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Plasma level of big endothelin-1 predicts the prognosis in patients with hypertrophic cardiomyopathy☆

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ABSTRACT

Background: Cardiac remodeling is one of major pathological process in hypertrophic cardiomyopathy (HCM). Endothelin-1 has been linked to cardiac remodeling. Big endothelin-1 is the precursor of endothelin-1.
Methods: A total of 245 patients with HCM were enrolled from 1999 to 2011 and partitioned to low, middle and high level groups according to their plasma big endothelin-1 levels.
Results: At baseline, significant associations were found between high level of big endothelin-1 and left atrium size, heart function and atrial fibrillation. Big endothelin-1 was positively correlated with N-terminal B-type natriuretic peptide ($r = 0.291$, $p < 0.001$) and late gadolinium enhancement (LGE) on magnetic resonance imaging ($r = 0.222$, $p = 0.016$). During a follow-up of 3 (range, 2–5) years, big endothelin-1 level was positively associated with the risks of all-cause mortality, cardiovascular death and progression to NYHA class 3 or 4 ($p = 0.020$, 0.044 and 0.032, respectively). The rate of above events in the highest tertile were 18.1%, 15.7%, 24.2%, respectively. After adjusting for multiple factors related to survival and cardiac function, the significance remained in the association of big endothelin-1 with the risk of all-cause mortality (hazard ratio (HR) = 4.94, 95% confidence interval (CI) 1.07–22.88; $p = 0.041$) and progression to NYHA class 3 or 4 (HR = 4.10, 95%CI 1.32–12.75, $p = 0.015$).
Conclusion: Our study showed that high level of plasma big endothelin-1 predicted prognosis for patients with HCM and it can be added to the marker panel in stratifying HCM patients for giving treatment priority to those at high risk.
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1. Introduction

Hypertrophic cardiomyopathy (HCM) is one of the most common inherited cardiac diseases with a prevalence of approximately 0.2% in USA [1] as well as in China [2]. The majority HCM are caused by mutations in 11 sarcomere genes [3–5]. The disease affects all age groups with a common feature of marked clinical and genetic heterogeneities [3] ranging from an asymptomatic longevity to a malignant prognosis such as sudden cardiac death (SCD), progressive heart failure or stroke (atrial fibrillation-related thromboembolism).

Identification of patients with HCM at high risk of malignant prognosis has a great clinical impact on preventing premature death as well as the disease progression. The major risk factors for HCM-related SCD have generally been recognized as the family history of SCD, unexplained syncope, non-sustained ventricular tachycardia on ambulatory monitoring, severe cardiac hypertrophy (left ventricular wall thickness ≥30 mm); and abnormal blood pressure response to exercise [6,7]. Two additional risk modifiers are the significant left ventricular outflow tract obstruction and late gadolinium enhancement (LGE) on cardiac MRI scanning. At the same time, some of the factors above could also be considered as predictors for heart failure. And there are some other risk factor of progression to heart failure in other cardiac disease, such as aging,

☆ These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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atrial fibrillation, and some biomarkers, including ET-1, may be associated with the prognosis of HCM patients should also be considered and need to be proved [8,9].

The pathology of HCM is not only confined to disease-causing mutations in genes encoding sarcomeric proteins, resulting in general myocyte hypertrophy and regions of myocyte disarray but also involves connective tissue elements leading to different types of cardiac fibrosis. Cardiac fibrosis is a substrate for heart failure and ventricular arrhythmia-induced SCD. Compared with structurally normal hearts, the collagen network has been shown morphologically abnormal and increased in size in the cardiac tissue in HCM patients. An increase in myocardial fibrosis has been identified in endomyocardial biopsy tissue from the right ventricle and the increased fibrosis is associated with a worse prognosis [10]. In the heart of HCM patients, intercellular junctions responsible for electromechanical coupling are dispersed over the surface of the myocytes instead of being confined to intercalated discs in regions with myocyte disarray [11]. Increased cardiac fibrosis has also been linked to cardiac conduction block and reentry in either isolated-perfused animal or diseased human cardiac tissues and promotes arrhythmias [12–16].

