Association between serum N-terminal pro-B-type natriuretic peptide levels and characteristics of coronary atherosclerotic plaque detected by coronary computed tomography angiography

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Abstract. The aim of the present study was to explore the association between the levels of serum N-terminal pro-B-type natriuretic peptide (NT-pro BNP) and the characteristics of coronary atherosclerotic plaque detected by coronary computed tomography angiography (CCTA), in patients with unstable angina (UA). A total of 202 patients (age range, 47-82 years) were divided into the following three groups: Non-cardiac disease group (57 patients); stable angina pectoris (SAP) group (62 patients); and UA group (83 patients). There were significant differences between the serum NT-pro BNP levels among the three groups (P=0.007). However, in multivariant diagnoses, NT-pro BNP level was not an independent risk factor for UA. The levels of serum NT-pro BNP were observed to be positively correlated with the number of vessels involved (r=0.462; P<0.001), SIS (r=0.475; P<0.001), segment-stenosis score (r=0.453; P<0.001), coronary calcification score (r=0.412; P=0.001), number of obstructive diseases (r=0.346; P<0.001), and the number of segments with non-calcified plaque (r=0.235; P=0.017), mixed plaque (r=0.234; P=0.017) and calcified plaque (r=0.431; P<0.001). The levels of serum NT-pro BNP were significantly higher in patients with UA and left main-left anterior descending (LM-LAD) disease, compared with UA patients without LM-LAD disease (P<0.001). In addition, serum NT-pro BNP was significantly higher in patients with obstructive disease and UA than in those without obstructive disease (P<0.001). The area under the curve of log(NT-pro BNP) was 0.656 (P=0.006; optimal cut-off value, 1.74; sensitivity, 77.6%; specificity, 51.9%). In conclusion, the levels of serum NT-pro BNP are associated with the burden and severity of coronary artery atherosclerotic disease in patients with UA, and may be helpful in risk stratification of patients with UA.

Introduction

B-type natriuretic peptide (BNP) is predominantly secreted by ventricular cardiomyocytes in patients with chronic cardiac disease (1). It serves a key role in the regulation of circulation and the balance of water and electrolytes (2), and it is closely associated with the systolic and diastolic functions of myocardial cells (3). At present, BNP is considered to be an effective index of evaluation for myocardial function (4). However, the levels of serum N-terminal pro-BNP (NT-pro BNP) are closely associated with BNP, and NT-pro BNP is stable enough to be detected using laboratory tests (5).

Coronary heart disease (CAD) is one of the most frequent causes of morbidity and mortality worldwide, and it is well known that the predominant factor of CAD is atherosclerosis, which is a chronic and progressive inflammatory disease (6). The pathogenesis of acute coronary syndrome (ACS) includes the rupture or erosion of a vulnerable plaque, which is characterized by infiltration of inflammatory cells, a large necrotic core and a thin fibrous cap (7). It is believed that the earlier the detection of UA, the better chances exist regarding treatment and prognosis.

Numerous studies have demonstrated that the levels of serum NT-pro BNP are associated with the severity and prognosis of coronary atherosclerotic disease (8-11). At present, computed tomography angiography (CTA) is the optimal non-invasive method for assessing the burden and components of coronary plaques (12). This technique is highly consistent with optical coherence tomography (OCT) and intravascular ultrasound (IVUS), which are widely considered as the 'gold standard' methods for assessing plaque characteristics (13). Currently, coronary CTA (CCTA) is widely used to evaluate the risk and stability of coronary atherosclerotic plaques in patients with unstable angina (UA) (14-16).

Zhou *et al* (17) oserved that the concentration of BNP was significantly higher in patients with carotid plaque compared with those without carotid plaque, and the presence of the

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plaque positively correlated with carotid intima-media thickness (17). Hong *et al* (18) demonstrated that patients with high NT-pro-BNP expression levels had more vulnerable plaque components (more non-calcified-containing lesions and a higher frequency of thin-cap fibroatheroma, as assessed by virtual histology-IVUS). In addition, Peng *et al* (19) observed that patients with essential hypertension and moderate and elevated BNP had significantly higher left ventricular mass index, intima-media thickness, coronary calcification score (CCS) and microalbuminuria levels compared with those with normal BNP expression levels, as assessed by ultrasound and coronary CT examinations (19). The above studies were investigated the associations between carotid atherosclerosis plaque burden, coronary artery plaque calcification score and BNP/NT-pro BNP. Altintas *et al* (20) demonstrated that serum NT-pro BNP expression level was associated with total plaque burden and calcification volume in patients with stable chest pain (20). However, currently there are no studies investigating the association between serum BNP/NT-pro BNP expression level and characteristics of coronary artery plaque in patients with ACS, in particular with regards to the burden and composition of plaques, as assessed by CT.

