Associations Between Multiple Circulating Biomarkers and the Presence of Atrial Fibrillation in Hypertrophic Cardiomyopathy with or Without Left Ventricular Outflow Tract Obstruction

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Summary

Atrial fibrillation (AF) is the most common arrhythmia in patients with hypertrophic cardiomyopathy (HCM). Data regarding the correlations of biomarkers and AF in HCM patients are rather limited. We sought to explore the associations between the presence of AF and circulating biomarkers reflecting cardiovascular function (N-terminal pro-brain natriuretic peptide, NT-pro BNP), endothelial function (big endothelin-1, big ET-1), inflammation (high-sensitivity C-reactive protein), and myocardial damage (cardiac troponin I, cTnI) in HCM patients with and without left ventricular outflow tract obstruction (LVOTO).

In all, 375 consecutive HCM in-hospital patients were divided into an AF group (n = 90) and a sinus rhythm (SR) group (n = 285) according to their medical history and electrocardiogram results.

In comparison with the SR group, peripheral concentrations of big ET-1, NT-pro BNP, and cTnI were significantly higher in patients with AF. Only the biomarker of big ET-1, together with palpitation and left atrial diameter (LAD), was independently associated with AF in HCM patients. Ln big ET-1 was positively related to Ln NT-pro BNP, LAD, and heart rate, but negatively related to left ventricular ejection fraction. Combined measurements of big ET-1 ≥ 0.285 pmol/L and LAD ≥ 44.5 mm indicated good predictive values in the presence of AF, with a specificity of 94% and a sensitivity of 85% in HCM patients.

Big ET-1 has been identified as an independent determinant of AF, regardless of LVOTO, and is significantly related to parameters representing cardiac function and remodeling in HCM. Big ET-1 might be a valuable index to evaluate the clinical status of AF in HCM patients.

Key words: Big endothelin-1, Cardiac remodeling

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disease, mainly caused by mutations in genes coding for cardiac sarcomeres.1,2 Atrial fibrillation (AF), as a common arrhythmia of HCM, harbors an estimated prevalence and annual incidence of 22.45% and 3.08%, respectively.3 Predisposing factors of AF in HCM mainly consist of elevated left atrial pressure and size, resulting from left ventricular (LV) myocardial hypertrophy, LV diastolic dysfunction, LV outflow tract obstruction (LVOTO), and mitral regurgitation (MR). AF affects quality of life and portends adverse prognosis in HCM patients.4,5 Previous studies have indicated that age and left atrial enlargement are predictors most closely associated with AF in HCM. Other reported risk factors include LVOTO, late gadolinium enhancement (LGE) on cardiovascular magnetic resonance (CMR), prolonged P-wave duration, ST-T changes on baseline electrocardiography (ECG), paroxysmal supraventricular tachycardia, premature ventricular contractions, abnormal coronary flow reserve, insulin resistance, obstructive sleep apnea, and exercise intolerance.3,6 However, data regarding the correlations of circulating biomarkers and AF are comparatively limited in HCM patients.

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between high levels of big endothelin-1 (big ET-1) and left atrium size, heart function, and AF. Cardiac biomarkers of big ET-1, NT-pro BNP, cTnI, and hs-CRP were found to be correlated with LV hypertrophy, left atrial diameter (LAD), and the presence of AF. However, most of these studies were of small scale and did not categorize HCM subjects according to LVOTO for data analysis. Therefore, we sought to systematically explore the associations of AF and circulating biomarkers representing cardiovascular function (NT-pro BNP), endothelial function (big ET-1), inflammation (hs-CRP), and myocardial damage (cardiac troponin I, cTnI) in HCM patients with and without LVOTO.

