Cutoff Value of Admission N-Terminal Pro-Brain Natriuretic Peptide Which Predicts Poor Myocardial Perfusion after Primary Percutaneous Coronary Intervention for ST-Segment-Elevation Myocardial Infarction

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Background: We explored the value of admission levels of N-terminal pro-brain natriuretic peptide (NTProBNP) that best predicts poor myocardial tissue perfusion following primary percutaneous coronary intervention (PPCI) in patients admitted with acute ST-segment-elevation myocardial infarction (STEMI).

Methods: We enrolled 90 consecutive patients admitted with acute STEMI who underwent PPCI and achieved post-procedural TIMI flow grade 3 in the infarct-related artery. We measured levels of NTProBNP from admission blood samples. Thereafter, we assessed post-procedural myocardial blush grade (MBG) at the end of PPCI, and further measured ST segment resolution (STR) 90 minutes following PPCI. The primary endpoint was STR < 50%; furthermore, the co-primary angiographic endpoint was postprocedural MBG 0/1.

Results: The mean age of study subjects was 53.6 ± 10.9 years (74.4% males). We found that NTProBNP was higher in patients with STR < 50% versus those with STR ≥ 50% (p < 0.001), and in patients with post-procedural MBG 0/1 versus those with MBG 2/3 (p < 0.001). A value of NTProBNP ≥ 420 ng/L was the optimal cutoff value that best predicted < 50% STR; it predicted < 50% STR with sensitivity, specificity, positive and negative predictive value of 98.4%, 92.3%, 96.9%, and 96%, respectively. Likewise, a value of NTProBNP ≥ 570 ng/L was the optimal cutoff value that best predicted postprocedural MBG 0/1; it predicted MBG 0/1 with sensitivity, specificity, positive and negative predictive value of 92.2%, 66.7%, 78.3%, and 86.7%, respectively.

Conclusions: In patients with STEMI who underwent PPCI and ended up with successful recanalization of the epicardial infarct-related artery, elevated admission levels of NTProBNP predicted incomplete post-procedural STR with good sensitivity and specificity, and predicted poor post-procedural myocardial blush with good sensitivity and moderate specificity.

Key Words: Myocardial blush grade • N-terminal pro-brain natriuretic peptide • Primary percutaneous coronary intervention • ST-segment-elevation myocardial infarction • ST-segment resolution

INTRODUCTION

Myocardial tissue perfusion plays a key role in recovery of left ventricular systolic function in patients with acute ST-segment-elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PPCI). Tissue-level perfusion after recanalization of the infarct-related artery is reflected by...
angiographic myocardial blush grade (MBG), and correlates with resolution of ST segment elevation in the infarcted territory in 12-lead surface electrocardiography (ECG). Early ST segment resolution (STR) is a strong predictor of lower short- and long-term adverse outcome.

N-terminal pro-brain natriuretic peptide (NTProBNP) is secreted from cardiomyocytes in response to increased wall stress, and elevated NTProBNP is a highly sensitive marker of left ventricular dysfunction after acute myocardial infarction. Moreover, elevated NTProBNP provides valuable prognostic information on short- and long-term mortality in patients with acute coronary syndrome. A recent study observed that patients with STEMI who had higher admission B-type natriuretic peptide (BNP) were more likely to develop inadequate myocardial tissue perfusion after PPCI. However, that study did not identify a cutoff value of BNP that predicts inadequate myocardial perfusion. Therefore, we sought to explore the optimal cutoff value of admission NTProBNP that best predicts poor myocardial tissue perfusion in patients with STEMI treated with PPCI, as reflected by STR and postprocedural angiographic MBG.

