Introduction of Metoprolol Increases Plasma B-Type Cardiac Natriuretic Peptides in Mild, Stable Heart Failure

Mark E. Davis, MBChB; A. Mark Richards, MD; M. Gary Nicholls, MD; Timothy G. Yandle, PhD; Christopher M. Frampton, PhD; Richard W. Troughton, MD

Background—The effect of β-blockade on the cardiac natriuretic peptides is poorly understood but could contribute to their beneficial treatment effect and may be relevant to clinical use of plasma brain natriuretic peptide (BNP)/N-terminal pro brain natriuretic peptide (NTproBNP) measurements in risk stratification and in titration of anti–heart failure therapy.

Methods and Results—Sixteen men with mild, stable heart failure (NYHA class II to III; left ventricular ejection fraction <40%) underwent serial blood sampling for plasma natriuretic peptide levels and received infusions of atrial natriuretic peptide (ANP) and BNP before and 6 weeks after the introduction and up titration of metoprolol or 6 weeks unchanged therapy in a randomized, parallel-group design. Plasma natriuretic peptides (BNP, NTproBNP, ANP, and NTproANP) were increased by metoprolol (P<0.01 for all). The natriuretic responses to ANP and BNP infusions were sustained with the introduction of metoprolol despite reduced renal perfusion pressure. The levels of the noninfused natriuretic peptide were increased by both ANP and BNP infusions, and this effect was enhanced by metoprolol. The early plasma half-life (t1/2) of BNP was prolonged by metoprolol (5.6±0.45 to 11±1.3 versus 5.7±0.8 to 6.6±1.3 minutes in control subjects; P=0.019).

Conclusions—Plasma cardiac natriuretic peptide levels increase significantly with the introduction of metoprolol in heart failure as a result of effects on secretion and clearance. Natriuretic responses to NP infusions are sustained with β-blockade despite reduced renal perfusion pressure. Clinicians should be aware that the introduction of metoprolol causes a rise in plasma BNP/NTproBNP that is unrelated to deterioration in clinical status and must be considered when measurements are undertaken for risk stratification or titration of treatment. (Circulation. 2006;113:977-985.)

Key Words: heart failure ▪ natriuretic peptides ▪ receptor blockers, adrenergic, beta

The B-type cardiac natriuretic peptides (NP; BNP and NTproBNP) are biomarkers of diagnosis,1,2 cardiac function, and prognosis in acute and chronic heart failure (HF).3-4 With emerging potential utility in acute coronary syndromes,5,6 valve disease,7 and asymptomatic groups harboring cardiovascular risk factors,8-9 Serial measurements may be useful for monitoring and titration of anti–HF therapy.10

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β-Blockade (BB) has become standard therapy in HF after trials showing a reduction in mortality in all NYHA classes of systolic HF.11-14 BB is now indicated in all symptomatic HF, including patients who are stable with mild (NYHA class II) symptoms. As general clinical practice alters to meet treatment guidelines based on evidence from the randomized controlled clinical trials, BB is being introduced in many cases of stable, mild HF. The effect of introducing BB therapy on plasma levels and biological actions of BNP may well be relevant to the use of plasma BNP measurements in the diagnosis, risk stratification, and titration of therapy. It is also possible that effects on NP levels may mediate some of the beneficial effects of BB in congestive heart failure. The effect of BB on plasma NP has been reported in population-based studies,15 in healthy control subjects,16 during exercise, in hypertension,17,18 in coronary disease,19 and in HF.20-30 The reported responses are widely divergent, presumably reflecting differences between specific β-blockers and the effects of dose and duration of treatment and clinical state. The setting of stable and mild HF, without major comorbidity, provides the best opportunity to accurately characterize the effect of introducing BB because results are less likely to be confounded by episodes of clinical instability and/or the need to alter other drugs that influence plasma NP levels. In such patients, it also is possible to safely introduce BB within a practical length of time according to a relatively rapid and standardized titration schedule. We have undertaken serial measurements of plasma NP and used infusions of ANP and BNP before and after the introduction of BB to elucidate the effects of introducing BB on plasma levels, plasma clearance, and biological activity of the NPs.
Methods

