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Review

Therapeutic benefits of increasing natriuretic peptide levels

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Abstract

Natriuretic peptides play an important role in water and salt homeostasis and in the regulation of the cardiovascular system. In recent years, exogenous administration of natriuretic peptides has primarily been used to improve our understanding of the role of natriuretic peptides. Also, it became evident that natriuretic peptides may be used therapeutically. Because of their peptide character, they cannot be administered orally and, therefore, may be used for short-term intravenous therapy only. In recent years, inhibitors of neutral endopeptidase, which degrades natriuretic peptides to inactive metabolites, have been investigated. This review focuses on the potential benefits of increasing natriuretic peptide levels, either through exogenous administration or inhibiting the degradation of endogenous natriuretic peptides. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Natriuretic peptide; Heart failure; Hypertension; Vasoactive agents; Hormones; ACE inhibitors

1. Rationale for the therapeutic increase in natriuretic peptides levels

Natriuretic peptides are importantly involved in water and sodium balance and cardiovascular homeostasis (Fig. 1). In response to an increase in filling pressures and stretch of the atrial and ventricular walls, atrial natriuretic peptide (ANP) and brain or B-type natriuretic peptide (BNP) are released into the bloodstream [1,2]. In addition, several neurohormones such as endothelin-1 (ET-1), arginine vasopressin (AVP), and catecholamines stimulate the secretion of natriuretic peptides [3,4]. This leads primarily to a reduction in preload by increasing water and sodium excretion, but also by shifting plasma from the intravascular to the extravascular space [5]. The effects of ANP and BNP are mediated by the transmembrane guanylyl-cyclase receptor type A, which promotes intracellular cGMP formation. Thus, they cause arterial and venous vasodilation [6]. Additional important properties include the ability to inhibit the activity of various neurohumoral systems, involved in the pathogenesis and development of arteriosclerosis, hypertension and progression of congestive heart failure (CHF) [7–9].

1.1. Natriuretic peptides in various cardiovascular diseases

The pivotal role of natriuretic peptides in the early development of CHF has been demonstrated in various animal studies. Prevention of the early rise of ANP in pacing-induced CHF by surgical removal of the atrial auricles may result in hemodynamic deterioration and in significant activation of the renin–angiotensin system [10]. In contrast to ANP, BNP is not or only minimally elevated in acute pacing-induced CHF [11]. Administration of BNP resulted in haemodynamic improvement and prevention of water and sodium retention [11], a finding we recently could confirm (unpublished data). However, further increase in already elevated serum ANP levels in this setting was without effect (unpublished data, Fig. 2). In patients suffering from large myocardial infarction the rise in BNP-levels results in left ventricular systolic dysfunction, which is seen as a compensatory mechanism to prevent further deterioration [12]. In chronic CHF, natriuretic

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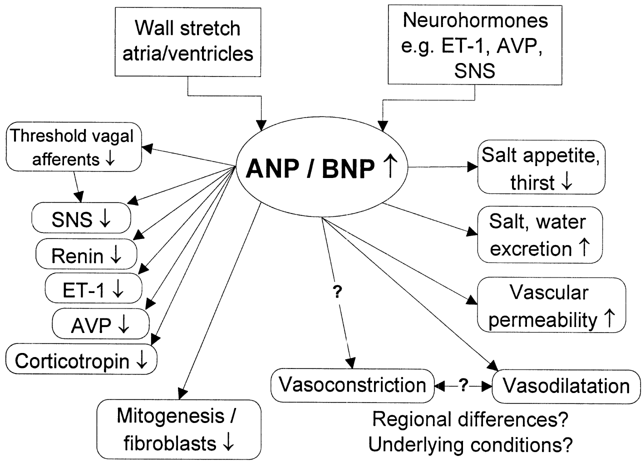

Fig. 1. Effects of natriuretic peptides released from the heart as a result of increased cardiac wall stretch (increased venous return) or various neurohormones. Both peripheral and central effects lead to reduction of the initial promoters. ? denotes effects or mechanisms not yet completely elucidated. ANP, atrial natriuretic peptide; AVP, arginine vasopressin; BNP, brain natriuretic peptide; ET-1, endothelin-1; SNS, sympathetic nervous system.

peptides may contribute to maintenance of cardiac function in early, asymptomatic stages of disease. At a later stage, however, progression of CHF may be related to loss of efficacy of natriuretic peptides [13].

Natriuretic peptides may also play a role in arterial hypertension. Polymorphism of the ANP gene was found in some patients with essential hypertension [14]. Moreover, a lower ratio of the guanylyl-cyclase type A receptor to the clearance receptor was found in obesity-related hypertension [15]. Other evidence derives from animal models. Transgenic mice overexpressing ANP or BNP were shown to have lower blood pressure than control animals [16,17]. Disruption of the pro-ANP gene in mice elevated blood pressure, particularly in the presence of salt-rich diet [18]. Salt-resistant hypertension was observed in mice lacking the guanylyl cyclase type A receptor [19]. Further, ANP may play a role in counteracting excess of mineralocorticoids [20].

