Plasma N-Terminal Pro–Brain Natriuretic Peptide and Adrenomedullin
New Neurohormonal Predictors of Left Ventricular Function and Prognosis After Myocardial Infarction

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Background—Newly discovered circulating peptides, N-terminal pro–brain natriuretic peptide (N-BNP) and adrenomedullin (ADM), were examined for prediction of cardiac function and prognosis and compared with previously reported markers in 121 patients with myocardial infarction.

Methods and Results—The association between radionuclide left ventricular ejection fraction (LVEF) and N-BNP at 2 to 4 days ($r = -0.63, P < 0.0001$) and 3 to 5 months ($r = -0.58, P < 0.0001$) after infarction was comparable to that for C-terminal BNP and far stronger than for ADM ($r = -0.26, P < 0.01$), N-terminal atrial natriuretic peptide (N-ANP), C-terminal ANP, cGMP, or plasma catecholamine concentrations. For prediction of death over 24 months of follow-up, an early postinfarction N-BNP level $\geq 160$ pmol/L had sensitivity, specificity, positive predictive value, and negative predictive values of 91%, 72%, 39%, and 97%, respectively, and was superior to any other neurohormone measured and to LVEF. Only 1 of 21 deaths occurred in a patient with an N-BNP level below the group median (Kaplan-Meier survival analysis, $P < 0.0001$). For prediction of heart failure (left ventricular failure), plasma N-BNP $\geq 145$ pmol/L had sensitivity (85%) and negative predictive value (91%) comparable to the other cardiac peptides and was superior to ADM, plasma catecholamines, and LVEF. By multivariate analysis, N-BNP but not ADM provided predictive information for death and left ventricular failure independent of patient age, sex, LVEF, levels of other hormones, and previous history of heart failure, myocardial infarction, hypertension, or diabetes.

Conclusions—Plasma N-BNP measured 2 to 4 days after myocardial infarction independently predicted left ventricular function and 2-year survival. Stratification of patients into low- and high-risk groups can be facilitated by plasma N-BNP or ADM measurements, and one of these could reasonably be included in the routine clinical workup of patients after myocardial infarction. (Circulation. 1998;97:1921-1929.)

Key Words: brain natriuretic peptide • atrial natriuretic factor • peptides • myocardial infarction • ventricles • prognosis

A number of circulating factors reflect LV function and/or predict cardiovascular prognosis in a spectrum of cardiovascular disease ranging from severe heart failure from different causes to well-defined asymptomatic ischemic LV impairment.1–14 Recently, the cardiac peptides have received close attention as cardiovascular markers.5–14 We have recently reported that the 76–amino acid residue amino terminal portion of pro-BNP (N-BNP) circulates in human plasma15 and that levels are elevated in cardiac impairment.15,16 In normal subjects, levels are similar to those of BNP (10.8 ± 1.3 versus 9.7 ± 0.5 pmol/L, respectively, NS), whereas in cardiac impairment, the proportional and absolute increment above normal levels of the N-BNP peptide exceeds that for BNP, which suggests that it may be the more discerning marker. ADM is a newly discovered 52–amino acid peptide with structural homology with calcitonin gene–related peptide.17 Originally isolated from human pheochromocytoma cells, immunoreactive ADM has been detected in other tissues including adrenal medulla, heart, brain, lung, kidney, and gastrointestinal organs.17,18 The limited data available concerning the biologic activity of ADM suggest that it has powerful direct vasodilator effects and is able to increase cardiac output and induce diuresis and natriuresis.19–22 Plasma ADM levels are typically in the lower picomolar range in

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1921
normal humans but are reported to be increased in hypertension, congestive heart failure, and chronic renal failure in proportion to the severity of disease. In heart failure, plasma ADM is inversely related to LVEF and positively associated with LVEDP. The potential value of plasma ADM levels as indicators of cardiovascular prognosis is unknown.