MATERIALS AND METHODS

Patient selection
Prospectively, we enrolled 90 consecutive patients who presented to our intensive care unit with acute STEMI from October 2013 to October 2014. All patients had persistent ischemic-type chest pain or other acute symptoms consistent with myocardial ischemia, at rest or with minimal exercise, lasting for more than 20 minutes. STEMI was defined by persistent ST segment elevation in two contiguous ECG leads, with a rise of biochemical markers of myocardial necrosis [cardiac troponin T (cTnT) and/or creatinine kinase-MB fraction (CK-MB)] at least twice the upper reference limit. To be eligible, patients needed to have chest pain for less than 12 hours. We excluded patients with previously diagnosed coronary artery disease, those with congestive heart failure, and those with conditions that interfere with assessment of ST segment recovery such as left bundle branch block, accelerated idioventricular rhythm, paced rhythm, and wide QRS complex. Before enrollment, informed written consent was obtained from each patient after full explanation of the study protocol. The study protocol was reviewed and approved by the Research Ethics Committee of our center as it conforms to the ethical guidelines of the 1964 Declaration of Helsinki, as revised in 2013.

Laboratory assessment
Venous blood samples were collected before PPCI for assessment of the NTProBNP, cTnT, CK-MB, C-reactive protein and serum creatinine levels. The blood samples were allowed to clot, centrifuged, and stored at -20°C. We used electrochemiluminescence immunoassay with a sandwich method for measurement of NTProBNP with an Elecsys 2010 Immunoassay analyzer (Roche, Germany). The analytic range of NTProBNP assay extended from 5 to 35,000 ng/L, and inter-and intra-assay coefficients of variation were < 3.1% both (Roche Diagnostics). We determined cTnT and CK-MB by standard analysis methods using electrochemiluminescence immunoassay. CK-MB was considered normal if < 25 μg/L, and cTnT if < 0.1 μg/L (Roche Diagnostics).

Twelve-lead ECG
Patients underwent 12-lead ECG both upon admission and 90 minutes following PPCI. The diagnosis of STEMI was confirmed by ST segment elevation in at least two contiguous leads of ≥ 2 mm in men or ≥ 1.5 mm in women in leads V2-V3 and/or of ≥ 1 mm in other contiguous chest leads or the limb leads. These elevations must be present in anatomically contiguous leads: I, aVL, V5, V6 correspond to the lateral wall; V1-V2 to the septal wall; V3-V4 to the anterior wall; and II, III, aVF to the inferior wall. An experienced investigator blinded to NTProBNP assay results evaluated ST-segment deviation in all available ECG recordings. ST-segment deviation was measured with a handheld caliper and magnifying glass at 80 milliseconds after the J-point in all available leads. ST segment deviation was measured to the nearest 0.5 mm, with the TP segment taken as the isoelectric baseline. STR was defined as the percent change in the summation of ST segment deviation between the preprocedural and 90-minute postprocedural ECG. We defined incomplete STR as < 50% STR in the postprocedural, compared with the preprocedural ECG.
Angiographic assessment

All patients underwent PPCI employing the contemporary standard techniques. It should be noted that all patients had successful recanalization of the infarct-related artery (prerequisite for enrollment), defined as post-procedural TIMI flow grade 3, with residual stenosis < 20%, in the absence of dissection or thrombosis. Post-procedural MBG was scored according to the method described by Van’t Hof et al.:5

a. Grade 0: No myocardial blush (relative to contrast density in uninvolved areas)
b. Grade 1: Minimal myocardial blush
c. Grade 2: Moderate myocardial blush
d. Grade 3: Normal myocardial blush

When myocardial blush persisted (persistent staining), it was graded as grade 0.5 An expert interventional cardiologist blinded to NTProBNP assay results performed grading on cine at 25 frames per second; final angiographic run was long enough to see the venous phase of contrast passage. Briefly, the right anterior oblique 30°/cranial 30° or lateral projection was chosen for the left anterior descending coronary artery, right anterior oblique 30°/caudal 30° projection for the left circumflex artery, and left anterior oblique 30° or right anterior oblique 30° projection for the right coronary artery.12 We classified post-procedural myocardial blush as either poor (MBG 0 or 1) or adequate (MBG 2 or 3).18

