Clinical research

Comparison of echocardiography and plasma B-type natriuretic peptide for monitoring the response to treatment in acute heart failure

Andrzej Gackowski¹,², Richard Isnard¹,*,², Jean-Louis Golmard³, Françoise Pousset¹, Alain Carayon¹, Gilles Montalescot¹, Jean-Sébastien Hulot¹, Daniel Thomas¹, Wieslawa Piwowarska², Michel Komajda¹

¹ Institute of Cardiology, Hospital Pitie-Salpetriere, Paris, France
² Department of Coronary Disease, Institute of Cardiology, Krakow, Poland
³ Department of Biostatistics, Pitie-Salpetriere Hospital, Paris, France

Received 5 November 2003; revised 14 June 2004; accepted 15 July 2004
Available online 17 September 2004

See page 1763 for the editorial comment on this article (doi:10.1016/j.ehj.2004.08.012)

Aims Comparison of the value of echocardiography and B-type natriuretic peptide (BNP) in monitoring response to treatment in patients admitted for acute heart failure (HF).

Methods and results Ninety-five consecutive patients admitted with acute HF underwent bedside Doppler echocardiography and BNP measurements on admission, after 24 h of intravenous treatment, and at day 7. We then studied the association between the clinical status, the Doppler echocardiographic findings, the BNP measurements and subsequent 60-day adverse outcome (death, resuscitated cardiac arrest, urgent heart transplantation, readmission).

On admission and during hospitalisation, relationships were found between plasma BNP and Doppler echocardiographic findings, and between their changes. During a 60 day follow-up, 37 events occurred. Multivariable analysis taking into account clinical factors, Doppler echocardiography and BNP showed that the two best models to predict outcome were (1) early evaluation at day 2 (previous CHF treatment, dobutamine use, relative BNP change during first 24 h) and (2) late evaluation at day 7 (previous CHF treatment, dobutamine use, BNP at day 7). Patients with a decrease in plasma BNP >10% at day 2, or with plasma BNP <300 pg/ml at day 7 had a better outcome than the others (19% versus 65% and 16% versus 72% events, respectively, p < 0.0001).

Conclusions Serial BNP measurements during the treatment of acute HF provide incremental prognostic information over clinical presentation and repetitive echocardiographic examination.

© 2004 The European Society of Cardiology. Published by Elsevier Ltd. All rights reserved.

KEYWORDS
B-type natriuretic peptide; Acute heart failure; Echocardiography; Prognosis

*A Corresponding author. Tel.: +33 1 42 16 30 09; fax: +33 1 42 17 67 19/16 30 20.
E-mail address: richard.isnard@psi.ap-hop-paris.fr (R. Isnard).

¹ Andrzej Gackowski was a visiting research fellow of the Polish Cardiac Society funded by an unrestricted grant from Servier International.
² A.G. and R.I. contributed equally to this work.

0195-668X/S - see front matter © 2004 The European Society of Cardiology. Published by Elsevier Ltd. All rights reserved.
Introduction

Acute decompensated heart failure (HF) is a major cause of hospitalisation and is associated with high rates of mortality and repeated hospitalisation. In this very high risk group of patients, early prognostic stratification may be useful in order to guide treatment intensity. Although in chronic heart failure (CHF), there are guidelines for prognostic evaluation, little is known about risk stratification in acute HF. Early prediction of the outcome based solely on clinical observation is useful but of limited reliability. The monitoring of pulmonary pressures using a Swan-Ganz catheter is no longer used routinely, given its potential risk of complications. Therefore, there is a need for an alternative and non-invasive method that can be easily used in larger patient populations, allowing the assessment of an early response to therapy and the prediction of individual risk.

Echocardiography provides important information on the mechanism of HF and can estimate left ventricular filling pressure in CHF. However, the value of repetitive bedside echocardiography for monitoring response to treatment has not been demonstrated in acute heart failure.