Methods

Study population: Patients who were admitted for HCM at Fuwai Hospital (Beijing, China) from January 2014 to December 2016 were retrospectively recruited in this study. All subjects received blood tests on the circulating biomarkers of big ET-1, NT-pro BNP, cTnI, and hs-CRP on admission. They also underwent comprehensive cardiac evaluation, including 12-lead ECG, 24-hour ambulatory ECG, echocardiography, and CMR. Detailed medical histories were obtained by reviewing de-identified medical records. All patients met the diagnostic criteria of HCM, which was based on the detection of a maximum LV wall thickness ≥15 mm in adults (or 13-14 mm with a definite family history of HCM) by echocardiography or CMR, in the absence of other accountable cardiac or systemic diseases. LVOTO was defined as an instantaneous peak Doppler LVOT gradient (LVOTG) ≥30 mmHg at rest or during physiological provocation. AF was defined according to the international consensus on AF definition. The diagnosis of AF was based on a previously reported medical history or according to the AF documentation in 12-lead ECGs or 24-hour ambulatory ECGs on admission. Patients who had myocardial infarction, valvular heart disease, congenital heart disease, pulmonary heart disease, renal dysfunction, connective tissue disease, neoplasm, or infection, or with a history of alcohol septal ablation, septal myectomy, coronary revascularization, or permanent mechanical device implantation were excluded from the study. Finally, 375 HCM patients were enrolled in the current study. Our study was compliant with the Declaration of Helsinki and was approved by the Ethics Committee at Fuwai Hospital.

Laboratory examination: Venous blood samples were collected in the morning on admission for measurement of the following biomarkers under resting conditions. Plasma big ET-1 was measured using a commercial enzyme immunoassay (BI-20082H big endothelin-1, Biomedica, Wien, Austria) with a detection limit of 0.02 pmol/L. Plasma NT-pro BNP was measured using an electrochemiluminescent immunoassay (Elecsys pro-BNP II assay, Roche Diagnostics GmbH, Mannheim, Germany) with a detection limit of 0.6 pmol/L. Serum cTnI was measured using an immunochemiluminometric assay (Access AcctnI, Beckman Coulter, CA, USA) with a detection limit of 0.01 ng/mL. Serum hs-CRP was measured using a particle-enhanced immunoturbidimetric assay (Ultrason sensitive CRP kit, Orion Diagnostica, Espoo, Finland) with a detection limit of 0.25 mg/L.

Cardiac evaluation: Examinations of echocardiography were performed using a Philips iE33 Color Doppler Ultrasound System (Philips Healthcare, Andover, MA). The parasternal acoustic window was used to record two-dimensional and M-mode images of LA, LV, and wall thickness. The LV ejection fraction (LVEF) was calculated using the modified Simpson’s rule method. The severity of MR was assessed by color Doppler flow imaging semiquantitatively. The LVOTG was measured in all patients with LVOTO using continuous-wave Doppler echocardiography. CMR studies were performed using a 1.5-T scanner (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany). Cine images consisting of LV two-chamber and four-chamber long-axis view, LVOT view, and LV short-axis view were acquired through true fast imaging with a steady-state precession sequence. Images of LGE were obtained 10–15 minutes after a bolus injection of 0.2 mmol/kg gadolinium-diethylene triamine pentaacetic acid (Gd-DTPA, Magnevist, Schering AG, Berlin, Germany).

Statistical analysis: Continuous variables, expressed as mean ± standard deviation or median (25th-75th percentile), were compared using the unpaired Student’s t-test or the nonparametric test. The chi-square test or Fisher’s exact test was utilized to compare categorical variables, which were expressed as a proportion. The correlation between 2 continuous variables was determined using Pearson’s correlation test. Because the levels of big ET-1, NT-pro BNP, cTnI, and hs-CRP followed lognormal distribution, they were converted into natural logarithmic transformations for t-tests, correlation tests, and regression analyses. Univariate and multivariate binary logistic regression analyses were performed to identify independent indexes associated with AF in HCM patients. The stepwise forward selection algorithm was performed with criteria of P < 0.05 for inclusion in and P > 0.05 for exclusion from the multivariate logistic regression model. Variables included in the multivariate model were age, gender, history of palpitation or syncope, body mass index, heart rate (HR), New York Heart Association functional class III or IV, Ln big ET-1, Ln NT-pro BNP, Ln cTnI, Ln hs-CRP, LAD, LV end-diastolic diameter (LVEDD), thickness of the interventricular septum (IVS), LVEF, moderate to severe MR, LV diastolic dysfunction, LVOTO, peak LVOTG flow velocity, peak LVOTG, and LGE. Adjusted odds ratios and 95% confidence intervals (CIs) were calculated. The area under the curve (AUC) and optimal cutoff values of big ET-1 and LAD in predicting AF were identified using receiver-operating characteristic (ROC) curve analysis. The sensitivity, specificity, and positive and negative predictive values were calculated for selected big ET-1 and LAD cutoff points. The statistical package SPSS 21.0 (SPSS Inc., Chicago, IL) was used for all statistical analyses. A two-tailed P-value of < 0.05 was considered to be statistically significant.
Clinical characteristics: The demographics, clinical features, pharmacologic therapy, and biomarkers of HCM patients with or without AF are summarized in Table I. Our study consisted of 375 HCM patients, with a mean age of 54.0 ± 10.0 years (range: 23-77 years) and 58.9% males. Of these, 245 patients (65.3%) manifested with hypertrophic obstructive cardiomyopathy (HOCM) and the remaining 130 (34.7%) with nonobstructive HCM. Ninety patients (24.0%) diagnosed with AF were classified into the AF group, and the other 285 patients (76.0%) with sinus rhythm (SR) were categorized as the SR group. Comparisons between the AF and SR groups in HCM patients (Table II).