The present study explores the association between the levels of serum NT-pro BNP and the characteristics of atherosclerotic plaques, as determined by CCTA.

Materials and methods

Subjects. A total of 202 patients (age range, 47-82 years; mean age, 74.5 years; male to female ratio, 1.8:1) were recruited for the present study between January 2013 and 2014 in the Chinese General Hospital of the PLA (Beijing, China). Informed patient consent was obtained prior to the collection of blood samples for the detection of serum NT-pro BNP. The study was approved by the Institutional Ethics Committee for human subjects, and was approved by the ethics committee of the Chinese General Hospital of the PLA. Written informed consent was obtained from the patients.

Inclusion criteria. Patients with stable angina pectoris (SAP) and UA, diagnosed according to the AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes (21), were included in the study.

Exclusion criteria. Patients were excluded from the study if they matched any of the following criteria: Acute myocardial infarction, cardiomyopathy, valvular disease, cardiac dysfunction, coronary revascularization (including percutaneous coronary intervention, stenting and coronary artery bypass grafting), renal insufficiency, iodine allergy, poor tolerance to CCTA examination, pregnancy and minors.

Study design. All subjects underwent CCTA examination and blood samples were taken for the detection of serum NT-pro BNP within 12-48 h following the onset of illness or admission to hospital. Blood samples were drawn prior to the CTTA examination and stored at -80˚C until assays were performed. Arterial hypertension was defined by the use of antihypertensive drugs prescribed by a physician, or reported systolic blood pressures >140 mmHg. Hyperlipidemia was defined by

200 mg/dl total cholesterol, or the use of statins to treat hyperlipidemia at present or in the past. Patients with UA (n=83) were analyzed as the experimental group, and patients with SAP (n=62) and non-cardiac diseases (n=57) were treated as control groups.

Scan protocol and image reconstruction. Scans were performed according to SCCT guidelines (22) for the performance of CCTA with a multidetector computed tomography (CT) scanner (256 iCT; Philips Healthcare, Andover, MA, USA). Helical scan data was obtained using retrospective or prospective electrocardiographic gating. Prior to performing the CCTA, 50-60 ml iodinated contrast media (370 mg I/ml, Bayer AG, Leverkusen, Germany) was injected followed by a 35-40 ml saline flush (4.5-5 ml/s). The threshold tract trigger mode of the region of interest was adopted (23). Images were reconstructed at 40, 45 and 78% of the cardiac cycle, consistently and immediately following the completion of a scan. The optimal phase reconstruction was assessed by comparison with the phase that had the least amount of coronary artery motion. The images were evaluated using transaxial two-dimensional image stacks (raw data), multiplanar reformations, maximum intensity projections, curved multiplanar reformations and volume-rendering technique reconstructions. If a coronary artery segment was uninterpretable (characterized by artifacts, such as motion, beam hardening, metal or calcium-related partial volume averaging, and adequacy of over contrast concentration or opacification) (24), it was not included in the analysis. IntelliSpace Portal 6 (Philips Healthcare, Andover, MA, USA) was used to analyze the images.

Image analysis and definition of atherosclerotic plaque in the coronary artery. In each coronary artery segment, coronary atherosclerosis was defined as the presence of tissue structures >1 mm^2 that existed within the coronary artery lumen or adjacent to the coronary artery lumen that could be discriminated from surrounding pericardial tissues, epicardial fat or the vessel lumen itself. Coronary artery segments were identified according to the 15-Segment American Heart Association model (25). Calcification of plaques was graded according to the following criteria: Non-calcified plaque (<20% calcification; mean CT, ≤150 HU); mixed plaque (20-80% calcification); and calcified plaque (>80% calcification; mean CT, >130 HU).

