Renoprotective Action of Fenoldopam in High-Risk Patients Undergoing Cardiac Surgery
A Prospective, Double-Blind, Randomized Clinical Trial

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Background—Acute renal failure is a serious complication of cardiac surgery causing high morbidity and mortality. The aim of this study was to evaluate the usefulness of fenoldopam, a specific agonist of the dopamine-1 receptor, in patients at high risk of perioperative renal dysfunction.

Methods and Results—A prospective single-center, randomized, double-blind trial was performed after local ethical committee approval and after written consent was obtained from 80 patients undergoing cardiac surgery. Patients received either fenoldopam at 0.05 μg/kg per minute or dopamine at 2.5 μg/kg per minute after the induction of anesthesia for a 24-hour period. All these patients were at high risk of perioperative renal dysfunction as indicated by Continuous Improvement in Cardiac Surgery Program score >10. Primary end point was defined as 25% creatinine increase from baseline levels after cardiac surgery. The 2 groups (fenoldopam versus dopamine) were homogeneous cohorts, and no difference in outcome was observed. Acute renal failure was similar: 17 of 40 (42.5%) in the fenoldopam group and 16 of 40 (40%) in the dopamine group (P=0.9). Peak postoperative serum creatinine level, intensive care unit and hospital stay, and mortality were also similar in the 2 groups.

Conclusions—Despite an increasing number of reports of renal protective properties from fenoldopam, we observed no difference in the clinical outcome compared with dopamine in a high-risk population undergoing cardiac surgery.

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Key Words: cardiopulmonary bypass ■ diuretics ■ anesthesia ■ fenoldopam ■ kidney failure, acute

Acute renal failure (ARF) is a serious complication after cardiac surgery resulting in significant in-hospital and long-term morbidity and mortality, as well as prolonged hospital stay.1,2 The risk of ARF ranges from 5% to 31%3–5 and is even greater in high-risk populations or when more inclusive definitions are used.6 When it is severe enough to require renal replacement therapy, the mortality rate is close to 60%.

Fenoldopam mesylate, a benzazepine derivative, is the first selective dopamine-1 receptor agonist that has been approved for clinical use (hypertensive urgencies and emergencies). The selective dopaminergic action of fenoldopam appears to improve renal performance in situations of reduced renal blood flow such as severe hypertension,7,8 hypertensive patients with preexisting impaired renal function,9 and ventilation with positive end-expiratory pressure.10 These effects are mediated by increased renal blood flow to both cortex and medullary regions. Fenoldopam may have some utility during cardiopulmonary bypass (CPB) because renal ischemia is thought to contribute to postbypass renal dysfunction.

Data on fenoldopam clinical efficacy are sparse, and there is still virtually no definitive evidence of efficacy, particularly in high-risk patients. We therefore performed a prospective, randomized, double-blind clinical trial to evaluate the renoprotective action of fenoldopam in a selected high-risk group of patients undergoing cardiac surgery.

Methods

Study Population

The study was performed according to the principles of the Declaration of Helsinki. The ethics committee approved the study protocol. Patients provided written informed consent.

Consecutive eligible patients, aged ≥18 years, scheduled for cardiac surgery at a tertiary university hospital were randomly assigned to receive either fenoldopam or dopamine.

Patients were included if the Continuous Improvement in Cardiac Surgery Program (CICSP) score was >10. This recently developed risk-stratification algorithm is the best predictor of ARF in a cardiac surgery population.6,11,12 It includes the following: low ejection fraction <35% (2 points); valvular surgery (3 points); chronic obstructive pulmonary disease (2 points); NYHA functional class IV (2 points); peripheral vascular disease (2 points); preoperative use of an intra-aortic balloon pump (5 points); prior heart surgery (3 points); pulmonary rale (2 points); systolic blood pressure >160 mm Hg and CABG surgery (3 points); systolic blood pressure <120 mm Hg and valvular surgery (2 points); and creatinine
Randomization to receive either fenoldopam at 0.05 μg/kg per minute or dopamine at 2.5 μg/kg per minute after induction of anesthesia for cardiac surgery to prevent ARF in high-risk patients.

