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Original Research Article

The study of brain natriuretic peptide level and heart rate turbulence in acute coronary syndrome

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This study aims to investigate the effect of serum brain natriuretic peptide (BNP) level and heart rate turbulence (HRT) phenomena on changes in acute coronary syndrome (ACS) patients, and their roles in predicting the evaluation of recent cardiovascular event. According to clinical diagnosis and coronary artery angiography results, 102 patients were divided into three groups; ST-elevation myocardial infarction (STEMI), non ST-elevation myocardial infarction (NSTEMI) and unstable angina (UA). The BNP and HRT results were determined upon performance of parallel color doppler ultrasound examination. Major adverse cardiac events (MACE) during hospitalization and within 90 days after discharge were analyzed. BNP level significantly differed between ACS and control groups (P < 0.05). With ACS degree aggravating, the classification of HRT in HRT2 increased significantly. Comparisons between with and without MACE shows an increase in BNP level, HRT2 ratio and Turbulence Onset (TO) with a decrease in turbulence slope (TS). The levels of BNP in patients with ACS are good indicators of the severity of ACS. HRT phenomenon is associated with ACS type. BNP and HRT are correlated with recent adverse cardiovascular events.

Key words: acute coronary syndrome, brain natriuretic peptide, heart rate turbulence, major adverse cardiac events.

INTRODUCTION

With improvements in living conditions and an aging population, coronary heart disease is a serious threat to human health in China. Acute coronary syndrome (ACS) is an acute symptom of coronary heart disease, often resulting in angina pectoris and sudden cardiac death. ACS, especially in the left coronary anterior descending artery, in the 30-50 years age group has rapidly increased with an average annual rate of 8.6%,. ACS is a syndrome caused by plaque instability, of which the clinical feature shows variations including unstable angina, as well as a wide range of myocardial infarction and even cardiogenic shock. Currently, there are more and more studies on brain natriuretic peptide (BNP) and heart rate turbulence (HRT) in ACS; both are referred to as effective factors of severity of myocardial ischemic injury, and the prognosis of ACS. This study investigated the association between serum BNP and HRT with the severity of ACS and the predictive value of MACE in patients with ACS.

MATERIALS AND METHODS

Inclusion criteria

A total of 102 cardiology patients were enrolled from November 2014 to 2015 December in the Third Affiliated Hospital of Nantong University. ACS diagnostic criteria was according to the Chinese Medical Association, Cardiovascular Branch of the Standard (Chen et al., 2000; Gao, 2001).

ACS classification

STEMI: Patients have acute ischemic chest pain history; ischemic chest pain for >30 min; no relief with the use of nitrates. ST-segment elevation of at least >0.1mv in two limb leads or >0.2mv in chest lead using the electrocardiogram; with dynamic changes; myocardial enzymes; increased cTnI; coronary angiography showing at least one branch diameter stenosis of >50%.

NSTEMI: Patients have chest pain with determination of acute myocardial ischemia; chest pain of >30 min; signs like left bundle branch block / T wave inversion / ST segment depression were seen on the electrocardiogram; myocardial enzymes and cTnI increased; coronary angiography showing at least one coronary artery stenosis of >50%.

UA: Patients with new ischemic chest pain within one month or original stable angina showing increased frequency and severity for prolonged duration and changes in incentives within one month; ischemic evidence on electrocardiogram, cTnI test was negative and at least one coronary artery diameter stenosis of > 50%.

Control group criteria: The control group comprised of patients with organic heart disease based on clinical data and coronary angiography results within the same hospital period.

Exclusion criteria: Elderly (> 75 years); family history of cancer; surgical history within one year, organ infection, severe liver function damage with transaminase of more than twice the normal average; chronic respiratory complications diagnosed as COPD, immune disorders with installation of temporary and permanent pacemaker; atrial fibrillation; atrial flutter; atrioventricular block and other cardiovascular disease patients; comorbidities suspected to interfere with plasma BNP concentration (hyperthyroidism, renal failure, primary aldosteronism, etc.). This study was approved by the hospital's Ethics Committee and informed consent of the patients was sought.

Clinical data: Baseline demographics collected included age, sex, smoking, past hypertension, diabetes and the current treatment upon hospitalization.

HRT: All subjects underwent a 12-channel 24-hour monitoring using the MGY-TOP Holter system. The record was replayed by experienced technicians and automatically analyzed with computer software. A continuous recording of a single typical ventricular contraction was chosen. The typical record is defined as fully compensated pause, which has 15 after and 2 before sinus rhythm. The two evaluation parameters of HRT: turbulence onset (TO) and turbulence slope (TS) were calculated.

