B-Type Natriuretic Peptide Predicts Sudden Death in Patients With Chronic Heart Failure

Rudolf Berger, MD; Martin Huelsman, MD; Karin Strecker, MD; Anja Bojic, MD; Petra Moser; Brigitte Stanek, MD; Richard Pacher, MD

Background—Given the high incidence of sudden death in patients with chronic heart failure (CHF) and the efficacy of implantable cardioverter-defibrillators, an appropriate tool for the prediction of sudden death is desirable. B-type natriuretic peptide (BNP) has prognostic significance in CHF, and the stimuli for its production cause electrophysiological abnormalities. This study tests BNP levels as a predictor of sudden death.

Methods and Results—BNP levels, in addition to other neurohormonal, clinical, and hemodynamic variables, were obtained from 452 patients with a left ventricular ejection fraction (LVEF) ≤35%. For prediction of sudden death, only survivors without heart transplantation (HTx) or a mechanical assist device and patients who died suddenly were analyzed. Up to 3 years, 293 patients survived without HTx or a mechanical assist device, 89 patients died, and 65 patients underwent HTx. Mode of death was sudden in 44 patients (49%), whereas 31 patients (35%) had pump failure and 14 patients (16%) died from other causes. Univariate risk factors of sudden death were log BNP (P=0.0006), log N-terminal atrial natriuretic peptide (P=0.003), LVEF (P=0.005), log N-terminal BNP (P=0.006), systolic blood pressure (P=0.01), big endothelin (P=0.03), and NYHA class (P=0.04). In the multivariate model, log BNP level was the only independent predictor of sudden death (P=0.0006). Using a cutoff point of log BNP <2.11 (130 pg/mL), Kaplan-Meier sudden death–free survival rates were significantly higher in patients below (99%) compared with patients above (81%) this cutoff point (P=0.0001).

Conclusion—BNP levels are a strong, independent predictor of sudden death in patients with CHF. (Circulation. 2002;105:2392-2397.)

Key Words: heart failure ■ death, sudden ■ prognosis ■ natriuretic peptides

Up to 50% of total mortality in patients with chronic heart failure (CHF) is attributable to sudden death. The proportion of sudden death is higher in mild heart failure (NYHA classes I and II) compared with advanced stages (NYHA classes III and IV), whereas the proportion of fatal pump failure increases with the severity of disease. Nevertheless, the incidence of sudden death also rises with total mortality in advanced heart failure; 1-year mortality attributable to sudden death ranges from 2% to 4% for patients in NYHA classes I and II and from 5% to 12% for patients in NYHA classes III and IV.1 Most sudden death events in ambulatory patients are caused by ventricular tachyarrhythmias. However, pulmonary emboli, stroke, ruptured aneurysm, myocardial infarction, and hyperkalemia may also present as sudden death.2,3 Bradyarrhythmias and electromechanical dissociation account for approximately half of the unexpected in-hospital cardiac arrests.2

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A specific treatment for the prevention of sudden death is only indicated if it also reduces overall mortality. Several placebo-controlled trials of amiodarone were performed in patients with CHF or reduced left ventricular dysfunction after myocardial infarction. Only 3 of the trials demonstrated a significant reduction of total mortality. A meta-analysis including 6500 patients from 13 trials reported a survival benefit of 13% to 15% attributable to amiodarone.4 Three secondary prevention trials including patients who resuscitated from cardiac arrest or hemodynamically significant ventricular tachycardia compared the efficacy of amiodarone versus implantable cardioverter-defibrillators (ICDs).5 The Antiarrhythmics Versus Implantable Defibrillator (AVID) study demonstrated an overall survival benefit with the ICD. The findings of the Canadian Implantable Defibrillator Study (CIDS) and Cardiac Arrest Study Hamburg (CASH) point in the same direction, although with less statistical power. Two trials of primary prevention in patients with ischemic cardiomyopathy, nonsustained ventricular tachycardia, and inducible ventricular tachycardia during electrophysiological testing (Multicenter Unsustained Tachycardia Trial [MUSTT]) and Multicenter Automatic Defibrillator Implantation Trial

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From the Department of Cardiology, Ludwig Boltzman Institute of Experimental Endocrinology and Ludwig Boltzman Institute of Cardiovascular Research, University of Vienna, Austria.

