Predictors of Mortality in Patients With Acute Myocardial Infarction and Cardiogenic Shock

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Background Although cardiogenic shock (CS) is the leading cause of death for acute myocardial infarction (AMI) patients, reliable predictive factors in the acute stage, such as cardiovascular peptides, have not yet been identified.

Methods and Results In 42 consecutive AMI patients with CS on admission, successfully treated by primary percutaneous coronary intervention (PCI) within 12 h of onset, related factors including brain natriuretic peptide (BNP), atrial natriuretic peptide (ANP), renin, aldosterone, catecholamines, and adrenomedullin, were investigated 24 h from onset, as well as the 1-year mortality rates. During the 12-month follow-up period, 15 patients died from cardiovascular causes (group D). There were no significant differences in patient characteristics, angiographic findings, and left ventricular systolic function between group D subjects and the survivors (group S: n=27). Multivariate analysis identified high levels of adrenomedullin as an independent predictor of 1-year mortality (risk ratio: 6.42, 95% confidence interval, 1.49–43.31, p<0.05).

Conclusions The acute-phase plasma concentration of adrenomedullin may be a reliable predictor of mortality in patients with AMI complicated by CS and successfully treated by direct PCI, as may be BNP concentration, peak-creatine kinase value, and ventricular fibrillation. (Circ J 2005; 69: 83–88)

Key Words: Cardiogenic shock; Myocardial infarction; Peptides; Prognosis

In recent years there has been a significant improvement in mortality rates for acute myocardial infarction (AMI) patients through the increased use of reperfusion therapy and intensive care in the coronary care unit (CCU), but despite this, cardiogenic shock (CS) remains the leading cause of death for these patients. To date, however, reliable predictive factors in the acute stage of subsequent mortality have not been clarified.

During the neurohumoral activation in AMI patients with associated heart failure, the plasma concentrations of the cardiovascular peptides, such as brain natriuretic peptide (BNP), atrial natriuretic peptide (ANP), adrenomedullin, renin, aldosterone, and catecholamines, are elevated in proportion to clinical severity. However, it is unclear which of these peptides are the most useful acute-phase predictor of subsequent mortality in AMI patients who have undergone successful primary percutaneous coronary intervention (PCI). Therefore, the purpose of this study was to evaluate the useful predictors of mortality, including neurohumoral activation, in the acute stage of AMI patients with CS.

**Methods**

**Patient Population** This was a retrospective study of 394 patients with AMI who were admitted to hospital within 12 h of onset between February 1999 and May 2003. All patients gave informed consent, and the study was approved by the Committee on Human Investigation. There were 58 consecutive patients with AMI complicated by CS. The diagnosis of AMI was made on the basis of the following criteria: (1) chest pain; (2) electrocardiographic ST segment elevation of >0.1 mV in 2 or more limb leads, or >0.2 mV in 2 or more precordial leads, or presentation of left-bundle branch block; and (3) elevated total serum creatine kinase (CK) more than twice the upper limit of the normal range. We excluded 3 patients who had renal failure on admission (defined as serum creatinine concentration >3.0 mg/dl), 4 patients who reached hospital >12 h after onset, 4 patients in whom we could not obtain Thrombolysis in Myocardial Infarction (TIMI) grade-III flow after direct PCI, and 5 patients who died before the initial blood samples were taken. The final study group comprised 42 consecutive patients (27 males, 15 females; mean age 72±11 years, range 49–92). We defined CS as blood pressure <90 mmHg (without inotropic or intraaortic balloon support), signs of hypoperfusion (cold extremities, impaired mental status, or urine output <30 ml/h), and evidence of pulmonary congestion on chest X-ray. Subjects were divided into 2 groups according to the 1-year mortality: those who survived 1 year were group S (n=27), and those who died within the year comprised group D (n=15).