The current study was designed to test the following hypotheses: (1) That after myocardial infarction, plasma N-BNP is equal or superior to other cardiac peptides, the second messenger cGMP and plasma catecholamines as an indicator of LV function both early and late after myocardial infarction, and of cardiovascular prognosis. (2) Plasma adrenomedullin is related to LV function, cardiovascular prognosis, and to other neurohormonal markers after myocardial infarction.

Methods
A consecutive series of 121 patients (Table 1) admitted to the Christchurch Hospital Coronary Care Unit with acute myocardial infarction between November 1994 and June 1995 were studied. All patients gave written informed consent for participation in the study. The protocol was approved by the Southern Regional Health Authority Ethics Committee (Canterbury). Acute myocardial infarction was defined by the presence of typical cardiac ischemic symptoms, the presence of ischemic changes on the ECG in two or more ECG leads, and peak elevation of plasma creatine kinase to at least twice normal (400 U/L). Inclusion criteria included age >80 years, absence of cardiogenic shock, and survival for at least 24 hours after myocardial infarction. Blood samples were taken between 24 and 96 hours after the onset of symptoms, in the morning (7 AM to 1 PM), through an indwelling intravenous cannula placed at least 30 minutes before sampling, with the patient resting quietly while semirecumbent. Samples were taken into chilled EDTA Vacutainers, placed immediately on ice, centrifuged within 20 minutes at −2°C, and the plasma stored at −80°C before assay for N-BNP, BNP, N-ANP, ANP, cGMP, ADM, and plasma catecholamines (NE and EPI).

LV function was first assessed by radionuclide ventriculography within 24 hours of blood sampling and then repeated 3 to 5 months after infarction. Each study was performed with a General Electric 400 AC gamma camera interfaced to a General Electric 3000i computer system after standard in vivo technetium-99m red blood cell labeling. Clinical events including death, heart failure (defined by the presence of new symptoms of dyspnea and/or edema, with one

**Table 1. Patients With Myocardial Infarction (n=121)**

<table>
<thead>
<tr>
<th>Demographic and Clinical Features</th>
<th>Neurohormone and Scan Data</th>
<th>Mean±SEM or %</th>
<th>ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>N-BNP, pmol/L</td>
<td>1867±1444</td>
<td>10.89</td>
</tr>
<tr>
<td>Sex, male %</td>
<td>BNP, pmol/L</td>
<td>88±5</td>
<td>241±53</td>
</tr>
<tr>
<td>Body mass index, kg/m²^2</td>
<td>N-BNP, pmol/L</td>
<td>154±5</td>
<td>10.89</td>
</tr>
<tr>
<td>Position of infarct, %</td>
<td>ADM, pmol/L</td>
<td>214±18</td>
<td>88±5</td>
</tr>
<tr>
<td>Anterior</td>
<td>N-ANP, pmol/L</td>
<td>2103±127</td>
<td>154±5</td>
</tr>
<tr>
<td>Inferior</td>
<td>ANP, pmol/L</td>
<td>46±1</td>
<td>2103±127</td>
</tr>
<tr>
<td>Other</td>
<td>cGMP, nmol/L</td>
<td>2103±127</td>
<td>46±1</td>
</tr>
<tr>
<td>Peak creatine kinase, U/L</td>
<td>EPI, pmol/L</td>
<td>46±1</td>
<td>2103±127</td>
</tr>
<tr>
<td>Peak troponin T, U/L</td>
<td>LVEDV, mL</td>
<td>500</td>
<td>2103±127</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>LVEF, %</td>
<td>500</td>
<td>2103±127</td>
</tr>
<tr>
<td>Previous history, %</td>
<td>LVEDV, mL</td>
<td>500</td>
<td>2103±127</td>
</tr>
<tr>
<td>Angina</td>
<td>smoker</td>
<td>500</td>
<td>2103±127</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>smoker</td>
<td>500</td>
<td>2103±127</td>
</tr>
<tr>
<td>Previous heart failure</td>
<td>smoker</td>
<td>500</td>
<td>2103±127</td>
</tr>
<tr>
<td>Hypertension</td>
<td>smoker</td>
<td>500</td>
<td>2103±127</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>smoker</td>
<td>500</td>
<td>2103±127</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>smoker</td>
<td>500</td>
<td>2103±127</td>
</tr>
<tr>
<td>Diabetes</td>
<td>smoker</td>
<td>500</td>
<td>2103±127</td>
</tr>
</tbody>
</table>