Correspondence to Rudolf Berger, MD, University of Vienna, Department of Cardiology, Waehringer Guertel 18-20, A-1090 Vienna, Austria. E-mail rberger@gmx.at

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ventricles and increased pressure within them are both stimuli for ICD. In these patients, the ICD will not improve overall pump failure in the near future are unlikely to benefit from the therapy. Therefore, subcategorizing of risk stratification with regard to sudden and pump-failure death is of essential importance.

To achieve the maximum benefit by ICD therapy, the selection mode for eligible patients should contain the following criteria. First, patients must have an increased risk of sudden death. Patients with negligible risk are exposed to the potential risks of invasive procedures without benefit. Moreover, the indiscriminate use of ICDs is an economically costly undertaking. Second, patients with high risk of death from pump failure in the near future are unlikely to benefit from the ICD. In these patients, the ICD will not improve overall mortality but has the potential to hasten death and negatively impact quality of life and should be avoided. Thus, patients with CHF either at negligible risk of sudden death or at high risk of death from pump failure should be excluded from ICD therapy. Therefore, subcategorizing of risk stratification with regard to sudden and pump-failure death is of essential impact.

B-type natriuretic peptide (BNP) levels have prognostic significance in patients with CHF, especially in patients with mild to moderate symptoms. Volume overload of the ventricles and increased pressure within them are both stimuli for enhanced BNP production and are reported to cause electrophysiological abnormalities. Thus, a relationship between BNP levels and arrhythmic activity is suggested. This study tests the value of BNP levels for prediction of sudden death in a large ambulant patient population with a LVEF <35%.

**Methods**

The study population consisted of 452 ambulatory patients with a LVEF <35% (by radionuclide ventriculography) who were referred to the Heart Failure Center at the Department of Cardiology, University of Vienna, between July 1, 1995, and July 30, 1999. Follow-up closing date was January 1, 2000. All data were obtained at time of first evaluation on the same day, except for LVEF, which was measured within 1 month before or after entry into the study. An institutional review committee approved the study, and all patients gave informed consent.

**Laboratory**

Venous blood samples were obtained after 30 minutes of supine rest from an indwelling catheter. Test tubes were placed on ice and centrifuged immediately. Plasma samples were stored at −70°C until analysis. Commercially available assay kits were used for determination of N-terminal atrial natriuretic peptide (N-ANP) (by ELISA), N-BNP (by ELISA), and big endothelin (by RIA) purchased from Biomedica and for determination of BNP (by ELISA) purchased from Biosite Diagnostics.

**Treatment**

In addition to digitals, patients received ACE-I and β-blocker therapy, which was uptitrated stepwise to an individual maximum dose. The diuretic regimen was adjusted to daily weight, symptoms, and increased vasodilator therapy. In case of refractoriness to medical treatment (ongoing NYHA class III or IV) and documented low output (cardiac index <2.5 L/min per m², pulmonary capillary wedge pressure >20 mm Hg), patients were treated with an intravenous bridging therapy (prostaglandin E₁ or dobutamine). In the absence of contraindications, these patients were considered heart transplantation (HTx) candidates and given higher priority according to the urgent request mode of Eurotransplant. A team of cardiologists and transplant surgeons who were unaware of the neurohormonal status determined the grade of listing for HTx.

**Mode of Death**

In case of death, the underlying cause was obtained from the hospital chart or from interviews with relatives. Deaths were classified as sudden death, pump failure, or resulting from other causes. Sudden death was defined as witnessed cardiac arrest or death within 1 hour after the onset of acute symptoms or unexpected, unwitnessed death (ie, during sleep) in a patient known to have been well within the previous 24 hours. Deaths resulting from deterioration of CHF with progression of congestive symptoms were classified as pump failure.