Statistical analysis

Continuous variables were presented as mean ± SD, in the event they were normally distributed. Data were tested for normal distribution using the Kolmogorov-Smirnov test. Categorical variables were described with absolute and relative (percentage) frequencies. Comparisons between 2 study groups (patients with incomplete versus those with complete STR, and patients with MBG 0-1 versus those with MBG 2-3) were performed using the unpaired t-test or the Mann-Whitney U test for continuous variables, and Pearson’s χ² test for categorical variables, as appropriate. Receiver operating characteristics curves were constructed to identify the optimal cutoff value of NTProBNP that best predicts < 50% STR in the postprocedural ECG, and its optimal cutoff value that best predicts poor postprocedural myocardial blush. Multivariable linear regression analysis was performed to identify the independent predictors of < 50% STR in the postprocedural ECG. All tests were two-sided, and a probability value of p < 0.05 was considered statistically significant. Analyses were performed with SPSS version 16.0 statistical package (SPSS Inc., Chicago, IL, USA).

RESULTS

The mean patient age in this study was 53.6 ± 10.1 years, 74.4% were males, and 35.6% were diabetic. The mean duration of chest pain was 4.3 ± 2 hours, and the mean post-procedural left ventricular ejection fraction was 59.6 ± 10.2%. Incomplete STR occurred in 64 (71.1%) patients, whereas poor post-procedural myocardial blush occurred in 39 (43.3%) patients. The baseline clinical and angiographic characteristics of the 2 main study groups (patients with incomplete versus those with complete STR) are shown in Table 1. Patients with incomplete STR had a longer duration of chest pain, compared with those with complete STR (p < 0.05). They were more likely to have ended up with poor post-procedural myocardial blush (p < 0.05) (Table 1). NTProBNP, cTnT and CK-MB were all higher in patients with incomplete versus those with complete STR (p < 0.05 for all) (Table 2). Other clinical and angiographic characteristics, and laboratory data were comparable between the 2 groups (p > 0.05 for all) (Table 2 and 3). Similarly, NTProBNP, cTnT and CK-MB were higher in patients who ended up with poor (MBG 0 or 1) versus those who ended up with adequate (MBG 2 or 3) post-procedural myocardial blush (p < 0.05 for all) (Table 3). Among patients with incomplete STR, those who ended up with poor (MBG 0 or 1) postprocedural myocardial blush (n = 35) had a higher NTProBNP (657.2 ± 62.5 versus 524.3 ± 61.4 ng/L, p = 0.041), higher cTnT (1.9 ± 0.7 versus 1.0 ± 0.6 ng/L, p = 0.035), and higher CK-MB (81.3 ± 19.7 versus 48.8 ± 19.6 ng/L, p = 0.05), versus those who ended up with adequate (MBG 2 or 3) post-procedural myocardial blush (n = 29).

A value of NTProBNP ≥ 420 ng/L was the optimal cutoff value that best predicts < 50% postprocedural STR. Using this cutoff value, NTProBNP was able to predict < 50% postprocedural STR with sensitivity, specificity, positive and negative predictive value of 98.4%, 92.3%, 96.9%, and 96%, respectively (Figure 1). Likewise, a value of NTProBNP ≥ 570 ng/L was the optimal cutoff value that best predicts poor post-procedural
myocardial blush. Using this cutoff value, NTProBNP was able to predict poor post-procedural myocardial blush with sensitivity, specificity, positive and negative predictive value of 92.2% and 66.7%, 78.3%, and 86.7%, respectively.

Multivariable linear regression analysis revealed no independent predictors of < 50% STR in the postprocedural ECG.

**DISCUSSION**

The current study demonstrated that in patients with STEMI who underwent PPCI and ended up with successful recanalization of the epicardial infarct-related artery, elevated admission NTProBNP level predicted poor post-procedural myocardial perfusion (as reflected by < 50% post-procedural STR and poor post-procedural angiographic myocardial blush). A value of NTProBNP ≥ 420 ng/L predicted < 50% post-procedural STR with good sensitivity and specificity, whereas a value ≥ 570 ng/L predicted poor post-procedural myocardial blush.