Correlations between circulating big ET-1 and other clinical variables: Correlations between plasma big ET-1 and other clinical variables were examined using linear correlation analyses (Table IV, Figure 1), in which parameters with a P-value < 0.05 were included in the multivariate linear regression model. The results demonstrated that Ln big ET-1 was positively related to Ln NT-pro BNP in both HOCM and nonobstructive HCM patients (Table III), whereas NT-pro BNP, cTnI, and hs-CRP were not.

ROC curve analysis: ROC curve analysis was performed to evaluate the predictive efficiency of big ET-1 and/or compared with their counterparts in the SR group (Table II). Cardiac evaluation indicated that patients with AF, especially in the HOCM cohort, possessed relatively increased LVEDD, lower LVEF, thicker IVS, and a higher proportion of LGE, but without statistical significance (Table II). Univariate and multivariate logistic regression analyses to identify independent determinants of AF in HCM patients: Multivariate analyses indicated that only the biomarker of big ET-1, together with palpitation and LAD, was an independent determinant of AF in both HOCM and nonobstructive HCM patients (Table III), whereas NT-pro BNP, cTnI, and hs-CRP were not.

Table I. Demographics, Clinical Features, Pharmacologic Therapy, and Biomarkers of HCM Patients with or without AF

|                      | All patients (n = 375) | AF group (n = 90) | SR group (n = 285) | P-value |
|----------------------|-----------------------|------------------|-------------------|--------|
| Male, n (%)          | 221 (58.9%)           | 53 (58.9%)       | 168 (58.9%)       | 0.992  |
| Age (years)          | 54.0 ± 10.0           | 55.8 ± 10.5      | 53.4 ± 9.8        | 0.052  |
| Dyspnea, n (%)       | 267 (71.2%)           | 63 (70%)         | 204 (71.6%)       | 0.773  |
| Chest pain, n (%)    | 292 (77.9%)           | 69 (76.7%)       | 223 (78.2%)       | 0.753  |
| Palpitation, n (%)   | 152 (40.5%)           | 66 (73.3%)       | 86 (30.2%)        | <0.001*|
| Syncope, n (%)       | 61 (16.3%)            | 15 (16.7%)       | 46 (16.1%)        | 0.906  |
| Current smokers, n (%) | 158 (42.1%)         | 34 (37.8%)       | 124 (43.5%)       | 0.337  |
| Alcohol drinking, n (%) | 96 (25.6%)           | 22 (24.4%)       | 74 (26%)          | 0.773  |
| FH of sudden death, n (%) | 13 (3.5%)            | 1 (1.1%)         | 12 (4.2%)         | 0.284  |
| FH of HCM, n (%)     | 35 (9.3%)             | 13 (14.4%)       | 22 (7.7%)         | 0.056  |
| Hypertension, n (%)  | 177 (47.2%)           | 41 (45.6%)       | 136 (47.7%)       | 0.720  |
| Diabetes mellitus, n (%) | 45 (12%)             | 9 (10%)          | 36 (12.6%)        | 0.503  |
| AF, n (%)            | 90 (24%)              | 90 (100%)        | 0                 |        |

Correlations between circulating big ET-1 and other clinical variables: Correlations between plasma big ET-1 and other clinical variables were examined using linear correlation analyses (Table IV, Figure 1), in which parameters with a P-value < 0.05 were included in the multivariate linear regression model. The results demonstrated that Ln big ET-1 was positively related to Ln NT-pro BNP in both HOCM and nonobstructive HCM patients (Table III), whereas NT-pro BNP, cTnI, and hs-CRP were not.