**Statistical Analysis**

Continuous variables are expressed as mean±SD. Differences between survivors, patients with sudden death, and patients with pump failure were analyzed using 1-factor ANOVA followed by Tukey’s studentized range test for continuous variables. Pairwise comparisons were performed by means of the χ² test for categorical variables. Probability value of the χ² test and of the 1-factor ANOVA are reported in the Tables, and differences between continuous variables of subgroups are marked as significant at a P<0.05. A Cox proportional hazard regression analysis was performed to identify independent predictors of sudden death, including only survivors without HTx and without implantation of a mechanical left ventricular assist device and patients with sudden death. The model was built stepwise, and P value for entering and staying in the model was set at 0.05. Because BNP, N-BNP, and N-ANP were not normally distributed, log BNP, log N-BNP, and log ANP plasma levels were used for analysis. A log BNP cutoff point was selected to define a large patient group with low risk of sudden death. Kaplan-Meier lifetime analysis was used for survival comparison between patient groups stratified according to this cutoff point. Differences were considered significant at P<0.05.

**Results**

The study population included 452 ambulatory patients with a mean observation period of 592±387 days. Patient characteristics are given in Table 1, and neurohormones are given in Table 2.

**Clinical Outcome**

Of the 452 ambulatory patients with heart failure, 298 survived without HTx, 65 underwent HTx, and 89 died. The mode of death was sudden in 44 patients (49%), whereas 31 patients (35%) had pump failure and 14 patients (16%) died from other causes (5 patients during or after implantation of a mechanical assist device, 1 patient with myocardial infarction, 1 patient with stroke, 1 patient during aneurysm surgery, 3 patients with pneumonia, 2 patients with pancreatic cancer, and 1 patient with thyroid cancer) (Table 3).
Patient Characteristics and Neurohormones According to Clinical Outcome

Patient characteristics according to the clinical outcome are given in Table 1. All 4 neurohormones differed significantly between survivors and patients who died from pump failure. In addition, log BNP and log N-BNP showed a significant difference between survivors and patients who died from sudden death, whereas log N-ANP and big endothelin differed between patients who died suddenly and patients who died from pump failure (Table 2).

Univariate and Multivariate Predictors of Sudden Death

Table 4 shows the results of the univariate and multivariate Cox proportional hazards model analyses for sudden death.

Log BNP was the single independent predictor of sudden death.

Kaplan-Meier Survival Estimation

Survival rates, as evaluated by a Kaplan-Meier lifetime analysis, were significantly higher in patients with log BNP \(<2.11\) (according to a BNP level of \(\approx 130\) pg/mL) compared with patients with log BNP values above this cutoff point \((P=0.0001)\). Using this cutoff point, only 1 of 110 patients (1%) below the cutoff point, but 43 of 227 patients (19%) above the cutoff point, died suddenly (Figure).

Discussion

Of 452 ambulatory patients with heart failure with a LVET \(<35\%\), 298 survived without HTx, 89 died, and 65 underwent...
HTx. The mode of death was sudden in 44 patients (49%), whereas 31 patients (35%) had pump failure and 14 patients (16%) died from other causes. The proportion of 10% sudden deaths in this patient population during a mean observation period of 592 days is exactly in accordance with the literature. Of 16 neurohormonal (BNP, N-BNP, N-ANP, and big endothelin), clinical, and hemodynamic variables, log BNP was the only independent predictor of sudden death. In accordance, in a population with mild to moderate heart failure, where sudden death is the main cause of death, BNP was reported to be a powerful prognostic parameter.10,11

