

Role of natriuretic peptides in cardiovascular surgery

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Acute kidney injury is a major complication of cardiovascular surgery. Therapies to reduce or prevent acute kidney injury are highly desirable, and recent advances have helped refine the targets for such therapy, albeit with surprises and controversies. Among these therapies, natriuretic peptides have received the most scrutiny owing to the difficulty in explaining the conflicting evidence for effectiveness in some, but lack thereof, in other studies. This article examines the possible reasons for the conflicting results reported with natriuretic peptides in various clinical conditions.

KEYWORDS: acute kidney injury • cardiovascular surgery • natriuretic peptide

Physiological effects

Natriuretic peptides (NP) are peptide hormones that are synthesized within the atria and ventricles in response to atrial distension, angiotensin II stimulation, endothelin and sympathetic stimulation. They are the natural antagonists of the renin–angiotensin system and are involved in the long-term regulation of the sodium and water balance, blood volume and arterial pressure. Atrial NP (ANP) and B-type NP (BNP) have both been used in clinical trials, although BNP is now the most commonly utilized NP in clinical practice. The actions of both peptides are qualitatively similar, despite their differing half-lives (ANP: 3 min; BNP: 20 min); both suppress the renin–angiotensin system and plasma norepinephrine concentrations to a similar degree. However, BNP induces a greater fall in blood pressure and a higher rate of natriuresis in patients with hypertension [1]. ANP and BNP exert their actions via the guanylyl cyclase-linked receptor NP receptor A and indirectly via B-type receptors on vascular smooth muscle cells, with resultant decreases in the level of intracellular calcium ions and sensitivity of the contractile processes [2]. Both peptides are equipotent in their stimulation of endothelial cGMP production, although A-type receptors have a higher affinity for ANP than BNP and are more abundant in the large blood vessels than the B-type receptors [1].

In normal and hypertensive individuals, NPs work preferentially on the venous system at low doses (<4 pmol/kg/min) to reduce preload by increasing venous compliance and

microvascular permeability [3,4]. However, in patients with congestive heart failure, even low doses (<4 pmol/kg/min) of BNP can cause a significant fall in blood pressure without inducing simultaneous changes in cardiac output or heart rate [1]. Chronic elevations of NP levels appear to decrease arterial blood pressure primarily by decreasing systemic vascular resistance, acting on sites within the CNS as well as through the inhibition of norepinephrine release by sympathetic nerve terminals. Thus, BNP appears to affect the vasculature in a dose-dependent manner – at lower doses, it dilates the venous circulation, while at higher doses, it dilates the arterial circulation [5]. NPs increase the glomerular filtration rate (GFR) by selective dilation of the afferent arterioles and constriction of the efferent arterioles without affecting renal blood flow [6]. Natriuresis is enhanced by inhibiting angiotensin-stimulated sodium and water reabsorption in the proximal tubules, and by blocking sodium reabsorption by the amiloride-sensitive cation-channels in the collecting ducts [7]. These observations may provide valuable insight regarding the conflicting evidence for the effectiveness of NPs in clinical applications.

Controversy of BNP in congestive heart failure

No discussion of NPs is complete without mentioning the controversy surrounding the use of BNP in heart failure patients. BNP and N-terminal pro-BNP are markers of congestive heart failure. BNP is the first in a new drug class

approved for the treatment of acutely decompensated congestive heart failure. Administration of BNP leads to a rapid and balanced vasodilatory effect, which results in significant decreases in right and left ventricular filling pressures and systemic vascular resistance and, at the same time, increases in stroke volume and cardiac output without causing a change in heart rate. However, the drug has been embroiled in enormous controversy due to associated increased risk for acute kidney injury (AKI; relative risk: 1.52; 95% CI: 1.16–2.0; $p < 0.003$) [8] and death (relative risk: 1.86; 95% CI: 1.05–3.27; $p = 0.03$) [9,10]. Determining the reason for the increase in incidence of acute renal failure, a risk factor for increased mortality, with the use of BNP in patients with congestive heart failure is complex. However, most of the reported studies administered higher doses (>4 pmol/kg/min) of BNP and documented an associated increased incidence of drug-induced hypotension [11–15]. While high doses of BNP peptide have little or no effect on blood pressure in normal or hypertensive patients, even low doses of BNP reduce the arterial blood pressure of patients with congestive heart failure [16–19] and increase the odds ratio for mortality in this cohort in a dose-dependent manner (odds ratios: 1.35, 1.90 and 2.58 for BNP doses of 0.01, 0.015 and 0.030 $\mu\text{g/kg/min}$, respectively) [8]. These findings may be explained by the increased activity of angiotensin, endothelin-1 and the sympathetic nervous system in congestive heart failure and the resultant vasoconstriction that predisposes to an enhanced degree of NP-induced vasodilatation [20]. In experimental models, use of NPs induced a higher degree of vasodilatation in precontracted versus normal afferent arterioles [6]. It is possible that the high levels of BNP in congestive heart failure act preferentially on the arterial vasculature to cause vasodilatation, as discussed previously [5].