Evaluation indicators. Images were analyzed for plaque and individual aspects. Evaluation indicators for individual aspects included left main-left anterior descending (LM-LAD) disease and obstructive diseases (stenosis degree of the coronary artery of ≥50%), and the number of segments of calcified plaque, non-calcified plaque and mixed plaque. Coronary calcium scoring computer programs typically identify pixels that exceed 130 HU as a level corresponding to calcium on a non-contrast study Plaques were evaluated according to the following criteria: CCS (Agaston score) (26); segment-involvement score (SIS; range 0-15); segment-stenosis score [SSS; range, 0-3; 0 = normal, 1 = mild (<50%), 2 = moderate (≥50-70%), 3 = severe (≥70%); obstructive disease = ≥2 points]; and the number of vessels (range, 0-4). Degrees of luminal stenosis were calculated on the basis of the vessel diameter. SSS ranged between 0 and 45 points.

Blind method. Each image was analyzed by two radiologists with experience of interpreting several thousands of CCTA scans. The radiologists had no knowledge of the clinical diagnosis and laboratory results of the patients.

Laboratory examination. Fasting blood samples (4.0 ml) were collected using vacuum tubes and serum was separated 30 min following sample extraction by centrifugation at 14,000 x g for 20 min at room temperature. An automatic biochemical analyzer (7600DDP; Hitachi, Ltd., Tokyo, Japan) was used to detect levels of serum NT-pro BNP.

Statistical analysis. Patient demographic characteristics were presented as the mean ± standard deviation or as medians (interquartile ranges) for continuous variables, and as proportions (percentages) for categorical variables. The levels of serum NT-pro BNP were normally distributed with logarithmic transformation. Non-parametric Mann-Whitney U or Kruskal-Wallis tests were used to compare continuous variables, and the Pearson's χ^2 test was used to evaluate differences in frequencies. Correlations between variables were analyzed using a linear and binary logistic regression model. Receiver-operating characteristic (ROC) curve analysis was used to evaluate the authenticity and reliability of the study and estimate the optimal threshold (cut-off value obtained from ROC). Statistical comparisons were performed using SPSS version 19.0 (SPSS, Inc., Chicago, IL, USA). P<0.05 was considered to indicate a statistically significant difference.

Results

Baseline information and levels of serum NT-pro BNP. There were no statistically significant differences between patient parameters, including heart rate and blood pressure, among the three groups (UA, SAP and non-cardiac disease groups; Tables I and II). The analysis of serum NT-pro BNP levels among the three groups is presented in Table III. Logarithmic values of NT-pro BNP serum levels are as follows: Non-cardiac disease group (1.57±0.57; n=57; 95% CI, 1.53-1.98); SAP group (1.93±0.50; n=62; 95% CI, 1.73-2.12); and UA group (2.16±0.53; n=83; 95% CI, 2.00-2.31). There were statistically significant differences in the log(NT-pro BNP) values between the three groups (Table III).

Atherosclerotic plaque characteristics assessed by CCTA. The data from the analysis of the atherosclerotic plaque CCTA characteristics among the three groups is presented in Table IV. There was no correlation between the levels of serum NT-pro BNP and the characteristics of atherosclerotic plaques, detected by CCTA, between the SAP and control group.

Association between serum NT-pro BNP expression levels and characteristics of plaques in patients with UA. The correlation analysis between the levels of serum NT-pro BNP and characteristics of atherosclerotic plaques detected by CCTA in patients with UA is presented in Table V. In the UA group, log(NT-pro BNP) had various degrees of linear correlation with the number of vessels (r=0.462, P<0.001), SIS (r=0.475, P<0.001), SSS (r=0.453, P<0.001), CCS (r=0.412, P<0.001), obstructive disease (r=0.346, P<0.001) and the number of

Table I. Patient information.

Parameter	NC	SAP	UA	F-value	P-value
Age	56.8±11	60.4±9.6	62.7±11	2.724	0.070
HR	71.6±12	73.5±11	75.5±15	0.786	0.458
SBP	135±19	136±16	138±23	0.300	0.741
DBP	80.0±11	77.0±8.0	77.0±11	0.614	0.543
BMI	26.0±2.8	26.7±5.0	25.7±3.2	0.568	0.568

The non-cardiac disease group served as the control. NC, non-cardiac group; SAP, stable angina pectoris group; UA, unstable angina group; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

Table II. Patient information (n=202).