Previous Studies Evaluating Sudden Death Risk Factors

In clinical practice, sudden death has been often attributed to ischemic events associated with coronary artery disease, and occurrence of ventricular arrhythmias was regarded as its foreteller. However, nonsustained ventricular tachycardia predicted sudden death in only 2 studies,21,22 and in other studies it did not.23–25 In addition, the prognostic value of other noninvasive electrophysiological tests, the heart rate variability as well as the signal-averaged ECG, is not conclusive.26 Limited data are available about QT dispersion as an independent predictor of sudden death risk.9 With regard to etiology, the Vasodilator-Heart Failure Trials (V-HeFTs) I and II found that the incidence of sudden death is not related to the underlying heart disease.23,25 Also, in the present study, the distribution of sudden death was similar in patients with ischemic (10%) and nonischemic (10%) heart failure etiology. On the other hand, the V-HeFT trials, among other studies, clearly suggested that sudden death is associated with the degree of LV dysfunction.23–25,27,28 In line with this notion, measuring, for example, pulmonary capillary wedge pressure to assess backward failure was also successful in predicting risk of sudden death.27,29

Stimuli of BNP Production as Promotor of Electrophysiological Abnormalities

Only a few neurohormonal parameters, such as plasma renin activity and plasma norepinephrine levels, have been tested as sudden death risk factors, and none have had significant prognostic impact.29 As discussed above, parameters of left ventricular function, especially LVEF, are predictive markers in many analyses. We recently reported a close negative correlation between LVEF and BNP plasma concentrations.11 BNP is largely of ventricular origin, released from the ventricles in proportion to intraventricular pressure or stretch of the ventricles.12 These stimuli of BNP production also cause various electrophysiological abnormalities, thereby favoring arrhythmogenesis in the failing heart. Myocardial

### TABLE 2. Neurohormones

<table>
<thead>
<tr>
<th>Patients (n=492)</th>
<th>Patients With Sudden Death (n=44)</th>
<th>Patients With Pump Failure (n=31)</th>
<th>P Value</th>
<th>All (n=452)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Big ET, fmol/mL</td>
<td>3.3±3.2</td>
<td>4.0±3.0</td>
<td>0.0001†</td>
<td>4.0±3.4</td>
</tr>
<tr>
<td>Log N-ANP</td>
<td>3.47±0.34</td>
<td>3.57±0.31</td>
<td>0.0001‡</td>
<td>3.58±0.37</td>
</tr>
<tr>
<td>Log BNP</td>
<td>2.28±0.70</td>
<td>2.63±0.39</td>
<td>0.0001‡</td>
<td>2.46±0.66</td>
</tr>
<tr>
<td>Log N-BNP</td>
<td>2.57±0.34</td>
<td>2.70±0.21</td>
<td>0.0001‡</td>
<td>2.64±0.31</td>
</tr>
</tbody>
</table>

ET indicates endothelin.

*Significant difference between survivors and patients with pump failure.
†Significant difference between patients with sudden death and patients with pump failure.
‡Significant difference between survivors and patients with sudden death.

### TABLE 3. Clinical Outcome

<table>
<thead>
<tr>
<th>Patients (n=452)</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>298 (66)</td>
</tr>
<tr>
<td>Patients with LVAD</td>
<td>5 (1)</td>
</tr>
<tr>
<td>HTx</td>
<td>65 (14)</td>
</tr>
<tr>
<td>Elective HTx</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Urgent HTx</td>
<td>47 (10)</td>
</tr>
<tr>
<td>Patients pretreated with LVAD</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Death</td>
<td>89 (20)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>44 (10)</td>
</tr>
<tr>
<td>Pump failure</td>
<td>31 (7)</td>
</tr>
<tr>
<td>Patients with LVAD</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Other reasons</td>
<td>9 (2)</td>
</tr>
</tbody>
</table>

LVAD indicates left ventricle assist device.

