EDITORIAL COMMENT

Cardiorenal Effects of Recombinant Human Natriuretic Peptides*

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The cardiorenal syndrome describes the complex interaction between the kidney and the heart (1). This complex interaction becomes particularly evident when we have to explain the effects of intravenous recombinant human natriuretic peptides (rhNPs) on renal function and outcome in patients with cardiovascular disease. Two examples of rhNPs are recombinant human B-type natriuretic peptide (BNP) (nesiritide) and recombinant human atrial natriuretic peptide (ANP) (carperitide). Carperitide was licensed in Japan in 1995, and nesiritide was licensed in the U.S. in 2001, both for the treatment of acute heart failure. Nesiritide and carperitide both bind to the natriuretic peptide receptor A in the heart, kidney, and other organs, mediating natriuresis, inhibition of renin and aldosterone, as well as vasorelaxant, anti-fibrotic, anti-hypertrophic, and lusitropic effects. No major differences between carperitide and nesiritide have been described. There is, however, continuing controversy on the effects of both nesiritide and carperitide on renal function.

In 2005, a meta-analysis of 5 randomized studies with 1,269 overall acute heart failure patients showed that intravenous nesiritide was associated with an increased risk of worsening renal function (2). However, in a large, randomized, double-blind, placebo-controlled trial, serial infusions of nesiritide were associated with a lower risk of worsening renal function in severe, chronic heart failure patients with renal impairment, although no effects on the primary end point of time to all-cause death or cardiovascular or renal hospital stay at 12 weeks were observed (3).

Besides acute heart failure, intravenous rhNPs are currently also under investigation for perioperative use in patients undergoing coronary bypass surgery. Coronary bypass surgery has many similarities with acute heart failure, such as hemodynamic changes, volume overload, decreased cardiac output, elevated filling pressures, and activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system, resulting in salt and water retention. Also, similar to heart failure, renal dysfunction is very frequently found in patients undergoing coronary bypass surgery and is clearly related to a poor outcome, both in-hospital and during long-term follow-up (4,5). In 2006 it was concluded, after several small studies, that the evidence of the clinical benefit of nesiritide on renal function in patients undergoing coronary bypass surgery was still controversial (6). In 2007, results of a larger, randomized, placebo-controlled trial were published (7). In 272 coronary bypass surgery patients with left ventricular dysfunction, nesiritide reduced the peak increase in serum creatinine, reduced the decrease in glomerular filtration rate (GFR), decreased the length of hospital stay, and lowered 180-day mortality. However, due to the limited sample size and because the mortality end point was added late in the study, the authors concluded that this was an exploratory trial, and these data needed further confirmation.

In this issue of the Journal, Sezai at al. (8) indeed confirm the data of the NAPA (Nesiritide Administered Peri-Anesthesia) trial in the NU-HIT (Nihon University working group study of low-dose Human ANP Infusion Therapy during cardiac surgery) trial. The NU-HIT randomized 133 coronary bypass surgery patients to rhANP or placebo (saline). Renal function was significantly better at 1 month and 6 and 12 months after surgery in the rhANP group compared with the placebo group. This was not accompanied by a reduction in early postoperative mortality (first primary end point), but it was associated with less perioperative complications (second primary end point). However, the sample size calculation was not properly justified, and obviously this trial was too small to allow definite conclusions about the effects of carperitide on clinical outcome. Therefore, although the NU-HIT trial confirmed the positive findings of the NAPA trial, still no definite recommendations on the perioperative intravenous rhNPs in coronary bypass surgery patients can be drawn.

Another reservation on the acceptance of the routine use of intravenous rhNPs in cardiovascular patients is that the mechanisms by which they should improve renal function are still not well-understood. The overall effect is a delicate balance of potentially beneficial and harmful effects on kidney function (= GFR). On the one hand, intravenous rhNPs will in general decrease blood pressure, leading to a decrease in renal plasma flow, which indeed was found with rhBNP (9). Because renal plasma flow is the main determi-

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nant driving GFR in heart failure patients (10), a decrease in GFR could be expected, but in that study, an increase in GFR was observed (9). The explanation for this might be 2-fold. First, a direct effect of intravenous rhNPs on afferent vasodilation has been proposed although not clearly demonstrated (9). Second, renal function is not only dependent on renal plasma flow but on central venous pressure as well (10,11). Because intravenous rhNPs induce a clear reduction in central venous pressure both by direct vasodilation, water and salt excretion, and decreased cardiac filling pressures, this might improve renal perfusion pressure by reducing “renal afterload.” In particular in patients after coronary bypass surgery, who are congested due to postoperative elevated cardiac filling pressures, this effect might outweigh the effects on renal plasma flow and inhibition of the RAAS. Besides hemodynamic effects, rhNPs also have hormonal effects on the kidney and the heart, through inhibition of the RAAS. The RAAS inhibition might preserve renal function in the long term, but in the short term, a decreased angiotensin II production would lead to efferent vasodilation, a decreased glomerular pressure, and therefore a decrease in GFR. In addition, intravenous rhNPs have multiple intrarenal effects on tubular function and several other vasoactive hormones, such as arginine vasopressin (9). These complex effects of intravenous rhNPs on central and renal hemodynamic status as well as intrarenal hormonal and functional actions might also explain why a positive effect on renal function was found in some studies, whereas in other studies no effect or even a deterioration of renal function was found.

How can the findings of these studies be translated into clinical practice? The effects of nesiritide on renal function and clinical outcome in acute heart failure patients remain to be established in an adequately powered study. Next year, the outcomes of the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) trial are expected (12). Data from the ASCEND-HF trial will establish whether nesiritide improves clinical outcome in more than 7,000 patients with acute heart failure. In patients undergoing coronary bypass surgery, the promising data of the NU-HIT trial together with the NAPA trial should be sufficient to initiate a well-designed trial, with sufficient power to detect meaningful differences in both renal and clinical outcome. Given the complex and multiple counteracting effects of intravenous rhNPs on renal and cardiac function, the clinical outcome will probably depend on the cause of renal and cardiac deterioration in the individual patient. To study the effects of drugs that primarily aim to improve renal function on cardiovascular outcome is not only important from a clinical perspective but it will further enhance our understanding of its interaction. As such, the present article adds to the unraveling of the cardiorenal syndrome, which has long been neglected (1) but has received increasing recognition in recent years.

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