B-type natriuretic peptide (BNP) has been extensively studied in recent years as a clinical marker of heart overload. BNP is produced mainly by the ventricular myocardium in response to increased intracavitary pressure and wall stress. It has been shown that the plasma BNP level is elevated in patients with heart failure and correlates to left ventricle filling pressures. Plasma BNP measurement is currently an accepted method for diagnosing heart failure. Moreover, the application of this biochemical marker for guiding the treatment in chronic heart failure has shown promising results. It has been proven that the BNP plasma level provides prognostic information in CHF and at discharge after treatment of acute decompensation. However, there is no data concerning the value of BNP for early risk stratification in acute HF. Although it has been shown that plasma BNP concentration can decrease rapidly after initiation of CHF treatment unloading the left ventricle, little is known about the prognostic significance of this phenomenon.

This study was performed to compare the usefulness of repetitive bedside echocardiography and plasma BNP measurements for the assessment of prognosis in patients hospitalised due to acutely decompensated heart failure.

Methods

Study population

From October 2001 to April 2002, we prospectively studied all the patients admitted for acute decompensated heart failure in the Intensive Care Unit, Institute of Cardiology, Pitie Salpetriere Hospital, Paris, France. The local Ethics Committee approved the study protocol and informed consent was obtained. All procedures were in accordance with institutional guidelines. The inclusion criterion was acute HF defined as progressive rest dyspnoea associated with clinical signs of pulmonary and/or peripheral congestion based on Framingham criteria, requiring urgent hospitalisation and treatment with an intravenous diuretic and/or dobutamine. Exclusion criteria were: inability to give informed consent, severe pulmonary, hepatic or renal (plasma creatinine >250 µmol/l) disease; acute coronary syndromes unless heart failure was the predominant manifestation or impossibility to obtain Doppler echocardiographic measurements of good quality. We screened 106 patients and excluded 11 (two patients requiring urgent surgery for aortic dissection, four patients from whom admission BNP sample was not obtained, four patients with a final diagnosis of pulmonary disease, and one patient with a very poor quality echocardiogram). Thus, the study group consisted of 95 patients (63 males and 32 females), with an age of 67 ± 16 years. A complete clinical examination was performed in all the patients at admission, at day 2 and day 7, and a clinical score adapted from Framingham criteria was calculated based on the following clinical signs: rest dyspnoea with respiratory rate >22/min (1 point); heart rate >100bpm (0.5 point), third heart sound (1 point), hepatojugular reflex positive (1 point), hepatomegaly (0.5 point), peripheral oedema (0.5 point), pulmonary crackles (1 point), systolic arterial pressure <100 mmHg (1 point).

Echocardiographic measurements

Doppler echocardiography (ECHO) was performed in all patients upon admission. It was repeated on the following day in all patients except four who died within 24 h of inclusion. The third examination was performed on the seventh day (or at discharge, whichever came first) in all except nine patients who had died by that time. All examinations were performed by the same echocardiographer on call with the use of a Sequoia machine (Acuson, Mountain View, CA, USA), recorded digitally and subsequently reviewed by another experienced echocardiographer. The following parameters were analysed: left ventricular end-diastolic diameter (LVEDD), left ventricle ejection fraction (LVEF, bipline Simpson method), mitral inflow E and A wave, maximal velocities (E, A), E/A ratio, E wave deceleration time (DT), inferior vena cava inspiratory diameter (IVC), right ventricle systolic pressure (RVSP), calculated as a sum of right atrial pressure (RAP) and the tricuspid regurgitation retrograde gradient. The RAP was estimated according to IVC diameter (RAP = 15 mmHg if IVC >20 mm; RAP = 10 mmHg if IVC in the range of 10 and 20 mm; RAP = 5 mmHg if IVC <10 mm). In case of atrial fibrillation (AF) the average of each parameter from 5 to 7 cardiac cycles was calculated. Mitral inflow pattern was considered as (i) restrictive if E/A > 2.0 or E/A between 1 and 2 with DT <150ms or DT = 120 ms in case of atrial fibrillation.; (ii) non restrictive when E/A < 1 or E/A between 1 and 2 and DT = 150 ms or DT = 120 ms in case of atrial fibrillation. At admission, the mitral flow pattern was non-interpretable in 28 patients (fusion between E and A wave due to tachycardia, mitral prostheses or mild mitral stenosis, permanent pacing). We considered there was an evidence of increased cardiac filling pressure when a restrictive pattern or a RVSP >50 mmHg were present. During follow-up, we defined an improvement of cardiac filling pressures assessed by Doppler echocardiography between admission and Day 2 or between admission and day 7 when one of the following was present: (1) in patients with sinus rhythm: change from restrictive to non-restrictive pattern or from fusion to non-restrictive pattern; (2) in patients with atrial fibrillation, development of non restrictive pattern when
conversion to sinus rhythm was achieved or increase of DT above 120 ms in case of persistent atrial fibrillation; and (3) decrease of RVSP by more than 20% compared to baseline.