### TABLE 4. Univariate and Multivariate Analysis for Prediction of Sudden Death

<table>
<thead>
<tr>
<th></th>
<th>χ²</th>
<th>P Value</th>
<th>χ²</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log BNP</td>
<td>11.8125</td>
<td>0.0006</td>
<td>11.8125</td>
<td>0.0006</td>
</tr>
<tr>
<td>Log N-ANP</td>
<td>8.9407</td>
<td>0.0028</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>LVEF</td>
<td>7.7377</td>
<td>0.0054</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Log N-BNP</td>
<td>7.6374</td>
<td>0.0057</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>6.0619</td>
<td>0.0138</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Big endothelin</td>
<td>4.5667</td>
<td>0.0326</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>NYHA class</td>
<td>4.3259</td>
<td>0.0375</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>AT II receptor blocker</td>
<td>2.8067</td>
<td>NS</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>1.8978</td>
<td>NS</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Rhythm</td>
<td>1.5282</td>
<td>NS</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>1.1854</td>
<td>NS</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Heart rate</td>
<td>1.1535</td>
<td>NS</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>ACE-I equivalence dose</td>
<td>0.584</td>
<td>NS</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.4122</td>
<td>NS</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>CAD</td>
<td>0.1207</td>
<td>NS</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>0.0245</td>
<td>NS</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease.
Kaplan-Meier analysis showing cumulative rates of survival in 337 patients with CHF (293 survivors and 44 patients who died suddenly) stratified into 2 groups according to BNP plasma concentration. Patients with log BNP >2.11 (~130 pg/mL) differed significantly from patients with log BNP values below this cutoff point (P=0.0001).

stretch attributable to volume overload slows conduction, enhances refractoriness, and triggers afterdepolarizations and ventricular ectopic beats.13–17 Cellular hypertrophy and fibrosis can prolong action potential duration,18 with the resulting arrhythmogenic consequences.19

Other Diagnostic and Prognostic Studies of BNP and N-Terminal BNP
In CHF, production of the B-type natriuretic peptides is stimulated. Hence, BNP and N-terminal BNP plasma levels are presently evaluated as biomarkers in assessment and management of these patients.10,11,30–35 First, abnormally elevated BNP plasma levels seem to be sensitive markers of symptomless LV dysfunction.31 In addition, N-BNP has the potential to predict LV dysfunction.32 Second, both plasma BNP and N-terminal BNP levels continue to rise along with the progression of LV dysfunction.33 Third, the prognostic impact of BNP was established in several studies. Tsutamoto et al10 were the first to show that a single BNP plasma level foretold 2-year mortality in 25 of 85 patients with LVEF <45% independent of pulmonary wedge pressure. Richards et al13 reported a reduction in risk of death or heart failure in patients with above-median N-terminal BNP levels, who were treated with carvedilol, to rates not significantly different from those observed in patients with levels below the median value but treated with placebo. Carvedilol might have reduced the stimuli responsible for the initially excessive BNP production. Moreover, most studies designed for prognostic purpose did not use repetitive BNP levels. Cheng et al34 demonstrated in patients admitted with decompensated CHF that changes in BNP levels during treatment are strong predictors for outcome. As recently reported from our group, repetitive measurement improves the predictive value of BNP plasma levels.11 These findings suggest that frequent BNP or N-terminal BNP measurements might be a useful blood test for detection of the progression of heart failure. Finally, as a consequence of the previous findings, Troughton et al35 used elevated N-terminal BNP plasma levels as targets for titration of therapy.

Nevertheless, until recently the routine use of plasma BNP levels as a diagnostic or prognostic aid outside research programs has not been established. Perhaps one reason is that the original assay for BNP is time consuming and more difficult to perform. The assay used in this study is practicable and allows rapid (15-minute) determination of BNP levels.

Clinical Implications
Survival rates were significantly higher in patients with log BNP <2.11 (99%) compared with patients with log BNP values above this cutoff point (81%). Thus, measurement of plasma BNP allows the specification of a patient group with higher risk of sudden death, a simple method to identify patients who may likely benefit from ICD implantation.

A limiting factor may be that the extension of survival by ICD is suggested to vary dependent on the severity of disease. In milder heart failure, secondary causes of sudden death, as mentioned above, are less frequent and there is less chance to die from pump failure. Thus, patients with mild heart failure are those who probably profit most from ICD implantation with regard to extension of survival.

Conclusions
The findings of the present study suggest that measurement of BNP plasma levels is a promising method for determining which patients may benefit from ICD implantation. To confirm these findings, additional studies in large heart failure populations are needed.

References


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