ROC curve analysis: ROC curve analysis was performed to evaluate the predictive efficiency of big ET-1 and/or compared with their counterparts in the SR group (Table II). Cardiac evaluation indicated that patients with AF, especially in the HOCM cohort, possessed relatively increased LVEDD, lower LVEF, thicker IVS, and a higher proportion of LGE, but without statistical significance (Table II). Univariate and multivariate logistic regression analyses to identify independent determinants of AF in HCM patients: Multivariate analyses indicated that only the biomarker of big ET-1, together with palpitation and LAD, was an independent determinant of AF in both HOCM and nonobstructive HCM patients (Table III), whereas NT-pro BNP, cTnI, and hs-CRP were not.

Correlations between circulating big ET-1 and other clinical variables: Correlations between plasma big ET-1 and other clinical variables were examined using linear correlation analyses (Table IV, Figure 1), in which parameters with a P-value < 0.05 were included in the multivariate linear regression model. The results demonstrated that Ln big ET-1 was positively related to Ln NT-pro BNP, LAD, and HR but negatively related to LVEF in patients with HCM (Table IV).
LAD as determinants of AF (Figure 2). The optimal cutoff value of big ET-1 was 0.285 pmol/L, with a sensitivity of 56% and a specificity of 75%. The optimal cutoff value of LAD was 44.5 mm, with a sensitivity of 66% and a specificity of 74%. Combining the 2 variables, the comprehensive efficiency of predicting concomitant AF in HCM patients was enhanced, with an AUC of 0.742 (95% CI: 0.681-0.803; P < 0.001; Figure 2). Compared with big ET-1 or LAD alone, the combination of big ET-1 ≥ 0.285 pmol/L and LAD ≥ 44.5 mm yielded a high specificity of 94% in predicting the presence of AF, whereas the association of either big ET-1 ≥ 0.285 pmol/L or LAD ≥ 44.5 mm generated a high sensitivity of 85% (Table V).

### Discussion

We have systematically investigated the associations between the presence of AF and multiple circulating biomarkers in HCM patients with or without LVOTO. The major findings were as follows: (1) Peripheral concentrations of big ET-1, NT-pro BNP, and cTnI were significantly elevated in HCM patients with AF. (2) Only plasma big ET-1 was independently associated with AF regardless of LVOTO, whereas NT-pro BNP, cTnI, and hs-CRP were not. (3) Big ET-1 was positively correlated with NT-pro BNP, LAD, and HR, but negatively correlated with LVEF in HCM patients. (4) Combined measurements of big ET-1 ≥ 0.285 pmol/L and LAD ≥ 44.5 mm indicated good predictive values in the presence of AF, with a specificity of 94% and a sensitivity of 85% in HCM patients.

ET-1, a 21-amino acid endothelium-derived vasoconstrictor peptide, is a well-established biomarker of endothelial damage. Increasing evidence has suggested that ET-1 was associated with the initiation and continuous presence of AF. The biological effects of ET-1 include activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS), modulation of neurohumoral factors, augmentation of myocardial
big ET-1 is a 38-amino acid precursor of ET-1, with a much longer half-life and slower tissue clearance. Moreover, ET-1 was reported to inhibit the L-type calcium current and muscarinic potassium current, causing hyperpolarization of the membrane and shortening of the action potential duration in mammalian atrial myocytes. Animal experiments also indicated that ET-1 was proarrhythmic and could induce arrhythmogenic Ca^{2+} signaling in atrial myocytes. All these facts demonstrated that ET-1 participated in the structural and electrical remodeling of myocardium and facilitated the occurrence of AF.

Big ET-1 is a 38-amino acid precursor of ET-1, with a much longer half-life and slower tissue clearance. Therefore, it is deemed to be a good indicator of the ET-1 system. The valsartan heart failure trial indicated that AF was independently associated with higher concentrations of big ET-1 in patients with symptomatic heart failure. Plasma big ET-1 levels have been identified to be increased in lone AF patients. Big ET-1 could predict AF recurrence after AF ablation. Higher big ET-1 levels were correlated with the elevated prevalence of AF in an HCM cohort. In our study, peripheral concentrations of big ET-1, NT-pro BNP, and cTnI were all increased in HCM patients with AF. However, multivariate analyses demonstrated that only big ET-1 was found to be independently associated with the presence of AF regardless of LVOTO, indicating a stronger correlation between big ET-1 and AF in HCM patients.

