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Norepinephrine Level as a Predictor of Mortality After First Myocardial Infarction*

D. Kotlaba, B. A. Rybicki, F. Khaja, E. J. Tanhehco, H. N. Sabbah, S. Goldstein

The objective of this study was to determine whether the magnitude of adrenergic activation, as measured by plasma norepinephrine concentration (PNE) in the acute phase of myocardial infarction, may be useful as an independent predictor of long-term morbidity and mortality following acute myocardial infarction (AMI). Plasma norepinephrine was obtained within 3 days of admission to the cardiac intensive care unit in 146 randomly selected patients presenting with their first AMI. We analysed the relationship between the initial PNE and the clinical outcomes of death, reinfarction, and congestive heart failure during the subsequent 18 months. Patients with initial PNE over 565 pg/ml (n = 54) were found to have a significantly higher likelihood of cardiac death within the following 18 months (RR = 4.22; p = 0.04), as compared with patients with a lower PNE (n = 98). Even adjustment for variables significant on the univariate level, the difference in mortality remained significant (RR = 4.67; p = 0.03). No correlation was found between PNE and subsequent incidence of reinfarction and congestive heart failure in these patients (RR = 0.087; p = 0.80 and RR = 1.00; p = 0.09, respectively). Our observations support the hypothesis that PNE obtained early in the course of myocardial infarction can be a useful independent prognostic tool for post-AMI mortality. J Clin Basic Cardiol 2005; 8: 55–8.

Key words: myocardial infarction, norepinephrine, cardiac death

The activation of the sympathetic nervous system early in the course of an acute myocardial infarction (AMI) manifested by increased concentrations of norepinephrine in the blood and urine has been of interest to investigators for almost three decades. Increased levels of plasma norepinephrine (PNE) have been associated with a number of adverse clinical events after myocardial infarction, including congestive heart failure, cardiogenic shock [1–3], ventricular arrhythmias [1, 2, 4, 5], and death [1, 4, 6, 7]. McAlpine et al. observed that in addition to plasma catecholamine elevation, renin and angiotensin II were elevated up to ten days after an AMI in patients with heart failure and ventricular tachycardia [1]. Elevation of these neurohormones was associated with death during hospitalisation due to pump failure and arrhythmias. Increase in PNE has also been correlated with higher levels of myocardial enzyme release [1, 6, 8], which signify the extent of myocardial damage.

These observations have given support for the use of beta-adrenergic blocking agents for the treatment of AMI. Since norepinephrine appears to be related to a number of adverse events occurring in the acute phase of myocardial infarction, it is possible that its concentration obtained during hospitalisation could provide an important predictor of long-term survival after an AMI. In order to examine the predictive potential of norepinephrine, plasma concentrations of norepinephrine were measured in patients within the first 72 hours of their first AMI. Patients were subsequently followed for occurrence of death, congestive heart failure (CHF) and reinfarction for 18 months after their initial hospitalisation.

Methods

Patients were enrolled consecutively into the study during a three-year period between 1991 and 1993. Study subjects were part of a larger study of 511 patients admitted to the Coronary Intensive Care Unit with their first AMI, based upon established electrocardiographic and enzymatic criteria (see below). From the total population of patients with their first AMI (Q-wave and non-Q-wave), 146 were randomly selected to have a blood sample drawn for plasma norepinephrine. The samples were taken within the first three days of admission, at an average time from admission of 2 days. All patients in the study underwent complete history and physical examination by a senior staff cardiologist, including a history of risk factors of coronary artery disease, family history of hypertension, hypercholesterolemia, diabetes mellitus, cigarette smoking, and drug abuse. At the time of admission, an electrocardiogram and serial cardiac enzymes were obtained.

ECG and Enzymatic Criteria for AMI

The diagnosis of a Q-wave AMI was based on the presence of typical symptoms, in association with a new Q-wave in at least two consecutive ECG leads. The anatomical location of the myocardial infarction was established using criteria described by Chou [9]. A non-Q-wave AMI was diagnosed in the presence of typical symptoms associated with concurrent changes in the ST and T waves without development of Q-waves. Enzymatic criteria for both Q-wave and non-Q-wave AMI included total peak serum creatine phosphokinase (CPK) > 400 IU/l and serum MB isoenzyme (CKMB) > 3 % total CPK. Enzyme evaluations were initiated upon admission and repeated 3 times, 8 hours apart.

Follow-Up

Patients had a two-dimensional transthoracic echocardiogram performed within 36 hours from admission and at discharge. During each follow-up visit, complete interval cardiac history, physical examination, and 2D-echo were performed.

* The study was supported by a grant from the National Heart, Lung and Blood Institute, HL49756-04

Received: March 3rd, 2003; accepted: February 18th, 2005.

