The efficacy and safety of B-type natriuretic peptide (nesiritide) in patients with renal insufficiency and acutely decompensated congestive heart failure

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Abstract

Background. Nesiritide (B-type natriuretic peptide) reduces preload and afterload, and causes natriuresis, diuresis and suppression of norepinephrine, endothelin-1 and aldosterone. In this study, we sought to explore the safety and efficacy of nesiritide in patients with acute congestive heart failure (CHF) and renal insufficiency (RI).

Methods. We studied the effects of nesiritide in patients with RI in the VMAC trial database, a multi-centre, randomized controlled trial (n = 489) of patients with acute decompensated CHF.

Results. The mean serum creatinine (SCr) in nesiritide-treated patients with RI (SCr ≥ 2.0 mg/dl, n = 60, range 2.0–11.1 mg/dl) and without RI (SCr < 2.0 mg/dl, n = 209) was 3.0 ± 1.51 and 1.2 ± 0.34 mg/dl, respectively. Pulmonary capillary wedge pressure (PCWP) was reduced significantly and similarly in both RI and no RI groups starting at 15 min into nesiritide infusion from a baseline of 29.9 ± 8.1 and 26.6 ± 6.0 mmHg, respectively. Addition of placebo to standard therapies yielded no further improvement in PCWP in patients with RI; in contrast, nesiritide significantly reduced PCWP at every time point during 24 h. The effects of nitroglycerin were less robust than those of nesiritide, and PCWP was not significantly reduced by nitroglycerin at the 3 h primary end-point. At 24 h, 83% of the RI patients and 91% of patients without RI treated with nesiritide reported improvements in dyspnoea. Nesiritide was well tolerated in patients with RI and no RI, and renal function was preserved in both groups.

Conclusions. In patients with RI, nesiritide was safe and improved haemodynamics and dyspnoea.

Keywords: brain natriuretic peptide; B-type natriuretic peptide; chronic kidney disease; haemodynamics; heart failure; nesiritide; renal insufficiency

Introduction

Patients with chronic RI have a disproportionate burden of cardiovascular morbidity and mortality. According to the Acute Decompensated Heart Failure National Registry (ADHERE™), September 2002 data cut of 27,645 patients admitted with a primary diagnosis of acute decompensated heart failure, 28% of patients had renal insufficiency (RI), 20% have a serum creatinine (SCr) of ≥ 2.0 mg/dl, and one in 20 was a dialysis patient [1]. Echocardiograms in dialysis patients reveal frequent left ventricular abnormalities. In one study, only 16% of 403 randomly selected haemodialysis patients had echocardiographically normal left ventricles [2]. Despite this, cardiac therapeutics, including those for acute heart failure, are seldom studied in patients with moderate and advanced RI.

Development of heart failure decompensation in patients with RI is common. Standard therapies such as nitroprusside, milrinone, dobutamine and diuretics for acute heart failure are less than ideal due to risks of metabolite or drug accumulation, proarrhythmic potential and reduced therapeutic effect in this population.

Nesiritide is the recombinant form of endogenously produced human B-type natriuretic peptide (BNP) and...
is approved by the Food and Drug Administration for management of patients with decompensated congestive heart failure (CHF). Based on data from earlier studies of nesiritide, dosing adjustment in patients with RI is not necessary [3].

Endogenous BNP is expressed by cardiac myocytes in response to myocardial stretch and is known to be elevated in patients with chronic RI who have echocardiographic left ventricular abnormalities, but not those without such findings [4]. BNP has lusitropic properties, which may facilitate ventricular relaxation in patients with diastolic dysfunction [5] and increases cardiac index secondary to afterload and preload reduction in patients with systolic dysfunction [6]. BNP also causes diuresis, natriuresis [6] and suppression on multiple levels of the renin–angiotensin–aldosterone axis [7] and other hormones that lead to renal vasoconstriction and/or sodium retention, such as norepinephrine [7] and endothelin-1 [8]. Glomerular filtration rate and renal blood flow are maintained during BNP treatment despite natriuresis and diuresis [7,9].

Although in patients with CHF the circulating BNP levels are elevated and correlate with New York Heart Association (NYHA) class, the levels produced endogenously are not sufficient to maintain compensation in patients with severe CHF. The ability of exogenously administered BNP to overcome the higher levels of endogenously circulating vasoconstrictive and sodium retentive hormones in CHF patients has been empirically determined in numerous clinical trials [6,10,11]. The efficacy and safety of nesiritide in patients with RI and CHF decompensation have not been described previously. We explored the efficacy and safety of nesiritide in the management of this population from the database of the Vasodilation in the Acute Management of CHF (VMAC) trial [10].