ULN indicates upper limit of normal defined as 2 SD above the mean in 168 age-matched normal subjects; nk, normal range not known.
or more concordant signs including ventricular gallop rhythm, pulmonary crepitations, elevated venous pressure, and/or radiologic evidence of left ventricular failure), unstable angina, and recurrent myocardial infarction were recorded for 24 months of follow-up in all patients.

**Statistical Analysis**

Values are expressed as mean±SD. For correlation analysis (Pearson product moment), the log of neurohumoral factors was used to normalize the distribution of data. Multiple logistic regression was undertaken to test for independent prediction of LVEF of <40% by one or more neurohumoral factors. The relative abilities of neurohumoral factors to predict death or clinical LVF were assessed by ROC analysis. Areas under the ROC curves for each marker were compared by the method of Hanley and McNeil. Optimal values for specificity and sensitivity were estimated by finding the position on the ROC curves with the minimum Euclidian distance to the point of perfect specificity and sensitivity (100%, 100%). Mean levels of neurohumoral factors and ventricular scan variables for patients incurring or spared specific adverse events were compared by use of independent t tests. Cumulative adverse event rates were compared by use of χ² tests (with Yates correction for low expected frequencies) with risk ratios (with 95% confidence intervals) and Kaplan-Meier survival curves calculated for groups with admission levels above and below the median of individual neurohumoral factors, ejection fraction, and LVESV and LVEDV. Multiple logistic regression analyses were conducted to test the independent predictive power of neurohormones, ventricular scan data, sex, age, and clinical history for two outcomes: death (all causes) and LVF within 24 months of myocardial infarction. Demographic and clinical variables forced into the model as standard predictors included age, sex, history of previous myocardial infarction, hypertension, diabetes, and previous heart failure. Concordant with the Kaplan-Meier survival curve and χ² event rate analyses, candidate predictors including LVEF, ADM, EPI, NE, the cardiac peptides, and cGMP were entered in the multiple logistic regression analyses as binary variables with values falling above or below the group median. For all analyses, a value of P<.05 was taken as statistically significant.

**Results**

The clinical and demographic features, together with plasma neurohumoral results and LV parameters, for the study group are given in Table 1. At discharge, the percentages of the group receiving aspirin, β-blockers, ACE inhibitors, and/or diuretics were 95%, 86%, 43%, and 25%, respectively. Mean plasma levels of both ANP and BNP were elevated (P<.001) well above the upper limit of normal (Table 1). Mean N-BNP levels were 12-fold the upper limit of normal. In contrast, mean plasma catecholamine levels were within the normal range. Worldwide, normal ranges for plasma N-ANP, cGMP, and ADM were yet to be formally established, but levels were all significantly greater than those observed in our laboratory in a group of 35 normal subjects (not matched for age with the current study group). Over the 4 months after infarction, LVEF rose marginally from 46±1% to 49±1% (P<.05).

**Hormone-Hormone Associations**

Strong positive relations were observed between plasma N-BNP levels and concurrent levels of BNP, N-ANP, ANP, and cGMP (Table 2), but associations with the catecholamines and ADM were weaker. The correlations between N-BNP and other neurohormones were strongest for N-BNP (r=.40, P<.001, n=116 to 121 for admission r values: (a) admission values plotted against admission values; (b) admission neurohormone levels plotted against 4-month LVEF and 4-month LVESV. For n=100 all r values >.32, P<.001; all r values 0.25 to 0.32, P<.01; and r values 0.20 to 0.25, P<.05.