The experimental protocol was approved by the Canterbury Ethics Committee of the Ministry of Health (New Zealand). All participants gave written informed consent. The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

We studied 16 men <80 years of age with treated stable congestive heart failure (ejection fraction <40% by echocardiography, predominantly NYHA functional class II, receiving an ACE inhibitor or angiotensin II receptor antagonist) in whom introduction of BB was indicated. All had been clinically stable for at least 3 months before the study, with a mean elapsed time of 3 years from the last episode of frank cardiac decompensation. Patients were excluded if they had impaired renal function (plasma creatinine >0.14 mg/dL), had reversible airways obstruction, had other con- traindications to or previous adverse reaction to β-blocker therapy, or had received a β-blocker within the month before the start of the study.

Study Protocol

The study used a randomized, balanced, controlled, parallel-group design. All subjects were studied before and 6 weeks after the introduction of metoprolol or a time-matched period of unchanged treatment. On the morning of the third and fifth days of 5-day controlled metabolic diets (sodium 80 mmol/d, potassium 100 mmol/d), patients ate breakfast, presented to the study room, and completed a 24-hour urine collection at 8 AM. Patients were weighed and then drank 10 mL/kg water, followed by 200 mL/h between 9 AM and 2 PM. Subjects remained seated throughout the day except when standing for urine collections. Venous canulas were placed in each forearm, 1 for the infusion of NP or placebo, and 1 for blood sampling. All patients received separate 3-hour infusions (9:30 until 12:30) of ANP and BNP (Clinalfa AG) (1 on day 3 and the other on day 5 in random order) at 4 pmol · kg⁻¹ · min⁻¹. Subjects were blinded to the order in which peptides were administered. Eight received ANP first; 8 received BNP first. The peptides were dissolved in normal saline and made up to a total volume of 50 mL. Serial venous samples were drawn before, during, and after each infusion at 9, 9:30, 10, 10:30, and 11:30 AM and 12:30, 1, and 2 PM for assay of ANP, NTproANP, BNP, NTproBNP, plasma cyclic guanosine monophosphate (cGMP), plasma renin activity, aldosterone, angiotensin II, adrenaline, noradrenaline, endothelin, adrenomedullin, and neutral endopeptidase 24.11 as previously published. Additional sampling for pharmacokinetics of NPs was undertaken at 9:40, 9:50, and 10:15, with further rapid, postinfusion sampling at 12:32, 12:34, 12:36, 12:40, and 12:45. Blood was collected into chilled tubes containing EDTA and centrifuged at 4°C, and the plasma stored at −80°C before assay. Measurements of plasma sodium, potassium, creatinine, and hematocrit were performed on samples before and at the completion of infusions and at the completion of the monitoring period. Urine was collected (for measurement of volume, cGMP, sodium, potassium, and creatinine) at 90-minute intervals (9:30, 11, 12:30, and 2). For each analyte, all samples from an individual were analyzed in a single assay. Intra-assay coefficients of variation were all <16.4%. Interassay coefficients of variation were all <18.5%.

During peptide infusions, arterial blood pressure, heart rate (PRO 300 monitor, Dinamap, Critikon), and cardiac output (Minnesota impedance cardiograph, model 304B, Surcom Inc) were recorded in duplicate at 30-minute intervals.

After baseline studies, patients were randomized to either the BB or the control group. Subjects in the BB group began long-acting metoprolol succinate starting at 47.5 mg/d, titrating at 2-week intervals to a target dose of 190 mg/d as tolerated over a 6-week period. In the control group, medications remained unchanged. After 6 weeks, all subjects received a repeated set of ANP and BNP infusions. At study completion, control patients began metoprolol therapy.

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics in the Treatment and Control Groups</th>
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<tr>
<td></td>
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<tr>
<td>Treatment (n=8)</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Age, y</td>
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<tr>
<td>Weight, kg</td>
</tr>
<tr>
<td>Creatinine (mean), mg/dL</td>
</tr>
<tr>
<td>Cause of HF, ischemic/total</td>
</tr>
<tr>
<td>LVEV, mL</td>
</tr>
<tr>
<td>LVEDV, mL</td>
</tr>
<tr>
<td>LVEF, %</td>
</tr>
<tr>
<td>NHYA class II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>Frusamide dose, mg (n patients)</td>
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<tr>
<td>ACE inhibition (enalapril equivalent), mg/d</td>
</tr>
</tbody>
</table>

LVEV indicates left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume; and LVEF, left ventricular ejection fraction.