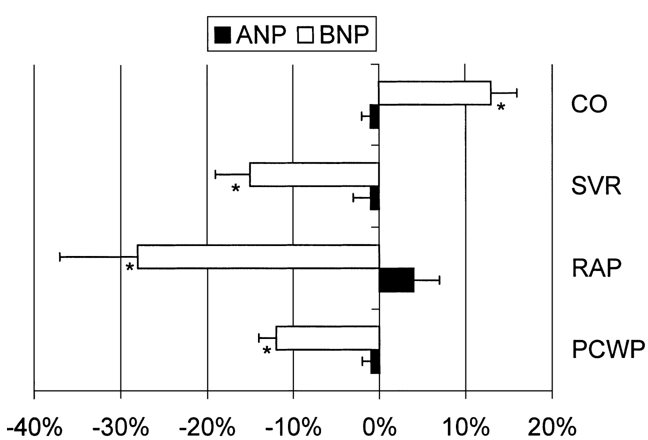

Fig. 2. Hemodynamic effects of equimolar doses of ANP and BNP (10 pmol/kg per min) in a crossover comparison in acute pacing-induced heart failure (AHF) in eight dogs (mean±S.E.M.). Tachycardic pacing was applied for 1 h to increase pulmonary wedge pressure (PCWP) to 15 mmHg before ANP and BNP was given for 30 min each in random order. Between infusions, there was a washout period of 30 min. *All differences between ANP and BNP $P<0.01$ (Wilcoxon Exact Test). CO, cardiac output; SVR, systemic vascular resistance; RAP, right atrial pressure.

1.2. Effects of natriuretic peptides on other neurohormones and mitogenesis

In addition to the well-described inhibitory effect on renin release [21], natriuretic peptides may also counteract other vasoconstrictor neurohumoral systems. Among others, natriuretic peptides may inhibit ET-1 secretion in vitro [8]. Moreover, there is general agreement that ANP inhibits sympathetic activity [9,22,23], despite some contradictory findings [24]. Effects of BNP in this context are less well known. We have recently found inhibition of systemic and regional sympathetic activity by exogenous BNP in both healthy controls and CHF patients [25], pointing to a potential role of natriuretic peptides in the regulation of the sympathetic nervous system.

Moreover, natriuretic peptides have antimitogenic activity. ANP and C-type natriuretic peptide (CNP) have been shown to inhibit mitogenesis in cultured vascular smooth muscle cells and in balloon injured carotid arteries [26,27]. These effects seem to be cGMP-mediated, implying that natriuretic peptides may modulate growth in the vessel wall and possess inhibitory properties on the development of arteriosclerosis [28]. ANP further inhibits growth of cardiac fibroblasts in vitro, independently of the underlying mechanism of stimulated proliferation [29,30]. Therefore, natriuretic peptides may favourably affect remodelling by reducing the myocardial proliferative response to injury.

2. Effects of systemic and local administration of natriuretic peptides

The hemodynamic effects of natriuretic peptides have been widely investigated in both health and cardiovascular disease. Whereas reduction in cardiac filling pressures has been almost uniformly reported, arterial vasodilatation as a response to natriuretic peptides is less consistent. In theory, one would expect reduction in systemic vascular resistance. Some studies showed an increase in cardiac output despite significant reduction in filling pressures [31–33]. Others have reported no effect on or even an increase in systemic vascular resistance [34–36]. The latter finding might be explained by a counterregulatory activation of baroreceptors with high doses of natriuretic peptides [28], despite their inhibitory effect on the sympathetic nervous system and the lowering of the activation threshold of vagal afferents [37].

The arterial response to exogenous natriuretic peptides may vary regionally. Natriuretic peptides cause vasodilatation in renal afferent arterioles but vasoconstriction in efferent arterioles [38], increasing the glomerular hydrostatic pressure, and thereby enhancing glomerular filtration rate. In healthy conscious dogs, natriuretic peptides have been shown to cause mesenteric vasoconstriction, but different responses have been observed in other vascular beds in the same animals. Interestingly, the vascular response was independent of the autonomic nervous system [39,40]. Thus, natriuretic peptides seem to be involved in the distribution of regional blood flow. Although the underlying mechanism for the vasoconstrictive effect of natriuretic peptides is still unexplained, it may be hypothesised that the arterial response to natriuretic peptides is not uniform and depends on the underlying conditions. So far, systemic vasodilatation has primarily been observed in patients with manifest cardiovascular or renal disorders [31–33,36].