Table 2) and fell in the range of r=.20 to .29 (P<.05 to .01) for NE, ANP, N-ANP, BNP, and cGMP.

**Hormones and LV Function**

In the early postinfarction period, the relations between LVEF and systolic volume with concomitant cardiac plasma peptide concentrations were strongest for N-BNP (r=-.63 and r=.61, respectively, both P<.0001) and BNP (Table 2). Multiple logistic regression analysis incorporating all the neurohormones except BNP indicated N-BNP alone remained independently predictive of LVEF <40% (P<.001), and a similar analysis that included BNP but not N-BNP indicated a similar finding for BNP (P<.001). Both the slope and strength of the relation between early postinfarction neurohormones and LV scan data were similar whether plotted against early or late (4-month) LVEF or LVESV measurements (Table 2; Fig 1).

Optimal levels of N-BNP and BNP for indicating LVEF ≤40% were 145 pmol/L and 30 pmol/L, respectively; yielding sensitivities of 71% and 68%, specificities of 69% and 69%, positive predictive values of 56% and 56%, and negative predictive values of 80% and 79%, respectively. Notably, N-BNP levels fivefold (70 pmol/L) and BNP twofold (20 pmol/L) the upper limit of normal retained both sensitivity and negative predictive values of ≥90% for LVEF <40%.

**Hormones and Clinical Events**

During 24 months of follow-up (complete for all 121 patients), 21 deaths (18 cardiovascular), 33 episodes of clinical heart failure, and 36 unstable ischemic syndrome events (nonfatal myocardial infarction or unstable angina) occurred, giving cumulative event rates of 17%, 27%, and 30%, respectively.

Mean early postinfarction values of all neurohormones except ADM and EPI were significantly higher for those dying during follow-up (Table 3). Similarly, all but ADM were increased in those later developing heart failure. Nota-

### Table 2. Correlations (r) of N-BNP and LVEF With Each Other and Other Neurohumoral Factors at Admission and 4 Months After Myocardial Infarction

<table>
<thead>
<tr>
<th></th>
<th>N-BNP(a)</th>
<th>LVEF(a)</th>
<th>LVESV(a)</th>
<th>LVEF(b)</th>
<th>LVESV(b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-BNP</td>
<td>. . .</td>
<td>- .63</td>
<td>.61</td>
<td>- .58</td>
<td>.59</td>
</tr>
<tr>
<td>BNP</td>
<td>.95</td>
<td>- .82</td>
<td>.60</td>
<td>- .59</td>
<td>.62</td>
</tr>
<tr>
<td>ANP</td>
<td>.69</td>
<td>- .50</td>
<td>.55</td>
<td>- .40</td>
<td>.53</td>
</tr>
<tr>
<td>cGMP</td>
<td>.64</td>
<td>- .51</td>
<td>.55</td>
<td>- .45</td>
<td>.47</td>
</tr>
<tr>
<td>N-ANP</td>
<td>.52</td>
<td>- .33</td>
<td>.40</td>
<td>- .31</td>
<td>.40</td>
</tr>
<tr>
<td>ADM</td>
<td>.40</td>
<td>- .26</td>
<td>.31</td>
<td>- .28</td>
<td>.32</td>
</tr>
<tr>
<td>NE</td>
<td>.33</td>
<td>- .27</td>
<td>.23</td>
<td>- .23</td>
<td>.15</td>
</tr>
<tr>
<td>EPI</td>
<td>.17</td>
<td>- .16</td>
<td>.17</td>
<td>- .16</td>
<td>.18</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.
bly, the ratio of mean neurohormone levels for those incurring over those spared both death and heart failure was greatest for N-BNP (Table 3). In contrast, baseline neurohormones did not differ between those destined to incur or to be spared a new acute ischemic coronary syndrome.