Statistical Analysis

The effects of treatment and NP infusions were analyzed with repeated-measures ANOVA and ANCOVA. Urine cGMP data were not normally distributed and therefore were analyzed by nonparametric analysis. Areas under the curve were calculated from the standard trapezoidal rule. Plasma half-lives (½) for ANP and BNP were calculated with a 1-compartment model during and after the infusion period (WinNonLin Professional 3.1, Pharsight Corp). A value of P<0.05 was accepted as indicating statistical significance. Results are presented as mean±SEM.

Results

Baseline variables and medications for the 2 study groups are given in Table 1. There were no significant differences in baseline hormone, biochemical, or hemodynamic variables between the treatment and control groups, except for heart rate (Table 2). No symptomatic hypotension or other adverse effects were noted for the duration of the infusion periods or for the subsequent monitoring periods. Consistent with the stable and mild degree of HF selected for this study, clinical status and non-BB medication dosages were unchanged for all subjects during the study period.

As expected, metoprolol treatment significantly decreased heart rate and blood pressure (Table 2). ANP and BNP infusions induced the expected diuresis and natriuresis (Table 3).

| Metoprolol significantly increased endogenous plasma BNP, NTproBNP, ANP, NTproANP, and second messenger urinary cGMP (Table 2 and Figure 1), with a trend (P=0.062) toward increased plasma cGMP. Plasma renin activity and angiotensin II fell significantly (Table 2 and Figure 2). The mean changes in BNP were 31±7 versus −7±7 pg/mL for the BB and control groups, respectively (P=0.001), with concurrent changes in NTproBNP (406±152 versus −93±152 pg/mL; P=0.012), ANP (31±9 versus 6±3 pg/mL; P=0.008), NTproANP (2.7±0.7 versus −0.8±0.5 ng/mL; P<0.001), and 24-hour uGMP (419 ng/h [interquartile range, 186 to 770 ng/h] versus −17 ng/h [interquartile range, −163 to 158 ng/h]; P=0.036). |

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Metoprolol treatment had no significant effect on plasma aldosterone, adrenomedullin, endothelin, noradrenaline, or adrenaline. Plasma sodium, potassium, and creatinine also remained unchanged (Table 2).

**NP Infusions**

Before the introduction of metoprolol, NP plasma levels before, during, and after NP infusions did not differ between groups (Table 2 and Figures 3 and 4). After 6 weeks of metoprolol treatment, infusions of ANP and BNP induced increases in plasma levels of the peptide similar to those seen in the control group (ANP, \( \text{P}=0.74 \); BNP, \( \text{P}=0.42 \)) albeit from higher baseline levels (Figures 3 and 4). Infusions of ANP and BNP consistently induced significant increments in plasma concentrations of the endogenous “sister” (noninfused) peptide (for increments in ANP levels during BNP infusion, \( \text{P}<0.001 \); for BNP increments during ANP infusion, \( \text{P}<0.001 \)). This effect was accentuated by metoprolol. Increments in plasma ANP during infusion of BNP were increased by metoprolol (39 ± 6 versus 24 ± 5 pg/mL compared with 16 ± 6 versus 23 ± 5 pg/mL observed in the control group; \( \text{P}=0.016 \) for intergroup comparison). BNP increments during ANP infusions also tended to increase after metoprolol (31 ± 7 versus 19 ± 2 pg/mL compared with 17 ± 5 versus 23 ± 3 pg/mL in control subjects; \( \text{P}=0.076 \) for intergroup comparison; Figures 3 and 4). During all ANP and BNP infusions, plasma levels of NTproANP fell slightly (by ≈0.2 ng/L; \( \text{P}<0.001 \) for all infusion data), and NTproBNP remained stable or fell minimally; this pattern was not affected by metoprolol.

