Percutaneous Coronary Revascularization Reduces Plasma N-Terminal Pro-B-Type Natriuretic Peptide Concentration in Stable Coronary Artery Disease

Samuel J. McClure, MBCChB, MRCP,* Scott Gall, MBCChB, MRCP,* Clyde B. Schechter, MA, MD, FACPM,† Mark Kearney, MBCChB, MRCP, MD,‡ Azfar G. Zaman, BSc, MBCChB, MD, FRCP§
Newcastle-upon-Tyne and Leeds, United Kingdom; and Bronx, New York

Objectives
The purpose of this work was to assess the effect of percutaneous coronary revascularization (PCR) on plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration.

Background
Left ventricular (LV) dysfunction is associated with increased plasma natriuretic peptide concentrations. The effect of ischemia resolution on plasma natriuretic peptide is not known.

Methods
Twenty-six patients with stable angina, normal LV systolic function, and isolated stenoses of the left anterior descending (LAD) coronary artery were studied. All patients had angiographically and physiologically significant lesions defined by cine-angiography and intracoronary pressure wire.

Results
After revascularization, 24 patients demonstrated significant decrease in mean plasma NT-proBNP 8 weeks after PCR (from 177.2 ± 190.8 pg/ml to 105.0 ± 92.4 pg/ml, p = 0.03). The mean decrease in log NT-proBNP was 0.533, corresponding to geometric mean decrease of NT-proBNP by a factor of 59% (95% confidence interval 48.2% to 71.4%, p < 0.00005). Reduction in NT-proBNP was independent of change in LV systolic function.

Conclusions
This study demonstrates that removal of fixed LAD stenosis reduces plasma NT-proBNP concentration. This has implications for interpretation of natriuretic peptide levels in clinical settings and as screening tool for LV systolic dysfunction. (J Am Coll Cardiol 2007;49:2394–7) © 2007 by the American College of Cardiology Foundation

The heart is both a pump and an endocrine organ. Cardiac stretch and overload stimulate secretion of natriuretic peptides, which have beneficial actions such as vasodilatation and natriuresis. B-type natriuretic peptide (BNP) is an established biomarker for diagnosis and risk stratification of patients with cardiovascular diseases (1).

Studies have explored the role for BNP (and its inactive, more stable pro-hormone amino-terminal fragment N-terminal pro-B-type natriuretic peptide [NT-proBNP]) as surrogate markers of left ventricular (LV) systolic dysfunction (2) and screening tools in patients with dyspnea (3). Elevated concentrations are predictive of poor prognosis in a variety of cardiovascular diseases (1,4).

Elevated plasma BNP and NT-proBNP in acute coronary syndromes predict mortality independently of LV systolic function (5). A strong correlation exists between BNP and extent of reversible ischemia in patients without LV dysfunction (6). This finding and others suggest that significant coronary stenoses per se may cause plasma natriuretic peptide elevation (7,8). The association of elevated natriuretic peptides with fixed coronary stenoses and acute cardiac ischemia is recognized (8,9).

We hypothesized that successful percutaneous coronary revascularization (PCR) would, by removing fixed coronary stenoses and ischemia, reduce plasma NT-proBNP.

Methods
This study was approved by the Joint Ethics Committee of Newcastle.

Six hundred and forty-eight patients referred for PCR were screened. Of these, 31 patients with angiographically significant (>90%) isolated proximal or mid-left anterior...
descending (LAD) artery stenoses, normal 12-lead electrocardiogram, normal resting LV, and normal valvar function on echocardiography with no history of acute coronary syndromes were recruited. Urea and creatinine levels were within normal laboratory values. The LAD was chosen for its major contribution to LV blood supply in most individuals. Patients were excluded if any angiographic disease was present in other vessels or in distal LAD.

Having obtained informed consent 2 weeks after cardiac catheterization (visit 1), all patients had cardiovascular medications stabilized to prevent possible changes to NT-proBNP concentrations. After stabilization for a minimum 8-week period, patients underwent echocardiography (performed and reported by a single experienced echocardiographer) to assess resting LV and valvar function (visit 2). A resting, supine plasma NT-proBNP sample was collected and stored at −30°C.

