Nesiritide Administration in Patients With Left Ventricular Dysfunction Undergoing Coronary Artery Bypass Surgery*

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Nesiritide has the same amino acid sequence as human B-type natriuretic peptide (BNP), which is secreted by the ventricles in response to myocardial stretch. B-type natriuretic peptide relaxes vascular smooth muscle and causes arterial dilatation (1–7). Although BNP may also cause venodilation, the fact that it does not reduce right-sided pressures in precapillary pulmonary hypertension suggests that it may be only a weak venodilator (8,9). B-type natriuretic peptide promotes sodium and water excretion (1–3,10). The filtration fraction and glomerular filtration rate increase consistent with vasoconstriction of efferent arterials and vasodilation of afferent arterials. Sodium reabsorption is inhibited in both proximal and distal tubules. Associated changes include decreased stimulation of the renin angiotensin and sympathetic nervous systems and decreased plasma aldosterone and endothelin-1 levels (4,11,12). Whether these changes are related to the hemodynamic effects of BNP or are direct effects is uncertain.

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As with other vasodilators, nesiritide is effective in treating acute decompensated congestive heart failure. In addition to symptomatic improvement, filling pressures and pulmonary vascular resistance are reduced and cardiac output is increased in a dose-dependent manner without an increased heart rate or plasma norepinephrine level (4). There is no apparent tachyphylaxis during infusions up to 48 h. Nesiritide was shown to be at least as effective as nitroglycerin in treating acute decompensated heart failure (5). However, a meta-analysis suggesting that long-term outcomes may be worse in patients treated with BNP (13) has created considerable controversy that remains to be resolved.

As reported by Mentzer et al. (14) in this issue of the Journal, the NAPA (Nesiritide Administered Peri-Anesthesia in Patients Undergoing Cardiac Surgery) trial was a placebo-controlled randomized study in which patients with left ventricular dysfunction (ejection fraction ≤40%) undergoing bypass surgery were administered nesiritide (low dose and no bolus) or placebo after induction of anesthesia for 24 to 96 h in addition to usual care. The focus was primarily on the effects of nesiritide on renal function. Patients were screened to ensure that blood pressure and filling pressures were not too low for them to safely receive an arterial dilator. The rationale was based on the association of renal dysfunction and worse outcomes after bypass surgery—improved renal protection might improve outcomes. Although serum creatinine increased in both groups, it returned to baseline within 12 h in those treated with nesiritide and remained elevated in the placebo group throughout hospitalization. There was better preservation of the glomerular filtration rate, and urine output was greater in those who received nesiritide. Renal protection was greatest in patients with preexisting renal dysfunction. Hospital length of stay was shorter, and mortality up to 180 days may have been lower in the treatment group.

The effects of nesiritide on renal function were clear; however, translation of those results to clinical outcomes remains to be demonstrated. Mortality was not a prespecified end point but was added during the course of the trial and, even more importantly, data collection was incomplete. There were few deaths, so the lack of follow-up in a substantial proportion of the patients precludes acceptance of the mortality difference with confidence despite the statistical significance of the results. Concomitant drug use would be of great interest. If nesiritide administration can reduce dependence on inotropic agents and diuretics to achieve similar or better hemodynamics in addition to renal protection, this would support considering its use. The mechanism of renal protection was unclear in the NAPA trial—hemodynamic results were similar in both groups. A direct renal protective effect is a viable but unproven hypothesis. Perhaps inotropes and vasoconstrictors may provide seemingly good acute responses but with negative downstream effects, as has been suggested in acute decompensated heart failure (15,16), but incomplete documentation of their use is a missed opportunity to test that hypothesis. Vasoactive agents, diuretics, and inotropes were listed, but the details, including doses, were such that no conclusion can be offered regarding the effects of nesiritide on concomitant drug use. It is also important to note that 303 patients were randomized in 54 participating centers.
over 15 months; therefore, the general applicability of the results in consecutive study-eligible patients is uncertain.

As stated by the authors, the NAPA trial should be considered exploratory. The results in patients with left ventricular dysfunction undergoing bypass surgery support the need for further study of nesiritide in this patient population, as well as in others with congestive heart failure. At this time, it remains unclear just where nesiritide best fits among agents available for parenteral treatment of heart failure. It is also important to assess the venodilating effects of nesiritide. If it is only effective as an arterial dilator, combined use with nitroglycerin may be appropriate in some patients, particularly in those with relatively low blood pressure in whom hypotension should be avoided (17–19).

Optimal dosing, including whether a bolus should be used, needs clarification. Low doses may improve renal function when blood pressure is maintained, whereas higher doses may cause hypotension and decrease renal perfusion, exaggerated by concomitant diuretic use (20). Experience with other parenteral vasodilators would suggest that doses should be titrated to desired effects rather than using arbitrary doses.

Although recent meta-analyses cause concern regarding outcomes, including worsening renal function with nesiritide in acute decompensated heart failure (13,21), results from ongoing clinical trials will soon address these issues. However, there is still much to learn regarding how best to use this promising agent. The NAPA trial provides encouraging results in one subgroup of patients who might benefit from the use of nesiritide, but more comprehensive data are required before promoting routine use in this population.

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REFERENCES