Cumulative (24-month) event rates for death (all causes) and LVF for those with early postinfarction neurohormone levels or LV function above the group median are compared with those with values below the median in Table 4. N-BNP yields the clearest separation for death, with only 1 death in 21 occurring within the half of the group with N-BNP values below the median. Median BNP and N-ANP are the next-ranked discriminators, with ANP, ADM, and LVF somewhat weaker. For LVF, median N-BNP, BNP, ANP, and LVESV display similar separation of events with 85% or more of 33 episodes of frank clinical heart failure occurring in those with early postinfarction levels of these indicators above the group median.

Kaplan-Meier survival curves by median levels of candidate indicators are shown in Figs 2, 3, and 4. Clear separation

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**Table 3. Adverse Events: Neurohormones and Left Ventricular Function (Mean±SEM)**

<table>
<thead>
<tr>
<th></th>
<th>ANP, pmol/L</th>
<th>N-ANP, pmol/L</th>
<th>BNP, pmol/L</th>
<th>N-BNP, pmol/L</th>
<th>cGMP, nmol/L</th>
<th>ADM, pmol/L</th>
<th>NE, pmol/L</th>
<th>EPI, pmol/L</th>
<th>LVESV, mL</th>
<th>LVEF, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>21</td>
<td>69±14</td>
<td>4182±698</td>
<td>55±7</td>
<td>366±56</td>
<td>8.4±1.2</td>
<td>20.1±2.3</td>
<td>2790±461</td>
<td>222±50</td>
<td>146±19</td>
</tr>
<tr>
<td>N</td>
<td>100</td>
<td>37±3</td>
<td>2114±145‡</td>
<td>30±2‡</td>
<td>150±13‡</td>
<td>5.9±0.3‡</td>
<td>16.4±1.0</td>
<td>1962±117*</td>
<td>212±20</td>
<td>76±3‡</td>
</tr>
<tr>
<td>Y/N</td>
<td>1.9‡</td>
<td>2.0‡</td>
<td>1.8‡</td>
<td>2.4‡</td>
<td>1.4‡</td>
<td>1.2‡</td>
<td>1.4‡</td>
<td>1.0‡</td>
<td>1.9‡</td>
<td>1.4‡</td>
</tr>
</tbody>
</table>

| Y | 33          | 75±10         | 3838±501    | 53±5          | 329±41      | 9.1±0.8     | 19.9±1.8   | 3098±346    | 280±38    | 131±13  | 35±3 |
| N | 88          | 30±2‡         | 1937±124‡   | 27±1‡         | 132±12‡     | 5.2±0.2‡    | 15.9±1.1   | 1733±91‡    | 190±20*   | 71±3‡   | 50±1‡ |
| Y/N| 2.5         | 2.0           | 2.0         | 2.5           | 1.8         | 1.3         | 1.8         | 1.5         | 1.8         | 1.4     |

**Ischemic syndromes**

| Y | 36          | 36±8          | 2736±454    | 35±5          | 203±37      | 6.7±0.7     | 16.4±1.8   | 2119±227    | 189±29    | 93±12   | 46±2 |
| N | 85          | 42±3          | 2337±170    | 34±2          | 179±17      | 6.1±0.3     | 17.2±1.1   | 2096±155    | 224±23    | 85±4    | 46±1 |
| Y/N| 1.1         | 1.2           | 1.0         | 1.1           | 1.1         | 1.0         | 1.0         | 0.8         | 1.1         | 1.0     |

Y indicates incurred adverse event; N, spared adverse event; Y/N, ratio of mean level of variable in those with event divided by that in those spared the event (ratio reversed for LVEF to aid comparison with other variables).