Left ventricular systolic function was assessed semiquantitatively (10). Left ventricular end-diastolic volume index, end-systolic index, ejection fraction, and left atrial size were assessed off-line (11) before and after PCR. Two weeks after second visit, patients were admitted for PCR performed by an experienced operator (A.G.Z.). Patients were prescribed clopidogrel (300 mg once daily) before PCR, and continued on 75 mg once daily until study completion. This was the only medication change during study. Lesions were assessed recording fractional flow reserve (FFR) using an intracoronary pressure wire (RADI Medical, Uppsala, Sweden). This validated measure defines physiologically significant stenoses as FFR of ≈0.75 after intracoronary adenosine injection (140 μg) (12). Patients with significant stenoses underwent PCR (n = 26). Intracoronary stents were employed in all and successful PCR confirmed by repeat coronary angiography (stenosis <20%) and postprocedure FFR of >0.90.

Eight weeks later, with medication unaltered, patients returned for resting, supine plasma NT-proBNP (stored at −30°C). Echocardiography was repeated.

**NT-proBNP assay.** Blinded samples were batch-analyzed using an electrochemiluminescence immunoassay (Roche Diagnostics Limited, West Sussex, United Kingdom) employing polyclonal antibodies recognizing epitopes located in the N-terminal part of NT-proBNP. In our laboratory, the coefficient of variation of measurement for BNP levels in the N-terminal part of NT-proBNP. In our laboratory, the coefficient of variation of measurement for BNP levels up to 195 pg/ml is 2.9% and for levels of 4,450 pg/ml, 2.3%. The measuring range is 5 pg/ml to 35,000 pg/ml; therefore no samples required dilution.

**Statistical analysis.** Statistical (chi-square) and graphical (normal quartile plot) exploration were performed to assess fit of NT-proBNP variables (before and after) to a log-normal distribution. These suggested good fit (not shown), and in subsequent analyses, this distribution was assumed.

Analyses were carried out using log transform of NT-proBNP, but changes in log NT-proBNP correspond to multiplicative changes in NT-proBNP itself. For example, a difference of 0.223 in log NT-proBNP reflects a change in NT-proBNP itself by a factor of 1.25 (≈e0.223). Arithmetic and geometric means of NT-proBNP were calculated before and after PCR. The significance of change in log NT-proBNP was tested using paired t test.

**Results**

Demographic data are presented in Table 1. Figure 1 shows changes in NT-proBNP. Of 31 patients identified with isolated angiographically severe proximal or mid-LAD lesions, 5 were excluded as FFR was >0.75. Mean preprocedure FFR was 0.57 and postprocedure 0.92.

Of 26 patients, 24 demonstrated a decrease, 1 an increase, and 1 recorded no change in NT-proBNP after revascularization.

Pre- and postprocedural mean plasma concentrations of NT-proBNP (pg/ml) for the PCR group were 177.2 and 105.0, respectively. The mean decrease in log NT-proBNP was 0.533, corresponding to a geometric mean decrease of NT-proBNP by a factor of 0.95 (95% confidence interval 0.92% to 0.70%, p < 0.00005).

There was 1 participant with baseline NT-proBNP levels exceeding 800 pg/ml. Before logarithmic transformation, this appeared to be an outlier. Within the log-transformed data, however, an appropriate fit on the normal distribution curve was seen and we, therefore, concluded not a cause for concern. Nevertheless, to ensure that results were not driven by an isolated case, the analysis was repeated excluding this.

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**Table 1**  Demographic and Medication Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PCR n = 26</th>
</tr>
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<tbody>
<tr>
<td>Mean age, yrs (SD)</td>
<td>59.3 (10.7)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28</td>
</tr>
<tr>
<td>Current smoker</td>
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</tr>
<tr>
<td>Ex-smoker</td>
<td>17</td>
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<tr>
<td>Hypertension</td>
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<td>Hypercholesterolemia</td>
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<tr>
<td>Diabetes mellitus</td>
<td>6</td>
</tr>
<tr>
<td>Aspirin</td>
<td>25</td>
</tr>
<tr>
<td>Preprocedure clopidogrel</td>
<td>4</td>
</tr>
<tr>
<td>Beta-blockade</td>
<td>18</td>
</tr>
<tr>
<td>Statins</td>
<td>23</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>11</td>
</tr>
<tr>
<td>Nicorandil</td>
<td>11</td>
</tr>
<tr>
<td>Long-acting oral nitrates</td>
<td>14</td>
</tr>
<tr>
<td>ACE inhibitors/ARB</td>
<td>18</td>
</tr>
<tr>
<td>Diuretics</td>
<td>4</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; PCR = percutaneous coronary revascularization.
case. The result (not shown) is not appreciably different from that previously reported. End-diastolic pressures were recorded in 22 patients before PCR (range 2 to 15 mm Hg, mean 8.5 mm Hg, median 8 mm Hg). No measurements were recorded after PCR. End-diastolic volume index (67.3 mls/m² vs. 67.4 mls/m²), end-systolic volume index (15.2 mls/m² vs. 15 mls/m²), ejection fraction (77.5% vs. 77.8%), and left atrial area (16.7 cm² vs. 16.8 cm²) showed no significant change after PCR (Wilcoxon signed rank test).

