Clinical research

Coronary angiography transiently increases plasma pro-B-type natriuretic peptide

Jens Peter Goetzea,b,*, Wang Yongzhonga, Jens F. Rehfeldb, Erik Jørgensena, Jens Kastrupa

a Medical Department B, Cardiac Catheterisation Laboratory, Rigshospitalet, University of Copenhagen, 9 Blegdamsvej, 2100 Copenhagen, Denmark
b Department of Clinical Biochemistry, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Received 3 June 2003; revised 2 February 2004; accepted 5 February 2004

Aims Increased plasma concentrations of B-type natriuretic peptide (BNP) and its precursor (proBNP) provide important prognostic information in patients presenting with acute coronary syndromes. Although a majority of these patients undergo early invasive assessment, the effects of coronary angiography per se on plasma BNP and proBNP concentrations are not known. We therefore sought to determine whether coronary angiography and ventriculography affect the cardiac secretion of these prognostic markers.

Methods and results Blood samples were collected before and two minutes after coronary angiography and ventriculography in patients with or without coronary artery disease (CAD) and normal left ventricular ejection fraction. In patients with suspected CAD and normal left ventricular ejection fraction, the plasma proBNP concentration transiently increased from 11 pmol/l (range 1–67 pmol/l) to 19 pmol/l (range 5–102 pmol/l, n = 29, P < 0.0001) two minutes after coronary angiography and ventriculography. The increase was similar in patients with or without CAD, although patients with stable CAD displayed higher plasma BNP and proBNP concentrations at baseline. In contrast, plasma BNP concentrations did not change after coronary angiography and ventriculography.

Conclusion Coronary angiography induces a transient increase in cardiac proBNP secretion. Blood sampling for plasma proBNP measurements in patient stratification and prognosis estimation should consequently be avoided immediately after coronary angiography.

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KEYWORDS
Angiography; BNP; Coronary disease; Heart failure; Natriuretic peptide; proBNP

Introduction

Increased plasma concentrations of B-type natriuretic peptide (BNP) and its precursor, proBNP, are markers of left ventricular systolic dysfunction.1,2 More recently, plasma BNP and proBNP concentrations have also been reported increased after acute myocardial infarction3–6 and in patients presenting with acute coronary syndromes.7–10 In these ischaemic heart disease patients, BNP and proBNP measurements provide independent prognostic information about the later risk of left ventricular dysfunction and death. Also, increased plasma proBNP concentrations may have prognostic value for
patients presenting with symptoms suggestive of acute coronary syndrome but with no ST-segment elevation on electrocardiography. Stable ischaemic heart disease patients and patients presenting with acute coronary syndromes are now recommended assessment by coronary angiography and revascularisation. As a result, BNP and proBNP measurements are likely to be used in patients undergoing invasive cardiac procedures, and plasma may sometimes be collected in connection with the procedure.

In this study, we examined the acute effects of diagnostic coronary angiography and ventriculography on cardiac secretion of BNP and proBNP. Blood samples were collected before and after the invasive procedures from patients with normal left ventricular systolic function referred for evaluation of suspected coronary artery disease (CAD). The specific aim was to assess whether these common diagnostic procedures per se affect the cardiac secretion of BNP and proBNP and, accordingly, may influence the interpretation of plasma measurements.

**Methods**

**Patients**

All patients were referred for evaluation of suspected CAD. Patients had to fulfil the following criteria: (1) normal left ventricular systolic function and valvular function assessed by two-dimensional echocardiography prior to referral, (2) no renal impairment (serum creatinine \(\leq 130\) \(\mu\)mol/l), and (3) no sustained arrhythmia, including atrial fibrillation. Blood samples were then obtained from 40 patients undergoing catheterisation (Table 1). From this group, the first 29 patients (12 women and 17 men, median age 62 years [range 38–74 years]) underwent coronary angiography and ventriculography. Blood samples were collected from the femoral artery immediately before and two minutes after the combined procedure and from a cubital vein the next day. The effects of ventriculography on cardiac proBNP secretion were examined separately in an additional 11 patients (5 women and 6 men, median age 57 years [range 37–70 years]), where blood samples were collected from the femoral artery immediately before and two minutes after ventriculography and simultaneously from the left ventricular cavity using a pigtail catheter inserted via the aorta (ventriculography group). The invasive examination was thereafter continued by coronary angiography. The left ventricular ejection fraction and left ventricular end-diastolic pressure were estimated from ventriculography. All patients gave informed written consent and the study was approved by the local ethics committee (KF 01-231/99).

