Peptides 52 (2014) 143–148

Contents lists available at ScienceDirect

Peptides

journal homepage: www.elsevier.com/locate/peptides

The severity of coronary artery disease and reversible ischemia revealed by N-terminal pro-brain natriuretic peptide in patients with unstable angina and preserved left ventricular function

Luhong Xu[a], Wenhao Qian[b,*], Wenhua Li[b], Jiali Liu[b], Haiyan He[a], Gonghao Li[a], Yan Cao[a], Yaren Yu[a]

[a] Institute of Cardiovascular Disease Research, Xuzhou Medical College, 84 West Huaihai Road, Xuzhou, Jiangsu 221002, China
[b] Department of Cardiology, The Affiliated Hospital of Xuzhou Medical College, 99 West Huaihai Road, Xuzhou, Jiangsu 221002, China

ARTICLE INFO

Article history:
Received 16 November 2013
Received in revised form
27 December 2013
Accepted 28 December 2013
Available online 8 January 2014

Keywords:
N-terminal pro-brain natriuretic peptide
Coronary artery disease
Coronary angiography
Fractional flow reserve

ABSTRACT

The association between the levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) and the severity of coronary artery disease (CAD) diagnosed by coronary angiography and other approaches has been investigated. The clinical application of NT-proBNP is restricted by the drawbacks of these techniques now available in screening out patients who need intensive or conservative treatment. Fractional flow reserve (FFR) is superior to coronary angiography and other functional indicators. Accordingly, we designed to investigate the association between NT-proBNP and myocardial ischemia from the perspective of anatomy and physiology in patients with unstable angina and preserved left ventricular function. Plasma samples were collected from 110 patients and NT-proBNP levels were measured by radioimmunoassay. The severity of coronary artery stenosis in patients was measured by coronary angiography and FFR. Stenosis ≥50% in the left main artery or stenosis of 70%, and fractional flow reserve (FFR) ≤0.80 in one or more coronary branches with diameter ≥2 mm were defined as "positive", which require revascularization. NT-proBNP levels increased progressively between patients with negative and positive angiographic results ($p < 0.05$), and between FFR-negative and FFR-positive patients ($p < 0.05$). A significant correlation was observed between log NT-proBNP and log GS (GS = Gensini score, $p < 0.001$). NT-proBNP level serves as a predictor of positive results of angiographic stenosis and FFR, with the area under the receiver operating characteristic curve being 0.697 and 0.787, respectively. NT-proBNP levels are correlated with the severity of anatomic coronary obstruction and inducible myocardial ischemia, but NT-proBNP per se is insufficient to identify clinically significant angiographic and physiological stenoses.

1. Introduction

N-terminal pro-brain natriuretic peptide (NT-proBNP) is a neurohormone predominantly synthesized and secreted by the ventricular myocardium [5,13,31,33] in response to increased ventricular stretching and wall tension [26,32,52]. Elevated NT-proBNP levels may be highly indicative and specific in the detection of ventricular dysfunction in patients with symptomatic heart failure [6,28]. Pre-proBNP is enzymatically cleaved to proBNP comprising 108 amino acids, and upon release into the circulation, it is cleaved in equal proportions into a biologically active peptide, BNP, consisting of 32 amino acids and representing the C-terminal fragment, and a biologically inactive N-terminal fragment, NT-proBNP, comprising 76 amino acids [47]. It is widely acknowledged that NT-pro-BNP may have more opportunities to reveal ischemia than BNP because of the sixfold longer half life (120 min for NT-pro-BNP vs. 20 min for BNP). Moreover, NT-proBNP is also directly released into the blood stream from myocardiocytes in response to myocardial ischemia in animals and humans as well [13,14]. It has been proposed that the levels of circulating NT-proBNP can serve to predict the onset of myocardial ischemia with preserved left ventricular function and stratify the risks of coronary artery disease (CAD) [13,14,17,18,45].

Coronary angiography is conventionally regarded as the "gold standard" of CAD diagnosis, but it has limitations in most clinical scenarios [9,22] and actually, symptomatic ischemia might not result from coronary stenosis, for which undue treatment rendered would involve revascularization in minor stenosis or failure to recanalize in significant cases. Conventional noninvasive methods in CAD diagnosis by coronary angiography, such as

* Corresponding author.
E-mail address: 15094346046@139.com (W. Qian).

0196-9781/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.peptides.2013.12.018

electrocardiography (ECG), treadmill exercise test and myocardial perfusion have drawbacks for their relatively low cost–effect ratio, sensitivity and specificity [10]. Perhaps for the mentioned reasons, the clinical application of NT-proBNP is restrained [16,39,41,46,49]. Fractional flow reserve (FFR), a recently proposed specific index of the functional significance of coronary artery stenosis, is defined as the ratio of maximum blood flow in a diseased artery to maximum flow if the same artery would be normal and a validated tool for detecting ischemia-inducing stenosis, and is superior to coronary angiography and other functional indicators [8,19,36,37,43,44].

Accordingly, this prospective cohort study was designed to investigate the association between NT-proBNP and myocardial ischemia from the perspective of anatomy and physiology in patients with unstable angina and preserved left ventricular function.

