Effect of systolic dysfunction and elevated left ventricular end diastolic pressure on 3-year clinical outcomes in patients with atrial fibrillation

YU HYEYON¹ and JIHUN AHN²

¹School of Nursing, College of Medicine, Soonchunhyang University, Asan, Korea

²Konkuk University Chungju Hospital

June 22, 2021

Abstract

Objectives: Systolic and diastolic dysfunctions are related to adverse clinical outcomes in patients with sinus rhythm. The aim of this study was to clarify the prognostic significance of systolic and diastolic dysfunctions in patients with chronic persistent atrial fibrillation (AF). **Methods:** We evaluated data for 114 consecutive patients with chronic AF who underwent measurement of LVEDP at our hospital between 1 March 2011 and 31 December 2014. In total, 114 consecutive patients with chronic AF were divided into two groups according to the left ventricular ejection fraction (LVEF): LVEF < 50 (reduced ejection fraction, REF group) and LVEF ≥ 50 (preserved EF, PEF group). The PEF group was further divided into two subgroups according to the left ventricular end-diastolic filling pressure (LVEDP): LVEDP >15 mmHg and LVEDP ≤ 15 mmHg. The 3-year clinical outcomes were compared between the PEF and REF groups and the LVEDP >15 mmHg and LVEDP ≤ 15 mmHg groups. **Results:** During the 3-year follow-up period, the rate of heart failure (HF) hospitalisation and incidence of AF with rapid ventricular rhythm (RVR) were higher in the REF group than in the PEF group. Multivariate analysis revealed that REF was the only significant predictor of HF hospitalisation (hazard ratio, 4.71; 95% confidence interval, 1.48–15.02; p=0.009). **Conclusions:** Our observations during a mid-term follow-up period revealed that systolic dysfunction could be an important predictor of HF hospitalisation in patients with AF. However, elevated LVEDP may not be associated with mid-term adverse clinical outcomes in patients without systolic dysfunction.

Effect of systolic dysfunction and elevated left ventricular end diastolic pressure on 3-year clinical outcomes in patients with atrial fibrillation HyeYon Yu RN, PhD¹, JiHun Ahn MD, PhD² **Affiliations:**

¹School of Nursing, College of Medicine, Soonchunhyang University, Asan, Korea

²Department of Internal Medicine, Konkuk University Chungju Hospital, Chungju, Korea

Correspondence

Ji Hun Ahn MD, PhD

Department of Internal Medicine, Konkuk University Chungju Hospital, Chungju, Korea

82, Gugwon-daero, Chungju-si, Chungcheongbuk-do, Korea

Mobile.: +82-10-6285-5204

Fax: +82-43-840-8888

Email: jichoona@gmail.com

ORCID: <https://orcid.org/0000-0003-1858-1803>

Short title: Prognostic value of diastolic dysfunction in AF

Funding statement

This work was supported by the Soonchunhyang University Research Fund (grant number 20170813).

KEYWORDS

Atrial fibrillation, heart failure, ejection fraction, left ventricular end-diastolic filling pressure

Conflicts of Interest

The authors report no financial relationships or conflicts of interest regarding the content herein.

ABSTRACT

Objectives : Systolic and diastolic dysfunctions are related to adverse clinical outcomes in patients with sinus rhythm. The aim of this study was to clarify the prognostic significance of systolic and diastolic dysfunctions in patients with chronic persistent atrial fibrillation (AF).

Methods : We evaluated data for 114 consecutive patients with chronic AF who underwent measurement of LVEDP at our hospital between 1 March 2011 and 31 December 2014. In total, 114 consecutive patients with chronic AF were divided into two groups according to the left ventricular ejection fraction (LVEF): LVEF < 50 (reduced ejection fraction, REF group) and LVEF $\geq$ 50 (preserved EF, PEF group). The PEF group was further divided into two subgroups according to the left ventricular end-diastolic filling pressure (LVEDP): LVEDP >15 mmHg and LVEDP $\leq$ 15 mmHg. The 3-year clinical outcomes were compared between the PEF and REF groups and the LVEDP $\leq$ 15 mmHg and LVEDP >15 mmHg groups.

Results : During the 3-year follow-up period, the rate of heart failure (HF) hospitalisation and incidence of AF with rapid ventricular rhythm (RVR) were higher in the REF group than in the PEF group. Multivariate analysis revealed that REF was the only significant predictor of HF hospitalisation (hazard ratio, 4.71; 95% confidence interval, 1.48–15.02; $p=0.009$).