Parameter	χ^2	P-value
Gender (male)	4.626	0.099
Hypertension	1.001	0.606
Diabetes mellitus	0.017	0.991
Dyslipidemia	0.588	0.745
Family history	0.115	0.944
Smoking	0.950	0.622

Table III. Levels of NT-pro BNP in the control (non-cardiac disease), SAP and UA groups.

Group	N	Log(NT-pro BNP)	95% CI	P-value
NC	57	1.57±0.57	1.53-1.98	0.007[a]
SAP	62	1.93±0.50[b]	1.73-2.12	
UA	83	2.16±0.53[c,d]	2.00-2.31	

[a]Multivariate analysis of all groups; [b]SAP, vs. the control group, P=0.363; [c]UA, vs. the control group, P=0.004; [d]UA, vs. the SAP group, P=0.14. NT-pro BNP, N-terminal pro-B-type natriuretic peptide; CI, confidence interval; NC, non-cardiac; SAP, stable angina pectoris; UA, unstable angina.

segments with non-calcified plaque (r=0.235, P=0.017), mixed plaque (r=0.234, P=0.017) and calcified plaque (r=0.431, P<0.001). However, following the adjustment of various conventional risk factors, log(NT-pro BNP) was not determined to be an independent risk factor of UA (Table VI).

Association between serum NT-pro BNP expression levels and LM-LAD disease in patients with UA. There were statistically significant differences between the prevalence of LM-LAD disease among the three groups. LM-LAD was most common in patients with UA (Fig. 1; χ^2=21.444, P<0.001) and the levels of serum NT-pro BNP were significantly higher in patients with UA and LM-LAD disease compared with UA patients without LM-LAD disease (2.12±0.52 vs. 1.64±0.48; P<0.001; Table VII).

Table IV. Univariant and multivariant analysis of the association between serum NT-pro BNP levels and US.

Parameter	NC	SAP	UA	P-value
Vessels	1.26±1.46	2.26±1.13[a]	2.13±1.27[b,c]	0.008
SIS	1.96±2.67	2.89±2.01[d]	3.56±3.22[e,f]	0.019
SSS	3.04±0.99	3.78±3.87	5.33±5.72	0.066
NCP	1.33±2.62	1.72±1.34	2.53±2.34	0.458
MP	0.07±0.27	0.56±0.90[g]	0.92±0.23[h,i]	0.009
CP	0.89±1.69	1.15±1.46	2.33±3.97	0.108
CCS	27.8±12.6	148.3±102.4	287.5±259.2	0.101

[a]SAP, vs. the control group, P=0.01; [b]UA, vs. the control group, P=0.012; [c]UA, vs. the SAP group, P=0.88; [d]SAP, vs. the control group, P=0.365; [e]UA, vs. the control group, P=0.037; [f]UA, vs. the SAP group, P=0.52; [g]SAP, vs. the control group, P=0.014; [h]UA, vs. the control group, P=0.002; [i]UA, vs. the SAP group, P=0.523. NC, non-cardiac group; SAP, stable angina pectoris group; UA, unstable angina group; SIS, segment-involvement score; SSS, segment-stenosis score; NCP, non-calcified plaque; MP, mixed plaque; CP, calcified plaque; CCS, coronary calcification score.

Table V. Correlation between N-terminal pro-B-type natriuretic peptide levels and coronary computed tomography angiography characteristics in patients with unstable angina.

Parameter	R-value	P-value
Vessel number	0.462	<0.001
SIS	0.475	<0.001
SSS	0.453	<0.001
OD	0.346	<0.001
NCP	0.235	0.017
MP	0.234	0.017
CP	0.431	<0.001
CCS	0.412	0.001

SIS, segment-involvement score; SSS, segment-stenosis score, OD, obstructive disease; NCP, non-calcified plaque; MP, mixed plaque; CP, calcified plaque; CCS, coronary calcification score.

Table VI. Analysis of log(N-terminal pro-B-type natriuretic peptide).