Management of Preoperative and Postoperative Medications

All preoperative medications were routinely omitted on the day of surgery. Aspirin was stopped 1 week before. Angiotensin-converting enzyme inhibitors were withdrawn on hospital admission (generally 1 day before surgery).

Operating Room and Intensive Care Management

Patients received standard monitoring and anesthesia. Heparin (3.0 mg/kg) was given to maintain the activated clotting time >480 seconds and reversed by protamine. CPB was conducted with an institutional custom pack including a coated membrane oxygenator, with mild hypothermia (32°C to 33°C). Pump flow was set at 2.4 L/min per square meter. At the end of the surgical procedure, patients were transferred to the intensive care unit and weaned from the ventilator as soon as they met the following criteria: hemodynamic stability, no major bleeding, normothermia, and consciousness with adequate pain control.

Study End Point

We tested the hypothesis that intravenous fenoldopam would reduce the incidence of postoperative ARF compared with intravenous dopamine. The study primary end point was the incidence of ARF after cardiac surgery, defined as an increase of serum creatinine levels of ≥25% from baseline to the maximum value obtained during postoperative hospital stay. Plasmatic creatinine was assayed by our hospital laboratory during the preoperative period, on arrival at the intensive care unit, 4 hours after the operation, and every day during the patients' hospitalization.

Management of ARF

Loop diuretics were administered early in the course of ARF to convert an oliguric to a nonoliguric state. Renal replacement therapy was started when ARF became oligoanuric (urine output <20 mL/h), when creatinine or urea doubled, or in the presence of severe hyperkalemia. Renal support was provided by continuous venovenous hemofiltration (Prisma CPM, Hospal Lyon) with the use of high-flux AN69 membranes with a surface of 0.60 m². A double-lumen catheter (Gam cath, Gambro Intern) was inserted into a femoral, internal jugular, or subclavian vein. The blood pump was set to deliver 120 to 150 mL/min; the goal was an ultrafiltration rate of 1.5 to 2 L/h in predilution or postdilution mode with bicarbonate buffer in the solution. Anticoagulation of the extra corporeal circuit was maintained with a heparin infusion (200 to 1000 U/h) through the inflow side of the circuit.

Power of the Study and Statistical Analysis

Sample-size calculations were based on a 2-sided α error of 0.05 and 80% power. On the basis of previous data investigating postoperative ARF in high-risk patients, we anticipated a 40% frequency of ARF in the standard treatment group and assumed a 50% reduction after treatment with fenoldopam. We calculated that we would need a sample size of 80 patients per group. Therefore, the total study population was 2×80 = 160 patients. A planned interim analysis was performed after 80 patients were included in the protocol following the suggestion of DeMets et al. with the 95% CIs based on the Wilson score for the difference between independent proportions as explained by Newcombe. This analysis showed that no 50% reduction in ARF was to be expected at the end of the study. In this case some authors suggest continuation despite null or adverse findings in order to provide more conclusive evidence against the new therapy (fenoldopam). The documented lack of efficacy of fenoldopam in improving renal outcome, the significant increased incidence of hypotension during CPB, and the suggestive intraoperative trend toward the use of vasoconstrictors caused the safety monitoring board to interrupt the study.

