

# Do engineered natriuretic peptides have greater therapeutic potential than do native peptides?

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**This editorial refers to ‘A novel chimeric natriuretic peptide reduces cardiomyocyte hypertrophy through the NHE-1–calcineurin pathway’ by A. Kilić *et al.*, pp. 434–442, this issue.**

As is well known, intravenously infused nesiritide [a recombinant form of brain-type natriuretic peptide (BNP)] antagonizes renin–angiotensin–aldosterone system activation and induces natriuresis, diuresis, and venous and arterial dilation. When administered to patients with acutely decompensated heart failure, a rapid reduction of pulmonary capillary pressure and consequent relief of dyspnoea often results. However, BNP-induced dilation of resistance (arterioles) and capacitance (veins) vessels taken together with the diuresis-associated reduction of blood (plasma) volume causes clinically significant systemic hypotension in some patients. Unfortunately, this hypotension can be associated with decreased renal perfusion and worsening of renal function, and the latter has been associated with increased morbidity and mortality in some clinical trials.<sup>1</sup> The hypotension and consequent complications can be attenuated by reducing the dose of nesiritide being administered.<sup>1</sup>

Recently, Burnett and colleagues speculated that they might be able to improve the therapeutic properties of natriuretic peptides by modifying their structures. Their goal was to generate a natriuretic peptide that retained the biological activities of BNP *sans* the capacity to dilate resistance vessels. Their first engineered chimeric natriuretic peptide (CD-NP) comprised the 15-amino acid C-terminus of the *Dendroaspis* peptide (a snake-derived natriuretic peptide) and the peptide ring component of the cardiac-type natriuretic peptide (CNP). CNP lacks renal actions but retains veno-dilator capacity and has only modest dilatory effects on resistance vessels. CD-NP had potent natriuretic and diuretic effects and retained veno-dilatory effects in normal dogs but did not cause significant systemic hypotension.<sup>2</sup> Moreover, in *in vitro* studies, CD-NP was shown to inhibit proliferation of cardiac fibroblasts.<sup>2</sup> In a preliminary pharmacological study performed in normal human volunteers, CD-NP was also found to have potent natriuretic and renin–angiotensin–aldosterone system antagonistic effects; notably,

it did not induce significant systemic hypotension.<sup>3</sup> CD-NP is now being evaluated in a Phase II clinical trial.

In the current report, Kilić *et al.*<sup>4</sup> examine the cellular effects of a newer chimeric molecule (designated CU-NP). In CU-NP, the ring structure of CNP is joined to the N- and C-termini of urodilatin. The latter is another natriuretic peptide with potent diuretic and natriuretic properties as well as arteriolar and venous dilatory effects. Preliminary studies of CU-NP in anaesthetized normal dogs had indicated that this agent increases the rates of glomerular filtration and renal sodium and water excretion. Further, although administration of CU-NP reduced pulmonary capillary wedge pressures, systemic hypotension did not occur. In this model, the natriuretic peptide urodilatin did induce significant arterial hypotension in addition to the aforementioned renal and veno-dilator effects (see cited references in Kilić *et al.*<sup>4</sup>).

That some natriuretic peptides antagonize hypertrophic signalling pathways in cardiomyocytes and fibrosis-associated signalling pathways in fibroblasts has been known for some time.<sup>4</sup> To determine whether CU-NP retained these potentially beneficial properties, Kilić *et al.*<sup>4</sup> tested the effects of CU-NP on selected hypertrophic signalling pathways following their activation (in neonatal rat cardiomyocytes) by classical G<sub>q</sub>-coupled receptor agonists. As expected, each agonist induced cardiomyocyte hypertrophy that was associated with significantly increased expression of the sarcolemmal sodium–hydrogen ion exchanger (NHE) mRNA, protein, and activity. A downstream consequence of increased NHE activity was increased calcineurin activity. This was presumably mediated by increased cytosolic entry of calcium (via the sodium–calcium exchanger) caused by the higher cytosolic sodium levels engendered by increased NHE activity. A significant consequence of calcineurin activation was greater nuclear localization of NFAT, a transcription factor known to activate many hypertrophy-associated genes. Notably, CU-NP abrogated this sequence of agonist-induced molecular responses with an efficacy comparable to that of native natriuretic peptides. These data are consistent with earlier reports that showed that direct inhibition of the NHE also antagonized the effects of pro-hypertrophic stimuli<sup>5</sup> in conjunction with normalization of the calcineurin pathway.<sup>6</sup> The precise mechanisms by