Analysis	P-value	OR	95% CI UL	95% CI LL
Univariable	0.008	2.892	1.326	6.309
Multivariable	0.053	2.723	0.985	7.526

OR, odds ratio; CI, confidence interval; UL, upper limit; LL, lower limit.

Association between serum NT-pro BNP expression levels and obstructive disease in patients with UA. There were statistically significant differences between the number of identified
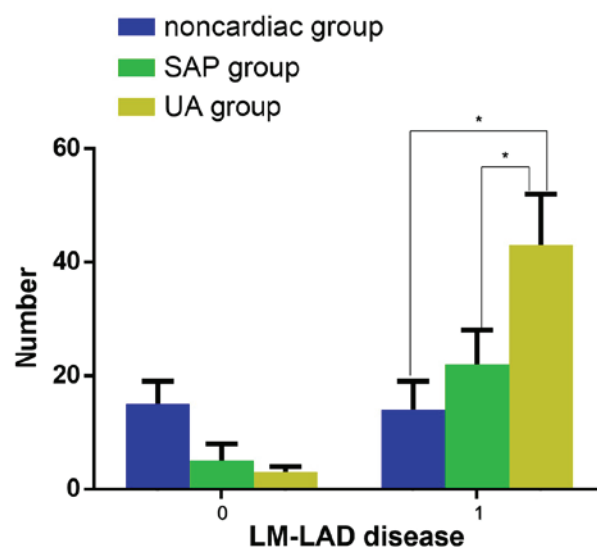

Figure 1. Presence of LM-LAD disease. There were significant differences between the prevalence of LM-LAD disease among the non-cardiac, SAP and UA groups. LM-LAD disease was the most common in patients with UA. *P<0.05. Blue, non-cardiac disease group; green, SAP group; yellow, UA group. LM-LAD, left main-left anterior descending; SAP, stable angina pectoris; UA, unstable angina.
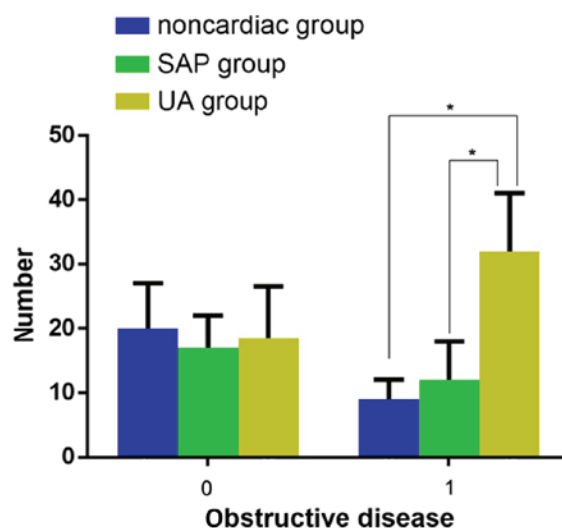

Figure 2. Presence of obstructive disease. There were significant differences between the prevalence of obstructive disease among the non-cardiac, SAP and UA groups. Obstructive disease was the most severe in patients with UA. *P<0.05. Blue, non-cardiac disease group; green, SAP group; yellow, UA group. SAP, stable angina pectoris; UA, unstable angina.

obstructive diseases among the three groups, and patients in the UA group experienced the most severe obstructive disease (Fig. 2; χ^2=10.113, P=0.006). In addition, in patients with UA the levels of serum N-pro BNP in those with obstructive diseases was significantly higher compared with those without obstructive diseases (Table VIII; 1.78±0.49, vs. 2.22±0.54; P<0.001); however, the levels of serum N-pro BNP did not increase when the number of obstructive vessels increased (P=0.400; Table IX).

ROC of serum NT-pro BNP expression levels and indexes of CCTA plaque characteristics to identify patients with UA.

Table VII. Levels of serum N-terminal pro-B-type natriuretic peptide in LM-LAD disease in patients with unstable angina.

Group	Log(N-pro BNP) (pg/ml)
With LM-LAD	2.12±0.52[a]
Without LM-LAD	1.64±0.48

[a]With LM-LAD, vs. without LM-LAD, P<0.001. LM-LAD, left main-left anterior descending.

Table VIII. Level of serum log(NT-pro BNP) in patients with obstructive disease and unstable angina.