**BNP measurements**

Blood samples (5 ml EDTA tube) were taken for BNP analysis upon admission (BNP1, 95 samples), after 24 h (BNP2, 91 samples), and on the seventh day (or at discharge, whichever came first) (BNP3, 86 samples). The blood was centrifuged and the spun serum was immediately frozen at −20 °C. Biochemical analysis was performed using the radioimmunoassay method. Cross reactivity of the used BNP-32 antiserum (Peninsula Laboratories Inc.) with a-ANP1-28, Endothelin-1, and Angiotensin II, was 0%. The assay detection limit was 10 pg/tube. The inter-assay and intra-assay variations were 11% and 8%, respectively. The normal BNP plasma concentration by the mentioned method in a local laboratory was previously calculated as 28 ± 12 pg/mL. The physicians in charge of the patients were blinded to the BNP results and participation in the study did not have any influence on diagnosis or therapy.

**Follow-up and statistical analysis**

All patients were followed-up for 60 days after admission. Combined endpoint of death, resuscitated cardiac arrest, urgent heart transplantation or repeated hospitalisation due to HF was considered.

In order to assess the prognostic value of different parameters in subsequent time-points, three analyses were performed, using different initial times. First, we considered all events occurring after admission to evaluate clinical data, evidence of increased cardiac filling pressure on echo and BNP. Then, we repeated the analysis in 91 patients surviving beyond the first 24 h (day 2), using clinical factors, data from two echocardiographic examinations (evidence of increased filling pressure at admission and day 2, and of echo improvement) and BNP data (BNP1, BNP2, and BNP relative change). The third analysis included 86 patients who survived until the moment of BNP3 sample collection (day 7), repeating the same analysis using clinical factors, echo data and BNP data from baseline, day 2 and day 7. For each analysis, the statistical methodology was the following: in the first step, univariate analysis was performed using univariate Cox models, and in the second step a multivariable analysis was performed using a stepwise regression based on the Cox model. All the variables considered in the univariate analysis were included as potential prognostic factors in the stepwise regression. Only the variables significant at the 0.05 level were kept in final models.

In order to assess the prognostic values of clinical data, echocardiography and BNP, complementary analyses were performed: for each initial time, models based on incremental source of information were fitted using stepwise Cox model regression. Since these models are not always embedded ones, model comparisons were based on the Akaike criteria.

Finally, for illustration purposes, the prognostic data of two subgroups of patients with and without events are shown in Table 1. At admission, 60 patients (63%) were on angiotensin converting enzyme (ACE) inhibitors, 45 (47%) diuretics, and 25 (26%) β-blockers. ACE inhibitors and β-blockers were temporarily withdrawn in nine and four patients, respectively. β-Blockers were not introduced during the initial 2 days. At Day 7, 85% of patients received an ACE-inhibitor, 31% a β-blocker and 85% a diuretic agent. Delay between admission and first Doppler echocardiography was 3.4 ± 2.8 h. During the 60-day follow-up, 37 patients exhibited at least one of the following events: 21 cardiac deaths, two urgent heart transplantations, three resuscitated cardiac arrests and 11 cardiac rehospitalisations. Four deaths occurred in the first 24 h and five deaths between day 2 and day 7. Baseline characteristics of the overall population and of subgroups of patients with and without events are shown in Table 1.