In comparison with group incurring event, *P<.05, †P<.01, ‡P<.001.
of curves, most clear-cut for N-BNP, was also demonstrated for ANP, N-ANP, and BNP. Survival curves for cGMP (not shown) did not separate significantly. ADM (Fig 3) curves exhibited a separation similar to that of ANP (Fig 2). All the cardiac peptides and ADM were superior to NE (Fig 3). Radionuclide data curves separate widely about median LVEF and LVESV with less though still significant distinction by LVEDV (Fig 4).

ROC analyses provided the optimal values of candidate markers for prediction of death and LVF, as shown in Table 5. For death, N-BNP had the strongest sensitivity, specificity, positive predictive value, and negative predictive value. An early postinfarction N-BNP value \( >160 \) pmol/L included 91% of those later to die, and in this group nearly 40% did die, whereas a value \( <160 \) pmol/L conferred a 97% probability of survival over 24 months of follow-up. For prediction of LVF, BNP performed marginally better than N-BNP, which, nevertheless, still exhibited sensitivity \( >80\% \) and negative predictive value \( >90\% \) at a cutoff of 145 pmol/L. Both N-BNP and BNP performed notably better than LVEF, LVEDV, and NE for both end points \( P<.01 \) for ROC curve comparisons. Values for ADM were comparable to those of NE (Table 5).
Multivariate analyses testing for independent predictive information among candidate cardiac markers for death and for heart failure are shown in Table 6. Overall N-BNP was the top-ranking neurohormonal predictor for death while also retaining independent predictive power for LVF. For both end points, when either N-BNP or BNP were included in the multivariate analysis, no additional independent information was provided by LVEF or other hormones including ADM, NE, or EPI. Age ($P=0.016$), a history of previous myocardial infarction ($P=0.044$), and N-BNP ($P=0.024$) level were all predictive of death independent of each other and of the other neurohormonal, LV scan, demographic, and clinical history variables tabled. A previous history of heart failure ($P=0.032$) and N-BNP ($P=0.013$) level were predictive of heart failure independent of each other and the other variables tabled. With serial substitution of the individual cardiac peptides and then cGMP in this model, age and a previous history of myocardial infarction retained their independent significance for prediction of death in all analyses. Of the other cardiac peptides, BNP ($P=0.041$) but not ANP, N-ANP, or cGMP ($P=0.139$ to .847) gave independent information for death.

For the end point of LVF, serial substitution of cardiac peptides, and then cGMP, gave more complex results. ANP ($P<0.001$) gave independent information together with NE ($P=0.047$) and LVEF ($P=0.015$). BNP ($P=0.009$) and a previous history of heart failure ($P=0.038$) were the independent variables (but not NE or LVEF) when BNP was substituted in the model. Previous heart failure ($P=0.048$), NE ($P=0.033$), and LVEF ($P=0.009$) but not N-ANP itself ($P=0.143$) were independently predictive when N-ANP was the cardiac peptide incorporated in the model. Finally, cGMP ($P=0.003$) and a previous history of heart failure ($P=0.044$) were the only independent variables when cGMP was examined.

**Discussion**

The current findings indicate that the plasma concentration of the newly discovered circulating N-terminal portion of pro-BNP, N-BNP, is equal or superior to the other cardiac peptides (ANP, N-ANP, and BNP), their second messenger (cGMP), ADM, and the plasma catecholamines as an indicator of LV function (both systolic volume and ejection fraction), both early and late after infarction. Similarly, the early postmyocardial infarction level of N-BNP is a powerful independent predictor of death or heart failure over the 2 years after myocardial infarction.

Plasma ADM levels have a statistically significant (but modest) inverse relation with LV function, which is comparable to that of NE. We report for the first time that plasma ADM is predictive of death in the 2 years after myocardial infarction, but this relation is generally far weaker than observed for N-BNP and does not retain independent significance by multivariate analysis. Plasma ADM levels in heart failure presumably reflect a systemic or peripheral response to cardiac impairment and may be mediated by a variety of mechanisms including induction.