All data were analyzed according to the intention-to-treat principle. Data were stored electronically and analyzed by use of Epi Info 2002 software (CDC) and SAS software, version 8 (SAS Institute). All data analysis was performed according to a preestablished analysis plan. Dichotomous data were compared by the use of 2-tailed χ² test with the Yates correction or Fisher exact test when appropriate; 95% CI estimation for the differences between independent proportions was performed with methods based on the Wilson score. Continuous measures were compared by ANOVA or the Mann-Whitney U test when appropriate; 95% CI estimate for the mean/median difference was performed. Two-sided significance tests were used throughout.
TABLE 1. Clinical Characteristics and Preoperative Data of 80 Patients Who Received Either Fenoldopam or Dopamine to Prevent ARF After Cardiac Surgery

<table>
<thead>
<tr>
<th>Variables</th>
<th>Fenoldopam (n=40)</th>
<th>Dopamine (n=40)</th>
<th>P</th>
<th>Mean/Percent Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68±8.2</td>
<td>69±8.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>9 (22.5)</td>
<td>13 (32.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>74±14.9</td>
<td>72±12.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.8±0.18</td>
<td>1.8±0.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CICSP score</td>
<td>13.7±2.7</td>
<td>13.2±2.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease, n (%)</td>
<td>9 (22.5)</td>
<td>10 (25.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>14 (35.0)</td>
<td>13 (32.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>29 (72.5)</td>
<td>20 (50.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contrast mean administration &lt;48 h, n (%)</td>
<td>6 (15.0)</td>
<td>6 (15.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous cardiac surgery, n (%)</td>
<td>7 (17.5)</td>
<td>10 (25.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular disease, n (%)</td>
<td>19 (47.5)</td>
<td>16 (40.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>44±16.7</td>
<td>43±15.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.56±0.78</td>
<td>1.54±0.59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance, mL/min</td>
<td>50±22.0</td>
<td>49±19.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-aortic balloon pump, n (%)</td>
<td>14 (35.0)</td>
<td>11 (27.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results

Between July 2002 and November 2003, 80 patients were randomly assigned to receive either fenoldopam 0.05 µg/kg per minute or dopamine 2.5 µg/kg per minute (Figure). The 2 groups of patients had similar incidence of postoperative ARF: 17 of 40 (42.5%) in the fenoldopam group and 16 of 40 (40%) in the dopamine group (P = 0.9). Renal replacement therapy was performed on 4 patients (10%) in each group (P = 0.9).

Baseline demographics and clinical characteristics are reported in Table 1. These 80 patients randomized to receive either fenoldopam (40 patients) or dopamine (40 patients) were at extremely high risk of developing ARF because the CICSP score was >10 in all patients (13.7±2.7 in the fenoldopam group and 13.2±2.4 in the dopamine group) and the creatinine clearance was 50±22.0 mL/min in the fenoldopam group and 49±19.2 mL/min in the dopamine group. All participants who underwent random allocation were analyzed according to group assignment.

Table 2 shows intraoperative data. Notably, the only difference within the 2 groups was noted in the development of hypotension during CPB (12 patients in the fenoldopam group and 4 patients in the dopamine group; P = 0.05). There was also a trend toward a more frequent use of norepinephrine during CPB (4 patients, all of them in the fenoldopam group; P = 0.06).

Table 3 shows postoperative data. ARF had the same incidence in the fenoldopam versus the dopamine group, irrespective of the definition used: 25% creatinine increase (42.5% versus 40.0%); 50% creatinine increase (25% versus 25%); and renal replacement therapy (10% versus 10%). Even the other major outcomes did not show any difference, including hospital mortality, length of hospital stay, and time on mechanical ventilation.

Serum creatinine in the overall population rose from a baseline level of 1.6±0.7 mg/dL to a peak postoperative value of 2.0±1.0 mg/dL (P = 0.009), whereas in the patients who developed ARF it showed a 63% increase, from 1.5±0.6 to 2.5±1.1 mg/dL.

Discussion

The principal finding of this prospective, double-blind, randomized trial is that the specific dopamine-1 agonist fenoldopam mesylate does not reduce the risk of ARF after cardiac surgery in high-risk patients compared with standard treatment (dopamine).