### Table III. Univariate and Multivariate Logistic Regression Analyses to Identify Independent Determinants of AF in Patients with HCM

|                      | All patients | HOCM | Nonobstructive HCM |
|----------------------|--------------|------|--------------------|
|                      | OR | 95% CI | P  | OR | 95% CI | P  | OR | 95% CI | P  |
| Univariate binary logistic regression analysis |   |      |    |   |      |    |   |      |    |
| n                    | 375 | 245  | 130 |
| Age                  | 1.029 | 0.996-1.064 | 0.086 | 1.057 | 1.005-1.112 | 0.032* | 1.011 | 0.954-1.072 | 0.715 |
| Male                 | 2.112 | 1.042-4.283 | 0.038* | 2.285 | 0.833-6.263 | 0.108 | 1.806 | 0.484-6.733 | 0.379 |
| Palpitation          | 9.103 | 4.641-17.856 | <0.001* | 9.302 | 3.647-23.726 | <0.001* | 21.472 | 5.437-84.796 | <0.001* |
| Syncope              | 1.046 | 0.456-2.402 | 0.916 | 0.916 | 0.339-2.476 | 0.863 | 5.485 | 0.753-39.936 | 0.093 |
| BMI                  | 1.010 | 0.913-1.118 | 0.842 | 0.960 | 0.835-1.104 | 0.571 | 1.160 | 0.959-1.404 | 0.126 |
| HR                   | 0.975 | 0.947-1.005 | 0.100 | 0.997 | 0.956-1.040 | 0.881 | 0.925 | 0.857-0.977 | 0.006* |
| NYHA III or IV       | 0.821 | 0.361-1.849 | 0.634 | 0.942 | 0.353-2.514 | 0.906 | 0.453 | 0.050-4.092 | 0.481 |
| Ln big ET-1          | 2.782 | 1.521-5.087 | 0.001* | 2.744 | 1.225-6.148 | 0.014* | 2.157 | 0.588-7.909 | 0.246 |
| Ln NT-pro BNP        | 1.275 | 0.885-1.837 | 0.192 | 1.373 | 0.801-2.354 | 0.248 | 1.529 | 0.781-2.996 | 0.215 |
| Ln cTnI              | 1.095 | 0.864-1.388 | 0.452 | 1.067 | 0.772-1.474 | 0.694 | 1.196 | 0.755-1.894 | 0.445 |
| Ln hs-CRP            | 0.969 | 0.789-1.191 | 0.766 | 0.832 | 0.639-1.085 | 0.175 | 1.111 | 0.711-1.734 | 0.644 |
| LAD                  | 1.095 | 1.045-1.148 | <0.001* | 1.082 | 1.014-1.155 | 0.018* | 1.132 | 1.029-1.245 | 0.011* |
| LVEDD                | 0.995 | 0.934-1.060 | 0.883 | 1.079 | 0.976-1.194 | 0.139 | 0.882 | 0.790-0.986 | 0.027* |
| IVS                  | 0.996 | 0.920-1.080 | 0.931 | 1.059 | 0.931-1.204 | 0.382 | 0.837 | 0.705-0.992 | 0.040* |
| LVEF                 | 0.984 | 0.952-1.016 | 0.323 | 0.985 | 0.932-1.041 | 0.597 | 0.978 | 0.926-1.032 | 0.420 |
| Moderate to severe MB| 0.939 | 0.435-2.028 | 0.873 | 1.217 | 0.470-3.153 | 0.685 | 8.306 | 0.507-136.150 | 0.138 |
| LV diastolic dysfunction | 0.790 | 0.396-1.578 | 0.505 | 0.690 | 0.262-1.820 | 0.453 | 1.920 | 0.546-6.748 | 0.309 |
| LVOTO                | 0.444 | 0.175-1.120 | 0.088 | - | - | - | - | - | - |
| Peak LVOT flow velocity | - | - | - | 1.103 | 0.065-18.707 | 0.946 | - | - | - |
| Peak LVOTG           | - | - | - | 0.975 | 0.898-1.059 | 0.553 | - | - | - |
| LGE ( + )            | 1.316 | 0.485-3.572 | 0.590 | 1.295 | 0.360-4.658 | 0.692 | 1.368 | 0.186-10.060 | 0.759 |

