Natriuretic Peptides

Renal Protective After All?* Guido Boerrigter, MD, John C. Burnett, Jr, MD Rochester, Minnesota

Renal dysfunction has emerged as an important independent predictor of adverse outcomes, renal as well as cardiovascular. Renal function is crucially affected by intrinsic renal factors (particularly remaining functional renal mass), hemodynamic function (renal perfusion pressure, renal venous pressure), oxygen delivery, and neurohumoral input.

The natriuretic peptides play an important role in cardiovascular homeostasis. The 28-amino acid atrial natriuretic peptide (ANP) and 32-amino acid B-type natriuretic peptide (BNP1–32) are secreted by the heart in response to cardiac stretch and stress. By activating guanylyl cyclase A (GC-A), they exert their pleiotropic actions, which include natriuresis, vasodilation, suppression of renin, angiotensin II, and aldosterone as well as antihypertrophic, antifibrotic, vascular regenerative, and cytoprotective properties (1,2).

Given this background, it is no surprise that clinical trials have tested the therapeutic benefit of administering exogenous ANP (approved in Japan as carperitide) and BNP1–32 (approved in the U.S. as nesiritide) in a variety of cardiovascular disease states. That has led to at times promising, neutral, or disconcerting results as it relates to overall benefit and renal function (3–9).

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Sezai et al. (10) in the NU-HIT for CKD trial in this issue of the Journal tested the renal effects of carperitide infused during and after coronary artery bypass graft surgery (CABG) with cardiopulmonary bypass (CPB) in patients (n = 285) with pre-operative chronic kidney disease (CKD), defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m–2. Carperitide was initiated at the start of bypass at 0.2 μg·kg–1·min–1, reduced to 0.1 μg·kg–1·min–1 at the beginning of oral medication, and discontinued 12 h thereafter. These investigators report that creatinine levels were lower with carperitide compared to placebo on the first day after surgery, and this effect was still present 1 year later. The same was true for aldosterone until 1 month after surgery. Although there was no significant difference in mortality at 1 year, the study was probably not powered for this endpoint. Fewer patients in the carperitide group had a cardiac event, and, importantly, fewer required dialysis.

This study complements 2 similar studies by the same authors with carperitide during and after CPB. In the first, in patients with normal eGFR and left ventricular (LV) function (n = 504), carperitide decreased creatinine compared to placebo during the 7-day post-operative observation period, and reduced the length of hospital stay (8). However, given the small number of events in this healthier group of patients, carperitide did not significantly reduce mortality (1.6% vs. 2.4%) or the need for dialysis (0% vs. 1.6%). In the other study, patients (n = 133) were enrolled with LV dysfunction defined as ejection fraction ≤35% (9). Carperitide decreased creatinine and increased LV ejection fraction compared to placebo for at least a year after surgery, and reduced perioperative complications and hospital length of stay. While all-cause mortality showed no difference, the carperitide group had fewer cardiac events.

Mentzer et al. (5) reported the results of an exploratory randomized trial with nesiritide, the NAPA (Nesiritide Administered Peri-Anesthesia in Patients Undergoing Cardiac Surgery) trial (n = 279) in patients undergoing CPB. Compared to placebo, nesiritide (0.01 μg·kg–1·min–1, no bolus) improved renal function, increased urine output, shortened hospital length of stay, and reduced 180-day mortality. Ejaz et al. (7) compared a 5-day infusion of nesiritide to placebo in patients (n = 94) undergoing high-risk cardiac surgery, in 77% for thoracic aortic aneurysm. Although nesiritide reduced creatinine compared to placebo, there were no differences between groups regarding need for dialysis, all-cause mortality, or both at 30 days. Likewise, the hospital length of stay was similar. Of note, per protocol, the dose of nesiritide was to be increased from 0.01 to 0.03 μg/kg to maintain post-operative urine output >1 ml·kg–1·h–1. This algorithm was probably the reason for a significantly increased use of vasopressors in the nesiritide group, and may conceivably have offset some potential benefit of nesiritide therapy. In a small proof of concept trial, we defined the actions of low-dose nesiritide (0.05 ng·kg–1·min–1) infused for 24 h started at the time of anesthesia in a double-blind placebo-controlled trial of patients with CKD (eGFR <60 ml/min/1.73 m2) undergoing CPB surgery with a focus on cystatin C and aldosterone. We observed a significant decrease in cystatin C with nesiritide compared to placebo and a lowering of aldosterone (6). Taken together, GC-A agonism with both ANP and BNP have shown promising beneficial results in patients undergoing CPB surgery.
What are the potential mechanisms? Given the pleiotropic actions of GC-A agonists, these are likely multifactorial and include suppression of neurohormones such as aldosterone, angiotensin II, and the sympathetic nervous system. Another mechanism could be an improved post-operative LV ejection fraction as was seen in patients with pre-operative LV dysfunction indicated above (9). In addition, GC-A activation may have improved renal perfusion and promoted cell survival, thus inhibiting the loss of functional renal tissue. In future studies, assessment of kidney injury markers, such as NGAL and KIM-1, may help to identify whether GC-A activation indeed reduces kidney injury.