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Echocardiographic Evaluation

Two-dimensional echocardiograms were used to quantify left ventricular (LV) mass, cavity volume, and regional wall motion in accordance with the recommendations of the American Society of Echocardiographers [10]. All echocardiographic studies were performed by an experienced sonographer and reviewed for quality by one of the investigators. End-systolic and end-diastolic cavity volumes were computed from the dimensions and area measures obtained from paired apical views. Left ventricular volumes were calculated using the disc summation method (modified Simpson rule) [11]. Left ventricular mass was determined by the method of Helak and Reichek [12].

Norepinephrine concentration was analysed in a pre-determined dichotomous fashion by separating patients above and below 565 pg/ml. The concentration of 565 pg/ml is the upper limit of normal norepinephrine levels used by the Henry Ford Hospital Biochemical Laboratory. This upper limit of normal equals the mean plus two standard deviations obtained by prior analysis of catecholamine levels in a group of 56 healthy volunteers.

Statistical Methods

Association of plasma norepinephrine levels with baseline characteristics and peak CPK concentrations between low and high PNE groups was performed. The three types of adverse cardiac events followed were cardiac death, reinfarction, and congestive heart failure. On a multivariate level, the association of plasma norepinephrine levels with adverse cardiac events as defined above was analysed using a Cox proportional hazards model (Proc. Phreg. in SAS). The outcome in all models was time to event. Time started three days after the date of AMI, the approximate date when PNE levels were drawn. Therefore, individuals who had heart failure or reinfection within three days of their AMI were excluded from the models that used heart failure or reinfection as the outcome event. This excluded 41 patients from the heart failure models and 2 individuals from the reinfection models. Individuals who did not experience an event were censored at their last day of follow-up or 18 months, whichever came first. Initial model fitting included only high PNE as an explanatory variable to obtain a crude risk ratio for survival. Additional model fitting included variables that were significant on the univariate level to obtain an adjusted risk estimate for high PNE. Time from study enrollment to each event was also analysed with Kaplan-Meier survival curves and log rank \( \chi^2 \)-square tests.
their first AMI and may be used as a convenient adjunct to other well established tests, such as two-dimensional echocardiogram or maximum serum CPK levels.

AMI is associated with the activation of the sympathetic nervous system and the renin-angiotensin system. This neurohumoral activation is expressed by the marked increase of plasma catecholamines, renin, vasopressin, brain (BNP), and atrial natriuretic peptide protein (ANP), prolactin, adrenocorticotropic hormone (ACTH), and glucagon [13, 14]. Elevated plasma levels of these markers are detected within minutes to hours after the ischaemic event and are not altered by early reperfusion [15]. Neurohumoral activation manifested by the marked elevation of catecholamine levels is also observed in patients with LV dysfunction without acute myocardial ischaemia [16]. Results of several studies suggest that elevations of ANP and PNE especially are prognostic markers in patients with AMI and/or LV dysfunction, and predict long-term clinical outcome [6, 7, 16–18]. In a subanalysis of 534 patients from the SAVE study, neurohormone levels, including PNE, were measured a mean of 12 days after an AMI. Higher PNE levels were independently related to later cardiovascular events by univariate analysis [18]. However, this relation was much weaker after adjusting for other known mortality correlates in the multivariate analysis [18]. Other studies have also shown that, after correction for clinical CHF or degree of LV dysfunction in these patients, increased PNE did not reach statistical significance as an independent outcome predictor [7]. In some studies, elevated PNE was related to the extent of myocardial damage reflected by peak CPK and development of clinical heart failure and cardiogenic shock [1, 2, 4, 6, 13, 16, 19, 20]. Therefore, it is still uncertain, whether acute elevation of norepinephrine after AMI is an independent prognostic marker after correction for the above covariates. We observed significantly better LV function as measured by baseline LV score index in the high PNE group compared with the low PNE group. We did not see any significant difference in peak CPK levels between the two groups.

Several investigators reported an association between the level of norepinephrine in patients with myocardial infarction and development of ventricular arrhythmias [1–5]. Hayashi et al. found a temporal relation of catecholamine elevations to the onset of arrhythmias by serial urine sampling [21]. This correlation could not be confirmed by a later study by Videbaek et al. [22]. Pathophysiologic mechanisms investigated in animal models proposed a relationship between elevated catecholamines and increased mortality. Catecholamines were shown to be involved in coronary thrombosis [23] and cardiotoxicity [24]. While epinephrine seemed to be thrombogenic in a canine model, norepinephrine had the opposite effect [23]. Infusion of exogenous norepinephrine