Turbulence Onset (TO): refers to the initial phase of sinus tachycardia phenomenon (after ventricular premature contraction, VPC). TO represents the initial acceleration of HRT and the formula is:

$$TO\ (\%) = 100 * [(RR1 + RR2) - (RR-1 + RR-2)] / (RR-1 + RR-2).$$

where RR1 + RR2 represents the RR interval of the first and second sinus rhythm after ventricular premature beats; RR-1 + RR-2 is the RR interval of the last two sinus rhythm before ventricular contraction. TO neutral value is 0%, TO <0% represents an acceleration of sinus rhythm after VPC acceleration, TO ≥ 0% indicates a deceleration of sinus rhythm after VPC (Cygankiewicz).

Turbulence slope (TS): This refers to the phenomenon of subsequent deceleration of the sinus heart rate, including TS regression line and values. Twenty consecutive sinus RR intervals were selected after compensatory pauses of VPC, and the regression line was drawn according to changes in the 20 RR intervals. The ordinate is the increasing number of ms, the horizontal axis is the sequential 20 RR interval, after mapping regression line can be obtained, in which the maximum positive slope is TS value. The neutral value of TS is 2.5 ms / RR interval, normal TS> 2.5 ms / RR interval, otherwise is abnormal. According to the results of the TO and TS HRT is classified as, Category 1(HRT0): TO < 0 and TS > 2.5 ms / RRI； Category 2 (HRT1: TO≥0 or TS≤2.5ms / RRI； Category 3 (HRT2): TO≥0; TS≤2.5 ms / RRI.

Cardiac Color Doppler Echocardiography

All subjects underwent Cardiac Color Doppler Sonography study (S5-1 probe, PHILPS IE-33, US) to detect cardiac LVEF (left ventricular stroke volume / left ventricular end diastolic volume), which is the indicator of left ventricular systolic function. It is calculated thus:

LVEF= (left ventricular end-diastolic volume-left ventricular end-systolic volume) / left ventricular end-diastolic volume × 100%, of which the normal reference value range of 67 ± 8%.

Coronary angiography

Coronary angiography was performed with Integris Alura-12 digital subtraction angiography system (Philips Integris Alura-12, Philips Medical Systems, Netherlands, 2000) using Seldinger arterial cannulation to establish radial artery pathway in the conventional position. Bilateral coronary angiography was taken according to the standard Judkin's method and a variety of different projection positions were included intraoperatively.

Follow-up

Major adverse cardiovascular events (MACE) were recorded

Table 1. Comparison of BNP, TO, TS, LVEF between examined group and control group ($\bar{X}$ ±s).

Group	n	BNP（pg/ml）	TO (%)	TS (ms/RRI)	LVEF (%)
STEMI	41	977.38±536.16*	2.49±2.43*	2.05±0.95*	34.88±7.60*
NSTEMI	27	567.33±187.94*	2.06±2.41*	2.58±1.34*	43.61±9.98*
UA	34	320.50±140.14*	0.04±1.49*	5.39±3.36*	51.57±7.67*
Control group	36	29.42±15.33	-1.42±0.82	8.18±2.79	69.53±8.42

* P <0.05 compared with the control group.

Table 2. Relationship between ACS types and HRT classification

Group	n	HRT_0 (%)	HRT_1 (%)	HRT_2 (%)
STEMI	41	5 (12.2)	9 (21.9)	27 (65.8)
NSTEMI	27	6 (22.2)	8 (29.6)	13 (48.1)
UA	34	21 (61.7)	7 (20.5)	6 (17.6)
Control group	36	27 (75.0)	9 (25.0)	0 (0)

during hospitalization and 90 days after discharge of all patients, by telephone follow-up and hospital visit follow-up to observe the occurrence of MACE events in patients. Primary endpoint: cardiac or all-cause death. Secondary endpoints: fatal or near-fatal cardiac arrhythmia (ventricular tachycardia, ventricular fibrillation), severe heart failure, the first myocardial infarction, recurrent myocardial infarction.

Group

A total of 102 patients were divided into two groups (STEMI/UA) according to the clinical diagnosis and angiographic results. The control group compromised 36 hospitalized patients in the same period, all with negative clinical data and coronary angiography to eliminate organic heart disease. The study was approved by the institution's Ethics Committee.

