. We have shown that BNP has more potent renal actions as compared with ANP attributable to its decreased susceptibility to degradation by the ectoenzyme neutral endopeptidase 24–11. We have recently reported that nonhypotensive low

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dose IV nesiritide (0.005 µg/kg/min) has renal enhancing actions which were not observed with standard dose nesiritide (2 µg/kg bolus followed by infusion at 0.01 µg/kg/min) in patients with heart failure and renal dysfunction. To date, the efficacy of IV low dose nesiritide in the prevention of worsening renal insufficiency post-CPB cardiac surgery remains undefined. Therefore, the objectives of the current study were to determine the renal and humoral responses to 24 hours of IV low dose nesiritide infusion started perioperatively after the induction of anesthesia before CPB in patients with pre-existing renal dysfunction undergoing cardiac surgery. Furthermore, we also sought to assess the effects of the 24-hour infusion on renal function at 48 and 72 hours.

Methods

Study Design

This was a double-blind placebo-controlled proof of concept pilot study.

Study Population

Subjects recruited were limited to men and women, aged 18 years and above undergoing CBP cardiac surgery with renal insufficiency preoperatively as defined by having an estimated CrCl of <60 mL/min determined by the Cockroft-Gault formula. Forty patients were randomized to IV nesiritide or placebo for 24 hours started after induction of anesthesia before cardiopulmonary bypass. Dose of nesiritide infusion was 0.005 µg/kg/min without bolus. Patients with cardiogenic shock or hypotension with systolic BP <90 mm Hg, patients with acute or chronic aortic dissection and patients who are enrolled in other studies that have an effect on the renal function were excluded. All patients gave informed consent, and the study was approved by the Institutional Review Board at our institution.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Measurements

Plasma cystatin, creatinine, BNP, cGMP and aldosterone were measured at baseline before surgery and repeated at the end of the 24-hour infusion and at 48 and 72 hours. Total fluid input and output during the 72 hours study period were recorded. Vital signs such as blood pressure, heart rate and oxygen saturation were also recorded. Plasma cystatin, creatinine, BNP, cGMP and aldosterone were determined by previously established methods. Renal function was determined by plasma cystatin and estimated CrCl determined by the Cockroft-Gault formula.

Sample Size

Our sample size calculation was based on the study by Sezai et al. In that pilot study, the authors demonstrated that the placebo group had a decrease in estimated CrCl of 10 mL/min while the estimated CrCl was preserved in the treatment group. Hence, using a standard deviation of 16 mL/min for the change in estimated CrCl, with 20 patients in each group, we have 80% power to detect a change of estimated CrCl of 10 mL/min or greater in either group. This calculation was based on a paired t test with a significance level of 0.05. Because this is a proof of concept pilot study, the sample size was chosen to detect a change of calculated CrCl of 10 mL/min or greater in either group but not powered to detect a difference in the change of estimated CrCl between groups.

Data Analysis

Continuous measurements are expressed as mean±SD (median) whereas categorical variables are reported as number (percent). χ² tests or Fisher exact tests were used to compare categorical variables between nesiritide group and placebo group, whereas 2-sample t tests or rank sum tests were used to compare the continuous variables between the 2 groups. Paired t tests or signed rank tests were used to compare within group changes. P<0.05 is considered statistically significant.

Results

Participants

We randomized 40 patients to receive nesiritide (n=20) or placebo (n=20). One patient randomized to the nesiritide group had the cardiac surgery performed off CPB and was excluded from the final analysis. Three patients had immediate postoperative complications during the 24-hour infusion period: 1 with hemorrhage and 2 with sepsis. Two of the 3 patients with immediate postoperative complications were randomized to nesiritide and 1 to placebo. The Data and Safety Monitoring Committee reviewed these events blinded and concluded that they were not study related but that they would affect the renal and humoral function regardless of the randomized therapy. Hence, the 3 patients were excluded from the final analysis, and thus we had n=17 in the nesiritide group and n=19 in the placebo group.

The baseline characteristics and intraoperative data for the study participants are reported in Tables 1 and 2 respectively. The groups were similar with regards to age, sex, weight, and existing comorbidities such as hypertension, diabetes, heart failure, history of myocardial infarction and preoperative medications except that more patients in the placebo group were taking diuretics before the surgery. The mean left ventricular ejection fraction in both groups was similar and was above 50%. Both groups had significantly reduced renal function as determined by plasma cystatin, plasma creatinine and estimated CrCl. More patients in the placebo group had valvular surgery only as compared to the nesiritide group.

