Relationship between exercise induced elevation of left ventricular filling pressure and exercise intolerance in patients with atrial fibrillation

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Abstract

Background Elevated left ventricular filling pressure (LVFP) is an important cause of exercise intolerance in patients with atrial fibrillation (AF). Exercise stress echocardiography could assess LVFP during exercise. The objective of this study was to investigate the relationship between exercise induced elevation of LVFP and exercise capacity in patients with AF.

Methods This study included 145 consecutive patients (81 men and 64 women; mean age 65.5 ± 8.0 years) with persistent non-valvular AF and normal left ventricular systolic function (left ventricular ejection fraction ≥ 50%). All patients underwent a symptom-limited cardiopulmonary exercise test (CPET). Doppler echocardiography was performed both at rest and immediately after exercise. Five consecutive measurements of early diastolic mitral inflow velocity (E) and early diastolic mitral annular velocity (e') were taken and averaged. E/e' ratio was calculated. Elevated LVFP was defined as E/e' > 9, and patients with elevated LVFP at rest were excluded.

Results Patients were classified into two groups according to LVFP estimated by E/e' ratio after exercise: 39 (26.9%) with elevated LVFP after exercise and 106 (73.1%) with normal LVFP. As compared with patients with normal LVFP, the ones with elevated LVFP after exercise had significantly lower peak oxygen uptake (VO2 peak) (21.7 ± 2.3 vs. 26.4 ± 3.8 mL/min per kilogram, P < 0.001), lower anaerobic threshold (19.9 ± 2.5 vs. 26.0 ± 4.0 mL/min per kilogram, P < 0.001), and shorter exercise time duration (6.2 ± 0.8 vs. 7.0 ± 1.3 min, P < 0.001). Multivariate analysis showed that age, gender and E/e' after exercise were significantly correlated with VO2 peak.

Conclusion Elevated LVFP estimated by E/e' ratio after exercise is independently associated with reduced exercise capacity in AF patients.

Keywords: Atrial fibrillation; Diastolic dysfunction; Exercise capacity, Exercise stress echocardiography

1 Introduction

Atrial fibrillation (AF) is the most common rhythm disorder. It is a risk factor for increased mortality.1 AF and left ventricular diastolic dysfunction often co-exist.1-4 It was proven in previous studies, that diastolic dysfunction promotes the initiation2 and recurrence of AF.3,4 On the other hand, patients with AF have a 3-fold higher risk of developing heart failure.1 Thus, early recognition and appropriate therapy of diastolic dysfunction is worthwhile to prevent progression to diastolic heart failure and subsequent death in AF patients. Among the echocardiographic parameters of diastolic dysfunction, the ratio of early diastolic mitral inflow velocity (E) to early diastolic mitral annular velocity (e') has been reported to be a useful parameter for estimating left ventricular filling pressure (LVFP).5 In the study by Li, et al.6 E/e' > 9 has a sensitivity of 72.7% and a specificity of 70.4% for identification of elevated LVFP (> 15 mmHg) in AF patients.

AF is always associated with exercise intolerance.7 Diastolic dysfunction could be an important cause of exercise induced dyspnea. Previous studies have shown that E/e' at rest correlates with exercise capacity in AF patients.8,9 However, in many cases it is only under conditions of cardiovascular stress that LVFP increases and exercise-limiting symptoms develop. Therefore, resting estimation of LVFP gives incomplete information. It has been reported that exercise stress echocardiography could assess LVFP during or after exercise, and is a non-invasive diagnostic test for early diastolic dysfunction.5 However, whether E/e' after exercise...
Exercise intolerance in AF patients was unknown. So we hypothesized that exercise induced elevation of LVFP estimated by E/e’ ratio is associated with reduced exercise capacity in AF patients.

2 Methods

2.1 Patient selection

This was a cross-sectional study. The study population consisted of 145 consecutive patients with persistent non-valvular AF and normal left ventricular systolic function (LVEF ≥ 50%), who were screened from January 2012 to December 2014 at Peking University Third Hospital. Patients with elevated LVFP at rest were excluded (as defined below). Other exclusion criteria were: significant valvular heart disease or congenital heart disease; LVEF < 50%; NYHA class IV; coronary heart disease; ECG or echocardiographic evidence of exercise-induced ischemia; uncontrolled baseline heart rate (> 100 beats/min); moderate or severe respiratory disease, or functional disability. This study was approved by the ethics review boards of Peking University Health Science Center. Patients were explained about the study and written informed consent was taken.