Because of the prevailing beneficial effects, there was early interest in the therapeutic use of ANP in humans [41]. Other atrial natriuretic peptides, such as urodilatin (i.e. proANP(95-126)) and vessel dilator (i.e. proANP(31-67)), and BNP received attention. Administration of natriuretic peptides has been investigated in patients with various cardiovascular conditions such as arterial hypertension [21], myocardial infarction, coronary artery disease [42,43], and CHF [44]. Moreover, therapeutic use of natriuretic peptides was considered in other conditions, such as renal insufficiency [45,46], liver cirrhosis [47,48], bronchial obstruction [49,50], and in the immediate postoperative period after cardiac surgery [51].

2.1. Administration of natriuretic peptides in arterial hypertension

In arterial hypertension, ANP has been shown to significantly reduce blood pressure in a dose-dependent manner [21,36]. In addition to increasing sodium and water excretion, which may be enhanced compared to healthy controls [52], natriuretic peptides may significantly reduce the activity of the renin–angiotensin–aldosterone system [21]. Moreover, infusion of BNP was found to improve diastolic function of the left ventricle in patients with isolated diastolic CHF due to hypertensive heart disease [53]. These effects are desirable and may be more favourable than those of other antihypertensive drugs, some of which may stimulate vasoconstrictor neurohumoral systems. However, lack of an oral form imposes limitations. Acute decompensation of pure diastolic CHF may be an exception to this notion [53]. Nevertheless, these studies expand the current pathophysiological understanding of arterial hypertension and set the stage for the use of drugs, which aim to increase the endogenous levels of natriuretic peptides (i.e. neutral endopeptidase inhibitors, see below).

2.2. Administration of natriuretic peptides in coronary artery disease

Natriuretic peptides have effects that are of potential benefit in coronary artery disease. Thus, infusion of ANP reduced the extent and severity of myocardial perfusion defects and prevented ST-segment depression during exercise [42]. Both ANP and BNP infused into the left main coronary artery increase coronary sinus blood flow and decrease coronary vascular resistance [54,55]. Natriuretic peptides may reduce chest pain and ECG changes in patients with vasospastic angina [56]. It has been suggested that ANP improves myocardial perfusion to areas of ischaemia by acting on collateral vessels [57]. Pacing-induced myocardial ischaemia has been attenuated in patients with coronary stenosis with but not in patients without collaterals [58]. Natriuretic peptides may therefore contribute to the local homeostatic regulation during conditions of myocardial ischaemia, similarly to the local distribution of blood discussed earlier [39].

There may be additional effects that are beneficial in the acute coronary syndrome. Neutrophils incubated in either ANP or BNP showed less adhesion and elastase release, and reduced detachment of endothelial cells [59]. Neutrophils are believed to contribute to endothelial cell damage in ischemic and reperfusion injury. They contain neutral endopeptidase, which is significantly increased in acute myocardial infarction [60]. Thus, deficient inhibition of neutrophils by natriuretic peptides in acute coronary syndrome may play an essential pathophysiological role. This may be seen in line with the relationship of elevated white blood cell counts to reduced myocardial perfusion and high incidence of new CHF in acute myocardial infarction [61]. Infusion of natriuretic peptides may therefore prove to be useful in patients with acute coronary syndromes.

2.3. Administration of natriuretic peptides in congestive heart failure

Several studies investigated the effects of natriuretic peptides on haemodynamics, renal function, and other circulating neurohormones in CHF. The majority of the human studies were conducted in patients with advanced CHF. Initial results were promising as they showed a significant reduction in filling pressures and systemic vascular resistance with an increase in cardiac output [62]. Sodium and water excretion were increased and both circulating noradrenaline and aldosterone decreased compared to placebo [44]. The expectations were slowed down when it became evident that the efficacy of natriuretic peptides may be lost over time as CHF progresses [63,64]. This phenomenon seems to correlate with the transition from asymptomatic to overt CHF [13]. In the human forearm model, both intra-arterial ANP and BNP caused less vasodilatation and local production of cGMP in patients with CHF than in healthy volunteers [63]. The production of cGMP in relationship to the extraction of ANP across the lung [65] and the leg [64] was significantly reduced in advanced compared to early CHF. One of the underlying factors for this observation may be downregulation of the guanylyl-cyclase type A receptor although this has not yet been specifically investigated in CHF. Downregulation of this receptor was found in patients with chronically elevated levels of natriuretic peptides in chronic but not in paroxysmal atrial fibrillation [66]. However, natriuretic peptides in CHF were not found in all studies [67]. Moreover, hyporesponsiveness may differ between various types of natriuretic peptides [68]. A recent study showed that vessel dilator strongly enhanced sodium and water excretion and had beneficial hemodynamic effects in patients with CHF [69]. In contrast, another fragment of pro-ANP (i.e. proANP(1-30) had significantly less diuretic and natriuretic effects in CHF compared to healthy controls. This reduced efficacy was significantly different to the effects of vessel dilator [68].