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics</th>
<th>Nesiritide (n=17)</th>
<th>Placebo (n=19)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>77±10 (79)</td>
<td>78±7 (80)</td>
<td>0.75</td>
</tr>
<tr>
<td>Gender, male</td>
<td>12 (71%)</td>
<td>10 (52%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>76±11 (75)</td>
<td>75±17 (79)</td>
<td>0.86</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>57±18 (60)</td>
<td>53±11 (55)</td>
<td>0.15</td>
</tr>
<tr>
<td>Plasma cystatin, mg/L</td>
<td>1.4±0.5 (1.3)</td>
<td>1.4±0.6 (1.4)</td>
<td>0.90</td>
</tr>
<tr>
<td>Plasma creatinine, mg/dL</td>
<td>1.7±0.5 (1.6)</td>
<td>1.7±0.7 (1.5)</td>
<td>0.68</td>
</tr>
<tr>
<td>Estimated CrCl, min/ml</td>
<td>41±11 (41)</td>
<td>38±10 (40)</td>
<td>0.44</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (71%)</td>
<td>12 (63%)</td>
<td>0.64</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7 (41%)</td>
<td>5 (26%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>11 (64%)</td>
<td>9 (47%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Previous MI</td>
<td>2 (12%)</td>
<td>5 (26%)</td>
<td>0.41</td>
</tr>
<tr>
<td>β-blocker</td>
<td>9 (53%)</td>
<td>9 (48%)</td>
<td>0.74</td>
</tr>
<tr>
<td>ACEI/AT1 blocker</td>
<td>4 (24%)</td>
<td>6 (32%)</td>
<td>0.59</td>
</tr>
<tr>
<td>ASA/NSAIDS</td>
<td>8 (47%)</td>
<td>8 (42%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Diuretics</td>
<td>3 (18%)</td>
<td>9 (47%)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Mean±SD (median) or No. (%). MI indicates myocardial infarction; ACEI, angiotensin-converting enzyme inhibitor; AT1, angiotensin receptor; ASA, aspirin; NSAIDS, nonsteroidal anti-inflammatory drugs.
Renal and Humoral Function at 48 and 72 Hours

Figure 2 illustrates both plasma cystatin and estimated CrCl at 48 and 72 hours as compared with the end of the 24-hour infusion.

There was 1 patient in the nesiritide group who had surgery for ascending aortic aneurysm only. There was a trend for the pump time and cross-clamp time to be longer in the nesiritide group as compared with the placebo group. The lowest systolic and diastolic blood pressure intraoperatively was similar between the 2 groups.

Humoral and Renal Responses to the 24-Hour Infusion

Figure 1 A and B illustrates the plasma BNP, plasma cGMP, plasma aldosterone and plasma cystatin levels preoperative (pre-op) and at the end of the 24-hour infusion. The nesiritide group had an increase in both plasma BNP and its second messenger plasma cGMP at the end of the 24-hour infusion whereas there was no significant change in the placebo group. Plasma aldosterone was significantly increased at the end of the 24-hour infusion as compared with pre-op in the placebo group, whereas in the nesiritide group, there was no significant increase in plasma aldosterone. Importantly, plasma cystatin was significantly reduced in the nesiritide group in contrast to the nonsignificant trend for a slight decrease in the placebo group. From a safety standpoint, there was no difference in the lowest systolic and diastolic blood pressure during the 24-hour infusion period between the nesiritide and placebo group (systolic blood pressure: nesiritide group: 80±15 [80] mm Hg versus placebo group: 85±16 [86] mm Hg, P=0.29; diastolic blood pressure: nesiritide group: 54±28 [44] mm Hg versus placebo group: 48±9 [49] mm Hg, P=0.66). The amount of furosemide administered during the 24-hour infusion period was similar in the nesiritide group and the placebo group (33±35 [40] mg/d versus 47±34 [40] mg/d, P=0.13). The total fluid input (2.4±0.9 [1.9] versus 2.2±0.9 [2.2] L/d, P=0.59) and output (2.6±0.9 [2.5] versus 2.8±1.4 [2.8] L/d, P=0.58) during the 24-hour infusion period was also similar between the 2 groups.