Conclusions : Our observations during a mid-term follow-up period revealed that systolic dysfunction could be an important predictor of HF hospitalisation in patients with AF. However, elevated LVEDP may not be associated with mid-term adverse clinical outcomes in patients without systolic dysfunction.

KEYWORDS

Atrial fibrillation, heart failure, ejection fraction, left ventricular end-diastolic filling pressure

INTRODUCTION

Atrial fibrillation (AF) is one of the most common forms of cardiac arrhythmia that is associated with not only increased mortality but also the progression of heart failure (HF) and an increased frequency of HF hospitalisation.^{1 2} The incidence and prevalence of AF are expected to double in the next 20 years, with corresponding increases in the mortality rate and medical cost.^{3 4} Some risk factors such as old age and combined coronary artery disease (CAD) are known predictors of adverse outcomes in patients with AF.⁵ In the setting of sinus rhythm, both systolic and diastolic dysfunctions are well-known risk factors of adverse outcomes such as mortality and HF hospitalisation.^{6 7} However, data regarding the relationship between diastolic dysfunction and adverse cardiac events in patients with AF are insufficient. Moreover, in the setting of chronic AF, prediction of the status of diastolic function is exceedingly difficult.⁸ During progression of diastolic dysfunction, elevated left ventricular end-diastolic pressure (LVEDP) reflects the extent of diastolic dysfunction.^{9 10} However, no studies have evaluated the relationship between elevated LVEDP and adverse cardiac outcomes in patients with chronic AF. Therefore, the aim of the present study was to clarify the prognostic significance of systolic and diastolic dysfunctions in patients with chronic

persistent AF by evaluating the relationship of systolic dysfunction as well as elevated LVEDP, which can reflect the extent of diastolic dysfunction, with the 3-year clinical outcomes.

METHODS

Study design and population

We evaluated data for 114 consecutive patients with chronic AF who underwent measurement of LVEDP at our hospital between 1 March 2011 and 31 December 2014. All patients presented with symptoms such as unexplained dyspnea, chest discomfort, and chest pain and underwent coronary angiography after providing informed consent. We excluded patients with paroxysmal AF, mitral stenosis, rheumatic disease, severe mitral regurgitation, moderate to severe aortic stenosis, severe aortic regurgitation, prosthetic valve disease and severe tricuspid regurgitation, and/or right ventricular dysfunction. The included patients were divided into two groups according to their left ventricular ejection fraction (LVEF): LVEF < 50 (n = 24; REF group) and LVEF [?] 50 (n = 90; PEF group). For evaluation of the outcomes with regard to diastolic dysfunction, the PEF group was further divided into two subgroups according to the left ventricular end-diastolic filling pressure (LVEDP): LVEDP >15 mmHg (n = 38) and LVEDP [?]15 mmHg (n = 52). Clinical data were obtained by face-to-face interviews in the outpatient clinic and/or telephone interviews, a complete review of electronic medical records, physical examinations, history taking, laboratory examinations, echocardiography, and haemodynamic measurements.

This single-centre study was performed at a university hospital, and the protocol was approved by the institutional review (IRB) board of the hospital (IRB approval number: 2015-14). All patients or their legal guardians were provided a thorough written and verbal explanation of the study procedures, following which they gave written consent for participation in the study.

Echocardiography and haemodynamic measurements

A single experienced physician performed baseline transthoracic echocardiography (TTE) with the patient in the left lateral decubitus position within 24 h before the measurement of LVEDP using a GE Vivid 7 device equipped with M4S transducers (GE Medical, Milwaukee, USA). All measured images were digitally recorded for subsequent analysis. Measured echocardiographic parameters included the ejection fraction (EF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left atrial volume, degree of mitral and aortic regurgitation, and stenosis. LVEF was calculated using the biplane modified Simpson's method.¹¹ Echocardiographic Doppler parameters were also measured and stored. The transmitral flow, mitral annular motion velocity, E-wave deceleration time (DT), and propagation velocity (Vp) were recorded for five consecutive cardiac cycles, and the results were averaged. LVEDP and the minimal LV filling pressure were measured using a 5-Fr pigtail catheter positioned at the left ventricle and aorta during coronary angiography. LVEDP was measured at the Z-point, which is identified on the left ventricular pressure trace as the point at which the slope of the ventricular pressure upstroke changes, and averaged over 10 consecutive beats.¹² An investigator blinded to the echocardiographic data acquired the pressure values.