2.2 Functional capacity assessment

All patients underwent a symptom-limited cardiopulmonary exercise test (CPET) with a treadmill using the Bruce protocol in accordance with the American Thoracic Society/American College of Chest Physicians (ATS/ACCP). Peak oxygen uptake (VO2 peak), anaerobic threshold (AT), carbon-dioxide production, and minute ventilation were measured during the test. VO2 peak and AT were computed as weighted terms (mL/min per kilogram). Patients were not asked to discontinue β-blockers, calcium channel blockers (CCBs) or digoxin before the test. A physician was present to encourage maximal exercise. The primary reason for discontinuing the exercise test included limiting dyspnea, chest pain, peripheral muscle fatigue, severe ST-segment depression, or severe ventricular arrhythmia.

2.3 Echocardiography

Comprehensive transthoracic echocardiography was performed using a Vivid S6 (GE) machine and a 3.5-MHz transducer. Standard M-mode, 2-dimensional, and color Doppler imaging were performed in parasternal and apical views with patients in the left lateral decubitus position before exercise. Doppler echocardiography was performed both at rest and immediately after exercise. E was measured using the pulsed wave Doppler method, by placing the sample volume at the level of the mitral valve leaflet tips. The e’ was measured from the lateral corner of the mitral annulus in the apical 4-chamber view. Five consecutive measurements of E and e’ were taken and averaged. E/e’ ratio was calculated. Studies were performed by a single experienced operator. Images were recorded on videotape and interpreted by another experienced operator.

LVFP was estimated by E/e’ ratio, and elevated LVFP was defined as E/e’ > 9. AF patients with normal LVFP (E/e’ ≤ 9) at rest were classified into two groups according to LVFP after exercise: patients with elevated LVFP after exercise (E/e’ > 9 after exercise) and the ones with normal LVFP (E/e’ ≤ 9 after exercise).

2.4 Statistics

Continuous variables are expressed as mean ± SD, and compared by Student’s unpaired t-tests between two groups. Percentage was calculated for categorical variables, and comparisons between groups were performed by Chi-Squared tests. Predictors of exercise capacity were identified by univariate analyses, and then all univariate predictors were entered in a stepwise manner into a multivariate linear regression model with the entry and retention set at a significance level of less than 0.10. Values for N-terminal pro-B-type natriuretic peptide (NT-proBNP) were normalized by logarithmic transformation (LnNT-proBNP). Spearman correlation was used to identify the bivariate correlations. Statistical significance was defined as P < 0.05. All analyses were performed with SPSS for Windows version 15.0 (SPSS, Chicago, IL).

3 Results

3.1 Clinical characteristics

A total of 145 AF patients (81 men and 64 women) were included in this study. The mean age was 65.5 ± 8.0 years. In all, 101 patients (69.7%) had a history of hypertension, 35 (24.1%) diabetes and 48 patients (33.1%) were current smokers.

Patients were classified into two groups according to LVFP estimated by E/e’ after exercise: 39 (26.9%) with elevated LVFP after exercise and 106 (73.1%) with normal LVFP. There were no significant differences in age, gender, body mass index (BMI), concomitant illnesses, medications, heart rate, systolic blood pressure, or LnNT-proBNP between the two groups (all P > 0.05, Table 1).
Table 1. Clinical characteristics of patients.