**Treatment Strategy** Following oral administration of 200 mg of aspirin and
200 mg of ticlopidine, all patients underwent direct PCI within 12 h of the onset of symptoms. In 6 patients, conventional balloon angioplasty was considered sufficient, and the remaining 36 underwent coronary stent implantation. All patients achieved TIMI grade-III flow. For 72 h after reperfusion therapy, patients were given intravenous lidocaine (1 mg/min) and heparin (10,000 units/day). All patients received either an angiotensin-converting enzyme inhibitor (quinapril 5 mg/day) or an angiotensin II receptor blocker (losartan, 50 mg/day).

**Blood Sampling**

The concentrations of the cardiovascular peptides are reported to peak approximately 24 h after the onset of AMI, so we chose that time to take blood samples from all subjects while they were supine. An immuno-radiometric assay (IRMA) was used to measure the adrenomedullin concentration and the concentrations of BNP, ANP, renin, epinephrine, norepinephrine, and aldosterone were all measured in those blood samples. Highly sensitive C-reactive protein (hs-CRP) was evaluated on admission and at 24 h and 48 h after onset. CK was serially determined every 4 h after admission for a period of 3 days and the peak value (peak-CK) was taken to reflect infarct size.

**Measurement of Cardiac Function**

All subjects underwent left ventriculography in a single-plane with a right anterior oblique of 30° during the acute phase (soon after recanalization) to evaluate the left ventricular (LV) ejection fraction (LVEF) and the LV end-diastolic volume index (LVEDVI), using the area–length method, and to evaluate regional wall motion (RWM), using the center-line method. These data were evaluated by 2 investigators who were unaware of the clinical findings. We excluded posterior infarctions from our evaluation because of associated issues of inaccuracy. We also evaluated the LV end-diastolic pressure (LVEDP). We used the Rentrop classification to evaluate collateral circulation prior to recanalization, and the TIMI classification to evaluate epicardial coronary blood flow. We also monitored major complications, such as cardiac rupture, ventricular arrhythmia (except reperfusion arrhythmia), subacute thrombosis, and acute closure.

**Statistical Analysis**

Values are expressed as mean ± standard-deviation (SD). All statistical tests were unpaired 2-tailed tests, and a p-value <0.05 was considered statistically significant. The chosen cutoff points for the concentrations of the cardiovascular peptides, peak hs-CRP, and peak-CK were based on tertiles in the overall sample. Multivariate logistic regression analysis was performed, with the independent variables being age, sex, history of myocardial infarction (MI), existence of pre-infarction angina pectoris, spontaneous recanalization, use of respirator, multivessel disease, ventricular arrhythmia, cardiac rupture, cardiopulmonary arrest on arrival, peak-CK value, location of MI, renin, aldosterone, ANP, BNP, epinephrine, norepinephrine, and adrenomedullin. The odds ratios (OR) and 95% confidence intervals (CI) were also calculated.

**Results**

The clinical characteristics for the 2 groups (group S and group D) are summarized in Table 1. There were no significant differences in age, gender, coronary risk factors, existence of pre-infarction angina, time since onset to arrival, or history of MI. In other words, the background of both groups of patients was not statistically different. Hemodynamic data at the time of admission and the treatment strategy are shown in Table 2. There were no significant differences between the 2 groups in the number of patients...
with cardiopulmonary arrest on arrival (CPAOA), in the heart rate or systolic blood pressure on arrival, or in the rate of use of coronary stents. Also, there were no significant differences in the frequency of use of intra aortic balloon pumping. There were, however, significantly more patients who required a respirator in group D than in group S (87% vs 47%, p<0.01).

Acute-phase angiographic results are shown in Table 3. There were no significant differences between the 2 groups in terms of culprit vessel location, the existence of spontaneous recanalization (TIMI grade 2 or 3 before intervention therapy), collateral circulation, good collateral circulation (Rentrop grade II or III).