**Relationship between Doppler echocardiographic findings and plasma BNP**

At admission, patients with an evidence of increased cardiac filling on echo (restrictive pattern or RVSP >50 mmHg) had higher plasma BNP levels than the others (396 ± 167 pg/ml versus 267 ± 158 pg/ml, p = 0.0005) (Fig. 1). Those who showed an improvement in cardiac filling pressures during hospitalisation had a higher decrease of plasma BNP compared to the others patients (between admission and day 2: −123 ± 157 versus −46 ± 78 pg/ml, p = 0.003; between admission and day 7: −154 ± 127 versus −40 ± 142 pg/ml, p = 0.0004).

**Univariate and multivariable analysis of adverse outcome**

Three different analyses were performed at admission, at day 2 and at day 7 (Table 2). Among clinical variables, a higher clinical score, a previous CHF treatment and the use of dobutamine infusion were always associated with adverse outcome in univariate analysis. On the opposite, other baseline clinical data (age, sex, CHF aetiology, creatinine level, initial Furosemide dose) did not show association with prognosis. Among echo variables, evidence of increased cardiac filling pressure and low LVEF were associated with outcome at the three different times in univariate analysis, while ECHO improvement did not. When we looked at the echo indices separately, restrictive filling pattern was associated to prognosis at admission (p = 0.044) and day 7 (p = 0.002) but not at day 2 (p = 0.14); right ventricular systolic pressure was associated to prognosis at day 2 (p = 0.039) and day 7 (p = 0.017) but not at admission (p = 0.17) in univariate analysis. Finally, plasma BNP was always associated with prognosis as did plasma BNP changes.

**Results**

**Admission data and events**

Ninety-five patients were enrolled into the analysis. Clinical characteristics of the patients at admission are shown in Table 1. At admission, 60 patients (63%) were on angiotensin converting enzyme (ACE) inhibitors, 45 (47%) diuretics, and 25 (26%) β-blockers. ACE inhibitors and β-blockers were temporarily withdrawn in nine and four patients, respectively. β-Blockers were not introduced during the initial 2 days. At Day 7, 85% of patients received an ACE-inhibitor, 31% a β-blocker and 85% a diuretic agent. Delay between admission and first Doppler echocardiography was 3.4 ± 2.8 h. During the 60-day follow-up, 37 patients exhibited at least one of the following events: 21 cardiac deaths, two urgent heart transplantations, three resuscitated cardiac arrests and 11 cardiac rehospitalisations. Four deaths occurred in the first 24 h and five deaths between day 2 and day 7. Baseline characteristics of the overall population and of subgroups of patients with and without events are shown in Table 1.
All possible models using previous BNP values, clinical and echocardiographic parameters, and their changes were used in the multivariable stepwise analysis (Table 2). In the first analysis considering all events that occurred after inclusion, the only independent predictors of prognosis were previous CHF treatment, dobutamine administration and evidence of increased cardiac pressure on echo. When only patients surviving at day 2 were analysed, percentage change of BNP during the first 24 h appeared to be a better predictor than BNP itself while previous CHF treatment and dobutamine use remained significant. Finally, when only patients who survived until the seventh day measurements were taken into consideration, the best model predicting subsequent prognosis was BNP3 associated again with previous CHF treatment and dobutamine usage. None of the echo indices (combined or taken separately) remained associated with prognosis in multivariable analysis at day 2 and day 7.

In order to evaluate the magnitude of the incremental value of serial BNP measurements over clinical and echo data, we compared successively the best models of clinical criteria alone, then clinical criteria plus echo, and finally clinical criteria plus echo and BNP at admission, day 2 and day 7: BNP clearly gave incremental prognostic information over clinical and echocardiographic data at day 2 and day 7, but not at admission (Table 3).

Identification of patients at high risk of adverse outcome based on BNP plasma levels

BNP changes in patients with and without events are shown in Fig. 2. No significant differences in BNP and BNP changes were found between patients who died and patients who were readmitted.