Role of NPs in cardiac surgery

The major risk factor for cardiac surgery-related mortality is postoperative AKI. Increased fluid balance due to aggressive resuscitation in the immediate perioperative period is a predictor of adverse outcomes in such patients. Interestingly, fluid retention following 'maze' and mitral-valve surgery are associated with diminished levels of NP and suggest a potential role for NPs in enhancing diuresis and influencing outcomes. Isolated case reports have shown a beneficial effect of ANP infusions [21]. However, a randomized, blinded, prospective pilot study comparing patients undergoing maze and mitral surgery, including excision of the left atrial appendage, was not able to demonstrate a favorable influence of the use of NPs on diuresis, diuretic dosage or time to extubation [22].

In critically ill patients with established acute tubular necrosis, short-term infusion of ANP was demonstrated to significantly reduce the need for renal-replacement therapy (23 vs 52%; $p < 0.05$) [23]. However, these promising results could not be reproduced in a larger, multicenter clinical trial using a similar protocol [24], nor in another subsequent clinical trial designed to study the effect of ANP on patients with oliguric acute tubular necrosis [25]. Moreover, a meta-analysis of 19 randomized clinical trials of NPs in high-risk patients for AKI reported that in established AKI, the use of NP was associated with a trend toward increased mortality and more adverse events [26]. By contrast, in

patients without established AKI, the administration of ANP at lower doses (50 ng/kg/min) was associated with a 30% increase in GFR, 30–35% increase in renal blood flow and 50–55% increase in urine output [27]. Similarly, a prospective, randomized clinical trial demonstrated that ANP decreased the probability of needing dialysis by 50% and significantly improved dialysis-free survival in patients undergoing cardiovascular surgery [28]. A retrospective analysis of the effect of BNP on renal outcomes in patients following cardiovascular surgery also reported a dramatic reduction in 21-day dialysis-free survival (odds ratio: 0.35; 95% CI: 0.14–0.87; $p = 0.024$) in patients with impaired renal function (serum creatinine level $> 1\text{mg/dl}$) [29]. In the Nesiritide Administered Peri-Anesthesia in Patients Undergoing Cardiac Surgery (NAPA) trial, the prophylactic use of BNP in patients undergoing bypass surgery with an ejection fraction of less than 35% was associated with statistically significant benefits in postoperative renal function and a decrease in mortality at 180 days (6.7 vs 14.7%; $p = 0.046$) [30]. Despite these promising results, a recently concluded prospective, randomized clinical trial did not demonstrate a benefit for the prophylactic use of BNP on the incidence of dialysis and/or death in patients undergoing high-risk cardiac surgery [31].

Right reasons but with the wrong approach?

There are distinct differences in study design, dose and duration of therapy, study cohort, and pre-existing renal function between studies reporting favorable versus negative outcomes with NPs. In general, unfavorable outcomes were associated with the use of high-dose NPs for short durations in established AKI in patients with advanced chronic kidney disease or patients undergoing high-risk surgical procedures [24,25,32]. They were also associated with an increased incidence of hypotension. Interventional trials to reverse established AKI have generally been unsuccessful owing to the presence of profound renal vasoconstriction and loss of renal blood flow autoregulation that accompany this entity [33]. Conversely, the prophylactic use of BNP has been associated with favorable outcomes, which are discussed later [29,30].

The comparison of clinical studies of NPs have been confounded by differing end points, shifting definitions of AKI [34] and the emerging understanding that even a mild degree of AKI that does not require dialysis induces increased long-term risk for renal failure and mortality [35]. The prophylactic use of BNP has been associated with a decreased incidence of AKI (according to the Acute Kidney Injury Network criteria [34]; 2.2 vs 22.4%; $p = 0.004$) and postoperative mean serum creatinine (1.18 ± 0.41 vs 1.45 ± 0.74 mg/dl; $p = 0.028$) despite the lack of benefit on the incidence of 21-day dialysis and/or death [31], particularly in subjects with pre-existing kidney disease (estimated GFR: <60 ml/min/ 1.73 m²). Similar renal protection by BNP has been reported in patients with pre-existing kidney disease [29,36,37] and in patients with poor cardiac function (ejection fraction $< 35\%$) who underwent cardiac surgery [30]. In view of the numerous studies that report subjects with less severe AKI to have better outcomes in terms of mortality and need for dialysis [35,38–41], the long-term effects of this observed renoprotection by NPs in the immediate postoperative period warrant further investigation.

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