Disease status	Log(NT-pro BNP)
Non-obstructive	1.78±0.49[a]
Obstructive	2.22±0.54

[a]Non-obstructive disease, vs. obstructive disease, P<0.001. NT-pro BNP, N-terminal pro-B-type natriuretic peptide.

Table IX. Level of serum NT-pro BNP (pg/ml) in patients in the unstable angina group with OD.

OD	N	Log(NT-pro BNP)	95% CI	P-value
Non-OD	57	1.78±0.49	1.65-1.92	<0.001[a]
1 OD	102	2.09±0.51[b]	1.89-2.38	
≥2 OD	43	2.12±0.56[c,d]	2.07-2.53	

[a]Multivariate analysis of all groups; [b]1 obstructive vessel, vs. non-obstructive vessel, P<0.001; [c]≥2 obstructive vessels, vs. non-obstructive vessel, P=0.022; [d]≥2 obstructive vessels, vs. 1 obstructive vessel, P=0.400. NT-pro BNP, N-terminal pro-B-type natriuretic peptide; OD, obstructive disease; CI, confidence interval.

Using the SAP and non-cardiac disease groups as control groups, ROC curves were plotted (Fig. 3). In patients with UA, the area under the curve (AUC) was 0.656 (95% CI, 0.55-0.762; P=0.006) and the optimal cut-off value was 1.74 (Fig. 3). The sensitivity, specificity, LR (likely ratio), Youden index, OR (odds ratio), CI and Kappa values of NT-pro BNP in patients with UA are presented in Table X. In addition, the AUC of vessels, SIS, SSS and the number of segments with calcified plaque, non-calcified plaque and mixed plaque are presented in Table XI.

Discussion

In the present study, the results demonstrated that the levels of serum NT-pro BNP have a positive correlation with atherosclerotic plaque, and specifically calcified plaque. It has been demonstrated that the pathogenesis of UA involves the rupture or erosion of vulnerable plaques and secondary thrombosis (27), leading to an acute occlusion of coronary

Table X. N-pro BNP parameters of patients in the unstable angina group.

Parameter	NT-pro BNP
Sensitivity	77.6%
Specificity	51.9%
Likely positive ratio	1.61
Likely negative ration	0.43
Youden index	0.295
Odds ratio	3.841
95% Confidence interval	2.077-7.102

Table XI. Receiver operating characteristic analysis of vessels, SIS, SSS, and the number of segments with NCP, MP and CP.

Parameter	AUC	P-value
Number of vessels	0.573	0.204
SIS	0.592	0.109
SSS	0.608	0.060
NCP	0.599	0.082
MP	0.591	0.112
CP	0.513	0.825

AUC, area under of the curve; Vessel, number of involved vessels; SIS, segment-involved score; SSS, segment-stenosis score; NCP, non-calcified plaque; MP, mixed plaque; CP, calcified plaque.
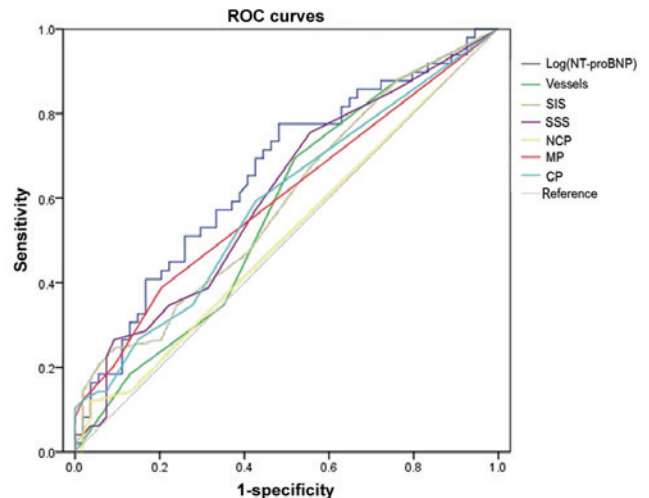

Figure 3. ROC curve of the unstable angina and control (stable angina pectoris and non-cardiac disease) group. For patients with unstable angina, the area under the curve is 0.656; 95% confidence interval, 0.55-0.762; P=0.006 (ROC analysis); optimal cut-off value, 1.74. ROC, receiver operating characteristics; SIS, segment-involvement score; SSS, segment-stenosis score; NCP, non-calcified plaque; MP, mixed plaque; CP, calcified plaque.

arteries. Acute myocardial ischemia is categorized under the Major Adverse Cardiovascular Events (MACE), which also includes UA, acute myocardial infarction (AMI) and sudden cardiac death. Numerous studies have demonstrated that there

is cross-talk between the endocrine and contractile functions of the heart, which acts as a pump as well as a multifunctional and interactive organ (28-31).