No cut-off BNP concentration clearly separating patients with and without events could be found. In contrast, a relative decrease of plasma BNP >10% after the first day of treatment and a plasma BNP concentration at day 7 <300 mg/ml were able to discriminate patients with a better prognosis (respectively, all events up to 60 days after admission in 19% versus 65%, p < 0.0001,

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Admission characteristics of study population (subgroups with and without events during 60-days of observation)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients n = 95</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67 ± 16</td>
</tr>
<tr>
<td>Males (%)</td>
<td>66</td>
</tr>
<tr>
<td>CHF treatment prior to admission (%)</td>
<td>48</td>
</tr>
<tr>
<td>CHF aetiology (%)</td>
<td></td>
</tr>
<tr>
<td>Ischaemic</td>
<td>48</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>22</td>
</tr>
<tr>
<td>Valvular</td>
<td>12</td>
</tr>
<tr>
<td>Other</td>
<td>18</td>
</tr>
<tr>
<td>Physical examination</td>
<td></td>
</tr>
<tr>
<td>HR (min⁻¹)</td>
<td>94 ± 23</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>120 ± 24</td>
</tr>
<tr>
<td>Respiratory rate (min⁻¹)</td>
<td>27 ± 6</td>
</tr>
<tr>
<td>S3 Gallop (%)</td>
<td>51</td>
</tr>
<tr>
<td>Signs of peripheral congestion (%)</td>
<td>80</td>
</tr>
<tr>
<td>Clinical score</td>
<td>3.6 ± 1.0</td>
</tr>
<tr>
<td>Use of dobutamine infusion (%)</td>
<td>40</td>
</tr>
<tr>
<td>Sinus rhythm (%)</td>
<td>68</td>
</tr>
<tr>
<td>Pulmonary congestion on X-ray (%)</td>
<td>75</td>
</tr>
<tr>
<td>Serum creatinine concentration (µmol/l)</td>
<td>129 ± 61</td>
</tr>
<tr>
<td>Furosemide dose within first 24 h (mg)</td>
<td>193 ± 127</td>
</tr>
<tr>
<td>Doppler echocardiogram findings</td>
<td></td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>58 ± 12</td>
</tr>
<tr>
<td>LVFS (%)</td>
<td>34 ± 16</td>
</tr>
<tr>
<td>RVSP (mmHg) (n = 80)</td>
<td>50 ± 15</td>
</tr>
<tr>
<td>Restrictive mitral flow pattern</td>
<td>49%</td>
</tr>
<tr>
<td>RVSP &gt; 50 mmHg</td>
<td>51%</td>
</tr>
<tr>
<td>Restrictive mitral flow pattern or RVSP &gt; 50 mmHg (n = 91)</td>
<td>63%</td>
</tr>
<tr>
<td>BNP, (on admission) pg/ml</td>
<td>346 ± 177</td>
</tr>
</tbody>
</table>

Data are expressed as the mean value ± SD for continuous variables and as percentage of patients in groups for qualitative variables.

CHF = congestive heart failure, HR = heart rate, SBP = systolic arterial pressure, LVEDD = left ventricle end-diastolic diameter, LVFS = left ventricle ejection fraction, RVSP = right ventricle systolic pressure, BNP = B-type natriuretic peptide plasma level.

Mitral flow pattern was interpretable in only 67 patients (70%).
and events in 16% versus 72% of patients, $p < 0.0001$) (Fig. 3).

**Discussion**

Acute heart failure is a critical condition and a common cause of hospitalisation. Early risk stratification reflecting also response to treatment is an important issue in these patients as it would allow physicians to discriminate patients who could be discharged early and safely from those who would need more intensive therapy. However, the difficulty of such an assessment explains the lack of practical, easy to use, and widely accepted prognostic algorithms. Without doubt careful clinical observation provides important prognostic information; however, due to the complexity of patients, who are usually old and present multiple co-morbid factors, it requires a great deal of experience, and can be frequently intuitive and difficult to quantify. In the present study, a simple clinical score based on Framingham criteria showed a strong association with prognosis in univariate analysis. However, its prognostic value was totally offset by two other clinical prognostic markers: previous CHF medication (reflecting chronicity of the disease aggravating in spite of treatment) and the dobutamine usage (fact integrating the severity of clinical presentation).