Subjects and methods

The VMAC trial was a multicentre, randomized, double-blind, placebo- and active-controlled trial that enrolled 489 patients with decompensated CHF and NYHA class IV symptoms on presentation and a pulmonary capillary wedge pressure (PCWP) of ≥20 mmHg (in patients with PA catheters), despite use of standard medical therapies (see below). The Institutional Review Board at each participating centre approved the protocol and all patients gave written informed consent.

Use of PA catheters was determined by investigator discretion, and patients were stratified according to whether they received a PA catheter (n = 246) or did not (n = 243). Inclusion criteria for the trial were broad, e.g. patients with renal disease (including end-stage renal disease), patients with either systolic or diastolic dysfunction, acute coronary syndromes, those on β-blockers and angiotensin-converting enzyme inhibitors (ACEIs) and those with serious arrhythmias were not excluded.

During the entire trial, patients were able to receive any needed oral and transdermal cardiovascular medications, i.v. diuretics, dopamine and dobutamine (collectively termed ‘standard therapy’) along with the assigned ‘study drug’.

During the first 3 h of the study, patients were randomized to i.v. nesiritide (2 μg/kg bolus, followed by a continuous infusion of 0.01 μg/kg/min), i.v. nitroglycerin (titrated as needed to maximize clinical effects) or placebo, each added to standard care. In an additional group, the nesiritide dose could be adjusted in increments of 0.005 μg/kg/min after 3 h of initial treatment at 0.01 μg/kg/min up to a maximum of 0.03 μg/kg/min. Following the placebo-controlled period, patients receiving placebo were placed on (pre-determined and still blinded) nitroglycerin or nesiritide for at least 24 h of treatment. The dual primary end-points for the trial were change from baseline vs placebo in 3 h PCWP (catheterized patients) and 3 h dyspnoea scores (all patients). Dyspnoea was rated by the patient, while blinded, on a 7-point scale (markedly improved, moderately improved, minimally improved, no change, minimally worse, moderately worse and markedly worse). A secondary end-point, the global clinical status, was based on either the physician’s or patient’s overall clinical evaluation (while still blinded), using the same 7-point ordinal scoring system. General adverse events were assessed up to study day 14. Serious adverse events other than death (hospital admissions and non-fatal, life-threatening events) were monitored up to study day 30, while mortality was assessed for 6 months. Results of the full VMAC trial are published elsewhere [10].

From the VMAC data set, we evaluated the efficacy and safety of nesiritide in the subset of patients whose SCr was ≥2.0 mg/dl at trial entry (termed, the ‘RI’ group). For purposes of qualitative comparison, we analysed data from the patients whose SCr was <2.0 mg/dl at trial entry (the ‘no RI’ group). The comparison of patients with and without SCr ≥2.0 mg/dl was pre-defined prior to the start of the study. Further, we examined reduction in PCWP in RI patients randomized to standard therapies plus either nitroglycerin, nesiritide or placebo. Data from nesiritide-treated patients with advanced RI, defined as those whose SCr was ≥4.0 mg/dl and/or were on chronic dialysis at trial entry, were specifically reviewed. A subgroup analysis in patients with SCr ≥2.0 mg/dl had been pre-defined prior to completion of the trial. Therefore, selection of this subgroup was not performed post hoc.

Changes relative to baseline in PCWP and systolic blood pressure were examined statistically using a paired Student’s t-test. Data are presented as means±SD, unless otherwise noted. As this was a subset analysis, power to detect statistically significant differences between groups was limited. A two-group t-test with a 0.050 two-sided significance level would have 55% power to detect the difference between the nitroglycerin group with mean PCWP reduction of −3.000 and the nesiritide group with mean PCWP reduction of −7.0, a difference in means of 4.000, assuming that the common SD is 6.0, when the sample sizes in the two groups are 17 and 28, respectively (a total sample size of 45).