Although not based on scientific grounds, it was postulated that hyporesponsiveness is also less pronounced for BNP than for ANP [70]. Intravenous administration of BNP caused a dose-dependent reduction in filling pressures and peripheral vascular resistance and an increase in cardiac output in patients with acutely decompensated CHF [70]. Most recently, the beneficial hemodynamic effects of BNP (nesiritide, i.e. recombinant human BNP) in symptomatic CHF were confirmed in two large studies [31,32].

The first of these studies investigated the hemodynamic effects of three different doses of nesiritide (0.015, 0.03, and 0.06 μg/kg per min) over 24 h compared to placebo in 103 patients with decompensated CHF [31]. Patients had a pulmonary capillary wedge pressure ≥18 mmHg and a cardiac index ≤2.7 l/min per m^2. Nesiritide had beneficial dose-dependent hemodynamic effects. The drug was generally well tolerated, but hypotension occurred more often with high doses of BNP ($P=0.027$ trend test). Unexpectedly, there were no significant effects on sodium or water excretion. This may be in contrast to the renal effects observed with vessel dilator [69], although no direct comparison of these two agents in CHF has been published. Hemodynamic peak effects of nesiritide were seen 3 h after the start of infusion and persisted to the end of the infusion (24 h). No rebound effect was observed after cessation of the infusion.

The largest trial investigating the therapeutic use of BNP in CHF has been published most recently [32]. In a first arm with 127 patients, efficacy of 0.015 and 0.03 μg/kg per min of nesiritide over 6 h was compared to placebo. The results showed beneficial hemodynamic changes (Fig. 3), increased urine production (mean urine output over 6 h: placebo vs. low dose vs. high dose nesiritide 380, 560 and 659 ml, respectively, $P=0.004$), and reduction in plasma aldosterone concentration (+17, −69, and −44 pmol/l, respectively, $P=0.03$). After 6 h, dyspnoea was improved in 56 and 50% of the patients receiving low and high dose nesiritide, respectively, but in only 12% of the patients receiving placebo ($P<0.001$). A similar reduction in fatigue (32 and 38%, respectively, vs. 5%, $P<0.001$) and improvement in clinical status (Fig. 4) were observed. In a second comparative arm, the two doses of nesiritide (0.015 μg/kg per min, $n=103$; 0.03 μg/kg per min, $n=100$) were compared with standard therapy ($n=102$; most commonly dobutamine) for up to 7 days to detect changes in symptoms and to evaluate safety. There were similar improvements in symptoms in all three treatment groups. Although the patients lost similar amounts of weight, intravenous diuretics were less often needed in patients assigned to nesiritide (84 and 75%, respectively) than in patients under standard treatment (96%, $P<0.001$). The

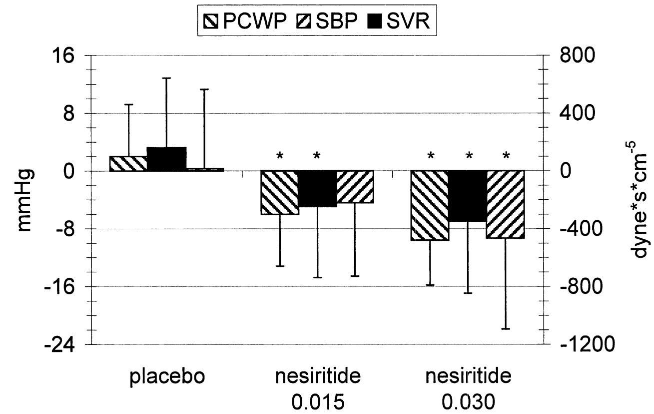

Fig. 3. Hemodynamic effects of two doses of nesiritide (human BNP, μg/kg per min) versus placebo in acute decompensated heart failure in 127 patients randomly assigned to one treatment group. Changes from baseline after 6 h of BNP infusion (mean±S.D.). Comparisons among all three groups $P\leq0.001$ by the omnibus F-test (one-way ANOVA); *$P<0.001$ for the pairwise comparison with placebo by the F-test. PCWP, pulmonary capillary wedge pressure; SBP, systolic blood pressure; SVR, systemic vascular resistance. Adapted from Colucci et al. [32].

