Is Human Atrial Natriuretic Peptide (hANP) Effective as an Additive to Cardioplegic Solution During Cardiac Surgery?

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Cardiovascular surgery has become an established procedure and various operative techniques have been refined since the introduction of safe chemical cardiac arrest by infusion of cardioplegic solution. Tremendous efforts have been made by many cardiac surgeons and basic researchers to develop better cardioplegic solutions in order to extend the safety margin of the duration of cardiac arrest for surgical procedures.\(^1\)\(^-\)\(^3\) Today, we can safely arrest the heart for approximately 3h without compromising postoperative cardiac function, if preoperative cardiac function is preserved.

However, more complex operative procedures have been developed to obtain better surgical results, not only for the early phase but also for long-term outcomes, including complex mitral valvuloplasty for degenerative or infective mitral regurgitation, root replacement with the native aortic valve preserved, and the Norwood procedure for congenital hypoplastic left heart syndrome, among others. In addition to these, we are operating on more patients with depressed cardiac function, in whom the duration of cardiac arrest during the procedure is critical for restoring postoperative cardiac function, even if the duration of cardiac arrest is short. Therefore, continuous improvements in the cardioplegia strategy are mandatory for achieving improvements in cardiac surgical results.

Atrial natriuretic peptide (ANP) was isolated and identified by Kangawa and Matsuo in 1984.\(^4\) ANP is synthesized mainly in the atrium and has been found to elicit potent diuretic and natriuretic activities, as well as vasorelaxant activity. An ANP preparation, carperitide (human ANP: hANP), has been developed and used for the treatment of heart failure and renal failure. In the field of cardiac surgery, low-dose continuous infusion of hANP from the beginning of cardiopulmonary bypass (CPB) has been reported to compensate for CPB shortcomings by inhibiting water retention in the third space, decreasing peripheral vascular resistance, suppressing the renin–angiotensin–aldosterone system, and exerting a strong diuretic effect without causing hypotension or rebound phenomena.\(^5\)\(^-\)\(^8\)

The effect of hANP as an additive to cardioplegic solution has been previously studied in experimental preparations,\(^9\)\(^,\)\(^10\) however, its use in a cardioplegic solution in a clinical setting has not been assessed. In this issue of the Journal, Sezai et al\(^1\) show, for the first time, the efficacy and safety of hANP administration into the coronary circulation (referred to as the “hANP shot”) after cardioplegic cardiac arrest during cardiac surgery. With regard to the primary endpoint, the authors found that the hANP group had significantly lower creatine kinase (CK)-MB levels at both 3h after surgery and on postoperative Day 1. The hANP group also had significantly lower troponin-I levels on postoperative Day 1 with significantly lower human-heart fatty acid-binding protein levels upon returning to the intensive care unit (ICU) as compared with the placebo group. The findings of this study indicate that myocardial damage may have been lowered in the hANP group as compared to the placebo group.

Regarding the mechanisms underlying the cardioprotective effects of hANP, the authors found that cyclic guanosine monophosphate (cGMP) levels were significantly higher in the hANP group than in the placebo group upon returning to the ICU. In a previous experimental study using pigs,\(^10\) the “hANP shot” group also demonstrated higher cGMP levels, not only in blood from the coronary sinus, but also in the myocardium. The authors also found that the myocardial calcium concentrations were significantly decreased during reperfusion, which was associated with elevated myocardial and blood cGMP levels. Therefore, it is suggested that hANP acts directly on the myocardium and inhibits calcium overload through cGMP, thereby improving the “stunned myocardium” caused by aortic cross-clamping. Using electron microscopy, the authors further found that hANP alleviated ischemic changes in the nuclei, myocardial fibers, and mitochondria; further, hANP also preserved myocardial ATP levels.

A confounding factor in the study by Sezai et al for evaluating the effects of the “hANP shot” is that continuous infusion of low-dose hANP (0.02 μg · kg\(^{-1}\) · min\(^{-1}\)) was performed in both the “hANP shot” and the placebo groups from the start of CPB.\(^11\) In previous clinical studies, a significant increase in plasma cGMP levels was reported during continuous low-dose hANP infusion (0.02–0.05 μg · kg\(^{-1}\) · min\(^{-1}\)), which was associated with improved hemodynamic parameters such as pulmonary capillary wedge pressure, right atrial pressure, cardiac index, left ventricular stroke work index, and systemic diastolic function.

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Received July 24, 2011; accepted July 25, 2011; released online August 4, 2011

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vascular resistance in the early postoperative phase, as well as favorable clinical findings such as a reduced incidence of postoperative arrhythmia and heart failure, not only in the early postoperative phase, but also in the long-term. Kitakaze et al reported the findings of a prospective multi-center study, which demonstrated that low-dose intravenous infusion of hANP (0.025 μg·kg$^{-1}$·min$^{-1}$) reduced infarct size, as evaluated by total CK levels, and increased left ventricular ejection fraction at 6–12 months after acute myocardial infarction.

The cardioprotective effects of hANP demonstrated by Sezai et al were likely associated with the continuous intravenous infusion of hANP during the procedure and the “hANP shot” immediately after the infusion of cardioplegic solution. Differentiating between the general effects of the hANP infusion and the topical effects of the “hANP shot” is not possible at this point. However, because the placebo group also received a continuous intravenous infusion of hANP, the “hANP shot” appears to have exerted additional cardioprotective effects, probably directly on the myocardium.

The dose of the “hANP shot” may also affect treatment efficacy. In the experimental study using pigs, a high-dose “hANP shot” (100 μg) was associated with higher blood cGMP levels and higher residual myocardial ATP levels compared with a low-dose “hANP shot” (25 μg), although myocardial calcium and cGMP levels were comparable. We do not yet know whether the effects of the “hANP shot” are dose-dependent and whether a dose of 100 μg is adequate for obtaining maximum cardioprotective effects.

Lastly, Sezai et al excluded patients who required more than 1 dose of cardioplegic solution because of prolonged aortic cross-clamping from their study. The average duration of aortic cross-clamping in this study was relatively short, at approximately 60 min. Because cardiac surgical procedures have become more complex, a longer aortic cross-clamping time is required and thus the cardioprotective effects of the “hANP shot” should be evaluated in patients experiencing a longer period of ischemia. Nevertheless, the “hANP shot” may be a potent and promising additive to the cardioplegic solution during cardiac surgery. Further investigations are required before using this method in more complex cases.

References