Fenoldopam mesylate is a unique vasodilator that selectively increases both renal cortical and outer medullary blood flow while decreasing systemic vascular resistance. 9,17,18 Fenoldopam has been shown to increase renal plasma flow in patients with and without chronic renal insufficiency,19,20 but there are at present no data from prospective clinical trials to support a reduction in the incidence of ARF. Despite the virtual absence of definitive evidence, the use of fenoldopam as a renal protective agent has become nearly standard practice in clinical situations that lead to impaired renal function, such as radiocontrast medium administration, shock, and cardiac or vascular surgery. Beneficial renal effects have been demonstrated at infusion rates as low as 0.03 µg/kg per minute, which are well below those usually required to lower the systemic blood pressure.19

TABLE 2. Intraoperative Data of 80 Patients Who Received Either Fenoldopam or Dopamine to Prevent ARF After Cardiac Surgery

<table>
<thead>
<tr>
<th>Variables</th>
<th>Fenoldopam (n=40)</th>
<th>Dopamine (n=40)</th>
<th>P</th>
<th>Mean/Percent Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPB time, min</td>
<td>83±4.5</td>
<td>85±52</td>
<td></td>
<td>–2 min (–25.9 to 20.8)</td>
</tr>
<tr>
<td>Cross-clamp time, min</td>
<td>55±30.9</td>
<td>61±27.7</td>
<td>0.3</td>
<td>–6 min (–20.7 to 7.2)</td>
</tr>
<tr>
<td>Urinary output during CPB, mL</td>
<td>420±237</td>
<td>460±389</td>
<td>0.8</td>
<td>–40 mL (–208 to 135)</td>
</tr>
<tr>
<td>Intraoperative diuretics, n (%)</td>
<td>21 (52)</td>
<td>18 (45)</td>
<td>0.7</td>
<td>7% (–13.9 to 27.9)</td>
</tr>
<tr>
<td>Oliguria during CPB, n (%)</td>
<td>6 (15)</td>
<td>5 (12)</td>
<td>0.9</td>
<td>3% (–13.4 to 18.3)</td>
</tr>
<tr>
<td>Hypotension during CPB, n (%)</td>
<td>12 (30)</td>
<td>4 (10)</td>
<td>0.05</td>
<td>20% (2.1 to 36.5)</td>
</tr>
<tr>
<td>Norepinephrine during CPB, n (%)</td>
<td>4 (10)</td>
<td>0</td>
<td>0.06</td>
<td>10% (–1.3 to 23.5)</td>
</tr>
<tr>
<td>Hemolysis, n (%)</td>
<td>9 (22)</td>
<td>5 (12)</td>
<td>0.4</td>
<td>10% (7.2 to 26.6)</td>
</tr>
</tbody>
</table>
Chertow et al showed that ARF is independently associated with preexisting conditions or by simultaneous nonrenal injury. Prognosis is determined either by preexisting renal insufficiency or underlying acid-base or metabolic imbalance associated with renal insufficiency.

In a study of 58 patients undergoing repair of thoracoabdominal aortic aneurysm and randomly assigned to receive fenoldopam or placebo, there was a trend toward a relative reduction in the mortality rate of 65%; 2 (7%) of 28 patients in the fenoldopam group versus 6 (20%) of 30 patients in the placebo group ($P=0.1$).

Several nonrandomized studies have shown a lower incidence of contrast nephropathy with fenoldopam and hydration compared with historical controls in stenting procedures. The only large randomized study on the preventive effects of fenoldopam in these high-risk subjects did not show any reduction in the incidence of ARF.

In the present prospective, double-blind, randomized clinical trial, fenoldopam mesylate did not prevent ARF in a high-risk population of cardiac surgical patients. ARF, defined as a postoperative serum creatinine level increase of $\geq 25\%$, developed in 42.5% of patients treated with fenoldopam versus 40% of patients treated with dopamine. Even when a stricter definition of ARF (50% serum creatinine increase) was used, this complication developed in 25% of patients in both groups.

Unfortunately, in this setting the mortality rate is distressingly high despite improvements in intensive care and dialytic technology. Prognosis is determined either by preexisting comorbid conditions or by simultaneous nonrenal complications, usually related to multiple organ dysfunction. Chertow et al showed that ARF is independently associated with early mortality after cardiac surgery, even after adjustment for comorbidity and postoperative complications.