Changes in ventricular wall tension, stimulation of myocardial cells and myocardial ischemia can immediately induce the secretion of BNP (32,33). When ventricular cardiomyocytes are stimulated, pre-pro BNP is released and cleaved into active BNP and inactive NT-pro BNP (34). Currently, BNP and NT-pro BNP are primarily used for the screening of heart disease, identifying the risk of congestive heart failure, detecting dysfunction of the left ventricle, differentially diagnosing dyspnea, and diagnosing acute and chronic heart failure (8,9,11).

Research into acute coronary syndrome (ACS) and AMI has demonstrated that levels of serum NT-pro BNP are closely associated with the severity and prognosis of coronary artery disease (35). Invasive examination, coronary angiography, optical OCT and intravascular ultra-sound IVUS are used in a large number of these studies (18,36-38). However, in the present study it was observed that the majority of patients with ACS preferred examination with noninvasive CCTA rather than the invasive methods discussed above. Although there are limitations to the detection of lipid necrotic cores and fiber caps using CCTA, with the development of scanning and post-processing techniques, CCTA may transform into a preferred option compared with OCT and IVUS, which are currently considered the 'gold standard' for detecting vulnerable plaques (13,15,39,40). In addition, the rupture or erosion of vulnerable plaques may increase the level of serum BNP and NT-pro BNP in a short period of time (5,41,42). Therefore, using CCTA in patients with UA to detect changes in serum NT-pro BNP levels and the characteristics of atherosclerotic plaques may have important clinical significance.

A previous study of IVUS demonstrated that the levels of serum NT-pro BNP are significantly associated with vulnerable plaques which have relatively large necrotic cores or thin fibrous caps (43). In the present study, high levels of serum NT-pro BNP were associated with a high volume of calcified plaque. In particular, serum NT-pro BNP levels were associated with the composition of atherosclerotic and calcified plaque (correlation coefficient, 0.431), as compared with non-calcified and mixed plaque that were not associated with serum NT-pro BNP (OR=0.235 and 0.234 respectively). To the best of our knowledge, these findings have not been previously reported.

The formation of atherosclerotic plaque is a complex process comprised of three stages: The formation of lipid plaques, fibrous plaques and complex lesions (44,45). Plaques in various stages present different characteristics on a CCTA, including low-density non calcified plaque, high-density non calcified plaque, mixed plaque and calcified plaque (46). Considering the limitations of detecting low-density and high-density non-calcified plaques using CCTA (11), these two types of plaque were considered to be non-calcified plaque in the present study.

Salama *et al* (47) observed that calcified plaques were commonly found in mid-to-late stage of atherosclerosis. In these stages, the severity and extent of the disease is more serious than in the early stages. In addition, the formation of atherosclerotic plaque was a non-linear process, in which stable

and unstable plaques coexisted and calcified, and non-calcified and mixed plaques could be observed in a patient at any time. Non-calcified and mixed plaques can be frequently unstable and vulnerable to rupture or erosion (48). However, calcified plaques often coexist with more severe luminal stenosis in mid- and late-stages of disease and are associated with inflammatory processes (49,50). Once the rupture or erosion of vulnerable plaque occurs, the degree of myocardial infarction can be more serious than that of early stage disease in which only non-calcified plaques exist. When plaques rupture or erode, the level of serum NT-pro BNP increases (51-53).

The results in the present study suggested that the increase of serum NT-pro BNP levels in patients with UA is a result of the rupture or erosion of vulnerable plaques, and is relative to the extent of lesion, degree of luminal stenosis and the number of segments that are affected by calcified plaques. The present study also demonstrated that the levels of serum NT-pro BNP in patients with UA are significantly higher, as compared with those in control groups, and that they are associated with the severity of the lesion, the degree of luminal stenosis and LM-LAD disease, and the number of segments affected by calcified plaques.