HCM remodeling, just like cardiac aging, is characterized with left ventricular hypertrophy (LVH) and fibrosis, leading to diastolic dysfunction and heart failure with preserved systolic function [17,18]. Endothelin-1 and angiotensin II signaling mediate interstitial and perivascular fibrosis in aging heart as well as in overloading-induced heart remodeling, perhaps in genetic mutation-induced cardiac remodeling as well. Endothelin-1 is a peptide with 21 amino acids and one of the most potent vasoconstrictors [19]. Endothelin-1 exerts also direct actions on the heart, such as chronotropic and inotropic effects, decrease of cardiac output, stimulation of myocardial hypertrophy and collagen synthesis in cardiac fibroblasts [20]. Big endothelin-1 is the precursor of endothelin-1 with 39 amino acids but has no biological function. Both big endothelin-1 and endothelin-1 have been known as strong independent predictors of survival in patients with heart failure [21]. Therefore, these markers allow easily identifying a population with high risk mortality eligible for more aggressive therapies.

In HCM patients, endothelin-1 levels have been reported to be significantly increased by more than two-fold compared with controls [22,23]. Endothelin-1 mRNA synthesis in the heart is also upregulated in hypertrophied hearts induced by pressure overload [24,25].

The precise mechanisms of endothelial dysfunction in HCM are unknown, whether the increase of endothelin is the cause of the hypertrophy or it contributes to the pathophysiology of HCM. However, there is a report that endothelin A receptor blockade can cause LVH induced by pressure overloading in vivo, suggesting a role of endothelin-1 in the development of cardiac hypertrophy [24].

We hypothesized that endothelin induces remodeling and fibrosis of the heart which play an important role in the progression of HCM. Plasma big endothelin-1 could serve as biomarkers of cardiac hypertrophy, cardiac fibrosis and remodeling, and provide valuable information for the risk stratification of patients with HCM. The objectives of the study were to compare the plasma levels of big endothelin-1, variables used for evaluation of the severity and HCM outcomes in a prospective study.

2. Methods

2.1. Study population

Three hundred and twelve unrelated consecutive patients with HCM were recruited at Fuwai Hospital, Chinese Academy of Medical Sciences, between January 1999 and March 2011. The HCM was ascertained on echochardiographic demonstration of LVH (maximum thickness of the left ventricular wall ≥15 mm, or ≥13 mm with a family history of HCM) in the absence of any other cardiac or systemic disease capable of producing the magnitude of hypertrophy evident, such as uncontrolled hypertension (home blood pressure monitoring ≥140/90 mm Hg), cardiac valve disease, congenital heart disease and amyloidosis.[6] Sixty-seven patients with coronary heart disease were excluded after coronary angiography or coronary computed tomography imaging. Finally, 245 patients were included and followed up for 3 years (range, 2–5).

The study approved by the Ethics Committees of Fuwai Hospital, Chinese Academy of Medical Sciences. Informed consent was obtained from all patients in accordance with the principle of the Declaration of Helsinki.

2.2. Clinical evaluation

The following clinical variables were recorded: medical history, symptoms, and alcohol intake, and smoking habit, current medications for coronary heart disease, hyperlipidemia, and diabetes. All patients underwent a complete cardiac evaluation, including physical examination, 12-lead electrocardiogram, M-mode, 2-dimensional and Doppler echocardiogram. Cardiac MRI (including LGE) was performed in 118 patients. Maximum left ventricular wall thickness was defined as the greatest thickness in any single segment on echocardiogram. Left ventricular mass index (LVMI) was calculated by the formula: LVMI (g/m^2) = $\{0.8 \times 10.4 \times [(\text{IVST (cm)} + \text{PWT (cm)} + \text{LVEDD (cm)})^3 - \text{LVEDD}^3\ \text{(cm)}] + 0.6\}$ / $[0.0061 \times \text{height (cm)} + 0.0128 \times \text{weight (kg)} - 0.1529]$. IVST indicates interventricular septum thickness; PWT, post wall thickness; LVEDD, left ventricular end-diastolic dimension.