Extracorporeal circulation is associated with multiple perturbations in renal physiology and function. These phenomena are precipitated by nonpulsatile blood flow, macroembolic and microembolic insults to the kidney (organic and inorganic debris), increases in circulating catecholamines and inflammatory mediators, and release of free hemoglobin from traumatized red blood cells. Therefore, during CPB there are substantive decreases (25% to 75%) in renal blood flow and glomerular filtration rate and increases in renal vascular resistance. The impact of these phenomena on clinical outcome is considerable.

Preoperative measures to prevent renal dysfunction include adequate hydration, elimination of medications with adverse effects on renal function, optimization of the hemodynamic status with inotropes and/or vasodilators, and the correction of acid-base or metabolic imbalance associated with renal insufficiency.

Recently, some published studies have suggested the use of fenoldopam as renal protection during CPB. Halpenny et al showed results to support this option in a study performed on a small group of patients. Only 2 studies on fenoldopam in cardiac surgery have been published thus far.

Garwood et al performed a single-center observational study comparing the results with a large multicenter trial and showing good results in patients receiving fenoldopam: reduced serum creatinine levels at hospital discharge compared with preoperative values. However, patients enrolled in this study cannot be considered at high risk of ARF. Each patient who received fenoldopam showed a postoperative increase in creatinine levels at hospital discharge compared with conventional management. Uncomplicated patients who received fenoldopam showed a postoperative reduction of creatinine compared with preoperative values.

Caimmi et al performed the only randomized controlled study on fenoldopam to prevent ARF in cardiac surgery. They included patients with serum creatinine $>1.5$ mg/dL who underwent uncomplicated procedures. Fenoldopam was compared with conventional management. Uncomplicated patients who received fenoldopam showed a postoperative reduction of creatinine compared with preoperative values.

They concluded that fenoldopam was an effective agent in the prevention of renal dysfunction after CPB. Because they compared a group with preoperative diuretic administration

<table>
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<tr>
<th>Variables</th>
<th>Fenoldopam (n=40)</th>
<th>Dopamine (n=40)</th>
<th>$P$</th>
<th>Mean/Percent Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARF (25% creatinine increase), n (%)</td>
<td>17 (42.5)</td>
<td>16 (40.0)</td>
<td>0.9</td>
<td>2.5% (−18.3 to 23.0)</td>
</tr>
<tr>
<td>ARF (50% creatinine increase), n (%)</td>
<td>10 (25)</td>
<td>10 (25)</td>
<td>0.8</td>
<td>0% (−18.7 to 18.7)</td>
</tr>
<tr>
<td>Renal replacement therapy, n (%)</td>
<td>4 (10)</td>
<td>4 (10)</td>
<td>0.9</td>
<td>0% (−14.6 to 14.6)</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>4 (10)</td>
<td>3 (7.5)</td>
<td>0.5</td>
<td>2.5% (−11.5 to 16.7)</td>
</tr>
<tr>
<td>Transfusion, n (%)</td>
<td>21 (56.8)</td>
<td>18 (51.4)</td>
<td>0.8</td>
<td>5.4% (−13.9 to 27.9)</td>
</tr>
<tr>
<td>Postoperative inotropes, n (%)</td>
<td>27 (67.5)</td>
<td>26 (65.0)</td>
<td>0.9</td>
<td>2.5% (−17.7 to 22.4)</td>
</tr>
<tr>
<td>Postoperative hemolysis, n (%)</td>
<td>6 (15)</td>
<td>1 (2.5)</td>
<td>0.054</td>
<td>12.5% (−1 to 26.9)</td>
</tr>
<tr>
<td>Mechanical ventilation, h, median (interquartile range)</td>
<td>20.5 (11.5−77)</td>
<td>21 (10.5−96)</td>
<td>0.7</td>
<td>−1 h (−42 to 19)</td>
</tr>
<tr>
<td>ICU stay, d, median (interquartile range)</td>
<td>3 (1−6)</td>
<td>3 (1−8.5)</td>
<td>0.9</td>
<td>0 d (−2 to 2)</td>
</tr>
<tr>
<td>Hospital stay, d, median (interquartile range)</td>
<td>13 (7−19)</td>
<td>10.5 (6−20.5)</td>
<td>0.8</td>
<td>2.5 d (−2.5 to 6)</td>
</tr>
<tr>
<td>Postoperative creatinine, mg/dL</td>
<td>1.4±0.74</td>
<td>1.4±0.60</td>
<td>0.9</td>
<td>0 mg/dL (−0.30 to 0.29)</td>
</tr>
<tr>
<td>Postoperative creatinine (after 24 h), mg/dL</td>
<td>1.7±0.86</td>
<td>1.6±0.69</td>
<td>0.4</td>
<td>0.1 mg/dL (−0.22 to 0.48)</td>
</tr>
<tr>
<td>Peak postoperative creatinine, mg/dL</td>
<td>2.0±1.01</td>
<td>1.9±0.94</td>
<td>0.5</td>
<td>0.1 mg/dL (−0.29 to 0.59)</td>
</tr>
</tbody>
</table>