| Characteristic            | LVFP elevated after exercise (n = 39) | LVFP normal (n = 106) | P    |
|---------------------------|--------------------------------------|-----------------------|------|
| Age, yrs                  | 67.4 ± 6.3                           | 64.9 ± 8.4            | 0.088|
| Male                      | 18 (46.2%)                           | 63 (59.4%)            | 0.153|
| BMI, kg/m²                | 26.4 ± 3.2                           | 25.6 ± 3.2            | 0.128|
| Hypertension              | 31 (79.5%)                           | 70 (66.0%)            | 0.118|
| Diabetes mellitus         | 10 (25.6%)                           | 25 (23.6%)            | 0.798|
| Current smokers           | 16 (41.0%)                           | 32 (30.2%)            | 0.219|
| Medications               |                                      |                       |      |
| β-blockers                | 25 (64.1%)                           | 65 (61.3%)            | 0.760|
| CCBs                      | 14 (35.9%)                           | 28 (26.4%)            | 0.264|
| digoxin                   | 4 (10.3%)                            | 7 (6.6%)              | 0.461|
| ACE inhibitors/ARB        | 13 (33.3%)                           | 32 (30.2%)            | 0.717|
| Antiplatelet agents       | 20 (51.3%)                           | 53 (50.0%)            | 0.891|
| Anticoagulants            | 12 (30.8%)                           | 22 (20.8%)            | 0.207|
| Heart rate peak, beats/min| 80.8 ± 9.6                           | 77.7 ± 9.3            | 0.208|
| Heart rate rest, beats/min| 154.0 ± 37.8                         | 150.9 ± 24.7          | 0.571|
| Systolic BP rest, mmHg    | 127.4 ± 22.3                         | 136.2 ± 23.5          | 0.317|
| Systolic BP stress, mmHg  | 171.5 ± 18.1                         | 172.2 ± 22.6          | 0.869|
| LnNT-proBNP               | 6.2 ± 1.1                            | 5.8 ± 1.1             | 0.111|

Data are represented as mean ± SD or n (%). ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; BMI: body mass index; BP: blood pressure; CCB: calcium channel blocker; LVFP: left ventricular filling pressure; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

3.2 Echocardiographic parameters and exercise capacity

The average E/e’ ratio of patients with elevated LVFP and normal LVFP were 10.2 ± 1.0 and 7.9 ± 0.7 separately. Table 2 summarizes the echocardiographic parameters and exercise capacity of the two groups. Echocardiographic parameters including left ventricular end diastolic diameter (LVEDD), left ventricular mass index (LVMI), LVEF and left atrial area (LAA) were not significantly different between the two groups (all P > 0.05). As compared with the patients with normal LVFP, the ones with elevated LVFP after exercise had significantly lower e’ (P = 0.005) and higher E/e’ at rest (P < 0.001), and higher E velocity (P = 0.001) and lower e’ (P < 0.001) after exercise (P < 0.001). However, E velocity at rest was not significantly different between the two groups (P = 0.920).

VO2 peak (21.7 ± 2.3 vs. 26.4 ± 3.8 mL/min per kilogram, P < 0.001), AT (19.9 ± 2.5 vs. 26.0 ± 4.0 mL/min per kilogram, P < 0.001) and exercise time duration (6.2 ± 0.8 vs. 7.0 ± 1.3 min, P < 0.001) were significantly lower in patients with elevated LVFP after exercise than the ones with normal LVFP.

3.3 Determinants of exercise capacity

Univariate regression analyses showed that age, gender,

Table 2. Echocardiographic parameters and exercise capacity of patients.

| Characteristic                  | LVFP elevated after exercise (n = 39) | LVFP normal (n = 106) | P    |
|---------------------------------|--------------------------------------|-----------------------|------|
| Echocardiography                |                                      |                       |      |
| LVEDD, mm                       | 42.3 ± 13.4                          | 40.9 ± 15.7           | 0.519|
| LVMI, g/m²                      | 73.9 ± 11.7                          | 71.3 ± 14.6           | 0.419|
| LVEF, %                         | 69.3 ± 5.3                           | 69.4 ± 5.1            | 0.909|
| LAA, cm²                        | 23.6 ± 4.3                           | 22.5 ± 5.5            | 0.319|
| E velocity rest, m/s            | 0.7 ± 0.2                            | 0.7 ± 0.1             | 0.920|
| e’ stress, cm/s                 | 9.2 ± 1.7                            | 10.4 ± 2.3            | 0.005|
| E/e’ rest                       | 7.9 ± 0.7                            | 7.1 ± 0.9             | <0.001|
| E velocity stress, m/s          | 1.1 ± 0.2                            | 1.0 ± 0.2             | 0.001|
| e’ stress, cm/s                 | 10.6 ± 1.6                           | 12.3 ± 2.7            | <0.001|
| Exercise capacity               |                                      |                       |      |
| VO2 peak, mL/min per kilogram   | 21.7 ± 2.3                           | 26.4 ± 3.8            | <0.001|
| AT, mL/min per kilogram         | 19.9 ± 2.5                           | 26.0 ± 4.0            | <0.001|
| Exercise time duration, min     | 6.2 ± 0.8                            | 7.0 ± 1.3             | <0.001|