Results

Patient distribution

Distribution of patients with and without RI by treatment group are shown in Figure 1.
Baseline characteristics and medication use during the study

Baseline characteristics of the nesiritide RI and no RI groups are shown in Table 1. Compared with the no RI group, the RI group had a greater burden of ischaemic heart disease and its complications, and, in turn, were more likely to have ischaemic cardiomyopathy. Compared with the no RI group, the RI group also had almost twice the likelihood of prior sudden death/near sudden death as well as higher use of class III antiarrhythmics (Table 2). There were some other notable differences in use of concomitant medications during nesiritide therapy between the RI and no RI groups. There was a 4-fold higher use of dopamine (20 and 5%) and 50% higher use of dobutamine (35 vs 23%) in the RI group vs the no RI group, respectively, and these differences were largely attributable to continuation of ongoing infusions of these medications into the VMAC trial. Use of other common medications in the RI and no RI groups, respectively, were as follows: angiotensin receptor blockers, 5% vs 7%; β-blockers, 22% vs 28%; and aldosterone inhibitors, 22% vs 19%. In both groups, 17% of patients received no oral or i.v. diuretics during the first 24 h of treatment with nesiritide. No patients received dialysis during the first 24 h of nesiritide treatment.

Pulmonary capillary wedge pressure

The baseline PCWP in patients with RI in the placebo, nitroglycerin and nesiritide groups was 27.8±4.4, 28.8±6.3 and 30.8±8.7 mmHg, respectively. The reduction in PCWP from baseline in each group during 24 h is depicted in Figure 2. Addition of placebo to standard therapies yielded no further improvement in PCWP in patients with RI; in contrast, nesiritide significantly reduced PCWP at every time point in this population during 24 h. The effects of nitroglycerin were less robust than those of nesiritide, and PCWP was not significantly reduced by nitroglycerin at the 3 h primary end-point.

The baseline PCWP in the groups with \( (n = 35) \) and without \( (n = 117) \) RI was 29.9±8.1 and 26.6±6.0 mmHg, respectively. Patients with and without RI had similar reductions in PCWP on nesiritide over a period of 48 h (Figure 3). As was found in the VMAC population overall (22), in the subset of patients with RI receiving nesiritide, PCWP decreased significantly relative to baseline at every time point during 48 h (Figure 3). Significant effects of nesiritide on PCWP in patients with RI were measured as early as 15 min after the start of treatment (Figure 3).

Systolic blood pressure

The baseline systolic blood pressure in the groups with \( (n = 43) \) and without RI \( (n = 158) \) was 122.8±26.4 and 119.4±22.5 mmHg, respectively. Nesiritide reduced systolic blood pressure relative to baseline in both groups. There was no consistent difference in blood pressure effects of nesiritide between patients with and without RI. However, those with RI generally had less reduction in systolic blood pressure than those without RI after the first hour of nesiritide treatment. The immediate effects on systolic blood pressure were more pronounced in those with RI. For example, at 15 min into nesiritide treatment, mean systolic blood pressure decreased by 6 mmHg in the group with RI compared with 3.4 mmHg in the group without RI.

Dyspnoea

At the end of the 3 h placebo-controlled period, 70% of nesiritide-treated patients with RI \( (n = 43) \) and 75% of
patients without RI ($n=158$) reported improvements in their dyspnoea. By 24 h, 84% of RI patients ($n=60$) and 91% of no RI patients ($n=209$) reported improvements in dyspnoea. The percentage of patients with RI who had improved dyspnoea at 0.25, 0.5, 1, 2, 3 and 24 h was 39, 40, 63, 60, 70 and 91%, respectively. Global clinical status at 24 h was improved in 83% of patients with RI and in 91% without RI. Seventy-four percent of the RI group had either moderate or marked improvement at 24 h.

**Safety**

In the VMAC trial overall, the incidence of adverse events was significantly higher for patients on nitroglycerin than for those on nesiritide (22). Likewise, there were significantly more adverse events on nitroglycerin compared with nesiritide amongst patients with RI (68% vs 58%, $P<0.001$). Amongst patients treated with nesiritide, the incidence of adverse events was similar in patients with and without RI. Selected adverse events in patients treated with nesiritide with and without RI, respectively, were as follows: headache, 3% vs 9%; abdominal pain, 3% vs 1%; symptomatic hypotension, 3% vs 5%; angina pectoris, 0% vs 2%; and ventricular tachycardia, 2% vs 4%. Mean SCr in nesiritide-treated patients with RI at baseline, day 2 and day 5 was 3.0±1.5, 2.9±1.6 and 3.0±1.6 mg/dl, respectively. Nesiritide-treated patients without RI had mean SCr at baseline, day 2 and day 5 of 1.2±0.3, 1.3±0.5 and 1.3±0.4 mg/dl, respectively. Mean SCr in nesiritide-treated patients with RI at baseline was similar in patients with and without RI. Selected adverse events in patients treated with nesiritide (titrated to effect) amongst patients with RI was –0.2 and –0.1 mg/dl, respectively ($P=0.03$). For the above treatment groups amongst patients without RI, median SCr changes were 0 and 0 mg/dl, respectively ($P=0.54$).