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**Table 1.** Baseline clinical and angiographic characteristics of the 2 main study groups

<table>
<thead>
<tr>
<th></th>
<th>Incomplete STR N = 64</th>
<th>Complete STR N = 26</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54.2 ± 11.7</td>
<td>52.2 ± 8.4</td>
<td>0.424</td>
</tr>
<tr>
<td>Male gender</td>
<td>44 (68.8%)</td>
<td>23 (88.5%)</td>
<td>0.052</td>
</tr>
<tr>
<td>Hypertension</td>
<td>26 (40.6%)</td>
<td>12 (46.2%)</td>
<td>0.630</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>23 (35.9%)</td>
<td>9 (34.6%)</td>
<td>0.905</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>11 (17.5%)</td>
<td>6 (23.1%)</td>
<td>0.540</td>
</tr>
<tr>
<td>Smoking</td>
<td>23 (35.9%)</td>
<td>8 (30.8%)</td>
<td>0.640</td>
</tr>
<tr>
<td>Duration of pain (hours)</td>
<td>5.1 ± 1.7</td>
<td>2.2 ± 0.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Culprit lesion</td>
<td></td>
<td></td>
<td>0.193</td>
</tr>
<tr>
<td>LAD</td>
<td>30 (46.9%)</td>
<td>15 (57.6%)</td>
<td>0.958</td>
</tr>
<tr>
<td>LCX</td>
<td>18 (28.1%)</td>
<td>4 (15.5%)</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>16 (25%)</td>
<td>7 (26.9%)</td>
<td></td>
</tr>
<tr>
<td>Anterior myocardial infarction</td>
<td>39 (60.9%)</td>
<td>16 (61.5%)</td>
<td></td>
</tr>
<tr>
<td>Non-anterior myocardial infarction</td>
<td>25 (39.1%)</td>
<td>10 (38.5%)</td>
<td></td>
</tr>
<tr>
<td>Postprocedural myocardial blush</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MBG 0-1</td>
<td>35 (54.7%)</td>
<td>4 (15.4%)</td>
<td></td>
</tr>
<tr>
<td>MBG 2-3</td>
<td>29 (45.3%)</td>
<td>22 (84.6%)</td>
<td></td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean ± SD, whereas categorical variables are presented as frequency (percentage). LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; MBG, myocardial blush grade; RCA, right coronary artery; SD, standard deviation; STR, ST-segment resolution.

**Table 2.** Laboratory data of the 2 main study groups

<table>
<thead>
<tr>
<th></th>
<th>Incomplete STR N = 64</th>
<th>Complete STR N = 26</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTProBNP (ng/L)</td>
<td>591.7 ± 126.1</td>
<td>258.9 ± 122.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>cTnT (µg/L)</td>
<td>1.4 ± 1.5</td>
<td>0.1 ± 0.2</td>
<td>0.002</td>
</tr>
<tr>
<td>CK-MB (µg/L)</td>
<td>63.2 ± 37.5</td>
<td>28.3 ± 30.3</td>
<td>0.003</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.1 ± 0.3</td>
<td>1.1 ± 0.2</td>
<td>0.196</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>7.1 ± 2.4</td>
<td>7.3 ± 2.8</td>
<td>0.188</td>
</tr>
</tbody>
</table>

Variables are presented as mean ± SD. CK-MB, creatine kinase MB fraction; CRP, C-reactive protein; cTnT, cardiac troponin T; NTProBNP, N-terminal pro-brain natriuretic peptide; STR, ST-segment resolution.