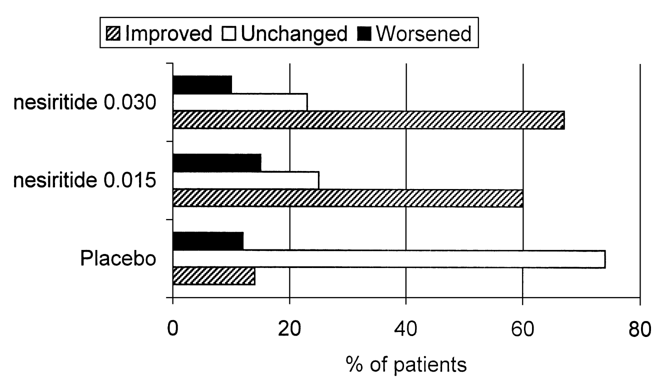

Fig. 4. Effects on overall symptoms of two doses of nesiritide (human BNP, μg/kg per min) versus placebo in acute decompensated heart failure ($n=127$). Symptoms were assessed on a five-category scale. Comparison among the three groups, $P<0.001$ by non-parametric ANOVA. Adapted from Colucci et al. [32].

most common side effect of nesiritide was dose-related, mostly asymptomatic hypotension (12 and 24%, respectively, vs. 7%, $P<0.01$). Bradycardia was more common in the nesiritide groups (4 and 5%, respectively, vs. 0%, $P<0.05$) and nonsustained ventricular tachycardia was noted less in the high dose nesiritide group (1%) than in the other two groups (low dose nesiritide 10%, standard therapy 8%, $P<0.05$).

These trials underline the potential benefit of nesiritide in decompensated CHF. Standard therapy in this setting still requires intravenous diuretics, dobutamine, milrinone, nitroglycerin, and sodium nitroprusside. All these therapies have significant drawbacks, including arrhythmias (dobutamine, milrinone [71], potentially augmented by electrolyte disturbances due to diuretics [72]), development of tolerance (nitroglycerin [73]), toxic effects (sodium nitroprusside), and stimulation of vasoconstrictor neurohumoral systems (pure vasodilators). Hypotension as the most common side effect of nesiritide might be overcome by careful uptitration, which so far has not been tested.

2.4. Administration of natriuretic peptides in acute renal failure

In experimental and small human studies, atrial natriuretic peptides showed beneficial effects in acute renal failure [74,75]. ANP was also investigated in an open-label, clinical study in 53 patients with acute tubular necrosis, transiently increasing creatinine clearance during infusion and decreasing the need for dialysis [45]. In contrast, a randomised double-blinded trial failed to show anatritide, a synthetic 25-amino-acid form of ANP, to ameliorate dialysis-free survival in 504 critically ill patients with acute tubular necrosis [46]. Nevertheless, in a predefined subgroup of patients with oliguria (i.e. <400 ml urine/day), a 24-h infusion of anatritide improved dialysis-free survival to 27% compared to 8% in the placebo treated group ($P=0.008$). However, anatritide was detrimental in the non-oliguric patient population (48 vs. 59% dialysis-free survival, $P=0.03$). Whether underlying pathophysiological conditions and/or the type of natriuretic peptide may be important in this regard needs to be tested. A recent study in rats with established ischemic non-oliguric acute renal failure found marked improvement in survival by vessel dilator [76]. In contrast, urodilatin did not reduce the incidence of renal replacement therapy in critically ill patients suffering form oliguric acute renal failure [77]. Additionally, urodilatin did not improve renal function in patients with acute renal failure after major abdominal surgery [78], but was effective in acute renal failure after cardiac surgery [74,79]. So far, the results of studies with natriuretic peptides in acute renal failure are controversial and at this time, there is no clear evidence to support a therapeutic role in this setting.

2.5. Administration of natriuretic peptides in other conditions

Similarly controversial conclusions were drawn in patients with liver cirrhosis. Both a blunted and a preserved response to natriuretic peptides have been found in advanced liver disease [47,48,80,81]. In theory, the renal effects of natriuretic peptides, if preserved, may help to reduce the pressure in the portal vein. Furthermore, although natriuretic peptides do not seem to have direct effects on hepatic vascular conductance [40], the reduction in mesenteric blood flow may further contribute to a reduced portal venous pressure [39]. This is in line with other experimental data, which show that natriuretic peptides may reduce portal venous pressure despite loss of renal effects in cirrhotic rats [81]. It remains to be seen whether this is of therapeutic significance in humans with portal hypertension.

In patients with bronchoconstriction, local (i.e. inhaled) and systemic application of natriuretic peptides consistently caused bronchodilation [49,50,82]. The combined use of a locally applied substance increasing cAMP (β2-stimulation) with systemic urodilatin, which increases cGMP, was significantly more effective than either therapy alone [50]. In addition, ANP may act as a bronchoprotective agent after allergic reactions [83]. Currently, there are insufficient data available about the long-term effects of natriuretic peptides in such patients with bronchoconstriction. Seemingly, rather high doses are needed to obtain significant effects with locally applied ANP [84]. Thus, cost-effectiveness may prevent natriuretic peptides from being used as a therapeutic agent for bronchoconstriction.