2. Materials and methods

2.1. Subjects

In this prospective single-center study, 110 patients with chief complaints of "chest pain and chest discomfort" were enrolled, who were refereed to the Department of Cardiology, the Affiliated Hospital of Xuzhou Medical College. Inclusion criteria were unstable angina pectoris (Canadian Cardiovascular Society [CCS] classes I–III), with preserved left ventricular function preserved (PLVF, ejection fraction [EF] > 50%). Unstable angina was defined according to the European Society of Cardiology (ESC) Guideline [15]. Exclusion criteria included ST-segment elevations on admission, valvular diseases, acute or chronic heart failure, cardiomyopathies, systolic dysfunction with an EF <50%, major arrhythmic complications (atrial or ventricular fibrillation, or ventricular tachycardia), renal dysfunction with creatinine clearance <50 ml/min, and hepatic or neoplastic diseases. Approval was obtained from the institutional review committee, and patients or their legally authorized representatives provided written informed consent.

2.2. Assessment of coronary lesions by angiography

After enrollment, all patients underwent coronary angiography performed by an experienced cardiologist in consistence with a standard process, in a cardiac catheterization laboratory equipped with a C-arm X-ray digital cardiac imaging system (Philips, the Netherlands or GE INNOVA2000). Two cardiologists independently reviewed the angiograms respectively, without being informed of NT-proBNP levels. Angiographically significant CAD is defined as either at least lumen diameter reduction by 70% in vessels with a diameter ≥2.0 mm, or ≥50% reduction in left main coronary artery or FFR ≤0.80 was defined positive, and thus the patients were advised for revascularization. Patients were classified as having one-, two- or three-vessel disease, and as having non-significant diffused CAD (defined as lumen irregularities, with reduced lumen diameter by 70%) or no CAD (no lumen irregularity).

The burden of coronary arteriosclerosis was assessed by the Gensini score (GS) [12]. The GS system yields a qualitative and quantitative evaluation of coronary angiogram, with grading of the narrowing percentage of lumen of the coronary artery as 1 for 25%, 2 for 26–50%, 4 for 51–75%, 8 for 76–90%, 16 for 91–99%, and 32 for total occlusion. This primary score is multiplied by a factor that considers the importance of the lesion site in the coronary arterial tree: score of 5 for the left main coronary artery, 2.5 for the proximal left anterior descending artery (LAD) or proximal left circumflex artery (LCX), and 1.5 for the mid-region, 1 for the distal LAD, and 1 for the mid-distal region of the LCX or right coronary artery.

2.3. Coronary pressure measurements and FFR calculations

Coronary pressure was measured in patients with 50–90% single-vessel stenosis by using a 0.014-in pressure guide wire (Radi Medical Systems, Austin, MA, USA), which was introduced through a 6F guide catheter, calibrated and advanced into the coronary artery, and positioned distal to the stenosis. Adenosine triphosphate (140 μg/kg/min) was intravenously administered to induce maximum hyperemia [11,24,25]. FFR was calculated as the ratio of mean hyperemic distal coronary pressure measured by the pressure wire to mean aortic pressure measured by the guiding catheter. Each measurement was performed twice, with the average of two values as FFR.

2.4. Measurements of NT-proBNP

On the next morning after admission, heparinized whole blood samples were collected and tested within 8 h by immunoassay (Roche CARDIAC proBNP+, Roche Diagnostics, Mannheim, Germany), with the measurement range of 20–9000 pg/mL.

2.5. Statistical analysis

Statistical analysis was performed with SPSS 13.0 for Windows. Normally distributed data were expressed as mean ± standard deviation (SD); abnormally distributed data were expressed as median and interquartile range, and categorical data were summarized as frequencies and percentages. Since NT-proBNP levels and the GS were not normally distributed, Mann–Whitney *U* test was used for comparisons of differences between groups. NT-proBNP levels and GS were log-transformed to log NT-proBNP and log GS which were both normally distributed, confirmed by Kolmogorov–Smirnov test, followed by assessment of their relationship by simple linear regression analysis. Between-group differences of quantitative data were compared by Student's *t*-test (two groups) and enumeration data by chi-square test. Data between groups were analyzed by one-way analysis of variance (ANOVA) followed by the Student–Newman–Keuls (SNK-q) multiple comparison test among multiple groups. The diagnostic ability of NT-proBNP for coronary lesions was evaluated by receiver operating characteristic (ROC) curve.

3. Results

3.1. NT-proBNP and clinical presentation

The clinical characteristics and associated risk factors in the 110 patients are listed in Table 1. The two groups did not differ significantly (p = ns) in terms of baseline characteristics, such as gender, age, history of hypertension and diabetes, as well as levels of total cholesterol, uric acid, and creatinine. As expected, the angiography-positive group had a more adverse cardiovascular risk profile versus the angiography-negative group, but the difference was not significant, and left ventricle ejection fraction (LVEF) was likewise. GS and NT-proBNP levels were significantly increased in the angiography-positive group compared with the negative group (GS, 1 (0 ± 6) vs. 32 (19 ± 50), $p < 0.05$; NT-proBNP, 45 (18 ± 76) pg/ml vs. 95 (33 ± 183) pg/ml, $p < 0.05$).

3.2. NT-proBNP and coronary vessel involvement

The NT-proBNP levels in relation to the severity of CAD are shown in Fig. 1. The NT-proBNP level and GS were not normally distributed, and thus were log-transformed. ANOVA revealed significant differences between groups ($p < 0.05$). Significant progressive differences were assessed between the nonevessel versus