We assumed that repetitive bedside echocardiography would provide the prognostic data and assess the effectiveness of instituted therapy. Without doubt this examination is crucial before making therapeutic decisions. It gives insights into the mechanism of CHF in a particular patient. However, in acute decompensated heart failure, the non-invasive assessment of cardiac filling pressures may be difficult in non-selected patients, because the transmtrial flow profile was interpretable in only 70% of the patients. This is why we used a combined index associating a restrictive pattern or an increase in right ventricular systolic pressure assessed by the tricuspid regurgitation gradient and the diameter of the inferior vena cava, reflecting the increase in pulmonary arterial pressure. Using this combined index we could assess the cardiac filling pressure in 91/95 patients. A relation was found between Doppler echocardiography findings and plasma BNP: actually, a higher plasma BNP was found in patients who had an evidence of increased cardiac filling pressure on admission and it decreased significantly only in those who showed an improvement in these criteria. Both high cardiac filling pressure and low ejection fraction were predictive factors of adverse outcome in univariate analysis and high cardiac filling pressure was an independent marker of prognosis at admission, while BNP levels at admission were not. However, the repetition of the echocardiographic examinations did not provide further independent prognostic information in multivariable analysis.

In contrast, measurement of BNP plasma level can be easily performed in virtually all patients. Our findings clearly show that serial measurements of BNP plasma levels provide incremental prognostic information over clinical and echocardiographic data in this very high-risk population. Few studies have assessed the prognostic value of serial measurements of BNP. In chronic heart failure, Bettencourt et al.27 showed that patients, who had an increase of BNP between two measurements separated by 8–12 months had a poorer survival compared with the others. In acute heart failure, Cheng et al.32 also showed that patients with a decrease of BNP between admission and discharge had a better outcome than patients with an increase or no change. To our knowledge, there are no data in the literature concerning the early prognostic value of BNP monitoring in acute heart failure. In our study, plasma BNP on admission was higher in patients with subsequent adverse events than in the others, however its predictive value was no more significant in multivariable analysis. More important is the change in BNP concentration as a result of effective treatment. Our observations not only confirm the findings that plasma BNP can rapidly decrease in patients responding well to therapy, but also show that these changes are directly related to the final clinical outcome.12,32 In patients with a poor outcome, treatment did not cause a significant decrease in plasma BNP. On the contrary, a cut-off value of BNP decrease >10% after
the first day of therapy appeared to be a marker of a favourable result for both hospital treatment and the outcome analysed up to 60 days after inclusion. In patients with a favourable 60-day outcome, a further BNP decrease between the second day and discharge was noted (Fig. 2); interestingly, this decrease was less pronounced than during the first day of treatment, confirming the importance of an early decrease in BNP. In patients who experienced cardiac death or rehospitalisation occurring later than collection of the third BNP sample, no significant plasma BNP changes throughout hospitalisation were noted, and the last measured BNP concentration was significantly higher than in the group with a better future outcome. This was consistent with other studies showing the value of delayed or pre-discharge BNP sampling for predicting death or rehospitalisation after discharge in decompensated CHF.28,29