**Figure 3.** Kaplan-Meier survival curves for subgroups with early postinfarction plasma peptide (ADM and NE) concentrations above (solid line) and below (dashed line) the group median in 121 patients with myocardial infarction.

**Figure 4.** Kaplan-Meier survival curves for subgroups with radionuclide scan indicators of LV function (LVEF, LVESV, and LVEDV) above (solid line) and below (dashed line) the group median in 121 patients with myocardial infarction.
of endothelial production of ADM, elevated levels of endothelin, or other humoral and neural mechanisms. There is little knowledge of the possible effects of heart failure on ADM clearance. Hence ADM appears an indirect reflector of LV function and has a weaker association with LV size or contractile function or prognosis than BNP or N-BNP. The latter two peptides are the true “ventricular” hormones studied. Their release is mediated by ventricular wall stress, and their synthesis is increased with cardiac injury (especially in the peri-infarct zone). The superior performance of BNP and N-BNP as cardiac markers is consistent with their site of synthesis and its regulation.

**Hormones and LV Function**

We have shown for the first time that the relations of N-BNP with LVEF and LVESV were comparable with those observed for BNP and clearly stronger than for any of the other neurohormones examined (Table 2). Furthermore, the relation between early postinfarction N-BNP and LVEF is as strong for late (3 to 5 months after infarction) LVEF as for concurrent LVEF, and therefore early postinfarction N-BNP can aid in prediction of LV function some months after acute infarction. The current results concur with those reported by Davidson et al,8 Yamamoto et al,9 and Motwani et al14 and contrast with Omland et al11 in showing that the inverse relation of LVEF with BNP is stronger than with ANP or N-ANP (and now cGMP). However, in contrast to the preliminary report on 16 patients from Motwani et al,14 despite the superior strength of the relation of BNP (and now N-BNP) with LVEF (compared with other hormones), the positive predictive value for LVEF <40% is only fair at ≈40%.

**Hormones and Clinical Events**

By multiple forms of analysis, N-BNP emerged as the single most powerful predictor of death. Only 1 of 21 deaths occurred in those with early postinfarction N-BNP levels below the group median (and none within the first 18 months of follow-up).

Univariate analyses (Tables 3 and 4 and figures) showed the expected association of many individual hormonal and LV scan features with both death and heart failure. Multivariate analyses demonstrated that N-BNP and BNP both retained statistically significant power for prediction of death and LVF independent of other demographic, clinical, hormonal, and LV scan variables.

The two end points of death and heart failure contrasted with respect to predictive factors in that age and history of previous myocardial infarction remained powerful predictors of death in all multivariate analyses. In contrast, for heart failure, neurohormones (a cardiac peptide and/or NE), a history of previous heart failure, and/or LVEF remained statistically independent. This presumably reflects the importance of age and previous cardiac injury in the overall likelihood of deaths that occurred evenly over the 2 years of follow-up (Figs 2, 3, and 4). Many heart failure events were brief, and the majority occurred in the predischarge, postinfarction period. In this setting it appears that neurohormonal...
indicators are more powerful independent indicators of incipient or imminent frank (though often transient) LVF than age, previous clinical history, or LVEF.

Although mean levels were higher in those dying during follow-up, in other analyses NE proved to be of little value in predicting death. However, event rates above and below the group median level of NE did differ for heart failure (Table 4), and NE added information beyond that given by some individual cardiac peptides and/or LVEF for prediction of LVF in most multivariate analyses. Generally, our findings are in accord with the bulk of reports that attest to the superior power for heart failure.

In this first report of the potential postinfarction utility of the plasma concentrations of the cardiac peptide second messenger, plasma cGMP maintained obvious relations with concurrent plasma cardiac peptide concentrations (most notably ANP and N-BNP), but it was clearly a less powerful indicator of LVEF or of death than N-BNP or BNP. This presumably reflects the fact that plasma cGMP is merely spillover of a tiny proportion of that produced intracellularly and responds to a number of stimuli, such as nitric oxide as well as cardiac peptide levels. However, in multivariate analyses it remained a powerful independent predictor of LVF.