Clinical outcomes

The 3-year clinical outcomes were evaluated and compared between the REF and PEF groups and the two LVEDP groups. Clinical outcomes, including the mortality rate; incidences of stroke, AF with rapid ventricular rhythm (RVR), and bleeding; and rate of HF hospitalisation, were recorded for all patients. RVR was defined as a ventricular response of >100 beats/min at presentation. Bleeding referred to major bleeding that was fatal or intracranial or affected another critical anatomical site, or overt bleeding causing a decrease in haemoglobin of [?]20 g/L or necessitating transfusion of [?]2 units of erythrocytes.

Data analyses

Intergroup differences in continuous variables, presented as means $\pm$ standard deviations, were evaluated by Student's t-test. Differences in categorical variables, expressed as numbers and percentages, were analysed

using the χ^2 test or Fisher's exact test as appropriate. Kaplan–Meier curves were generated for determination of the time-dependent HF hospitalisation rate, with comparisons performed using the log-rank test. Cox proportional hazards models were used to estimate the risk factors for HF hospitalisation during the 3-year period, with calculation of hazard ratios (HRs) and 95% confidence intervals (95% CIs). A two-sided p-value of <0.05 was considered statistically significant in all tests. All statistical analyses were performed using SPSS 20 (IBM SPSS., Chicago, IL, USA).

RESULTS

Descriptive clinical characteristics of the participants

The baseline clinical characteristics of the 114 patients enrolled in this study are presented in Table 1. The REF and PEF groups showed no significant differences in terms of sex, age, the prevalence of hypertension and diabetes mellitus, a history of myocardial infarction (MI), and the presence of CAD (Table 1). Baseline laboratory, haemodynamic, and echocardiographic data for all patients are presented in Table 1. There were no significant differences in laboratory and haemodynamic data, including LVEDP, between the REF and PEF groups. However, EF during the index admission was $37.8\% \pm 9.2\%$ in the REF group and $60.9\% \pm 5.2\%$ in the PEF group, with a significant difference between groups ($p < 0.01$). With regard to echocardiographic parameters of diastolic function, EF, E/e', and E/Vp ($p < 0.01$ for all) were significantly worse in the REF group than in the PEF group, whereas the left atrial volume index (LAVI) showed no significant difference between groups (Table 1). With regard to the baseline clinical characteristics of patients in the two LVEDP subgroups in the PEF group, no significant differences were observed in terms of sex, age, the prevalence of hypertension and diabetes mellitus, a history of MI, and the presence of CAD (Table 2). Baseline laboratory, haemodynamic, and echocardiographic data for the LVEDP > 15 mmHg and LVEDP ≤ 15 mmHg subgroups are shown in Table 2. LAVI, E/e', and E/Vp were significantly worse in the former group than in the latter group ($p < 0.01$ for all).

Clinical outcomes of the participants according to LVEF

The 3-year clinical outcomes of all patients (REF vs. PEF groups) are presented in Table 3. The mortality rate and the incidences of stroke and bleeding were not significantly different between the two groups. Two patients died during the observation period; the causes were hepatic encephalopathy with liver cirrhosis and newly diagnosed terminal cancer in the REF and PEF groups, respectively. However, the rate of HF hospitalisation (29.2% vs 8.9% , $p < 0.02$) and incidence of AF with RVR (20.8% vs 3.3% , $p < 0.01$) were significantly higher in the REF group than in the PEF group. Time-dependent Kaplan–Meier analyses and log-rank tests revealed a high rate of HF hospitalisation in the REF group (Fig 1a). Cox proportional hazards models with univariate and multivariate analyses found that reduced LVEF ($< 50\%$) was an important independent predictor of HF hospitalisation (Table 4).

Clinical outcomes of the participants according to LVEDP

The 3-year clinical outcomes of patients in the LVEDP > 15 mmHg and LVEDP ≤ 15 mmHg groups are presented in Table 5. There were no significant differences between the two groups. Although the rate of HF hospitalisation tended to be higher in the LVEDP > 15 mmHg group, the difference was not statistically significant (15.4% vs 21.1% , $p = 0.58$). Time-dependent Kaplan–Meier analyses and log-rank tests showed no difference in the rate of HF hospitalisation between the two groups (Fig 1b).