Renal and Humoral Function at 48 and 72 Hours

Figure 2 illustrates both plasma cystatin and estimated CrCl at 48 and 72 hours as compared with the end of the 24-hour infusion. Plasma cystatin increased and estimate CrCl decreased at 48 and 72 hours as compared with the end of the 24-hour infusion in the placebo group. In contrast, estimated CrCl was not significantly changed at both time points in the
nesiritide group, whereas there was a trend for the plasma cystatin to increase only at 72 hours in the nesiritide group. The amount of furosemide administered daily at 48 and 72 hours was similar between the nesiritide group and the placebo group (42±51 [40] and 46±45 [40] mg/d versus 54±41 [40] and 46±26 [40] mg/d, P=0.20 and P=0.63 respectively for 48 and 72 hours). The total fluid input (1.7±0.8 [1.4] and 1.4±0.6 [1.3] L/d versus 1.6±0.5 [1.5] and 1.4±0.6 [1.4] L/d, P=0.87 and P=0.94) and output (1.8±0.9 [1.5] and 1.9±1.0 [1.5] L/d versus 1.9±0.8 [1.9] and 1.8±0.8 [1.8] mg/d, P=0.08 and P=0.96) at 48 and 72 hours was similar between the 2 groups.

At 72 hours, plasma BNP increased significantly (8 change of 172±236 [106] pg/mL, P=0.006) as compared with pre-op levels in the placebo group. However, in the nesiritide group, there was no significant increase in plasma BNP (8 change of 97±289 [62] pg/mL, P=0.21) at 72 hours as compared with pre-op levels.

### Postoperative Outcomes

The post-op outcomes are reported in Table 3. Two patients in the nesiritide group and 5 patients in the placebo group had an increase of plasma cystatin of ≥0.3 mg/L at 72 hours. There were 2 patients in the placebo group whereas no patient in the nesiritide group had a decrease of estimated CrCl of ≥10 mL/min at 72 hours. Seven patients in the placebo group required isotropic support for >48 hours whereas only 2 patients in the nesiritide group required isotropic support for >48 hours. The mean Intensive Care Unit stay was 2.1 days for the nesiritide group and 2.8 days for the placebo group.

### Adverse Events

The adverse events are reported in Table 4. We have included the 3 patients with immediate post-op complication within the first 24 hours. There were 5 patients with 7 adverse events in the nesiritide group and 3 patients with 4 adverse events in the placebo group. There was 1 in-hospital mortality in the nesiritide group and it was one of the patients who developed sepsis postoperatively. Two patients in the placebo group had hemorrhage post-op and required reoperation. One patient in both groups required dialysis, and similarly 1 patient in each group developed atrial fibrillation post-op. The patient in the nesiritide group who developed atrial fibrillation also had an ischemic stroke. One patient in the nesiritide group developed a transient post-op confusion for 24 hours but recovered without consequence.

### Discussion

The objectives of the current study were to define the effects of 24-hour infusion of IV low dose nesiritide infusion at 0.005 µg/kg/min started perioperatively after the induction of anesthesia before CPB in patients with pre-existing renal dysfunction undergoing cardiac surgery on renal function at 48 and 72 hours. Furthermore, we also sought to assess the renal and humoral responses to 24 hours of this IV low dose nesiritide infusion. In this proof of concept pilot study, we demonstrated that 24 hours of IV low dose infusion of nesiritide at 0.005 µg/kg/min resulted in the preservation of renal function in the nesiritide group at 48 and 72 hours as compared with the end of the 24-hour infusion, whereas in the placebo group, there was a decline in renal function at 48 and 72 hours as compared with the end of the 24-hour infusion. We also determined that this low dose of nesiritide is biologically active with increased plasma BNP and activation of the natriuretic peptide receptor resulting in a significant increase of its second messenger cGMP. Consistent with the aldosterone inhibiting actions of BNP, there was no activation aldosterone in the nesiritide group at the end of the 24-hour infusion in contrast to the placebo group where there was activation of aldosterone. From a safety stand point, the lowest blood pressure during the 24-hour infusion period was similar between the nesiritide group and the placebo group suggesting that this low dose of nesiritide did not result in significant reduction in blood pressure.