**Table 3. Relationship between study risk factors and adverse cardiac outcomes**

<table>
<thead>
<tr>
<th>Variable</th>
<th>YES (n = 10)</th>
<th>NO (n = 136)</th>
<th>p-value</th>
<th>YES (n = 19)</th>
<th>NO (n = 89)</th>
<th>p-value</th>
<th>YES (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNE &gt; 565 (%)</td>
<td>647 ± 246</td>
<td>516 ± 338</td>
<td>0.230</td>
<td>445 ± 247</td>
<td>518 ± 366</td>
<td>0.413</td>
<td>526 ± 274</td>
</tr>
<tr>
<td>Age</td>
<td>64.3 ± 18.8</td>
<td>57.9 ± 13.3</td>
<td>0.158</td>
<td>60.5 ± 12.2</td>
<td>56.2 ± 13.4</td>
<td>0.206</td>
<td>61.1 ± 20.0</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>80.0</td>
<td>62.5</td>
<td>0.328</td>
<td>47.4</td>
<td>72.1</td>
<td>0.037</td>
<td>46.7</td>
</tr>
<tr>
<td>Black race (%)</td>
<td>30.0</td>
<td>33.8</td>
<td>0.805</td>
<td>21.1</td>
<td>33.7</td>
<td>0.282</td>
<td>33.3</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>0</td>
<td>20.0</td>
<td>0.209</td>
<td>31.6</td>
<td>15.1</td>
<td>0.092</td>
<td>20.0</td>
</tr>
<tr>
<td>HTN (%)</td>
<td>60.0</td>
<td>47.1</td>
<td>0.521</td>
<td>79.0</td>
<td>37.2</td>
<td>0.001</td>
<td>73.3</td>
</tr>
<tr>
<td>Peak CPK</td>
<td>3262 ± 2217</td>
<td>2022 ± 1507</td>
<td>0.017</td>
<td>3023 ± 2043</td>
<td>1766 ± 1309</td>
<td>0.020</td>
<td>2806 ± 1837</td>
</tr>
<tr>
<td>Ant MI (%)</td>
<td>50.0</td>
<td>29.4</td>
<td>0.285</td>
<td>36.8</td>
<td>23.3</td>
<td>0.251</td>
<td>40.0</td>
</tr>
<tr>
<td>EF (%)</td>
<td>50.3 ± 7.8</td>
<td>50.8 ± 10.6</td>
<td>0.895</td>
<td>49.2 ± 11.1</td>
<td>52.4 ± 14.4</td>
<td>0.230</td>
<td>44.5 ± 10.3</td>
</tr>
<tr>
<td>ESVI</td>
<td>27.4 ± 10.3</td>
<td>27.5 ± 9.4</td>
<td>0.982</td>
<td>27.3 ± 7.8</td>
<td>27.2 ± 9.4</td>
<td>0.952</td>
<td>31.5 ± 10.4</td>
</tr>
<tr>
<td>Thrombolytics (%)</td>
<td>100.0</td>
<td>56.6</td>
<td>0.006</td>
<td>52.6</td>
<td>61.6</td>
<td>0.469</td>
<td>73.3</td>
</tr>
</tbody>
</table>

*Adjusted for variables significant for each outcome by univariate analysis at p < 0.10 level; #41 individuals omitted from the analysis due to reinfarcted before entry into study.
caused multifocal microscopic myocardial necrosis in rabbits [25] and significantly increased the infarct area in isolated rabbit hearts, with or without β-blockers [24]. Treatment with metoprolol prevented norepinephrine-induced myocardial damage in isolated rat hearts [26]. It has been proposed that catecholamines are cardio toxic by their autoxidation and release of oxygen free radicals [24]. Overall, the possibility of catecholamines having any direct effect upon the infarct size, subsequent left ventricular dysfunction or arrhythmias deserves further investigation.

For the purpose of the dichotomous analysis, we chose a PNE level cut-off of 565 pg/mL, i.e. the upper limit of normal range in our laboratory. Norepinephrine levels are typically elevated in the acute phase of myocardial infarction and this somewhat arbitrary level provided a very practical cut-off point for the dichotomous statistical analysis.

Although the study excluded patients with overt heart failure, a known predictor of norepinephrine elevation, it is possible that even subclinical heart failure was present and provided a sufficient stimulus for catecholamine release. It has been documented in prior studies that elevated catecholamines tend to persist in subjects developing CHF after a myocardial infarction, whereas they decrease in those without clinical signs of heart failure [1, 6, 20, 27, 28]. However, the incidence of CHF in the post-MI period did not correlate with the initial PNE.

Our observations support the hypothesis that an increase in PNE early after myocardial infarction may provide, together with other established criteria such as assessment of LV function and volumes, peak CPK, and clinical CHF/shock, a useful prognostic tool for long-term clinical outcome. More research is still needed to explain the role of early catecholamine release in the pathophysiology of post-AMI morbidity and mortality.

References:
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