The results of the present study were concordant with those of a previous study conducted by Palazzuoli *et al* (54), who demonstrated that the level of NT-pro BNP is positively correlated with SIS, SSS and the number of involved vessels. Palazzuoli *et al* (54) observed that the level of NT-pro BNP is higher in patients with >3 vessels implicated. Sadanandan *et al* (55) observed that the levels of serum NT-pro BNP increased in the coronary angiography when the degree of luminal stenosis was >76% or LM-LAD was present, and Radwan *et al* (41) reported similar findings when using IVUS. It can therefore be speculated that high degree stenosis and extensive lesions may weaken the compensatory abilities of the myocardium, exacerbate myocardial ischemia and provoke the ongoing release of NT-pro BNP and BNP. However, the same correlation in patients with SAP was not observed in the current study. Furthermore, the results from the present study were not concordant with those reported by Weber *et al* (56), although that particular study did not mention the incorporation of a time frame in which they extracted blood samples, which is a critical stage in testing for serum NT-pro BNP. However, an insufficient sample size in the present study may have led to inaccurate results.

In the current study, the AUC of serum NT-pro BNP levels in patients with UA was 0.656, which is marginally higher than that of non-ST-elevated myocardial infarction, but lower than that of ST-elevated myocardial infarction (47). The serum NT-pro BNM optimal cut-off value was 55 pg/ml, sensitivity was 77.6% and specificity was 51.9%. There are large discrepancies between the results of the present study and those reported by Liu *et al* (57), which may be due to the use of different patient types; Liu *et al* (57) used patients with ACS. The levels of serum NT-pro BNP were higher in patients with non-ST-elevated myocardial infarction compared with patients with UA. In addition, Liu *et al* (57) described blood samples being drawn immediately following admission to hospital, not at T_{max}, which would lead to inaccurate results; it is difficult to identify the Tmax in patients with non-cardiac disease (58), therefore, blood samples were taken 12-48 h

following admission in the present study. Furthermore, the use of different experimental methods in the laboratory would also lead to inconsistent results (8,59,60).

Univariant analysis in the present study concluded that the OR of log(NT-pro BNP) was 3.841, but following multivariant analysis, log(NT-pro BNP) was not categorized as an independent risk factor of UA when atherosclerotic plaques were detected by CCTA. In addition, the results of the present study demonstrated that there were no statistically significant differences between conventional risk factors of coronary heart disease among the three experimental groups. Therefore, it can be concluded that conventional risk factors have a limited value in predicting MACE.

It has been demonstrated that the pathogenesis of UA is not associated with the extent of lesions and the degree of luminal stenosis, but rather with plaque stability (61,62). It was observed that a large amount of non-calcified plaque was unstable and vulnerable to rupture or erosion, and that the number of segments with non-calcified plaque was higher in patients with UA compared with the non-cardiac disease and SAP group. However, in the present study there were no statistically significant differences between the number of segments with non-calcified plaque among the three patient groups. It can be speculated that this was due to secondary thrombosis caused by plaque rupture or erosion that may have activated fibrinolytic systems in the body. Clots autolyzed subsequently. In coronary angiography, negative results were often obtained; clot autolysis was further confirmed by the HORIZONS-AMI Trial (63).

The limitations of the present study are as follows: The study was a single center study, and further studies would be required to acquire more accurate results; joint analysis with regular blood biomarkers was not performed; and the prognostic value of serum NT-pro BNP levels in patients with different compositions of atherosclerotic plaques requires further research.

In conclusion, the present study demonstrates that the expression level of NT-pro BNP is associated with coronary plaque, in particular calcified plaque, LM-LAD disease, and the severity of vessel stenosis in patients with UA. It can be suggested that NT-pro BNP is a marker of cardiac failure, and indicates the severity of coronary artery atherosclerotic disease. Although the expression level of NT-pro BNP was not an independent risk factor of UA, it may be helpful in risk stratification in patients with UA. Further research is required in order to explore the value of NT-pro BNP and plaque detection by CCTA in the risk stratification and prognosis of patients with UA.

Acknowledgements

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