|                      | 375 | 245  | 130 |
| Multivariate binary logistic regression analysis |   |      |    |   |      |    |   |      |    |
| n                    | 375 | 245  | 130 |
| Palpitation          | 8.197 | 4.409-15.238 | <0.001* | 6.281 | 2.884-13.679 | <0.001* | 11.943 | 4.192-34.031 | <0.001* |
| Ln big ET-1          | 3.224 | 1.884-5.520 | <0.001* | 2.553 | 1.390-4.689 | 0.003* | 3.217 | 1.193-8.675 | 0.021* |
| LAD                  | 1.089 | 1.048-1.131 | <0.001* | 1.109 | 1.051-1.170 | <0.001* | 1.113 | 1.043-1.188 | 0.001* |

HCM indicates hypertrophic cardiomyopathy; HOCM, hypertrophic obstructive cardiomyopathy; AF, atrial fibrillation; SR, sinus rhythm; BMI, body mass index; HR, heart rate; NYHA, New York Heart Association; big ET-1, big endothelin-1; NT-pro BNP, N-terminal pro-brain natriuretic peptide; cTnI, cardiac troponin I; hs-CRP, high-sensitivity C-reactive protein; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; IVS, interventricular septum; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; LVOTO, left ventricular outflow tract obstruction; LVOTG, left ventricular outflow tract gradient; LGE ( + ), late gadolinium enhancement positive; OR, odds ratio; and CI, confidence interval. *P < 0.05.
dial inotropic and chronotropic effects on the heart and reduce cardiac output.\(^3\) Our findings that big ET-1 was negatively associated with LVEF might further support these phenomena. In our study, big ET-1 was significantly related to several parameters representing cardiac function and structure, suggesting its underlying associations with cardiac remodeling in HCM.

ET-1 levels have been reported to be elevated by more than twofold in HCM patients compared with controls.\(^2\)\(^3\)\(^4\)\(^5\) However, whether the increased level of ET-1 was the cause of HCM, or vice versa, still remained uncertain. Some studies have shown that ET-1 could induce hypertrophy in cultured heart muscle cells.\(^6\) ET-1 mRNA synthesis in the heart was upregulated in hypertrophic hearts caused by pressure overload.\(^7\)\(^8\) ET-1 could induce pathological phenotypes such as cardiomyocyte hypertrophy and intracellular myofibrillar disarray in HCM.\(^9\) Big ET-1 levels were positively associated with cardiac fibrosis in CMR.\(^10\) All these findings seemed to suggest that ET-1 participated in the hypertrophy, remodeling, and fibrosis of hearts and played a role in the progression of HCM. On the contrary, it has been reported that the secretion of ET-1 is promoted by stretching, pressure overload, and increased wall shear stress.\(^11\)\(^12\) The preexisting structural remodeling of heart in HCM might lead correspondingly to the enhanced secretion of ET-1, resulting in the further aggravation of cardiac remodeling and the development of AF. It has been reported that a number of anatomical features such as systolic anterior motion of the mitral valve leaflets, septal hypertrophy, narrowing of the LVOT, and abnormalities of the mitral apparatus were predisposing factors of the LVOTO in HCM.\(^13\) In our study, we found that patients with LVOTO manifested severer cardiac remodeling (more dilated LA, thicker IVS, higher proportions of moderate to severe MR, and LV diastolic dysfunction). Accordingly, the concentrations of big ET-1 in these HOCM patients were higher. Considering all these data, we hypothesized that the elevated plasma ET-1 levels might participate in the cardiac remodeling process and were associated with the occurrence of AF in HCM patients.

AF can be detrimental, even lethal, to HCM patients. Although ECG is the golden standard for the diagnosis of AF, the ambulatory ECG monitoring on Chinese patients is not currently sufficient to allow widespread use in HCM patients for AF detection. Therefore, exploring potential predictive factors of AF for early diagnosis is of great clinical significance. Our study indicated that big ET-1 was independently associated with the presence of AF in both HOCM and nonobstructive HCM patients. Because the measurement of plasma big ET-1 is relatively easy and noninvasive, it has the potential to be used clinically as part of a routine assessment for HCM patients, together with LAD, providing a more integrated picture for clinicians to evaluate the status of AF.