Discussion

Our study suggests that successful PCR of clinically and physiologically significant isolated LAD coronary artery stenoses leads to substantial falls in plasma NT-proBNP concentration. The study group was highly selected (therefore small in number) to allow confident localization and successful resolution of ischemia territory after revascularization.

Elevated plasma natriuretic peptides are seen in many different cardiovascular diseases. The heart is recognized as an endocrine organ, and natriuretic peptides are used clinically as biochemical markers in heart failure (13). Several reports identify elevated levels of natriuretic peptides (7,8) and one identifies increased BNP gene expression (14) in the presence of ischemia. A possible mechanism is ischemia leading to LV dysfunction before an elevation in natriuretic peptide concentration.

After PCR, studies report changes in atrial natriuretic peptide levels occurring acutely due to immediate release from storage in the stretched atrial wall (15). Measures of BNP concentrations have been reported in the very short term after PCR, making it difficult to separate effect of injury from ischemia resolution on BNP release. Little information exists on long-term influence of revascularization of stable ischemic heart disease by PCR on ventricular-derived natriuretic peptide. Our study differs from others in 3 important respects:

1. Drugs with potential to influence BNP were stabilized and maintained unchanged after procedure. The only change was addition of clopidogrel. There are no published data to suggest its influence on natriuretic peptides.
2. Patients were selected on clinical symptoms, angiographic assessment, and assessment of the physiological significance of coronary stenosis.
3. Timing of repeat samples was based on change in concentration after surgical revascularization (16) and need to avoid influence of restenosis (a later phenomenon) and ischemia recurrence.

Implications for clinical testing. A major issue is the widespread application of natriuretic peptides assays to identify LV dysfunction. Occult ischemia may have influenced results in many of the clinical settings in which the assay was validated.

Investigators have suggested diastolic dysfunction as the cause when elevated natriuretic peptides could not be attributed to impaired LV systolic function or valvular heart disease (17). Pathological conditions associated with diastolic dysfunction undoubtedly do raise natriuretic peptides levels (18). It is acknowledged that ischemia may produce diastolic dysfunction (19). Thus, it is likely that some cases of “diastolic dysfunction,” and specifically of elevated natriuretic peptides in the absence of LV systolic dysfunction or valvular disease, may result from coronary ischemia. Indeed, in the first report linking BNP to diastolic dysfunction, all subjects had ischemic heart disease (17).

Natriuretic peptides have also been shown to be superior to LV ejection fraction in risk stratification of patients after myocardial infarction (20). Elevation of plasma natriuretic peptide, therefore, may be secondary to significant untreated coronary disease rather than LV dysfunction. This could explain the lack of utility of natriuretic peptide measurement in identifying specific degrees of LV dysfunction seen in some postmyocardial infarction studies (21).

Study limitations. Interpretation of study data is limited due to the small number of selected patients and absence of control subjects. The ideal group would be identified as having significant isolated LAD stenosis with NT-proBNP measurement before invasive study and repeated at 8 weeks, without PCR. This was not feasible for ethical reasons and limited numbers. Moreover, the coefficient of variation of the assay is low, and differences noted in our study are likely
to be real. It should be noted, however, that a low coefficient of variation does not necessarily imply low intraindividual variability. This study does not provide evidence of mechanism of reduction of NT-proBNP, but the most likely cause involves alteration of wall stress, which was not directly measured.

Conclusions

We have demonstrated, in patients with coronary ischemia, removal of angiographically and physiologically significant coronary stenosis results in decrease of plasma NT-proBNP. Due to the high prevalence of ischemic heart disease, this finding may have implications for future measurement of natriuretic peptides in cardiovascular medicine.

Acknowledgments

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Reprint requests and correspondence: Dr. Azfar G. Zaman, Freeman Hospital and University of Newcastle, Newcastle-upon-Tyne, NE7 7DN, United Kingdom. E-mail: azfar.zaman@nuth.nhs.uk.

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