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Univariate and multivariable analysis of plasma BNP, clinical and echocardiographic variables found to be associated with 60 days outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors</td>
<td>Univariate</td>
</tr>
<tr>
<td></td>
<td>$\chi^2$</td>
</tr>
<tr>
<td><strong>Admission</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical score (1)</td>
<td>24.9</td>
</tr>
<tr>
<td>Previous CHF treatment</td>
<td>11.4</td>
</tr>
<tr>
<td>Dobutamine infusion</td>
<td>23.9</td>
</tr>
<tr>
<td>LVEF</td>
<td>7.6</td>
</tr>
<tr>
<td>Restrictive or RVSP &gt; 50 (1)</td>
<td>8.9</td>
</tr>
<tr>
<td>BNP (1)</td>
<td>5.6</td>
</tr>
<tr>
<td><strong>Day 2</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical score (1)</td>
<td>16.5</td>
</tr>
<tr>
<td>Clinical score (2)</td>
<td>24.5</td>
</tr>
<tr>
<td>$\Delta$ clinical score (1–2)</td>
<td>9.7</td>
</tr>
<tr>
<td>Previous CHF treatment</td>
<td>10.4</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>19.7</td>
</tr>
<tr>
<td>LVEF</td>
<td>5.1</td>
</tr>
<tr>
<td>Restrictive or RVSP &gt; 50 (1)</td>
<td>7.2</td>
</tr>
<tr>
<td>Restrictive or RVSP &gt; 50 (2)</td>
<td>3.8</td>
</tr>
<tr>
<td>Echo improvement</td>
<td>0.21</td>
</tr>
<tr>
<td>BNP (1)</td>
<td>1.6</td>
</tr>
<tr>
<td>BNP (2)</td>
<td>9.6</td>
</tr>
<tr>
<td>$\Delta$% BNP (1–2)</td>
<td>16.6</td>
</tr>
<tr>
<td><strong>Day 7</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical score (1)</td>
<td>13.9</td>
</tr>
<tr>
<td>Clinical score (2)</td>
<td>19.9</td>
</tr>
<tr>
<td>Clinical score (3)</td>
<td>24.5</td>
</tr>
<tr>
<td>$\Delta$ clinical score (1–2)</td>
<td>10.9</td>
</tr>
<tr>
<td>$\Delta$ clinical score (1–3)</td>
<td>17.9</td>
</tr>
<tr>
<td>Clinical score (2–3)</td>
<td>0.6</td>
</tr>
<tr>
<td>Previous CHF treatment</td>
<td>13.8</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>16.4</td>
</tr>
<tr>
<td>LVEF</td>
<td>4.8</td>
</tr>
<tr>
<td>Restrictive or RVSP &gt; 50 (1)</td>
<td>6.5</td>
</tr>
<tr>
<td>Restrictive or RVSP &gt; 50 (2)</td>
<td>3.4</td>
</tr>
<tr>
<td>Restrictive or RVSP &gt; 50 (3)</td>
<td>8.0</td>
</tr>
<tr>
<td>Echo improvement (1–2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Echo improvement (1–3)</td>
<td>2.0</td>
</tr>
<tr>
<td>Echo improvement (2–3)</td>
<td>0.23</td>
</tr>
<tr>
<td>BNP (1)</td>
<td>3.1</td>
</tr>
<tr>
<td>BNP (2)</td>
<td>9.7</td>
</tr>
<tr>
<td>BNP (3)</td>
<td>24.7</td>
</tr>
<tr>
<td>$\Delta$% BNP (1–2)</td>
<td>7.3</td>
</tr>
<tr>
<td>$\Delta$% BNP (1–3)</td>
<td>15.0</td>
</tr>
<tr>
<td>$\Delta$% BNP (2–3)</td>
<td>5.9</td>
</tr>
</tbody>
</table>

LVEF: LV ejection fraction; restrictive or RVSP > 50: restrictive mitral flow pattern or right ventricular systolic pressure > 50 mmHg; (1) admission, (2) day 2; (3) day 7; (1–2) changes between admission and day 2; (1–3) changes between admission and day 7; (2–3) changes between day 2 and day 7.

* Hazard Ratio for an increase of one SD of $\Delta$% BNP 1–2.
** Hazard Ratio for an increase of one SD of BNP3.
evaluation of cardiac filling pressure and their changes (Fig. 1), serial BNP measurements appear to be more informative than repetitive echos for prognostic stratification; we may hypothesise that besides information on intracardiac pressure, BNP concentrations and their variations may also integrate complex determinants such as systolic or diastolic myocardial stress, or neurohumoral BNP secretory mechanisms.

Our findings may also have economic impact. Repetitive bedside echocardiography, if performed routinely, can induce significant costs related to availability of both the experienced echocardiographer and the ultrasound machine. Serial BNP measurements might therefore identify a subgroup of patients at high risk (i.e., those without BNP decrease), who should require closer monitoring. In contrast, our results suggest that an early decrease in plasma BNP could allow an earlier and safe discharge of the patient. Finally, patients with persistent high plasma BNP after one week of treatment could benefit from an intensive ambulatory follow-up after discharge to avoid costly rehospitalisations.