The current study confirms and extends our recent report that nonhypotensive low dose nesiritide infusion in patients with congestive heart failure had renal glomerular filtration rate enhancing actions. The current study also suggests that the favorable renal effect is also associated with the suppression of aldosterone which is in contrast to the known aldosterone-stimulating actions of diuretics such as furosemide, which are commonly used in this clinical setting. Recently, the results of the Nesiritide Administered Peri-Anesthesia in Patients Undergoing Cardiothoracic Surgery (NAPA) trial were published. The investigators reported that perioperative infusion of nesiritide in patients with left ventricular dysfunction undergoing CABG resulted in preservation of renal function post-op. The dose of nesiritide used

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**TABLE 3. Postoperative Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>Nesiritide (n=17)</th>
<th>Placebo (n=19)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Plasma cystatin ≥0.3 mg/L</td>
<td>2 (12%)</td>
<td>5 (26%)</td>
<td>0.20</td>
</tr>
<tr>
<td>↓ Estimated CrCl ≥10 mL/min</td>
<td>0 (0%)</td>
<td>2 (11%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Inotropic support &gt;48 hours</td>
<td>2 (12%)</td>
<td>7 (37%)</td>
<td>0.23</td>
</tr>
<tr>
<td>ICU stay, day</td>
<td>2.1±1.6 (2)</td>
<td>2.8±2.9 (2)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

No. (%) or mean±SD (median);
↑ indicates increase; ↓, decrease; ICU, intensive care unit.

**TABLE 4. Adverse Events**

<table>
<thead>
<tr>
<th></th>
<th>Nesiritide (n=19)</th>
<th>Placebo (n=20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients with adverse events</td>
<td>5 (26%)*</td>
<td>3 (15%)†</td>
<td>0.45</td>
</tr>
<tr>
<td>No. of adverse events</td>
<td>7 (37%)</td>
<td>4 (20%)</td>
<td>0.30</td>
</tr>
<tr>
<td>In-hospital Mortality</td>
<td>1 (5.3%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>2 (11%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>0 (0%)</td>
<td>2 (10%)</td>
<td></td>
</tr>
<tr>
<td>Dialysis</td>
<td>1 (5.3%)</td>
<td>1 (5%)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (5.3%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1 (5.3%)</td>
<td>1 (5%)</td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td>1 (5.3%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

No. (%).

*There were 5 patients with 7 adverse events; †there were 3 patients with 4 adverse events.
in the NAPA study was 0.01 μg/kg/min without the bolus of 2 μg/kg. The patient population of the NAPA study was distinctly different from the current study. The main inclusion criterion for the NAPA study was an ejection fraction of 40% or less. However in the current study, the main inclusion criterion was a baseline estimated CrCl of 60 mL/min or less. The mean ejection fraction in the current study was above 50%. However, despite the difference in patient population, the NAPA study and the current study suggest that IV nesiritide administered at doses less than the standard dose may have favorable renal effects in patients undergoing cardiac surgery. Because both the NAPA study and our study were unassociated with hypotension with nesiritide, one might speculate that such doses are more renal enhancing as compared with the standard dose of nesiritide with bolus administration preceding the intravenous administration.

BNP has been shown to decrease pulmonary capillary wedge pressure and improve left ventricular relaxation. Sezai et al recently reported that low dose ANP infusion peripherally, suppressed aldosterone and improved left ventricular remodeling. In the current study, at 72 hours, there was a significant increase in plasma BNP levels in the placebo group and not in the nesiritide group. Plasma BNP has been recognized as a good biomarker for left ventricular function and filling pressure, thus the absence of an increase of BNP in the nesiritide group may suggest favorable left ventricular effects of the nesiritide infusion. This may account for the observation that 7 patients in the placebo group as compared with 2 patients in the nesiritide group required inotropes for >48 hours post-op. However, it must be stressed that the current pilot study is not powered to assess clinical outcomes and thus further sufficiently powered studies need to be done to confirm these observations.

Limitations of the Study
This is a pilot study and the small number of patients is a limitation. Therefore, further adequately powered studies will be required to determine whether these physiological observations can be translated to improve patient outcomes and to assess the safety of this strategy.

Conclusion
This proof of concept pilot study demonstrated that 24 hours of IV nesiritide at 0.005 μg/kg/min is biologically active with the increase in plasma cGMP its second messenger and the suppression of aldosterone. Further studies are needed to demonstrate the clinical benefit and safety of this strategy.

Acknowledgement
We would like to acknowledge Lenore A Marcotte, the study coordinator for this study for all her hard work and all our colleagues in the Division of Cardiovascular Surgery and Division of Cardiovascular Anesthesia for supporting this study.

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Disclosures
Dr Chen and Dr Burnett have received research grants and honoraria from Scios Inc. There are no other conflicts of interest to report.

References
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