Over 30 days, there were no significant differences between nesiritide-treated and nitroglycerin-treated patients in the overall frequency of serious adverse events, with 47 and 45% of RI patients, respectively, and 26 and 25% of patients without RI, respectively, experiencing serious adverse events. Over 30 days, there were no significant differences in death/readmission rates between nesiritide-treated and nitroglycerin-treated patients; this occurred in 33.3 and 40.9% of RI patients, respectively, and in 23.1 and 23.2% of patients without RI, respectively. There were no significant differences with respect to 6-month mortality rate between nesiritide-treated and nitroglycerin-treated patients, occurring in 42.9 and 40.9% of RI patients, respectively, and in 20.6 and 15.8% of patients without RI respectively.

**Patients with advanced RI**

There were seven nesiritide-treated patients (two catheterized, five non-catheterized) with advanced RI, defined as SCr ≥4.0 mg/dl. SCr and calculated creatinine clearance (Cockcroft–Gault) in these patients ranged from 4.1 to 11.1 mg/dl (mean 6.0±2.8 mg/dl) and from 7.0 to 21.2 ml/min (mean 14.2±5.1 ml/min), respectively. Baseline characteristics and clinical parameters during the treatment course of these patients are summarized in Table 2. Compared with the overall VMAC population, these patients were somewhat older (mean age 62.0±13.0 years vs 68.3±12.6, respectively) and they were more frequently treated with i.v. vasoactive therapies within the 24 h preceding the trial (42% vs 29%, respectively). Additionally, patients with RI received a typically longer course of treatment with nesiritide (mean ~3–7 days vs ~48 h in the full study population). The two patients with the lowest creatinine clearances did not receive any concomitant diuretics, presumably because they were not expected...
<table>
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<tr>
<th>Patient number</th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<td>54-year-old female</td>
<td>77-year-old male</td>
<td>80 year-old male</td>
<td>86-year-old female</td>
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<td>Diabetes</td>
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<td>NYHA class prior to decomposition</td>
<td>NYHA IV</td>
<td>NYHA III</td>
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<td>Ischaemic CM</td>
<td>Ischaemic CM</td>
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<td>Ischaemic CM</td>
<td>Ischaemic CM</td>
<td>Hypertensive CM</td>
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<td>Hospital course</td>
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<td>Admission SCr (mg/dl)</td>
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<td>8.6</td>
<td>11.1</td>
<td>4.7</td>
<td>4.1</td>
<td>4.1</td>
<td>5.3</td>
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<td>17.5</td>
<td>16.8</td>
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<td>Nesiritide</td>
<td>Nesiritide</td>
<td>Placebo</td>
<td>Placebo</td>
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<td>3-Hour dyspnoea score</td>
<td>Markedly better</td>
<td>Markedly better</td>
<td>Minimally better</td>
<td>Minimally better</td>
<td>No change</td>
<td>Minimally worse</td>
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<tr>
<td>24-Hour global clinical status</td>
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<td>Moderately better</td>
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<td>Markedly better</td>
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<td>SCr on last day of nesiritide treatment (mg/dl)</td>
<td>3.5</td>
<td>9.0</td>
<td>10.6</td>
<td>5.2</td>
<td>4.5</td>
<td>3.1</td>
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<td>No</td>
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<tr>
<td>Concomitant use of i.v. or p.o. diuretics?</td>
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<td>Yes</td>
<td>No</td>
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<td>Yes</td>
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<tr>
<td>Concomitant parenteral vasoactive medications?</td>
<td>Dobutamine</td>
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<tr>
<td>Re-admitted within 30 days?</td>
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<td>No</td>
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</tr>
</tbody>
</table>

CM = cardiomyopathy; CrCl = creatinine clearance; NYHA = New York Heart Association Class; SCr = serum creatinine.

* Dobutamine or dopamine treatment was ongoing prior to initiation of nesiritide and was continued during nesiritide treatment. Dopamine, dobutamine and norepinephrine were added onto nesiritide treatment on study day 3.