2.3. Determination of big endothelin-1

Blood was drawn from the antecubital vein for determination of big endothelin-1 as well as N-terminal pro-brain natriuretic peptide (NT-pro-BNP, in 241 patients), and high-sensitivity C-reactive protein (hs-CRP, in 232 patients). The big endothelin-1 concentrations were determined following the instruction of Big Endothelin-1 ELISA Kit (CAT. NO. BI-20082H, 12 × 8 TESTS) supplied by Biomedica Medizinprodukte GmbH & Co KG, Austria.

2.4. Outcomes

At the entry and during follow up, the primary events were all-cause mortality, including cardiovascular death (SCD, heart failure-related death and fatal stroke) and non-cardiovascular deaths. SCD was defined as sudden and unexpected death within 1 h from the onset of symptoms in patients previously experiencing a relatively stable or uneventful clinical course. The secondary outcomes included progression to chronic heart failure (New York Heart Association, NYHA class 3 or 4), ventricular tachycardia and/or fibrillation (VT/VF), implanted cardioverter defibrillator (ICD) discharge, non-fatal stroke, atrial fibrillation (AF), transient heart failure, implantation of ICD or pacemaker and septal reduction therapy (including myoectomy and alcohol ablation). Chronic heart failure was diagnosed according to typical clinical manifestation and signs of shortness of breath at rest or during exertion, and/or fatigue; signs of fluid retention such as ankle swelling [26]. The follow-up ended in the October of 2012.

2.5. Statistical analysis

In our study, the median of concentration of Big ET-1 was 0.65 pmol/l (inter quartile range 0.51–0.88 pmol/l; mean ± SD 0.87 ± 0.69 pmol/l), and the grouping was according to the level of big endothelin-1 divided the cohort into tertiles: tertile 1, low level (<0.55 pmol/l); tertile 2, middle level (≤0.55 pmol/l, but <0.78 pmol/l); tertile 3, high level (≥0.78 pmol/l).

Normally distributed data were expressed as mean ± standard deviation and skewed distributed data, as median (25th–75th percentile), and were tested by using the unpaired Student *t*-test and non-parametric test, respectively. The chi-square test was utilized to compare non-continuous variables, which were expressed as a proportion. The Pearson and Spearman correlations were used to determine the association between biomarkers and clinical risk factors. Survival curves were constructed according to the Kaplan-Meier method, and comparisons were performed using the log-rank test. Both univariable and multivariable Cox proportional hazard regression models were used to calculate hazard ratio (HR) and 95% confidence interval (CI). The factors should be adjusted were selected from age, symptoms of syncope (without any invasive treatment, including implantation of ICD, pacemaker and septal reduction therapy), family history of SCD, maximum left ventricular wall thickness >30 mm, AF, left ventricular outflow tract obstruction (without septal reduction therapy) and NYHA functional class 3 or 4 at enrolment [5,27]. Multivariate regression model was used for adjusting confound factors, into which each variable with a *p*-value ≤0.05 based on univariate analysis was entered. A *p*-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS software, version 13.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Baseline characteristics

The baseline characteristics of the patients with HCM were stratified by using big endothelin-1 levels and presented in Table 1. High big endothelin-1 level was significantly associated with an increase in left atrial size ($P < 0.001$), NT-pro BNP level ($P < 0.001$), the prevalence of NYHF class 3 or 4 ($P < 0.005$) as well as atrial fibrillation ($P < 0.003$). The correlation coefficient between big endothelin-1 and the variables was as follows: NT-pro-BNP ($r = 0.291$, $p < 0.001$), left atrium diameter ($r = 0.235$, $p < 0.001$) and LGE on MRI ($r = 0.222$, $p = 0.016$).

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