N-ANP has previously been reported to reflect LVEF and prognosis.\textsuperscript{5-8} N-ANP was consistently and significantly related to the other cardiac peptides and to cGMP as well as to LVEF and to adverse outcomes, at least in univariate analyses. However, it clearly performed less well than N-BNP, BNP, or ANP as an indicator of LVEF. This seems intuitively acceptable because N-BNP and BNP released from the ventricle (the only truly “ventricular” hormones measured in the study) in response to LV wall stress might logically relate most closely to LV status. The finding conflicts with other studies\textsuperscript{8,11} reporting N-ANP equal or superior to BNP in predicting LVEF \(\leq45\%\) in smaller groups including LV impairment of different causes.\textsuperscript{8} The current study indicates that within days or months of myocardial infarction, N-ANP will be less closely related to LV parameters and to later prognosis than N-BNP or BNP.

Notably, nonfatal ischemic events over follow-up were not predicted by any of the hormones measured or by LV scan data. Presumably this reflects the weakness of any possible association of intracardiac distending pressures (the main regulator of cardiac peptide release) and the risk of renewed coronary atherosclerotic plaque rupture and subsequent thrombosis.

The strong relations of N-BNP to LV function and cardiovascular prognosis have been observed despite the heterogeneity of the group under study. Wide variation in age, previous blood pressure, preinfarction LV function, or history of previous ischemic events is present, together with some variation in acute management (eg, use of thrombolytic therapy, \(\beta\)-blockers, and other vasoactive drugs). It will be of interest to see whether any particular clinical or therapeutic subgroups exhibit an altered relation between cardiac peptides and LV function or prognosis. However, this task is beyond the current study; the population described would not provide adequate statistical power to appropriately examine these questions, which should be the subject of later prospective studies in larger populations.

A shortcoming of the current study and all similar studies is the necessary limit to the number of potential neurohumoral markers assessed. Renin was not measured because many of the group received converting enzyme inhibitors, thus distorting any relation between renin and ventricular function or cardiovascular prognosis. Endothelin has shown promise despite its diffuse vascular (rather than specific cardiac) origin and warrants further study.\textsuperscript{32,33} Similarly, further consideration of cytokines including tumor necrosis factor is also required.\textsuperscript{34} The list of circulating factors with potential prognostic utility will inevitably expand with time.

Among plasma cardiac peptides, cGMP, ADM, and catecholamine levels, the ventricular hormones N-BNP and BNP best reflected LV function and gave prognostic information (independent of age, sex, clinical history, and LVEF) regarding the risk of death or heart failure in the 2 years after myocardial infarction. Stratification of patients into low- and high-risk groups can be facilitated by plasma N-BNP or BNP measurements, and one of these could reasonably be included in the routine clinical workup of patients after myocardial infarction.

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<th>Variable</th>
<th>Death T Ratio</th>
<th>Death P</th>
<th>Heart Failure T Ratio</th>
<th>Heart Failure P</th>
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<td>Age</td>
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<td>1.42 NS</td>
<td>1.62 NS 0.99 NS</td>
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<tr>
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<td>0.81 NS 1.69 NS</td>
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<tr>
<td>Hypertension</td>
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<td>1.21 NS 0.41 NS</td>
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<tr>
<td>LVEF</td>
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<tr>
<td>N-BNP</td>
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<td>2.49 NS</td>
<td>2.26 * 2.49 NS</td>
<td>2.26 * 2.49 NS</td>
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</tbody>
</table>

\(\text{MI indicates myocardial infarction; HF, heart failure, } *P<.05.\)
Department technical and nursing staff, and Coronary Care nursing staff. Secretarial assistance was provided by Barbara Griffin.

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