** Fenoldopam added on study day 1 (5 h and 49 min into nesiritide treatment).
to respond to these. Amongst those with SCr \( \geq 4.0 \text{ mg/dl} \), there was little correlation in urine volumes to quantity of furosemide administered (data not shown). Despite lack of homogeneity in urine output, all patients who received active nesiritide had improved dyspnoea at 3 h (Table 2). In contrast, those receiving placebo in the first 3 h tended to have unchanged or worsening dyspnoea. Global clinical status at 24 h improved in five out of six patients and was not available in one patient. Clinical parameters and (where available) haemodynamics improved on nesiritide in a manner unrelated to urine output response. For example, patient 3 (Figure 4), who had an SCr of 11.1 mg/dl on trial entry, had improvements in filling pressures, pulmonary pressures and cardiac output consistent with the nesiritide trial population overall despite a urine output of 100 ml during the first 24 h. Dyspnoea scores also progressively improved during therapy. The patient experienced two adverse events: headache (treated with acetaminophen) and nausea (not treated).

SCr levels at the end of nesiritide treatment were similar to those pre-nesiritide (Table 2). None of the seven patients with advanced RI were dialysed while on
nesiritide. Two of the seven patients died during their hospitalization: one due to respiratory failure from ongoing bacterial endocarditis and acute post-infectious glomerulonephritis, and the second from a cardiac arrest after discontinuation of an automatic internal cardiac defibrillator (Table 2). The remaining five patients survived, were discharged and were not readmitted to hospital during the 30 days of readmission follow-up.

Discussion

In this study, we found that nesiritide was effective at improving haemodynamics and clinical parameters such as dyspnoea and overall clinical status in patients with moderate and advanced RI. The observations we make in this subset analysis are consistent with the described effects of nesiritide in the entire VMAC trial population [10]. The efficacy of nesiritide in patients with moderate to severe RI is particularly notable given that the VMAC population was comprised of a refractory group of patients. For example, 42% of the RI group had already failed to respond or responded inadequately to treatment with parenteral vasoactive therapies (Table 1), as evidenced by the fact that despite treatment with the above during the 24 h prior to trial entry, the patients met the entry criteria for VMAC, i.e. PCWP ≥20 mmHg (if catheterized) and dyspnoea at rest or with minimal exertion. In fact, mean PCWP on enrolment into VMAC in the RI patients was 29.9 ± 8.1 mmHg. When clinically determined standard therapies, including diuretics, nitrates, β-blockers, ACEIs, dopamine and dobutamine, were added to placebo, there was no significant further reduction in PCWP at any time point in RI patients. In contrast, nesiritide significantly reduced PCWP at every time point over 24 h, starting at 15 min, in this population. The effects of nitroglycerin were less robust than those of nesiritide and not significantly different vs baseline at the 3 h primary end-point.

We chose to use SCr rather than calculated creatinine clearance using various formulae, such as Cockcroft–Gault [12] and the equation used in the Modification of Diet in Renal Disease (MDRD) Trial [13], in this analysis for several reasons. First, SCr itself has been related to poor outcomes among hospitalized heart failure patients [14]. Secondly, because these formulae were derived for patients with chronic RI, their reliability in patients with acute changes in renal function (as often occurs in the setting of decompensated CHF) is not well defined. Further, the formulae...
have not been validated in the CHF population. Finally, calculated creatinine clearance measurements based on body weight will be inaccurate in patients with a significant degree of volume overload, such as those with acute heart failure.