**Study limitations:** Firstly, this was a single-center, cross-sectional study. Although our results suggested an independent association between big ET-1 and AF in HCM patients, the retrospective nature of this study limited our ability to determine a causal relationship. Secondly, despite previous medical records and the documentation of AF on 12-lead ECGs or ambulatory ECG monitoring, the

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**Table IV. Correlations Between Ln Big ET-1 and Other Clinical Variables**

| Linear correlation                        | r      | P-value | β regression coefficients | P-value |
|-------------------------------------------|--------|---------|---------------------------|---------|
| Age (years)                               | 0.110  | 0.033*  |                           |         |
| BMI (kg/m²)                               | 0.003  | 0.949   |                           |         |
| SBP (mmHg)                                | 0.015  | 0.766   |                           |         |
| DBP (mmHg)                                | −0.013 | 0.801   |                           |         |
| HR (beats/minute)                         | 0.133  | 0.010*  |                           |         |
| Ln NT-pro BNP (pmol/L)                    | 0.377  | < 0.001*|                           |         |
| Ln cTnI (ng/mL)                           | 0.216  | < 0.001*|                           |         |
| Ln hs-CRP (mg/L)                          | 0.144  | 0.005*  |                           |         |
| LAD (mm)                                  | 0.338  | < 0.001*|                           |         |
| LVEDD (mm)                                | 0.047  | 0.365   |                           |         |
| IVS (mm)                                  | 0.010  | 0.842   |                           |         |
| LVEF (%)                                  | −0.124 | 0.017*  |                           |         |
| CO (L/minute)                             | −0.042 | 0.418   |                           |         |
| LVEDV (mL)                                | 0.048  | 0.350   |                           |         |

**Multiple linear regression analysis**

|                                | r       | P-value | β regression coefficients | P-value |
|--------------------------------|---------|---------|---------------------------|---------|
| Ln NT-pro BNP (pmol/L)         | 0.282   | < 0.001*|                           |         |
| LAD (mm)                      | 0.243   | < 0.001*|                           |         |
| HR (beats/minute)             | 0.130   | 0.005*  |                           |         |
| LVEF (%)                      | −0.098  | 0.034*  |                           |         |

Big ET-1 indicates big endothelin-1; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; NT-pro BNP, N-terminal pro-brain natriuretic peptide; cTnI, cardiac troponin I; hs-CRP, high-sensitivity C-reactive protein; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; IVS, interventricular septum; LVEF, left ventricular ejection fraction; CO, cardiac output; and LVEDV, left ventricular end-diastolic volume. * P < 0.05.
detection of every episode of AF, particularly in asymptomatic patients, was quite difficult to achieve. Therefore, we might have somehow underestimated the incidence of AF in our study. Thirdly, the conclusions were only based on the one-time measurement of circulating biomarkers. Serial measurements of these parameters would be more useful to further explore the dynamic correlations among them.
Table V. Accuracy of Big ET-1 and LAD in Predicting the Presence of AF in HCM Patients

| Variables                          | Sensitivity | Specificity | Positive predictive value | Negative predictive value |
|------------------------------------|-------------|-------------|---------------------------|---------------------------|
| Big ET-1 ≥ 0.285 pmol/L            | 56%         | 75%         | 41%                       | 84%                       |
| LAD ≥ 44.5 mm                      | 66%         | 74%         | 44%                       | 87%                       |
| Big ET-1 ≥ 0.285 pmol/L and LAD ≥ 44.5 mm | 41%         | 94%         | 62%                       | 83%                       |
| Big ET-1 ≥ 0.285 pmol/L or LAD ≥ 44.5 mm | 85%         | 56%         | 37%                       | 90%                       |

Big ET-1 indicates big endothelin-1; LAD, left atrial diameter; AF, atrial fibrillation; and HCM, hypertrophic cardiomyopathy.

Conclusions

To the best of our knowledge, this is the first study that has systematically investigated the associations of different circulating biomarkers (big ET-1, NT-pro BNP, cTnI, and hs-CRP) and AF in a relatively large-scale Chinese HCM cohort. Plasma big ET-1 is significantly related to parameters representing cardiac remodeling in HCM and can be used as an independent determinant of AF regardless of LVOTO. Big ET-1 might be a valuable index to evaluate the clinical status of AF in patients with HCM.

Disclosures

Conflicts of interest: None.

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