The diuretic and natriuretic responses to peptide infusions and concurrent excretion of creatinine were sustained with BB (\( \text{P}<0.001 \)) (Table 3) despite a substantial reduction in arterial and therefore renal perfusion pressure. There was no effect of BB on these responses (all \( \text{P}>0.05 \)). Intra-infusion mean arterial pressures averaged 6.3 and 3.5 mm Hg lower after the introduction of metoprolol for ANP and BNP infusions, respectively, compared with no significant change.
in the control group (1.8 and 1.2 mm Hg, respectively; P<0.01 for intergroup comparisons).

Pharmacokinetics

Calculated early plasma half-life (t½α) for BNP extended significantly after metoprolol treatment (5.6±2.0 to 11.0±1.3 minutes compared with 5.8±0.8 to 6.6±1.3 minutes for control subjects; P=0.019). Calculated t½α for ANP showed no significant change compared with control subjects. There was no significant change in the formally calculated plasma metabolic clearance rate of either ANP or BNP alone during infusions. Intra-infusion metabolic clearance rates of ANP were 4.0±0.4 and 4.0±0.5 L/min before and after the introduction of metoprolol compared with 4.5±0.4 and 4.0±0.5 L/min with unchanged treatment. BNP metabolic clearance rates were 4.6±1.1 and 4.5±0.6 L/min before and after metoprolol compared with 5.6±1.1 and 4.7±0.6L/min in the control group. The sum of increments in plasma ANP plus BNP during NP infusions tended to be increased by metoprolol (Figures 3 and 4), although this did not achieve statistical significance.

Discussion

We report the first controlled examination of the effects of introducing BB in mild and stable HF on plasma levels of both endogenous plasma A- and B-type cardiac NPs and on the pharmacokinetics and bioactivity of infused ANP and BNP. The findings are free of confounding by clinical deterioration or any change in drugs other than BB reflecting the stable and mild degree of HF selected for the study. After 6 weeks of uptitration of metoprolol, we observed unequivocal and substantial increments in plasma BNP, NTproBNP, ANP, and NTproANP. These changes were accompanied by increased 24-hour urinary excretion of cGMP, the intracellular second messenger for the NPs.

The plasma concentration of any peptide is the net result of secretion and clearance. The concurrent rise in plasma levels of both amino terminal and carboxy terminal derivatives of both proANP and proBNP strongly suggests a common enhancement of cardiac NP secretion because both peptides are secreted in parallel in response to alterations in transcardiac pressures and NTpro-peptide and carboxy terminal fragments of both propeptides are cosecreted 1:1. Clear-

### Table 3. Urinary Indexes During NP Infusion

<table>
<thead>
<tr>
<th></th>
<th>Pretreatment</th>
<th>Infusion</th>
<th>Posttreatment</th>
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<tbody>
<tr>
<td></td>
<td>Preinfusion</td>
<td>Infusion (0–180)</td>
<td>Postinfusion (180–270)</td>
</tr>
<tr>
<td>ANP infusions</td>
<td></td>
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<td></td>
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<tr>
<td>Metoprolol</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Vol, mL/h</td>
<td>79±23</td>
<td>233±21</td>
<td>139±16</td>
</tr>
<tr>
<td>Na+, mmol/h</td>
<td>2.1±0.5</td>
<td>5.8±0.8</td>
<td>4.6±0.6</td>
</tr>
<tr>
<td>Cr, mmol/h</td>
<td>0.4±0.08</td>
<td>0.61±0.07</td>
<td>0.50±0.01</td>
</tr>
<tr>
<td>cGMP, nmol/h</td>
<td>34±14</td>
<td>178±25</td>
<td>98±8.4</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vol, mL/h</td>
<td>140±50</td>
<td>271±59</td>
<td>142±18</td>
</tr>
<tr>
<td>Na+, mmol/h</td>
<td>2.6±0.7</td>
<td>6.2±1.1</td>
<td>4.1±1.1</td>
</tr>
<tr>
<td>Cr, mmol/h</td>
<td>0.48±0.10</td>
<td>0.61±0.04</td>
<td>0.53±0.14</td>
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<tr>
<td>cGMP, nmol/h</td>
<td>38±8</td>
<td>181±26</td>
<td>95±13</td>
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<tr>
<td>BNP infusions</td>
<td></td>
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<tr>
<td>Metoprolol</td>
<td></td>
<td></td>
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<tr>
<td>Vol, mL/h</td>
<td>108±31</td>
<td>245±24</td>
<td>128±20</td>
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<tr>
<td>Na+, mmol/h</td>
<td>1.5±0.4</td>
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<td>3.4±0.7</td>
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<tr>
<td>Cr, mmol/h</td>
<td>0.46±0.10</td>
<td>0.57±0.11</td>
<td>0.45±0.07</td>
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<tr>
<td>cGMP, nmol/h</td>
<td>34±7</td>
<td>134±17</td>
<td>103±6</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vol, mL/h</td>
<td>136±44</td>
<td>271±25</td>
<td>124±18</td>
</tr>
<tr>
<td>Na+, mmol/h</td>
<td>2.8±0.7</td>
<td>6.0±0.7</td>
<td>3.2±0.5</td>
</tr>
<tr>
<td>Cr, mmol/h</td>
<td>0.48±0.08</td>
<td>0.58±0.04</td>
<td>0.51±0.05</td>
</tr>
<tr>
<td>cGMP, nmol/h</td>
<td>39±1.0</td>
<td>126±19</td>
<td>88±11</td>
</tr>
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</table>