Data are represented as mean ± SD. AT: anaerobic threshold; E: early diastolic mitral inflow velocity; e’: early diastolic mitral annular velocity; LAA: left atrial area; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; LVFP: left ventricular filling pressure; LVMI: left ventricular mass index; NT-proBNP: N-terminal pro-B-type natriuretic peptide; VO2 peak: peak oxygen uptake.

Table 3. Clinical and echocardiographic variables as determinants of VO2 peak.

| Variable                  | Univariate β | t     | P     | Multivariate β | t     | P     |
|---------------------------|--------------|-------|-------|               |-------|-------|
| Age                       | −0.390       | −5.062| <0.001| −0.274         | −3.559| 0.001 |
| Gender (female)           | −0.351       | −4.489| <0.001| −0.239         | −3.500| 0.001 |
| BMI                       | −0.017       | −0.220| 0.826 |
| Hypertension              | −0.063       | −0.824| 0.411 |
| Diabetes mellitus         | −0.049       | −0.634| 0.527 |
| Current smokers           | −0.036       | −0.470| 0.639 |
| β-blockers                | −0.109       | −1.434| 0.153 |
| Heart rate rest           | −0.019       | −0.226| 0.822 |
| Heart rate peak           | −0.046       | −0.537| 0.592 |
| LVMI                      | −0.048       | −0.504| 0.615 |
| LVEF                      | −0.099       | −1.147| 0.253 |
| LAA                       | −0.013       | −0.148| 0.883 |
| E velocity rest           | 0.071        | 0.928 | 0.355 |
| e’ rest                   | 0.360        | 5.038 | <0.001|
| E/e’ rest                 | −0.402       | −5.725| <0.001|
| E velocity stress         | 0.025        | 0.321 | 0.748 |
| e’ stress                 | 0.467        | 6.877 | <0.001|
| E/e’ stress               | −0.632       | −9.746| <0.001|
| LnNT-proBNP               | −0.165       | −1.999| 0.048 |

BMI: body mass index; E: early diastolic mitral inflow velocity; e’: early diastolic mitral annular velocity; LAA: left atrial area; LVEF: Left ventricular ejection fraction; LVMI: left ventricular mass index; NT-proBNP: N-terminal pro-B-type natriuretic peptide; VO2 peak: peak oxygen uptake.
e’ and E/e’ at rest, e’ and E/e’ after exercise, and LnNT-proBNP were associated with VO2 peak. Multivariate analysis identified 3 significant variables that were predictive of VO2 peak: age (r = −0.351, P < 0.001), gender (26.4 ± 4.4 and 23.6 ± 3.0 mL/min per kilogram for male and female separately, P < 0.001) and E /e’ after exercise (r = −0.632, P < 0.001) (Figure 1).

Figure 1. Linear regression of E/e’ ratio with VO2 peak. E: early diastolic mitral inflow velocity; e’: early diastolic mitral annular velocity; VO2 peak: peak oxygen uptake.

4 Discussion

In this study, our data showed that elevated LVFP after exercise was present in 26.9% of AF patients with normal LVFP at rest. Elevated LVFP after exercise was associated with reduced exercise capacity. Multivariate regression analysis showed age, gender and E/e’ after exercise were independently associated with VO2 peak.