**Table 3.** Comparison of laboratory data between patients with final myocardial blush grade 0/1 versus those with final myocardial blush grade 2/3

<table>
<thead>
<tr>
<th></th>
<th>MBG 0/1 N = 39</th>
<th>MBG 2/3 N = 51</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTProBNP (ng/L)</td>
<td>620.1 ± 144.2</td>
<td>405.7 ± 177.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>cTnT (µg/L)</td>
<td>1.6 ± 1.8</td>
<td>0.7 ± 1.0</td>
<td>0.004</td>
</tr>
<tr>
<td>CK-MB (µg/L)</td>
<td>69.8 ± 40.4</td>
<td>43.2 ± 31.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.1 ± 0.3</td>
<td>1.1 ± 0.3</td>
<td>0.953</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>7.1 ± 2.8</td>
<td>7.2 ± 2.3</td>
<td>0.957</td>
</tr>
</tbody>
</table>

Variables are presented as mean ± SD. CK-MB, creatine kinase MB fraction; CRP, C-reactive protein; cTnT, cardiac troponin T; MBG, myocardial blush grade; NTProBNP, N-terminal pro-brain natriuretic peptide.
with good sensitivity and moderate specificity. To the best of the authors’ knowledge, this is the first study to identify the optimal cutoff value of admission NTProBNP that best predicts poor myocardial tissue perfusion in patients with STEMI treated with PPCI.

Ito et al. first described the “no reflow” phenomenon which signifies absence of reperfusion at myocardial tissue level, despite a patent infarct-related artery (TIMI flow grade 3), following revascularization of acute myocardial infarction. No reflow after revascularization of acute myocardial infarction is associated with poor recovery of left ventricular function, and worse outcome, since it is a marker of more extensive myocardial tissue damage. MBG is among several indices of inadequate perfusion at the myocardial tissue level. It predicts infarct size, and is related to long-term mortality after PPCI.

Left ventricular wall tension regulates the secretion of natriuretic peptides. BNP concentration predicts left ventricular systolic function and long-term survival after myocardial infarction. The results of the current study support the findings in an earlier study, Woo et al., which reported a correlation between NTProBNP and STR (index of myocardial tissue perfusion) in patients with STEMI. Moreover, in a recent report by Seo et al., patients who underwent PPCI for STEMI and had admission BNP ≥ 80 pg/ml were more likely to develop worse myocardial tissue perfusion (as revealed by STR and MBG), and had higher 1-month all-cause mortality, compared with those who had admission BNP < 80 pg/ml. These data suggest that higher left ventricular load on admission in patients with STEMI predicts poor myocardial tissue perfusion after PPCI, even with adequate final epicardial coronary flow. The current study supports the previous data, and provides the optimal cutoff values of admission NTProBNP that best predict poor myocardial tissue perfusion following PPCI for STEMI. In view of the current data, we recommend estimation of admission NTProBNP in patients with STEMI scheduled for PPCI, hence taking the appropriate prophylactic measures (adjuvant pharmacological agents) in order to prevent distal embolization, and preserve myocardial tissue perfusion in those with admission NTProBNP level above the cutoff value.

Limitations of the study

There were limitations to our study. Primarily, our findings are based on a single-center study with a relatively small sample size, although the results can provide a hypothesis-generating foundation. However, multi-center studies employing the same protocol in a larger cohort are needed to confirm the current results. Moreover, the study could not trace STEMI patients who developed left bundle branch block, ventricular arrhythmias, wide QRS complex, and those who needed external pacing during PPCI. In addition, subjective angiographic assessment of MBG is another limitation. Furthermore, the values of NTProBNP are substantially lower than those reported in the literature, which may be due to the exclusion of patients with congestive heart failure. If patients with heart failure were also in-
cluded, the optimal cutoff values would have been different. Finally, many different assays of NTProBNP have been developed; and the optimal cutoff value of NTProBNP would be different for the different assays.

CONCLUSIONS

In patients with STEMI who underwent PPCI and ended up with successful recanalization of the epicardial infarct-related artery, elevated admission levels of NTProBNP predicted poor postprocedural myocardial tissue perfusion. In fact, NTProBNP predicted incomplete postprocedural STR with good sensitivity and specificity, and predicted poor postprocedural myocardial blush with good sensitivity and moderate specificity.

ACKNOWLEDGMENTS

The current study was accepted as an abstract for poster presentation in the 4th Congress of the Acute Cardiovascular Care Association, October 2015, Vienna, Austria.

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest.

FUNDING

This research received no grant from any funding agency in the public, commercial or not-for-profit sectors.

REFERENCES