Although the ideal situation would be to have a clinical trial or trials of acute heart failure therapeutics specifically in patients with moderate and severe RI that were of sufficient power to make comparisons between various therapeutic strategies, such studies have not been performed. However, because heart disease is a major problem in patients with RI, information on treatment of these patients is important. We therefore feel the publication of the findings from the VMAC trial in this patient population, although not powered for statistical comparisons between groups, does provide new and important information on heart failure therapy in RI patients. Although the primary intent of the VMAC trial was not to evaluate the effects of nesiritide in patients with moderate to severe RI, such patients were included in the trial and this is the largest clinical trial database to date of use of nesiritide or, to our knowledge, any other acute heart failure therapeutic in this patient population. Trials of acute cardiovascular therapeutics often exclude patients with moderate to severe RI. For example, the recently completed OPTIME trial evaluating milrinone for acute heart failure excluded patients with SCr ≥3.0 mg/dl [15]. The worth of using clinical trial databases to examine the effects of therapeutic agents in patient populations in whom separate trials have not yet been or cannot be performed has been described previously [16]. The VMAC trial as a whole demonstrated that in patients with acute heart failure, nesiritide was superior to placebo + standard therapies (including i.v. diuretics, oral and transdermal cardiac medications and, in some cases, dopamine and dobutamine) and also superior to nitroglycerin + the above standard therapies. Our goal in performing this analysis was to assess qualitatively whether response and safety to nesiritide were similar in patients with and without RI. Patients with moderate to severe RI were not precisely matched with respect to baseline characteristics. The differences in baseline characteristics are interesting and they define the nature of patients presenting with acute heart failure and moderate to severe RI as compared with those with acute heart failure with more normal renal function. Further, the baseline differences in PCWP, extent of class III antiarrhythmic use and the percentage of patients having received and done poorly on a parenteral vasoactive drug within 24 h of randomization into the present trial suggest that patients with moderate to severe RI were a sicker group than those without RI and, if anything, their response to therapy should be inferior. The latter was not observed. Our findings, therefore, suggest that nesiritide has pharmacological effects in patients with and without RI that are not dissimilar.

The comparison of the RI vs no RI patients was intended to be of a qualitative nature as the VMAC trial was not powered to look at differences amongst these patient subsets. For this reason, formal statistical tests comparing the two groups were not performed. In this situation, absence of ‘statistical significance’ could not be interpreted confidently as lack of significant differences between the two groups. Likewise, statistical differences between treatment groups in PCWP in RI patients were not interpretable due to inadequate power. Instead, change from baseline in PCWP was examined statistically for each group separately.

Patients with chronic RI are known to have a high prevalence of ischaemic heart disease. We found that even within a population of patients with severe CHF, the presence of RI was associated with a greater burden of ischaemic heart disease: 75% had a history of coronary artery disease, 57% had a known prior history of myocardial infarction and 47% had previously had either a coronary artery bypass graft or coronary angioplasty procedure. The above underscores the importance of minimizing use of drugs such as dopamine and dobutamine, which increase myocardial oxygen demand and may precipitate acute coronary events in this patient population.

In both VMAC [10] and prior clinical trials [6,10,17], nesiritide increased urine output and/or decreased diuretic usage. The dependence of nesiritide-induced filling pressure reductions on removal of total body volume had not been evaluated previously. Our review of patients with advance RI suggests that symptomatic and haemodynamic improvements can be robust even in the absence of fluid removal. Our findings are consistent with previous work with atrial natriuretic peptide, which demonstrated improvements in oxygenation and haemodynamics in patients with congestive heart failure and renal failure in the absence of diuresis [18]. Presumably, fluid is pooled in the venous circulation such that filling pressures decrease, cardiac output increases and dyspnoea improves. In the majority of haemodialysis patients who can rapidly undergo ultrafiltration to manage their acute heart failure, the clinical picture can be dramatically and suddenly improved without drug therapies. However, in situations where ultrafiltration cannot be performed within a time frame that is adequate for management of acute respiratory distress, stabilization of haemodynamics and symptoms with nesiritide until dialysis can be performed may be an option.

BNP has known lusitropic effects [5] in patients with isolated diastolic heart failure, and we found that it reduced blood pressure in patients with RI, much as it did in those without RI. These properties together suggest that nesiritide would be a particularly good therapeutic choice for the patient with decompensated CHF, diastolic dysfunction and hypertension, a common presenting triad in patients with chronic RI. Despite that fact that the patients with RI in VMAC were a severely compromised elderly group, nesiritide was well tolerated. Specifically, safety in patients with and without RI was similarly good. Nesiritide is not proarrhythmic in patients with decompensated CHF [19]. Our analysis also suggested that nesiritide does...
not aggravate pre-existing arrhythmias in RI patients, such as ventricular tachycardia, despite the higher prevalence of past history of sudden death and baseline arrhythmogenic use in the former group.

We conclude that in patients with RI, nesiritide is safe and improves haemodynamics and dyspnoea, even when urine output is minimal. In particular, risk of aggravating arrhythmias and myocardial ischaemia appears low with nesiritide. Lusitropic and blood pressure effects of BNP may make it particularly well suited for the RI patient with hypertension, left ventricular hypertrophy and CHF. Nesiritide should be considered a first-line agent for CHF management in patients with RI.

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References


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