4.1 Left ventricular diastolic dysfunction in AF patients

AF impairs cardiac function by several mechanisms, such as the loss of atrioventricular synchrony and atrial contraction, the reduction of the diastolic filling and the induction of a tachycardia-induced cardiomyopathy.[11] The study by Kosiuk, et al.[12] showed that diastolic dysfunction was present in 37% of patients referred for AF catheter ablation. Park, et al.[13] reported that E/e’ ratio was a useful independent prognostic parameter for predicting mortality in patients with AF whose left ventricular systolic function was preserved. In these studies, echocardiography was all done at rest. However, resting estimation of LVFP gives incomplete information. During exercise, to maintain adequate left ventricular filling and stroke volume, the filling pressures raise provoking symptoms to patients with diastolic dysfunction.[5,14] Previous studies confirmed that in subjects with normal myocardial relaxation, E/e’ remained unchanged during exercise because of a proportionally increase in both E and E’ velocities. In patients with impaired myocardial relaxation, however, the increase in e’ with exercise was lower than that of E velocity, so that the E/e’ ratio increased.[5] Takagi, et al.[15] reported that elevated E/e’ ratio after exercise was valuable in predicting new-onset of AF in non-ischemic elderly patients. This study found that elevated E/e’ after exercise was present in 26.9% of AF patients with normal LVEF at rest, indicating a presence of early diastolic dysfunction in these patients.

4.2 Determinants of exercise capacity in AF patients

Exercise intolerance is one of the most important symptoms in patients with AF. The study by Kosiuk, et al.[12] showed that diastolic dysfunction was correlated with symptom severity in AF patients. Lee, et al.[8] reported a negative correlation between E/e’ at rest and exercise capacity in AF patients. Because many patients may have normal LVFP in the resting state and cardiac symptoms may be precipitated only by exertion, it may be important to assess LVFP during exercise. Studies had shown LVFP during or after exercise was associated reduced exercise capacity in patients with heart failure[16] as well as non-obstructive hypertrophic cardiomyopathy.[17] However, the value of E/e’ during exercise in AF patients were uncertain. As far as we know, this study was the first to show that AF patients with elevated E/e’ after exercise had lower exercise capacity than patients with normal E/e’. So we concluded that early diastolic dysfunction detected by exercise stress echocardiography was associated with reduced exercise capacity.

In this study, both E/e’ at rest and after exercise were correlated with VO2 peak in univariate analysis. However, multivariate regression analysis showed that E’/e’ after exercise, but not E/e’ at rest, was an independent predictor of VO2 peak.

In this study, heart rates neither at rest nor during exercise were correlated with VO2 peak in univariate analysis. However, multivariate regression analysis showed that E’/e’ after exercise, but not E/e’ at rest, was an independent predictor of VO2 peak.

This study also showed age and gender were independently associated with VO2 peak in AF patients. It had been reported that elderly women were predominantly observed among patients with heart failure with preserved ejection fraction.[18] Previous study also showed that age and female gender were associated with heart failure in AF patients.[19] In this study, heart rates neither at rest nor during exercise were correlated with VO2 peak. It has been proved that lenient heart rate control is as effective as strict rate control in terms of major clinical events.[20] However, previous studies had controversial results about the relationship between heart rate control and exercise capacity.[5,21] In the study by Lee, et al.[8] heart rate at rest was an independent
predictor of VO₂ peak, while Cooper, et al. found that heart rate was not significantly associated with 6-minute walking distance.

NT-proBNP, an established biomarker for heart failure, could predict exercise capacity in patients with heart failure. In this study, patients with elevated E/e’ after exercise did not have elevated LnNT-proBNP than patients with normal E/e’. Thus, NT-proBNP may be not as sensitive as E/e’ in identifying early diastolic dysfunction in AF patients. In univariate regression analysis, LnNT-proBNP was associated with VO₂ peak, however, LnNT-proBNP was not an independent predictor of VO₂ peak in multivariate regression analysis.

4.3 Limitations
The accuracy and reproducibility of E/e’ has been debated in AF patients because of the beat-to-beat variations. However, Li, et al. demonstrating a good correlation between LVFP and E/E’ in AF patients. In this study, five consecutive measurements of E and e’ were taken and averaged in order to reduce the effect of variance from beat to beat.

4.4 Conclusions
Elevated LVFP estimated by E/e’ ratio after exercise was independently associated with reduced exercise capacity. Exercise stress echocardiography could be a useful diagnostic test for early diastolic dysfunction in AF patients.

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