Table 3 - Angiographic Findings in the Acute Stage of Infarction

<table>
<thead>
<tr>
<th></th>
<th>Group S (n=27)</th>
<th>Group D (n=15)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culprit lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMT</td>
<td>2 (7)</td>
<td>1 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>LAD</td>
<td>11 (41)</td>
<td>8 (53)</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>11 (41)</td>
<td>2 (13)</td>
<td></td>
</tr>
<tr>
<td>LCX</td>
<td>3 (11)</td>
<td>4 (27)</td>
<td></td>
</tr>
<tr>
<td>Spontaneous recanalization</td>
<td>4 (15)</td>
<td>1 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>Collateral circulation</td>
<td>8 (30)</td>
<td>3 (20)</td>
<td>NS</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>13 (48)</td>
<td>8 (53)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are number (%).

LMT, left main trunk; LAD, left anterior descending artery; RCA, right coronary artery; LCX, left circumflex coronary artery; Spontaneous recanalization, TIMI grade 2 or 3 before intervention therapy; Collateral circulation, good collateral circulation (Rentrop grade II or III).

Table 4 - Laboratory Findings

<table>
<thead>
<tr>
<th></th>
<th>Group S (n=27)</th>
<th>Group D (n=15)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak-CK value (IU/L)</td>
<td>3,706±3,658</td>
<td>5,377±4,730</td>
<td>NS</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>436±403</td>
<td>1,270±958</td>
<td>0.0009</td>
</tr>
<tr>
<td>ANP (pg/ml)</td>
<td>80±69</td>
<td>160±180</td>
<td>0.07</td>
</tr>
<tr>
<td>Renin (ng·ml⁻¹·h⁻¹)</td>
<td>6.77±8.14</td>
<td>8.5±6.95</td>
<td>NS</td>
</tr>
<tr>
<td>Aldosterone (pg/ml)</td>
<td>96±70</td>
<td>228±205</td>
<td>0.005</td>
</tr>
<tr>
<td>Adrenomedullin (fmol/L)</td>
<td>4.74±1.89</td>
<td>13.6±11.39</td>
<td>0.003</td>
</tr>
<tr>
<td>Epinephrine (pg/ml)</td>
<td>116±117</td>
<td>3,008±8,062</td>
<td>0.09</td>
</tr>
<tr>
<td>Norepinephrine (ng/ml)</td>
<td>1.666±1.635</td>
<td>20.56±44.675</td>
<td>0.05</td>
</tr>
<tr>
<td>Peak-hs CRP (mg/dl)</td>
<td>8.92±5.21</td>
<td>10.20±6.90</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>206±34</td>
<td>204±39</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>49±13</td>
<td>50±14</td>
<td>NS</td>
</tr>
</tbody>
</table>

Peak-CK value, peak value of creatine kinase; BNP, brain natriuretic peptide; ANP, atrial natriuretic peptide; peak-hs CRP, peak value of highly sensitive C-reactive protein.

Table 5 - Major Complications

<table>
<thead>
<tr>
<th></th>
<th>Group S (n=27)</th>
<th>Group D (n=15)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAT</td>
<td>1 (4)</td>
<td>1 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>VT</td>
<td>18 (67)</td>
<td>13 (87)</td>
<td>NS</td>
</tr>
<tr>
<td>VF</td>
<td>7 (27)</td>
<td>10 (67)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cardiac rupture</td>
<td>1 (4)</td>
<td>2 (13)</td>
<td>NS</td>
</tr>
<tr>
<td>Acute closure</td>
<td>1 (4)</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are number (%).

SAT, subacute thrombosis; VT, ventricular tachycardia; VF, ventricular fibrillation.

Major complications in the first 30 days are shown in Table 5. In terms of clinical severity, there were significantly more patients with ventricular fibrillation in group D than in group S (67% vs 27%, p=0.01). There were no significant differences in the frequency of other complications, such as sub-acute in-stent thrombosis, acute closure, ventricular tachycardia, and cardiac rupture.

Table 6 shows LV function in the acute phase (soon after recanalization). There were no significant differences in LVEDP, LVEDVI, RWM, or LVEF; that is, in the acute phase, LV systolic function in these 2 groups of patients did not significantly differ.