**Angiography**

The standard Seldinger and Judkins technique using 6-French catheters was performed in all patients. A single-plane ventriculography was obtained in right anterior oblique projection. We infused 50 ml (10 ml/s) contrast agent through a 6-French pigtail catheter. Left ventricular function was also visually estimated by an experienced interventional cardiologist. A minimum of 6 projections for the left coronary and 3 projections for the right coronary artery were recorded. A nonionic contrast agent (Iomeron\textsuperscript{8}, Bracco, Italy) was used in all procedures.

**Plasma BNP and proBNP analysis**

Blood was collected in tubes containing Na\(_2\)-EDTA (1.5 mg/ml) and in tubes containing Na\(_2\)-EDTA (1.5 mg/ml) with aprotinin (500 KIU/ml). Plasma was obtained after centrifugation and stored at \(-80\) °C for later analysis. For BNP measurements, we used a commercial assay (Shionogi, Osaka, Japan). This immunoradiometric assay detects the BNP-32 peptide and has no cross-reactivity with atrial natriuretic peptide. The lowest level of detection is 0.6 pmol/l and the upper reference limit is listed as 5.3 pmol/l (1 pmol/l BNP-32 equals 2.17 pg/ml). The assay imprecision within-runs is 9.4% at 8.3 pmol/l and 12% at 168.9 pmol/l. Plasma proBNP was measured using a processing-independent assay recently developed in our laboratory. This type of assay quantifies the total proBNP concentration in plasma utilising a pre-analytical enzymatic step. Briefly, plasma is treated with a protease (trypsin) to cleave all proBNP forms at a monobasic cleavage site. The enzymatic reaction is then terminated and all N-terminal fragments (proBNP 1–21) released are subsequently measured with a specific proBNP radioimmunoassay. The assay sensitivity is 0.2 pmol/l, with an upper reference limit in individuals without cardiac disease of 15 pmol/l (confidence interval: 9–16 pmol/l, where 1 pmol/l proBNP equals 2.17 pg/ml). Assay imprecision within-run is 12% at 13 pmol/l and 5% at 130 pmol/l.

**Statistics**

Results are presented as medians with ranges unless otherwise stated. The changes in concentrations within-groups were

<table>
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<tr>
<th>Table 1 Patient characteristics</th>
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<tr>
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<td>Coronary angiography and ventriculography ((n = 29))</td>
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<tr>
<td>Age in years (median with range)</td>
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<tr>
<td>Male gender (%)</td>
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<tr>
<td>History of diabetes (%)</td>
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<tr>
<td>History of hypertension (%)</td>
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<tr>
<td>CCS class (0, 1, 2, 3 [%])</td>
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<tr>
<td>LVEF, % (median [range])</td>
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<td>LVEDP, mmHg (median [range])</td>
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<td>Haemoglobin, mmol/l (median [range])</td>
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<td>Plasma creatinine, (\mu)mol/l (median [range])</td>
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CCS class: Canadian Cardiovascular Society functional classification, LVEF: Left ventricular ejection fraction, LVEDP: Left ventricular end-diastolic pressure. Both LVEF and LVEDP were obtained from ventriculography.
analysed using the Wilcoxon matched pairs test, and between-
groups by logarithmically transforming data prior to analysis
with an unpaired t-test with Welch’s correction. To assess the
association between BNP and proBNP plasma concentrations, we
used Pearson’s correlation analysis on logarithmically trans-
formed data. \( P \) values (two-sided) of less than 5% were consid-
ered significant.

Results

All patients were referred for elective evaluation of
suspected CAD. Of the 40 patients included, 23 were
found eligible for later percutaneous coronary interven-
tion or coronary artery bypass grafting surgery, whereas
17 patients had no findings of CAD on angiography. All
patients had a normal left ventricular ejection fraction
on ventriculography (Table 1).