Statistical analysis

All analyses were performed using Stata 10.0 software. Quantitative data were presented as mean ± standard deviation ($\bar{X}$ ±s). t test was used for comparison between groups, and χ 2 test was used for categorical data analysis. A P value of <0.05 was considered statistically significant.

RESULTS

Among 102 patients, 41 patients were STEMI (35 male, 6 female; aged 68 ± 7 years); 27 patients were in NSTEMI group (22 males and 5 females; 68 ± 6 years of age); 34 cases of UA group (28 males and 6 females; aged 66 ± 9 years).

There were significant differences in BNP concentration between each ACS group and control group (P <0.05). BNP concentration in STEMI group was the highest among groups. There were significant differences in TO, TS and LVEF between ACS groups and control group (Table I).

Proportion of HRT classification in each ACS type is significantly different from control group (P <0.05). Proportion of HRT2 increased significantly with the severity of ACS. (Table 2; Figure 1).

The value of BNP, TO and LVEF in patients with MACE were significantly different from those without MACE (Table 3); TS was significantly lower in MACE group (2.16 ± 0.95 vs. 5.48 ± 3.30, P <0.05) (Table 3). The proportion of HRT2 in the MACE group was higher (Table 4).

DISCUSSION

ACS is a syndrome which refers to coronary occlusion caused by coronary atherosclerotic plaque rupture and thrombosis, leading to angina and acute myocardial infarction. BNP is a polypeptide hormone containing thirty-two amino acid residues that has been used as an objective serum biochemical marker for HF. In recent years, BNP concentrations were found to be associated with mechanical strain and wall tension in the development of ACS lesions. Ham's animal experiments (Horio et al., 1992) found that in the rat myocardial infarction model, the main regional distribution of BNP synthesis and release are in the junction of the ischemic area which constitutes a necrotic area of myocardial infarction and non-necrotic region. Stained ischemic myocardium cells particularly increased in residual necrotic areas. The increased secretion of BNP may be due to the fact that the mechanical tension of the ventricular wall is most concentrated and the gene expression of BNP in the myocardium of the infarcted area and surrounding survival area is greatly increased. Studies have shown that BNP reflects the cardiac contractile function and diastolic function changes caused by insufficient

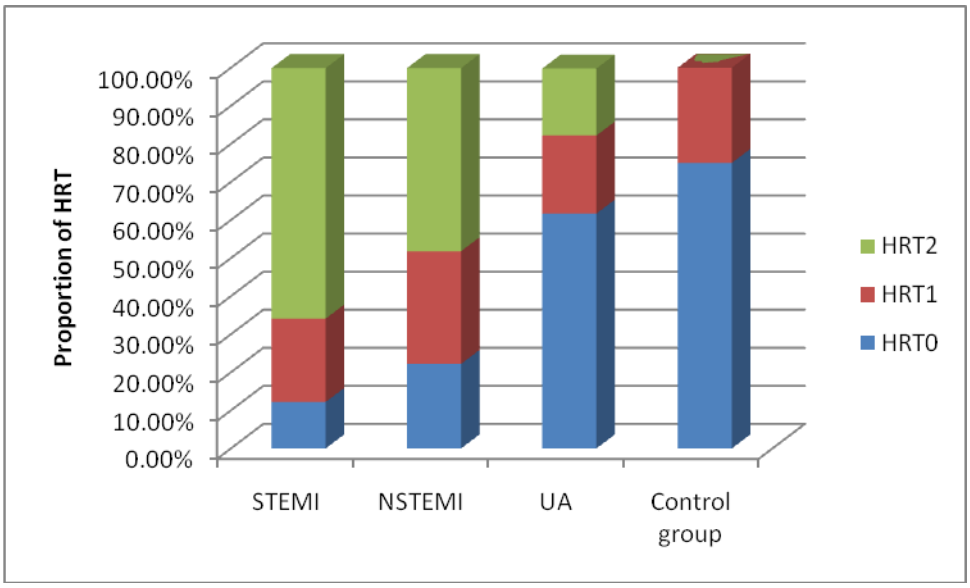

Figure 1: Relationship between ACS types and HRT classification

Table 3. Comparisons of BNP, TO, TS, and LVEF between with/without MACE($\bar{X}$ ±s).