Natriuretic peptides have also been investigated during cardiac surgery [51,85,86]. A low ANP dose had favourable effects given during and for the first 24 h after coronary bypass grafting, improving hemodynamics and respiratory index and reducing neurohumoral stimulation, use of diuretics, and pleural effusions [51]. Similarly, ANP improved hemodynamics and augmented urinary excretion given on the first postoperative day after open-heart surgery [85]. The same was found in patients undergoing Fontan operation [86]. Therefore, administration of natriuretic peptides during the perioperative period may be beneficial and may deserve further investigation.

3. Increasing endogenous levels of natriuretic peptides

Long-term increase in natriuretic peptides may be a desirable therapeutic target. So far, the only means to achieve this goal is to reduce the degradation of natriuretic peptides by neutral endopeptidase inhibition [87]. Selective neutral endopeptidase inhibition increases the levels of natriuretic peptides, resulting ultimately in increased excretion of sodium, water, ANP, and cGMP without altering urinary potassium excretion [88]. However, neutral endopeptidase inhibition has demonstrated only a limited ability to lower systemic blood pressure [89], which may be related to vasoconstrictive properties of selective neutral endopeptidase inhibition [90]. In addition to the vasoconstrictive potential of natriuretic peptides [39], other mechanisms may be accountable for these findings. Neutral endopeptidase is involved not only in degradation of ET-1 [91] but possibly also in its formation [92]. Thus, selective inhibition of neutral endopeptidase might cause both an increase and decrease in endothelin-1. Increased levels of circulating ET-1 could be demonstrated after administration of candoxatril, a selective neutral endopeptidase inhibitor [89]. Similarly, locally applied candoxatrilat caused vasoconstriction which could be reverted by a selective ET_A receptor antagonist [93]. Importantly, neutral endopeptidase is also involved in the degradation of angiotensin-II (Ang II). Consequently, inhibition of neutral endopeptidase leads to increased levels of Ang II [94]. Apart from bearing potential vasoconstrictive effects, Ang II may antagonise the effects of the natriuretic peptides. It down-regulates guanylyl cyclase receptors and up-regulates cGMP phosphodiesterases, both of which attenuate the generation of cGMP [30,95]. Therefore, simultaneous inhibition of both neutral endopeptidase and angiotensin converting enzyme (ACE) may be synergistic and a promising approach to modulate neurohumoral stimulation in cardiovascular diseases [88]. In line with this concept, simultaneous inhibition of both neutral endopeptidase and ACE in animal experiments exhibited hemodynamic and renal effects that were more than additive compared to those caused by inhibition of either one of these enzymes alone [96–98]. Recently, omapatrilat, a vasopeptidase inhibitor that inhibits both neutral endopeptidase and ACE, has been developed [99]. Omapatrilat shows equipotent, highly selective competitive inhibition of both enzymes, although the rate constant (K_i) is slightly higher for neutral endopeptidase (8.9±1.0 nmol/l) than for ACE (6.0±0.4 nmol/l). Therefore, omapatrilat acts primarily as an ACE inhibitor in low dosages while it inhibits both enzymes in higher dosages.

3.1. Vasopeptidase inhibition in hypertension

Preclinical studies showed the potential advantages of omapatrilat over pure ACE-inhibition in various models of hypertension [100,101]. Thus, omapatrilat lowered elevated blood pressure in conscious rats with high, medium, or low renin hypertension [100]. In comparison with a calcium antagonist and an ACE inhibitor, omapatrilat was superior in lowering blood pressure. More recently, the efficacy of omapatrilat was reported in hypertensive patients, where it lowered blood pressure in a dose-dependent manner [102]. Furthermore, omapatrilat normalised blood pressure in 71% of patients with mild hypertension [103]. The high response rate may relate to the fact that omapatrilat may be effective independently of the renin levels. Thus in patients with salt-sensitive low renin hypertension, as often observed in black individuals, ACE inhibitors usually are not as effective as in patients with normal or high renin levels [104]. In these patients, inhibition of neutral endopeptidase may be important as it enhances the levels of natriuretic peptides and lowers plasma volume. Although direct comparisons of omapatrilat with other blood pressure lowering agents are scarce, omapatrilat seems to be one of the most efficacious antihypertensive drugs yet known.

There are effects of omapatrilat beyond pure blood pressure lowering. As elevated neurohumoral stimulation is increasingly recognised as an important factor in the pathophysiology of CHF [105], this is also found to be true in hypertension [106,107]. Similarly, the recently published HOPE study could show that ACE inhibition favourably affects prognosis in patients with arteriosclerosis independently of the magnitude of blood pressure lowering [108]. Because of the additional properties of omapatrilat, one might speculate that long-term effects of this new therapeutic tool might prove even better in improving prognosis in this patient population.