Most recently at the 2011 meeting of the American Heart Association, the results of a key 7,000-patient clinical trial using nesiritide for acute decompensated heart failure (ADHF) were announced and have relevance to the use of natriuretic peptides as therapeutic agents for cardiorenal disease. This trial, ASCEND (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) (11), was conducted after safety concerns were raised regarding renal function and mortality on the basis of publicly available information on earlier trials with nesiritide for HF (3,4). The ASCEND trial showed that nesiritide for patients with ADHF was safe and, specifically, did not harm renal function. However, it also did not improve survival or reduce rehospitalization and only tended to improve symptomatic status (11). Nesiritide was infused at 0.01 μg·kg⁻¹·min⁻¹; an initial 2 μg/kg bolus could be given at the discretion of the investigator, which was the case in approximately 62% of patients. Of note, asymptomatic and symptomatic hypotension occurred more often with nesiritide (21.4% vs. 12.4% and 7.1% vs. 4.0%, respectively). While the demonstration of safety is reassuring, it remains to be seen whether specific groups of acute HF patients can be identified that derive clinically significant benefit from nesiritide.

Many more questions remain regarding GC-A agonists as therapeutic agents that need to be addressed in future studies. For example:

1. An important question is whether there are relevant clinical differences between carperitide and nesiritide, for example, as it relates to the incidence and duration of hypotension.

2. Degradation of NPs to an inactive metabolite is probably a multistep process, and some intermediate NP derivatives are likely to have a shorter half-life while still retaining bioactivity. Would it be safer to administer such a NP derivative with short half-life to patients with ADHF so that any developing hypotension would be less sustained? Do any of these endogenous NP derivatives have an activity profile that may be more appropriate for patients in critical hemodynamic condition (12)? For example, BNP₃₋₃₂, a BNP derivative reported to circulate at higher concentrations than BNP₁₋₃₂, levels in HF patients was natriuretic but not hypotensive in healthy canines (13).

3. Can we modulate the activity of GC-A agonists by combining them with inhibitors of their degradation, e.g., nepilysin inhibitors? Also, can we combine GC-A agonists with phosphodiesterase inhibitors to reduce degradation of the NP’s second messenger cGMP?

4. Should we also target GC-B, the receptor of C-type natriuretic peptide, which has important vascular and renal actions especially at the level of the podocyte (14)? Indeed, the use of a novel dual GC-A and GC-B agonist (cenderitide) designed by our group, which is currently in clinical trials, could have an important role in renoprotection in CPB surgery on the basis of such novel properties.

5. In the case of ADHF, would chronic therapy with NPs after hospital discharge improve survival and reduce rehospitalizations? This strategy is currently being pursued. Specifically, chronic subcutaneous delivery of the above-mentioned cenderitide is being evaluated using the same pump technology used for the treatment of diabetes mellitus.

In summary, Sezai et al. (10) remind us that GC-A agonism has shown promising cardiorenal protective effects in several studies, and that it remains an attractive therapeutic target worthy of continuing investigation.

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REFERENCES


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