ICU indicates intensive care unit.
(fenoldopam) with a group without preoperative diuretic administration, it was no surprise that patients receiving diuretics had an increased urinary output and a decrease in serum creatinine, particularly if they were patients with an uncomplicated perioperative course. Unfortunately, this has nothing to do with ARF or clinical outcome after cardiac surgery. Our study is different from the aforementioned investigations in that (1) we enrolled a high-risk population using the only accepted and validated risk score (CICPS) for cardiac surgery and (2) we defined a clear postoperative clinical outcome.

Study Limitations

The following limitations of the study should be considered:

(1) Did we use too low a dose of fenoldopam (0.05 μg/kg per minute)? Beneficial renal effects have been demonstrated at infusion rates as low as 0.03 μg/kg per minute,2,3 and other authors have studied even lower doses in cardiac surgery.27 It is unlikely that a different dose or infusion duration of fenoldopam would prove effective. In fact, even the 0.05-μg/kg per minute dose in the present study resulted in significant hypotension during CPB, and higher doses are likely to be poorly tolerated.

(2) We compared fenoldopam with dopamine and not with a placebo. Dopamine was the standard treatment for patients at high risk of developing ARF in our center, and we considered dopamine to be the best available treatment. Even if no evidence exists on the benefits of low-dose dopamine in preventing renal damage, it is “at least not harmful” if used for a limited period of time, as stated by recent review articles29 and meta-analysis.30 A notable finding of the recent meta-analysis is that dopamine does not appear to increase the risk of death, ARF, or hemodialysis. Indeed, dopamine seems to be a relatively safe agent, although it is totally ineffective for preventing or treating renal dysfunction.

(3) Although the present study size effectively rules out fenoldopam utility for the prevention of ARF in the study population as a whole, it is possible that subgroups might have been identified that could benefit had more patients been enrolled; similarly, it is also possible that low-risk patients could benefit from fenoldopam.

(4) One could argue that the random variation in serum creatinine assays due to laboratory variation would meet the criteria for ARF, but this is a randomized study, and this aspect cannot affect the analysis; furthermore, this definition of ARF is widely used.13,14

Conclusions and Clinical Implications

On the basis of the present study, fenoldopam should not be used as a prophylactic agent to prevent ARF in a high-risk cardiac surgical population. The negative finding of this investigation suggests that disturbances in intrarenal hemodynamics may not represent the critical pathophysiological insult that produces ARF after cardiac surgery. The authors acknowledge that they studied high-risk patients and that fenoldopam may be beneficial in other subgroups. In high-risk patients, the likelihood of developing ARF after cardiac surgery depends on factors linked to poor cardiac performance and advanced atherosclerotic vascular disease and not to vasodilatory effects.

Acknowledgments

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