3.2. Vasopeptidase inhibition in congestive heart failure

Despite significant advances in the medical therapy of CHF in recent years, prognosis of these patients remains poor [109,110]. On the one hand, vasoconstrictor neurohumoral systems may overcome the endogenous counterregulatory mechanisms, resulting in progression of CHF [111]. On the other hand, sodium and water retention cause significant problems in these patients. This may, in turn, result in deterioration of CHF and hospitalisation [112]. Standard loop-diuretics increase water and salt excretion, but also increase potassium excretion leading to an elevated risk of hypokalemia-induced arrhythmias [113]. In addition, they also stimulate vasoconstrictor neurohumoral systems, in particular the renin–angiotensin system. In contrast, vasopeptidase inhibitors may overcome this problem, by increasing water and sodium excretion and reducing preload without affecting potassium excretion and without stimulating vasoconstrictor neurohumoral systems [88]. In dogs, omapatrilat has been shown to improve cardiac function in pacing-induced CHF [114]. Furthermore, omapatrilat was not only able to improve left ventricular geometry compared to captopril, but also to improve survival in cardiomyopathic hamsters [98]. These studies might indicate the superiority of a combined inhibition of neutral endopeptidase and ACE compared to ACE inhibition alone.

Most recently, the IMPRESS trial randomly compared omapatrilat (target dose 40 mg daily) with the ACE inhibitor lisinopril (target dose 20 mg) in 573 CHF patients (ejection fraction≤40%) over 24 weeks [115]. Although there was no difference between the two treatment groups with respect to the primary endpoint of maximal exercise capacity, there were fewer cardiovascular serious adverse events in the omapatrilat group than in the lisinopril group (7 vs. 12%, $P=0.04$). Furthermore, there was a trend towards less combined endpoints of death and admission to hospital for worsening CHF and a significant reduction in the combined endpoint of death, admission to a hospital or discontinuation of study treatment due to worsening CHF (Fig. 5). There was also a trend towards improvements in symptoms of CHF, particularly in highly symptomatic patients. Although these data are very promising, one has to be cautious not to over-interpret them, as this study was not powered to investigate the prognostic effects of omapatrilat versus isolated ACE inhibition. Underpowered studies may lead to false positive results as recently shown in the ELITE-1 trial [116], which could not be confirmed in the properly powered ELITE-II study [117].

Another study compared different dosages of omapatrilat in patients with CHF, most of them previously treated with either an ACE inhibitor and/or angiotensin-II receptor antagonists [118]. There was a dose-dependent improvement in the clinical CHF status with good overall tolerability of the drug. Moreover, clinical and hemodynamic improvements were dose-dependent and significantly different between the three groups for arterial pressure and left-ventricular ejection fraction (Fig. 6). There was also a significant enhancement in water and sodium excretion and a reduction in blood volume. All these changes were dose-dependent. The increased cGMP production as measured by urinary cGMP seemed to be an important mechanism of the additional effects of omapatrilat. Nevertheless, large-scale controlled clinical trials have to prove the superiority of this concept over isolated ACE inhibition (±diuretics) before omapatrilat may be recommended for the treatment of CHF.

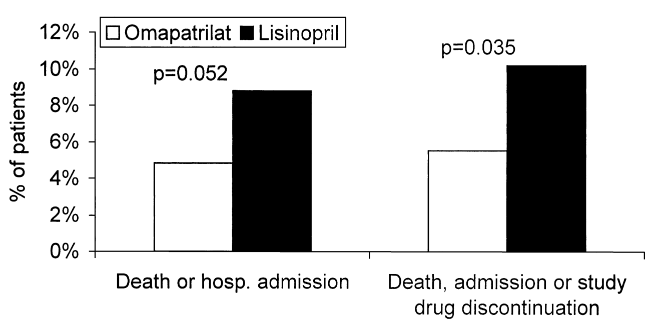

Fig. 5. Death and comorbid events of worsening heart failure in patients with congestive heart failure after 24 weeks of therapy with either omapatrilat 40 mg daily ($n=298$) or lisinopril 20 mg daily ($n=284$). Hosp. denotes hospitalization. Adapted from Rouleau et al. [115].