Our study population comprised 42 consecutive patients with an AMI and complicated by CS who were admitted within 12 h of onset. The follow-up period for this study was 12 months during which 15 patients died from cardiovascular causes. Pump failure was the cause in 11 and there were 2 cases of cardiac rupture, 1 case of ventricular fibrillation, and 1 case of sudden death out of hospital. The predictors of mortality by multivariate analysis are shown in Table 7. The highest tertile level of adrenomedullin (risk ratio: 6.42,
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95%CI: 1.89–43.31, p=0.02), use of respirator (risk ratio: 3.92, 95%CI: 1.22–21.01, p=0.04), and ventricular fibrillation (risk ratio: 3.87, 95%CI: 1.06–22.28, p=0.04), were identified as independent predictors of mortality at 12 months.

**Discussion**

In the past 20 years, the mortality rate for AMI patients has been significantly reduced as a result of pharmacological and mechanical reperfusion therapies. Nevertheless, AMI with the complication of CS remains the leading cause of death for these patients. Some reports have suggested that emergency mechanical revascularization improves the survival of patients with CS as compared with initial medical stabilization including thrombolytic treatment. However, at present, the 12-month mortality rate for patients with AMI complicated with CS is still high, at approximately 30–50%, and it remains difficult to predict the clinical prognosis (including mortality) in the early phase.

We have clarified that the useful predictors of mortality in AMI patients with CS are ventricular fibrillation, high peak-CK value and high concentrations of BNP and adrenomedullin. Ventricular fibrillation is the most severe arrhythmia, and often occurs in the end stage. The peak-CK value reflects infarct size, so has a close relation to severity in AMI, including mortality. With regard to circulating hormones, we conclude that the concentrations of BNP and adrenomedullin may be reliable predictors of mortality.

The circulating hormones participate in the regulation of cardiovascular system and are closely associated with cardiovascular conditions such as hypertension, LV hypertrophy, and heart failure. BNP, ANP, adrenomedullin, renin, catecholamines, and aldosterone are called cardiovascular peptides and are involved in the neurohumoral activation in patients with AMI and heart failure, their plasma concentrations increasing in proportion to clinical severity. Furthermore, it is known that the concentrations of these cardiovascular peptides in the early phase are closely related to mortality in patients with AMI. Little is known, however, about which of them is most closely related to the mortality rate in AMI complicated by CS.

The cardiovascular peptides have different actions on the cardiovascular system. BNP, ANP, and adrenomedullin have protective effects, reducing blood pressure through vasodilation and by decreasing total peripheral resistance, whereas the catecholamines, renin, and aldosterone have the opposite action. Catecholamines are elevated in heart failure, and in the present study we found...
higher concentrations of epinephrine and norepinephrine in group D than group S. However, they are not a predictor of mortality because not all patients in group D had high catecholamines and in fact, the 2 patients who died from cardiac rupture had significantly lower concentrations of catecholamines than the other patients in group D (epinephrine: 252±146 pg/ml vs 3,62±7,421 pg/ml, p=0.05; norepinephrine: 2.08±41,463 ng/ml vs 22,596±41,201 ng/ml, p<0.05). Adrenomedullin was also higher in the 2 dead patients than in the other group D patients, which suggests that adrenomedullin might be a more sensitive predictor of mortality than catecholamines.

At present, it is generally recognized that the acute-phase plasma concentration of BNP is a useful predictor of the clinical course, including mortality, in AMI. In our study, a high concentration of adrenomedullin in plasma was associated with higher concentrations of epinephrine and norepinephrine in patients with AMI with CS and successfully treated by direct PCI, as is the BNP concentration, peak-CK value and ventricular fibrillation.

Study Limitations

The small size of the study population means that our results require confirmation in a large-scale trial before any concrete significance is extrapolated. We excluded patients with renal failure on the basis that they would not be able to tolerate coronary angioplasty, but this may have introduced bias into our results, and we also excluded the patients who died within 24h of the onset of symptoms and therefore could not provide a blood sample.

Conclusions

From our data, it would appear that the acute-phase plasma concentration of adrenomedullin is a reliable predictor of mortality in patients with AMI complicated by CS and successfully treated by direct PCI, as is the BNP concentration, peak-CK value and ventricular fibrillation.

References


