Author: Chen, Liping; Wei, Tiemin; Wang, Lexin
Email address:- lwang@csu.edu.au
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Relationship between pericardial fluid B-type natriuretic peptide and ventricular function

Liping Chen[1], MD, Tiemin Wei[1], MD, Lexin Wang[2], MD, PhD.

From: [1] Department of Cardiology, the Fifth Affiliated Hospital of Wenzhou Medical College, Lishui, the People's Republic of China, and [2] School of Biomedical Sciences, Charles Sturt University, Wagga Wagga, NSW 2678, Australia.

Short title: pericardial BNP and ventricular function

Author for correspondence:

Lexin Wang, M.D., Ph.D., School of Biomedical Sciences, Charles Sturt University, Wagga Wagga, NSW 2678, Australia. Phone: +61 2 69332905, Fax: +61 2 69 332587,

E-mail: lwang@csu.edu.au,

Abstract

The pericardial fluid BNP and plasma BNP concentrations were measured in 18 patients underwent surgical repair of ventricular septal defect (VSD). The levels of BNP in the pericardial fluid (324.8 ± 137.3 pg/ml) were higher than that in the plasma (20.75 ± 6.05 pg/ml) (*P*=0.034). Pericardial fluid BNP was correlated with the plasma BNP (r=0.85, p<0.01). A good correlation was also found between the pericardial fluid BNP levels and left atrial diameter, left ventricular end-diastolic and end-systolic diameter, left ventricular ejection fraction, right ventricular diameter and mean pulmonary artery pressure (p<0.05). We conclude that the levels of BNP in pericardial fluid were higher than that in the plasma. Similar to plasma BNP, pericardial fluid BNP is also related to the ventricular diameter and function.

Key Words: natriuretic peptide, brain; pericardium, ventricular function, ventricular septal defect.

Introduction

B-type natriuretic peptide (BNP) is a neurohormonal substance secreted predominantly by the ventricular myocytes. This peptide serves as a compensatory mechanism to promote systemic arterial dilation, natriuresis, diuresiss and rennin inhibition (1-5). BNP has been found to be a sensitive and specific maker for ventricular dysfunction (6-10).

In most of the previous studies, BNP was measured from the plasma to study its physiological function and diagnostic significance in heart failure (1-10). BNP in the pericardial fluid was also found to be elevated in patients with myocardial ischemia or ventricular dysfunction (11-13). However, the relationship between pericardial fluid and plasma BNP levels in subjects without overt ventricular dysfunction is unclear.

In this study, the concentrations of pericardial fluid BNP were compared with plasma BNP in a group of patients underwent surgical repair of ventricular septal defect (VSD), and the correlation between pericardial BNP and ventricular function was investigated.

Patients and Methods

Patient selection

The investigation was approved by the Human Ethics Committee of the Fifth Affiliated Hospital of Wenzhou Medical College, and conforms to the principles outlined in the Declaration of Helsinki. Consent was obtained from all patients before the study.

Between June and December 2003, 18 consecutive patients (male 7, female 11, average age 12.4±1.5 years, range 4-28 years) underwent surgical repair of VSD were recruited in the study. Thorough physical examination, blood biochemistry, chest X-ray and echocardiography was performed in all patients.

Echocardiographic studies

The left ventricular function was assessed by two-dimensional and Doppler echocardiography

(Acuson Sequoia 512, transducer frequency 2.5-3.5 MHz) by two experienced cardiologists. Standard 2-dimensional images were obtained in the parasternal long and short axes, and in the apical 4- and 2-chamber views (8-10). Pulsed-wave Doppler tracings of mitral valve inflow were recorded at the leaflet tips. Left ventricular volumes and Doppler tracings were analysed using a digital echocardiography workstation. The left ventricular ejection fraction, left ventricular end-diastolic and end-systolic volume, left ventricular and atrial diameter, right ventricular end-diastolic parameter and pulmonary arterial pressure were measured.

BNP measurements

BNP was measured from the pericardial fluid collected after general anesthesia and surgical opening of the pericardium. Venous blood was drawn after the induction of general anesthesia and plasma BNP was also measured. We have recently reported the methodologies of BNP measurements, using Triage® BNP Test kit (Biosite, San Diego CA) (8-10). The device was run daily to confirm laser stability, alignment, and calibration. The measurable range of the test is from 5 to 5000 pg/mL.

Statistical analysis

Data were expressed as means $\pm$ SD. Student t test was used to analyze the differences in clinical parameters between groups. The correlations between BNP and the left ventricular anatomy or function were assessed with Pearson analysis. $P<0.05$ was considered to be statistically significant.

Results

The clinical characteristics and the echocardiographic study results from the 18 patients were summarized in Table 1. Mild left ventricular dysfunction (New York Heart Association functional class II) was identified in two of the 18 patients. The left ventricular function and diameter was within the normal range in the other 16 patients.

The average plasma BNP and pericardial fluid BNP in the 18 patients were 20.8±6.1 pg/ml and 324.8±137.3 pg/ml, respectively (P=0.034). There was a good correlation between the pericardial fluid BNP and plasma BNP (r=0.85, P=0.0001).

The correlation between the pericardial fluid BNP or plasma BNP and age, heart rate, blood pressure and echocardiographic data were shown in Table 2. Pericardial fluid BNP levels were correlated well with left atrial diameter, left ventricular end-diastolic and end-systolic diameter, right ventricular end-diastolic diameter, left ventricular ejection fraction and mean pulmonary artery pressure ($p<0.05$). A good correlation was also found between plasma BNP and the above parameters except left ventricular end-systolic diameter (Table 2).