which CU-NP prevents agonist-induced up-regulation of the sarcolemmal NHE remain unclear.

Notably, CNP and its derivative CU-NP can both activate the natriuretic peptide B and A receptors.<sup>4</sup> The B-type receptor, unlike the A-type receptor, is not down-regulated in failing cardiomyocytes.<sup>7</sup> Importantly, cardiac overexpression of CNP was shown to attenuate left ventricular hypertrophy produced by infarction in the mouse heart.<sup>8</sup> Hence, CU-NP might have more potent anti-hypertrophic effects in diseased hearts than does BNP, which primarily activates A-type receptors.<sup>4</sup>

Therefore, it is reasonable to hypothesize that the 'improved' haemodynamic profile of the new chimeric molecules may decrease the hazards of short-term (i.e. conventional) natriuretic therapy for decompensated heart failure; this view is consistent with clinical studies, suggesting that relatively low-dose nesiritide therapy (which induces less hypotension) also appears to be safe.<sup>1</sup>

Clinically, current (i.e. short-term) nesiritide dosing schemes are useful because of their renal and haemodynamic effects that result in relief of dyspnoea. However, the potential beneficial effects of natriuretic peptides on hypertrophic and fibrosis signalling pathways are likely not fully realized during (conventional) short-term periods of administration. Long-term administration of CU-NP (or CD-NP) variants appears to be feasible from a pharmacological standpoint and might become clinically practical if additional modifications could prolong their biological half-lives and eliminate the need for their intravenous delivery (i.e. a molecule suitable for subcutaneous or oral administration).

In support of the speculation that chronic natriuretic peptide administration might also be beneficial because of its potential anti-hypertrophic effects, animal studies have shown that chronic treatment with BNP favourably affected the course of post-myocardial infarction-induced left ventricular remodelling in the rat heart.<sup>9,10</sup> Further, in a limited study performed in patients with acute anterior myocardial infarction and successful percutaneous revascularization, a Mayo Clinic team (including several of the current investigators) reported that a 3-day period of low-dose BNP infusion (initiated shortly following the revascularization procedure) suppressed plasma aldosterone levels and attenuated the severity of post-infarction left ventricular structural and functional remodelling. The latter was evaluated (with echocardiography) before initiating BNP infusion and 1 month following the treatment period.<sup>11</sup> Because patients in both the control and BNP infusion groups were given an angiotensin-converting enzyme inhibitor following their infarctions, these preliminary clinical data suggest (but certainly do not prove) that chronic natriuretic peptide therapy has added beneficial effects beyond those achieved by chronic angiotensin-converting enzyme inhibitor administration. Limited clinical studies of the effects of atrial-type natriuretic peptide have also suggested that administration of this peptide for several days following myocardial infarction and

revascularization may limit the extent of subsequent left ventricular remodelling (for review, see Kasama *et al.*<sup>12</sup>).

To summarize: CU-NP (i) has a more favourable haemodynamic profile than does BNP and (ii) retains the renal, endocrine, and anti-hypertrophic effects of BNP. Hence, CU-NP may prove to be a beneficial addition to the current (acute) treatment protocol for patients with decompensated heart failure. Whether future iterations of natriuretic peptide molecules will prove to be useful anti-hypertrophic agents when administered chronically will require much more laboratory and clinical investigation.

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