Group	With-MACE (n=67)	Without- MACE (n=35)	P
BNP（pg/ml）	807.28±471.11	307.07±177.41	P<0.05
TO (s)	2.52±2.14	-0.51±1.15	P<0.05
TS (ms/RRI)	2.16±0.95	5.48±3.30	P<0.05
LVEF (%)	37.35±7.89	53.35±7.42	P<0.05

Table 4. Proportion of HRT between with/without MACE

Group	n	HRT_0	HRT_1	HRT_2	p
With-MACE	67	11 (16.4)	17 (25.3)	39 (58.2)	P<0.05
Without- MACE	35	19 (54.3)	12 (34.3)	4 (11.4)	P<0.05

myocardial blood supply. BNP levels of AMI patients before percutaneous coronary intervention were significantly increased, while postoperative BNP decreased significantly compared with preoperative BNP; the mechanism is that systolic and diastolic function decline sharply after myocardial infarction and along with relatively heavy capacity overload, the ventricular wall is stretched in excess thereby inducing rapid expression of myocardial BNP gene (Zhao et al., 2010). At the same time, the concentration of BNP increased with the severity of vascular stenosis and diseased vessels. When the perfusion of the coronary artery decreased, the corresponding regional myocardial blood supply results in elevated BNP levels. Long et al. (2012) researched on 63 cases of ACS patients involved in coronary artery lesions based on the number of coronary artery lesions involved and found that brain natriuretic peptide levels of multi-vessel disease group was significantly higher than the double-vessel disease group and single-vessel disease group in ACS patients. Meanwhile, BNP levels of the double-vessel disease group was significantly higher than the single-vessel disease group thus indicating that plasma levels of brain natriuretic peptide and myocardial ischemia severity are positively correlated. The research shows that there were significant differences in the concentration of BNP between the three groups and the normal control group. The BNP concentration in STEMI group was higher than in the other three groups; the BNP concentration of NSTEMI group was higher than that of UA group and normal control group while in UA group, it was higher than in the normal control group. The plasma BNP concentration was positively correlated with the severity of ACS. The levels of BNP in different types of ACS were statistically significant. Increased plasma BNP concentrations reflects that the more serious myocardial blood supply deficiency is, the worse cardiac function would be.

Plasma BNP determination of ACS patients to determine the prognosis remains to be further studied. Wang et al.'s (2005) follow-up study lasted nearly a year and found that

in patients with acute myocardial infarction, the higher blood BNP concentration was, the more significantly increased the possibility of clinical adverse events was. When BNP <100pg / ml, the probability is 13.8%; BNP is 100-200pg / ml, the probability is 39.1%; BNP is 200-400pg / ml, the probability is 43.3%; BNP is more than 400pg / ml, the probability is 46.4%. In a clinical study by de Lemos et al. (2001), the average plasma BNP concentrations monitored results of 2525 patients with ACS showed that the concentration of BNP is closely related to death, heart failure and 30d-after, 10 months-after myocardial infarction. NT-proBNP generates from the cleavage of brain natriuretic peptide precursor (Pro-BNP) during ventricular dysfunction. NT-proBNP is closely related to BNP concentrations. Yang et al. (2012) on the STEMI study found that increase in NT-proBNP is related to myocardial infarct size, left ventricular morphology, left ventricular prognosis which has an independent predictive value. The results of this study also showed that the value of BNP in ACS patients with or without recent MACS was statistically significant. The higher the plasma BNP concentration was, the greater the risk of MACS in ACS patients was. Therefore, elevated plasma BNP concentration is an important factor in the risk stratification of ACS and in guiding further treatment.