Discussion

Our study demonstrated that in patients with VSD but a relatively normal left ventricular function, the level of BNP in the pericardial fluid was higher than that in the plasma. Also, the pericardial fluid BNP levels correlated well with the plasma BNP. These results indicate that a high level of BNP is secreted into the pericardium in VSD patients without overt heart failure.

Ventricular secretion of BNP is largely stimulated by an increase in ventricular pressure or volume (1-3). The level of plasma BNP is associated with the severity of ventricular dysfunction, in particular the left ventricular ejection fraction (7-10). The present study in patients VSD but with relatively normal ventricular function has confirmed the previous findings that the level of both plasma and pericardial BNP is correlated well with the left atrial and ventricular diameter, left ventricular ejection fraction and mean pulmonary artery pressure.

The physiological or pathophysiological basis of higher BNP concentrations in the pericardial fluid is poorly understood. It has been proposed that BNP, which has a molecular weight of approximately 3,464, may be released directly from ventricular myocardium into the pericardial space in response to increased left ventricular overload (12). Because the volume of pericardial fluid is smaller than that of the plasma in the systemic circulation, a higher BNP concentration was found in the pericardial fluid. In addition, pericardial fluid BNP may have

a longer elimination half-life than that in the plasma, resulting accumulation and increased concentration in the pericardium (11, 12). Recent studies have shown that pericardium synthesis and releases endothelium-1 and prostaglandins (14). However, whether the pericardium directly secrets BNP is unclear.

In addition to endocrine actions, BNP appears to exhibit important autocrine and paracrine functions within the heart and coronary circulation. These include regulation of myocyte growth, inhibition of fibroblast proliferation and extracellular matrix deposition, a cytoprotective anti-ischemic (preconditioning-like) function, and influences on coronary endothelium and vascular smooth muscle proliferation and contractility (15, 16). Measurement of BNP levels in the pericardial fluid may facilitate the evaluation of the autocrine or paracine functions of BNP.

Release of BNP that occurs rapidly from ventricular myocardium during experimental or clinical ischemia also suggests that the natriuretic peptide receptor system may serve as an important autocrine or paracrine response to ischemia (17). A recent study has shown that patients with anterior myocardial infarction had elevated plasma and pericardial BNP, even when the left ventricular function was relatively normal (11). The plasma BNP levels were not increased in the patients with inferior or posterior myocardial infarction, but the pericardial fluid BNP concentrations in these patients were greater than in the patients with no history of myocardial infarction (11). The higher pericardial fluid BNP concentrations in post-infarction patients suggest that the BNP synthesis and release are augmented in the ventricular myocardium independent of the left ventricular ejection fraction (11).

The measurement and interpretation of plasma or pericardial fluid BNP in patients with VSD may have important clinical implications. Although left ventricular volume overload is expected in most patients with VSD, significant BNP elevation rarely occur before left ventricular dysfunction develops (18). In a recent study on 59 VSD patients, plasma BNP was found to be positively correlated with pulmonary to systemic flow ratio and mean pulmonary artery pressure (19). Plasma BNP of $\geq$ 20 pg/mL was able to identify children with a mean

pulmonary artery pressure of $\geq$ 20 mmHg, with a sensitivity and specificity of 82% and 89%, respectively (19). These results indicated that plasma BNP may reflect pressure and volume loads to the pulmonary arteries and the right ventricle, which may help to identify VSD children with pulmonary hypertension that needs early intervention.

Due to the small patient population in the present study, the value of plasma or pericardial fluid BNP in diagnosing pulmonary hypertension was not analyzed. However, a good correlation was found between plasma or pericardial fluid BNP and the mean pulmonary artery pressure. Further studies in a larger patient group are required to ascertain the diagnostic value of plasma BNP in pulmonary hypertension in these VSD patients.

In summary, our study has demonstrated that a higher level of BNP was present in the pericardial fluid in patients with uncorrected VSD. Similar to plasma BNP, pericardial BNP is closely related to the ventricular structure and function. Measurements of pericardial fluid BNP may facilitate the study of the autocrine or paracrine functions of BNP.

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Table 1. Patient's clinical and echocardiographic characteristics (n=18).

Items	Mean value (range)
Age (yrs)	12.4±1.5
Heart rate (beats/min)	82.8±2.7
Systolic BP (mmHg)	109.8±2.8
Diastolic BP (mmHg)	64.7±2.0
Left atrial diameter (mm)	28.1±1.3
Left ventricular end-diastolic diameter (mm)	38.9±1.0
Left ventricular end-systolic diameter (mm)	26.7±1.2
Right ventricular end-diastolic diameter (mm)	31.9±1.6
Left ventricular ejection fraction (%)	65.8±2.0
Mean pulmonary artery pressure (mmHg)	32.4±2.7

Table 2. Relationship between pericardial fluid or plasma BNP and patient's clinical or echocardiographic data (n=18)

	Plasma BNP		Pericardial BNP	
	Correlation coefficient	*P value*	Correlation coefficient	*P value*
Age (yrs)	-0.093	0.715	-0.042	0.869
Heart rate (beats/min)	0.391	0.109	0.455	0.058
Systolic BP (mmHg)	-0.121	0.633	-0.045	0.860
Diastolic BP (mmHg)	0.163	0.519	0.308	0.213
LA diameter (mm)	0.585	0.011	0.548	0.019
LV EDD (mm)	0.557	0.016	0.622	0.006
LV ESD (mm)	0.426	0.078	0.496	0.036
RV EDD (mm)	0.589	0.010	0.635	0.005
LV EF (%)	-0.686	0.002	-0.699	0.001
Mean PAP (mmHg)	0.707	0.001	0.750	0.0001

LA: left atrial; LV: left ventricular; EDD and ESD: end-diastolic and end-systolic diameter; EF: ejection fraction; RV: right ventricular; PAP: pulmonary artery pressure.