Table 3 Comparison of the prognostic values of clinical data, then clinical and echocardiographic data, then clinical, echocardiographic data and BNP values at admission, day 2 and day 7

<table>
<thead>
<tr>
<th>Variables included in the model</th>
<th>$-2\log(L)$</th>
<th>DF</th>
<th>Akaike criterion *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Admission</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical data(1)</td>
<td>248.85</td>
<td>[2]</td>
<td>254.85</td>
</tr>
<tr>
<td>Clinical data + echo (2)</td>
<td>244.39</td>
<td>[3]</td>
<td>252.39</td>
</tr>
<tr>
<td>Clinical data + echo + BNP1 &gt; 300 pg/ml</td>
<td>243.89</td>
<td>[4]</td>
<td>253.89</td>
</tr>
<tr>
<td><strong>Day 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical data (1)</td>
<td>226.27</td>
<td>[2]</td>
<td>232.27</td>
</tr>
<tr>
<td>Clinical data + echo (3)</td>
<td>221.88</td>
<td>[3]</td>
<td>229.88</td>
</tr>
<tr>
<td>Clinical data + echo + Δ% BNP 1-2 &gt; 10%</td>
<td>214.25</td>
<td>[4]</td>
<td>224.25</td>
</tr>
<tr>
<td><strong>Day 7</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical data (4)</td>
<td>167.58</td>
<td>[3]</td>
<td>175.58</td>
</tr>
<tr>
<td>Clinical data + echo (5)</td>
<td>166.46</td>
<td>[4]</td>
<td>176.46</td>
</tr>
<tr>
<td>Clinical data + echo + BNP 3 &gt; 300 pg/ml</td>
<td>158.17</td>
<td>[5]</td>
<td>170.17</td>
</tr>
</tbody>
</table>

(1) Previous CHF treatment and dobutamine; (2) restrictive pattern or RVSP > 50 mmHg at admission; (3) echo improvement 1–2; (4) previous CHF treatment, dobutamine, clinical score 3; and (5) restrictive pattern or RVSP > 50 mmHg at day 7.

* Akaike criterion $= -2\log L + 2 \times$ number of parameters allows comparison of non embedded models. The smaller the criterion, the better the model. DF: degree of freedom.

Fig. 2 Plasma B-type natriuretic (BNP) level changes during the treatment of acute heart failure in subgroups of patients with events and without events during the 60-day follow-up.

Fig. 3 Event free 60-day survival in subgroups of patients defined according to BNP change ($\Delta$BNP) after the first day of treatment (a) and to BNP concentration at day 7 (BNP3) (b).

Limitations

There were 37 observed events in the sample and the multivariable analyses performed at several timepoints can lead to an inflation of Type I error. However, even if the results of the analyses are not independent from a strict statistical point of view, we may consider that three separated analyses were performed, and each
multivariable analysis, based on a stepwise regression, found three risk factors, a finding in the usually accepted range (around 10% of the number of events). In addition, the results of the different analyses are consistent. Therefore we do not believe there is an overfitting problem in this study. Our population was not selected and represented the variety of consecutive patients treated in intensive care unit for acute heart failure. Interestingly, plasma BNP was a powerful prognostic marker in this heterogeneous population of patients with acute heart failure related to various underlying cardiac causes.

Conclusion

We demonstrate that serial evaluation of plasma BNP concentration is an effective method for assessing prognosis and response to therapy in a non-selected acute heart failure population. Lack of initial decrease of BNP plasma levels during first day as well as plasma BNP after the first week of treatment provided incremental prognostic information over clinical presentation and repetitive echocardiographic examination. Our results suggest an interesting and useful application of such a non-invasive biochemical monitoring in this severely ill group of patients. Further studies testing this approach in larger populations are warranted.

Acknowledgements

We are grateful to Prof. H.J. Dargie for kindly reviewing the manuscript. We thank Dr. Z. Boufrara, Dr. R. Dumaine, and the entire medical, nursing and analytical staff for outstanding co-operation during the study.

References

30. Johnson W, Omland T, Hall C et al. Neurohormonal activation rapidly decreases after intravenous therapy with diuretics and