The prognostic value of HRT for myocardial infarction has been demonstrated in a number of studies (Barthel et al., 2003; Chen et al.,2012). The simultaneous abnormity of TO and TS values is the most powerful risk classifications factors. Cardiac function, drugs, the number of PVC and other factors on the TO / TS indicators had no significant interference in the prediction of sudden death in high-risk patients, with relative independence. The principle of this predictive ability is still under study. Direct effects such as autonomic nervous tension, indirect effects of pressure reflex, and ventricular contractions led by indirect effects of pressure reflex, represent some of the mainstream speculative perspectives. Pressure reflex is related to heart rate, referring that pressure reflex receptor excitement and heart rate speed up while heart rate slows down. When ventricular contraction occurs, ventricular blood filling decreased and along with cardiac output, arterial blood pressure decreases. Exciting baroreceptors and the sympathetic nervous excitability is enhanced by stress reflex regulation mechanism thereby reducing vagal excitability, resulting in sinus tachycardia. This early acceleration only lasted in several premature ventricular contractions followed by a series of adaptations that resulted in adequate ventricular filling, increased cardiac output and blood pressure, decreased baroreceptor excitability, vagus nerve inversely increased, slow sinus that is, the late deceleration after ventricular contractions. ACS patients suffered from acute myocardial ischemia, injury, myocardial necrosis, fibrosis, got baroreceptor impaired and unresponsive, impaired vagal function, and autonomic dysfunction, all related to ACS severity of the lesion. The results of this study showed that the HRT phenomenon in ACS patients significantly reduced or was absent compared with the control group, the abnormal rate was significantly higher and the severity of coronary artery disease was positively correlated. It indicates that in ACS symptoms, the autonomic nervous system of the heart was damaged and the sensitivity of baroreceptors weakened with regulation abnormalities. As the literature reported, HRT classification according to the results of TO and TS are thus: Class 1 (HRT0): TO <0 and TS> 2.5 ms / RRI; Class 2 (HRT1): TO $\geq$ 0 or TS $\leq$ 2.5 ms / RRI; Category 3 (HRT2): TO $\geq$ 0 and TS $\leq$ 2.5 ms / RRI. Follow-up study of patients with ACS found that the composition ratio is a significant predictor of death. Jia et al. (2009) reported that ACS lesions reduced in AMI patients after undergoing revascularization while HRT degree improved. This study shows that: with increasing ACS severity, HRT2 in HRT classification increased significantly thereby indicating that TO and TS abnormalities are at the same time important indicators of diagnosing the prognosis of ACS.

Conclusion

In summary, BNP detection is easy, and HRT is a non-invasive ECG indicator. A combination of the two showed good prospects for the diagnosis and prognosis of ACS especially as they show significant superiority in risk assessment after myocardial infarction. However, sinus heart rate shock detection is also deemed deficient as only sinus rhythm category, non-sinus rhythm such as atrial flutter, atrial fibrillation, pacing rhythm, as well as conduction group lag special circumstances constitute unabnormal detection. The prognosis evaluation of ACS remains to be further studied. Future research should focus on the expansion of the number of cases, extension of follow-up time and test of comprehensive studies in relevant disciplines and research methods to further explore their clinical significance and practical value.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

REFERENCES

Barthel P, Schneider R, Bauer A, Ulm K, Schmitt C, Schömig A, Schmidt G(2003). Risk stratification after acute myocardial infarction by heart rate turbulence. Circulation 108(10):1221-1226.

Chen J, Ning T, Zhu W(2000). Diagnosis and treatment of unstable angina pectoris. Chinese J. Cardiol. 28(6): 409-412.

Chen Z, Yao H, Zhang Y(2012). [Changes of sinus rhythm and heart rate in elderly patients with unstable angina pectoris before and after percutaneous coronary intervention]. Modern Preventive Medicine 39(22).

Cygankiewicz I (2013). Heart rate turbulence. Prog Cardiovasc Dis 56(2):160-171.

de Lemos JA, Morrow DA, Bentley JH, Omland T, Sabatine MS, Mccabe CH, Hall C, Cannon CP, Braunwald E(2001). The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. New England J. Med. 345(14):1014-1021.

Gao R(2001). [A Guide to the Diagnosis and Treatment of Acute Myocardial Infarction]. Chinese J. Cardiol. 29(12):710-725.

Horio T, Kohno M, Takeda T(1992). Effects of arginine vasopressin, angiotensin II and endothelin-1 on the release of brain natriuretic peptide in vivo and in vitro. Clin Exp Pharmacol Physiol 19(8):575-582.

Jia F, Lei H, Qin S(2009). [Dynamic changes of cardiac autonomic nerve function in patients with acute myocardial infarction]. J. Chongqing Medical. University(10):1384-1388.

Long X(2012). [BNP in early diagnosis of ACS and its correlation with myocardial necrosis markers]. Chinese J. Cardiovascular Rehabilitation Medicine(03):250-253.

Wang LF, Wu S, Guan XR, Zhang L, Shen JX, Xue FH(2005). [Relationship between plasma brain natriuretic peptide concentration and clinical prognosis in patients of acute myocardial infarction]. Zhonghua Xin Xue Guan Bing Za Zhi 33(3):234-237.

Yang F, Ning X, Xiang X(2012). [Prognostic significance of N-terminal pro-brain natriuretic peptide levels in patients with acute non-ST-segment elevation myocardial infarction]. Chinese Practical Medical J. (20): 81.

Zhao X, Zhao X, Wang H(2010). [The changes and significance of serum MMP-9 and BNP in patients with acute myocardial infarction before and after PCI]. J. Cardiovascular Rehabilitation Medicine(05):461-463.