The plasma proBNP concentration in patients under-
going angiography and ventriculography \((n = 29)\) in-
creased two minutes after the procedure from 11 pmol/l
(range 1–67 pmol/l) to 19 pmol/l (range 5–102 pmol/l,
\( P < 0.0001 \)), and the concentration had returned to the
initial level the next day (10 pmol/l, range 1–65 pmol/l)
(Fig. 1). In contrast to this transient 1.7-fold increase in
plasma proBNP concentrations, we did not detect chan-
ges in cardiac BNP secretion two minutes after coronary
angiography and ventriculography (7 pmol/l [range 0–82
pmol/l] versus 8 pmol/l [range 0–110 pmol/l]) (Fig. 1).
The relative difference in plasma BNP and proBNP concentra-
tions calculated as percentage of baseline values showed a similar pattern (median BNP: 104% two minutes
after and 100% the next day; median proBNP: 163% two
minutes after and 97% the next day). Plasma proBNP and
BNP concentrations were associated before the proce-
dure \((r = 0.71, P < 0.0001, \text{ data not shown})\), and this
association was increased further in samples collected
two minutes after the procedure (Fig. 2). To elucidate if
the transient increase in cardiac proBNP secretion is
predominantly a feature in patients with CAD, the plas-
a concentrations were compared between the group of
patients with normal findings on angiography \((n = 12)\)
and the group of patients with CAD \((n = 17)\). Although
the baseline plasma BNP and proBNP concentrations
were significantly elevated in patients with CAD
(Fig. 3(a)), the transient plasma proBNP increase was
similar in the 2 groups (Fig. 3(b)).

Finally, we examined the isolated effect of ventricu-
lography on cardiac proBNP secretion by measuring
plasma concentrations in samples drawn from the left
ventricular cavity and the femoral artery immediately
before and two minutes after ventriculography \((n = 11)\).
No change in proBNP concentrations could be demon-
strated in the femoral artery (11 pmol/l [range 0–43
pmol/l] versus 11 pmol/l [range 0–51 pmol/l]) or the left
ventricular cavity (median 7 pmol/l [range 3–45 pmol/l]
versus median 9 pmol/l [range 0–52 pmol/l]). Compari-
son between patients undergoing both angiography and
ventriculography to patients undergoing ventriculogra-
phy corroborated that the increase in plasma proBNP
concentrations was only seen in the patients undergoing

![Fig. 1](#) Increased plasma proBNP but not BNP concentrations after
coronary angiography and ventriculography (top panel). Concentrations
are expressed as the picomolar change \((\Delta)\) from the concentration pre-
ceding the invasive procedure. Plasma proBNP concentrations had re-
turned to initial concentrations the following day (lower panel). One
patient displayed highly increased BNP and proBNP concentrations im-
mediately after the procedure and greatly reduced concentrations the
next day. This patient had severe CAD but otherwise normal find-
ings. Each point represents values obtained from an individual patient, and
median values are indicated by the horizontal lines \((n = 29)\).

![Fig. 2](#) Association between plasma proBNP and BNP. Plasma proBNP and
BNP concentrations were closely associated immediately after angiog-
raphy, even though only the proBNP concentration increased. Data are
logarithmically transformed prior to correlation analysis (Pearson) and
each point represents values from individual patients \((n = 29)\).
Discussion

The main findings of the present study are that plasma proBNP concentrations significantly increase after coronary angiography and ventriculography. In contrast, coronary angiography and ventriculography do not affect cardiac secretion of BNP. Evaluation of left ventricular function by ventriculography is not followed by increased plasma proBNP concentrations in patients with an overall normal left ventricular ejection fraction. Finally, plasma BNP and proBNP concentrations are both elevated in patients with stable CAD and normal left ventricular ejection fraction.

Increased plasma concentrations of BNP have been reported after percutaneous transluminal coronary angioplasty. The underlying mechanism for the increased cardiac BNP secretion was suggested to be transient myocardial hypoxia induced by coronary artery occlusion, which inevitably is introduced by the procedure. We have recently found that stable ischaemic heart disease patients display increased plasma concentrations of BNP and proBNP, and that the plasma concentrations are associated with BNP gene expression in the hypoxic myocardium of the left ventricle. The present finding that patients with CAD have increased plasma BNP and proBNP concentrations compared to patients with normal coronary arteries on angiography therefore corroborates the association of plasma BNP and proBNP concentrations to chronic myocardial ischaemia. Intracoronary contrast injection during angiography, however, only causes brief myocardial hypoxia and is not restricted to only one region of the left ventricle. As the plasma proBNP concentrations increased immediately after the procedure, it is likely that other mechanisms may also be involved. For instance, introduction of the contrast agent could represent an osmotic or chemical secretagogue causing instant proBNP release from myocytes.