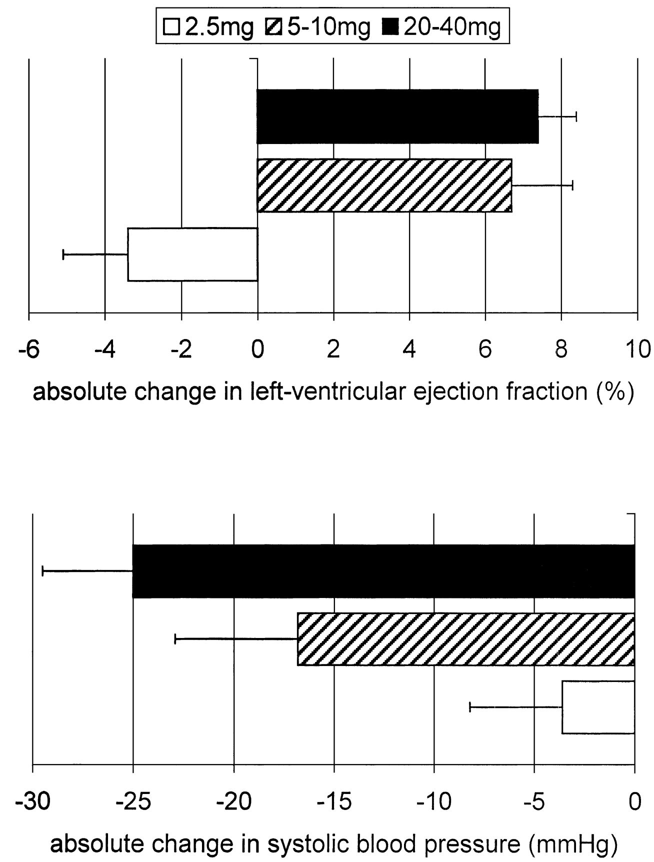

Fig. 6. Effects of different doses of omapatrilat for 12 weeks on left ventricular ejection fraction and systolic blood pressure (mean±S.E.M.) in humans with left ventricular ejection fraction ≤40%. Comparisons among the three groups $P<0.01$ by one-way ANOVA. Adapted from McClean et al. [118].

3.3. Tolerability of vasopeptidase inhibition

Despite the promising data in both arterial hypertension and CHF, there are important caveats. In both studies [115,118], only patients with prior ACE inhibitor treatment were included, with few exceptions. Therefore, it is not surprising that few ACE-inhibition specific adverse effects were reported. With this in mind, one has to be cautious when comparing the tolerability of omapatrilat with ACE inhibitors [119]. Though rare, a potentially fatal adverse effect of ACE inhibition is angioedema. The widespread use of ACE inhibitors may lead to a significant number of deaths due to angioedema. Inhibition of neutral endopeptidase not only increases the levels of endogenous natriuretic peptides but also of other vasodilators such as a prostacyclin, adrenomedullin and, more important in this context, bradykinin [97]. Accumulation of bradykinin is the most probable cause of angioedema in patients treated with ACE inhibitors [120]. Therefore, one may assume that angioedema is more common with vasopeptidase inhibitors than with ACE inhibitors. Angioedema occurred in 0.34% of the more than 4000 patients treated with ramipril in the HOPE study [108]. In data submitted for the new drug application of omapatrilat, 44 cases of angioedema occurred in more than 6000 patients (approx. 0.7%) with a threefold increase in incidence when the starting dose was at least 20 mg compared to lower doses [119]. Because of this dose dependence of angioedema, a pharmacodynamic side effect may be assumed. Since patients with a history of angioedema are strictly excluded from such clinical trials, the true incidence may be considerably underestimated by selection bias. The higher rate of gastrointestinal side effects reported in the IMPRESS trial in patients receiving omapatrilat may be an indicator for the higher rate of angioedema [115]. Gastrointestinal symptoms may be a less well-known presentation of angioedema [121]. Therefore, the risk–benefit ratio of this new class of drug has to be carefully evaluated, particularly in the treatment of arterial hypertension where the short- to medium-term mortality is relatively low.

4. Conclusions

Therapeutic strategies to increase the circulating levels of natriuretic peptides are attractive and promising therapeutic targets to improve the treatment of various cardiovascular diseases in the future. Administration of natriuretic peptides, particularly BNP, seems to be highly effective in the management of acute decompensated CHF. A definite role for natriuretic peptides in the treatment of other conditions cannot be attested yet and requires further study.

The inhibition of the degradation of endogenous natriuretic peptides seems to be a promising approach, particularly in combination with ACE inhibition. However, the inhibition of both neutral endopeptidase and ACE by new vasopeptidase inhibitors not only prevents formation of angiotensin-II and degradation of natriuretic peptides, but also influences various other auto- and paracrinely active peptides. Further studies are needed to better define the therapeutic potential of vasopeptidase inhibitors, but initial results are promising, particularly in CHF. Finally, it must be kept in mind that the true incidence of serious side effects has to be properly assessed before the widespread use of vasopeptidase inhibitors can be safely recommended.

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