Vol indicates volume; Cr, creatine. Comparison of urine indexes was conducted by repeated-measures ANOVA. Both ANP and BNP infusions significantly and consistently altered urinary volumes, Na+, and cGMP (P<0.001). There was no effect of metoprolol treatment on responses to NP infusions (all P>0.05). Values are mean±SEM.
of a generalized increase in plasma BNP, NTproBNP, ANP, and NTproANP (Figure 1). Furthermore, the early effects of BB include longer cardiac filling times and negative inotropism. In the absence of offsetting changes in other drugs such as ACE inhibitors or diuretics, these early effects of BB will promote elevation of cardiac pressures for a period until beneficial remodeling of the ventricle can occur, with a reduction in ventricular dimensions leading to reduced wall tension and subsequent falls in cardiac peptide secretion and plasma levels. This sequence may well require several months, a period considerably longer than the 6-week time span of the present study.

Our findings during ANP and BNP infusions also point to some effect of metoprolol on clearance, at least of the carboxy terminal peptides. During ANP and BNP infusions, increments in plasma concentrations of the infused peptide were little changed by metoprolol (albeit superimposed on higher baseline preinfusion levels), but interestingly, increments in levels of the noninfused peptide were increased substantially (Figures 3 and 4). Concurrent intra-infusion levels of NTproBNP and NTproANP either fell or were stable with or without metoprolol, suggesting that the enhanced levels of BNP during ANP infusions and of ANP during BNP infusions reflected competition for clearance rather than increased endogenous secretion. The known effects of infused NPs to reduce intracardiac pressures and the possible receptor-mediated negative feedback of NPs on their own cardiac secretion also make decreased clearance rather than increased secretion more likely to underlie the net increment in intra-infusion plasma peptide levels. The elevation of BNP with infusion of ANP and vice versa has been well documented previously in both humans and animal experiments. The mechanism through which BB enhances this interaction cannot be addressed through the present study. We could not support these findings with a clear demonstration of decreased steady-state plasma clearance of infused peptides after introduction of metoprolol. However, that may reflect limitations in our ability to accurately measure metabolic
clearance because of the cumulative errors involved in assays of baseline and intra-infusion peptide levels, the inability to define the possible degree to which endogenous secretion of ANP and BNP fell during infusion of exogenous peptide, the possible confounding effects of altered preinfusion baseline levels of peptides, and the lack of achieved true steady-state plasma peptide levels during infusions (Figures 3 and 4). Notably, the pharmacokinetic analyses from the offset of BNP infusions did demonstrate that metoprolol significantly prolonged the early plasma half-life of BNP (with a weak similar trend for ANP). Taken together, our findings suggest that the introduction of BB enhances cardiac secretion of all the A- and B-type NPs over at least 6 weeks with a possible additional contribution through reduced clearance of the carboxy terminal peptides, at least in the setting of abrupt increments in plasma ANP and/or BNP.