Interestingly, angiography was not followed by an increase in plasma BNP concentrations. It is known that BNP gene expression is predominantly a feature of atrial myocytes in the normal heart. In fact, we recently reported that proBNP is present in normal atrial — but not ventricular — tissue from pig hearts, and that proBNP localises in a granular pattern within the atrial myocytes. All patients in the present study had normal left ventricular ejection fraction on ventriculography so the acute release of proBNP may therefore reflect mostly atrial secretion. The selective increase in only proBNP after coronary angiography furthermore suggests that the released form is not processed prior to release. proBNP is thought to be cleaved by the transmembrane enzyme Corin, which generates the bioactive BNP-32 form. Even though understanding of the post-translational maturation of cardiac proBNP in cells still is incomplete, the present finding indicates that atrial proBNP is stored as the intact precursor and can be secreted instantly without concomitant enzymatic cleavage by Corin.

BNP and proBNP secretion by the endocrine heart reflects not only cardiac function but is also affected by other stimuli. Sudden changes in haemodynamics as well as some neurohormonal responses can directly stimulate cardiac secretion of natriuretic peptides. In chronic heart failure, the endocrine cardiac response can be
altered by drugs administered to ameliorate diminished cardiac function and these effects also seem to be mediated by mechanisms acting directly on the myocytes.\textsuperscript{23,24} Accordingly, the beneficial effects of angiotensin-converting-enzyme (ACE) inhibitors and beta-blockers can be monitored by serial measurements of plasma BNP and proBNP concentrations and may provide a more sensitive marker of overall cardiac status than standard clinical assessment.\textsuperscript{25–28}

All patients had an apparently normal left ventricular ejection fraction on ventriculography (Table 1). Two-dimensional echocardiography prior to referral and invasive assessment did not include information on other ventricular parameters, including diastolic function. It is therefore likely that some patients may have had some ventricular involvement despite an overall normal systolic function. In support of this, 2 of the 12 patients without CAD displayed slightly increased basal plasma BNP and proBNP concentrations, and one CAD patient had highly increased left ventricular end-diastolic pressure (22 mm Hg), where the latter indicates underlying diastolic dysfunction. Nevertheless, this CAD patient had normal basal BNP and proBNP plasma concentrations. In the clinical setting, it is most likely that regional ventricular dysfunction or diastolic disease will be present in some patients undergoing coronary angiography. The present finding of a transient increase in plasma proBNP concentrations may therefore not be limited only to patients with normal left ventricular systolic function with or without CAD, but also to patients with ventricular dysfunction not detected by ventriculography.

Increased plasma concentrations of proBNP after coronary angiography may become clinically relevant. Plasma measurements of BNP and proBNP are prognostic markers in patients with acute coronary syndrome and have been proposed as an integral part of standard evaluation of these patients.\textsuperscript{29} However, it seems reasonable to speculate that blood for plasma BNP or proBNP measurements sometimes may be sampled close to the time of angiography or perhaps even during the procedure. Hence, coronary angiography-induced proBNP secretion could influence the interpretation of the test and misguide investigators and physicians. Appreciation of the acute cardiac secretion of proBNP after coronary angiography will help to avoid such a pitfall. Furthermore, it is not always clear at what precise moment plasma was sampled in earlier studies that have suggested a prognostic importance of proBNP measurements in patients with acute coronary syndromes. In view of that, future studies on the prognostic utility of plasma proBNP measurements should include details on the exact time of blood sampling in relation to invasive assessment.

In conclusion, the present study shows that plasma proBNP concentrations increase immediately after diagnostic coronary angiography and ventriculography. This transient effect should be taken into account when using plasma proBNP as a biochemical marker in hospitals, where invasive assessment of CAD is an integral part of the cardiac evaluation.

Acknowledgements

The authors thank Lone Olsen and Mette Groos for expert technical assistance.

References