Infusions of ANP and BNP induced significant natriuresis and diuresis; these effects, together with sustained creatinine clearance and urinary excretion of cGMP, were preserved with the introduction of metoprolol. Preservation of natriuresis is the more notable in that this response to NPs is very sensitive to changes in renal perfusion pressure and metoprolol reduced arterial pressure (and therefore renal perfusion pressure) substantially. These findings suggest that increments in plasma NPs, most likely in concert with concurrent falls in plasma renin activity and angiotensin II, may ameliorate potential adverse effects of BB on renal sodium handling in HF.

The present study is the first to measure change in all 4 A- and B-type NPs with introduction of BB in stable HF in the absence of any other drug changes. It is also the first to assess the effects of BB on the pharmacokinetics and bioactivity of ANP and BNP using repeated infusions of exogenous peptides. However, numerous prior publications report changes in 1 or 2 of the NPs at various time intervals after the introduction of a variety of β-blockers in HF. In general, NPs are reported to rise when measured at intervals <6 months after initiation of BB, with falls commonly reported with longer follow-up. At least 2 reports with serial measurements showed an initial increase in plasma NPs (at 2 or 12 weeks), followed by later falls. Exceptions to this pattern often involve unstable situations, uncontrolled studies, or β-blockers with vasodilator activity. In 815 patients in the Carvedilol (Coreg) Prospective Randomized Cumulative Survival (COPERNICUS) study, NTproBNP fell at 13 and 26 weeks but did not differ from placebo. These patients were recently in NYHA class IV HF. Their treatment included recent increments in ACE inhibitor, angiotensin receptor blockade, and/or loop diuretic dose shortly before randomization to carvedilol or placebo. Hence, their overall therapy for severe HF would still be taking effect. Vasodilators and diuretics reduce plasma NPs through reductions in intracardiac pressures. Carvedilol itself has vasodilating α-adrenoceptor blocking activity. Hence, in this setting, it is not surprising that any specific effect of BB to elevate NP levels will be counterbalanced by improving cardiac function and drugs with an opposing effect on plasma NPs. The observation by Jourdain et al of a fall in plasma BNP 6 weeks after the introduction of carvedilol in 50 patients with NYHA class III HF may also reflect the vasodilator effects of carvedilol and concurrent changes in other drugs in an uncontrolled series. The probable significance of the vasodilator actions present in some β-blockers is reinforced by a report from Sanderson et al in which, over the 24 hours after introduction of drug, ANP and BNP were both clearly increased by metoprolol but modestly decreased by celiprolol. In summary, existing reports, together with our own findings, suggest that the introduction of nonvasodilating β-blockers in stable HF, in the absence of other drug changes, will increase plasma NPs over several weeks or months with a subsequent fall in NPs, possibly reflecting attainment of beneficial ventricular reverse remodeling with concomitant reductions in cardiac chamber wall tension.

Our findings have practical implications for clinical application of BNP and NTproBNP measurements in risk stratifi-
Figure 3. Plasma ANP and BNP with ANP infusions before and after introduction of metoprolol (●) or 6 weeks of unchanged treatment (○).

Figure 4. Plasma ANP and BNP with BNP infusions before and after introduction of metoprolol (●) or 6 weeks of unchanged treatment (○).
cation and titration of therapy when a nonvasodilating β-blocker is introduced in stable, mildly symptomatic HF. Specifically, the increment in BNP or NTproBNP observed in this setting need not imply worsening control of HF and/or a deteriorating prognosis. Our findings may not be extrapolable to vasodilating β-blockers such as carvedilol or celiprolol. The influence of β-blockers is unlikely to detract from the diagnostic application of BNP/NTproBNP in newly breathless patients presenting to the emergency department. In acute, severely symptomatic left ventricular failure, BNP/NTproBNP are elevated many-fold above normal, and the “noise” of BB is unlikely to substantially alter their diagnostic utility.1–2 In the present study, our stable patients had mean BNP and NTproBNP levels only moderately elevated above the normal range; it is in this setting that β-blocker–induced increments in peptide levels on the order that we observed (>70% increments; Table 2) are potentially misleading. Whether β-blockers may confound risk stratification in other non-HF settings such as acute coronary syndromes, hypertension, or other asymptomatic at-risk groups requires specific group-by-group investigation.

Acknowledgments
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Disclosures
None.

References


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