DISCUSSION

In the present study, we evaluated the relationship of systolic dysfunction as well as the level of LVEDP with the 3-year clinical outcomes in patients with chronic AF. The main results of our study were as follows. First, systolic dysfunction was related with adverse outcomes such as heart failure (HF) hospitalisation and the occurrence of AF with rapid ventricular rhythm during the 3-year observation period. In addition, systolic dysfunction (LVEDP $< 50\%$) was an important independent predictor of HF hospitalisation. Second, elevated LVEDP, which is the key finding in patients with diastolic dysfunction, was not associated with mid-term adverse outcomes. To our knowledge, this is the first study to assess the effect of increased LVEDP

on mid-term outcomes in patients with chronic AF. These results highlight the importance of paying more attention to a low EF detected by echocardiography than to diastolic parameters in patients with chronic AF.

AF is one of the most common forms of cardiac arrhythmia requiring treatment, and it is associated with increased rates of mortality and hospitalisation.¹⁻⁴ Some previous studies of patients with AF also showed that patients with systolic dysfunction more frequently exhibit all-cause mortality than do patients with a preserved EF.¹³⁻¹⁵ In a previous study, AF was theoretically associated with the development of rapid rhythm, loss of atrial contractility, and left atrial enlargement. These changes can lead to left ventricular wall thickening, neurohormonal changes, and systolic dysfunction, which is an important predictor of adverse cardiac outcomes.⁵⁻¹⁶ However, in the present study, the mortality rates for patients with REF and those with PEF were comparable; this was probably because of the relatively short observation period, small number of patients in the REF group, and event rates. Although many studies have demonstrated a high mortality rate and increased HF hospitalisation in patients with AF and reduced LVEF, a few studies showed that reduced LVEF did not increase the HF hospitalisation or stroke rate for patients with AF and HF, relative to the rates for patients with AF and diastolic dysfunction.¹⁷⁻¹⁸ In the present study, the HF hospitalisation rate was significantly higher in the REF group than in the PEF group, with the rate being as high as 29.2% in the former group. These findings could be carefully explained by the relatively old age of the enrolled patients and the presence of chronic persistent AF in all patients (patients with paroxysmal AF were excluded).

Notably, the prognostic utility of LVEF measurements for patients with AF is well established. However, in a very recent study, the authors compared the long-term prognostic implications of AF and sinus rhythm in patients with acute or chronic HF stratified according to the level of LVEF and found that AF was not associated with worse cardiovascular outcomes in patients with reduced LVEF.¹⁹ These varied results could be caused by the complexity of AF. Therefore, prediction of our results was difficult, and we carefully estimated that elevated LVEDP would be related with adverse clinical outcomes. Studies that investigated the relationship between LVEDP and clinical outcomes are very limited because of the invasiveness of measurement methods. Previously, some investigators reported that elevated LVEDP is an important risk factor for adverse clinical outcomes in patients with acute myocardial infarction.²⁰⁻²² To our knowledge, however, no study has evaluated the association between LVEDP and clinical outcomes in patients with chronic AF. Only left ventricular diastolic dysfunction (LVDD), measured by non-invasive tests such as echocardiography, was proven to be correlated with adverse clinical events such as hospitalisation and stroke.²³⁻²⁵ However, in the setting of AF, atrial contractile asynchronicity complicates the assessment of LVDD using classic echocardiographic parameters.²⁶⁻²⁷ The physiological hallmarks of LVDD are impaired relaxation and reduced diastolic compliance, which increase the LV filling pressure.²⁸⁻²⁹ Among patients with normal systolic function, elevated LVEDP could represent early diastolic dysfunction or could be the main physiological consequence of diastolic dysfunction.³⁰ We not only determined the relationship between LVEDP and clinical outcomes in patients with chronic AF and a preserved EF but also clarified the relationship between diastolic dysfunction and adverse clinical outcomes such as mortality, stroke, and HF hospitalisation. We found that echocardiographic parameters that represent diastolic function, such as E/e' and E/V_p , were worse in the $LVEDP > 15$ mmHg group. However, during the 3-year observation period, no significant differences were found in terms of adverse clinical outcomes between the $LVEDP > 15$ mmHg and $LVEDP \leq 15$ mmHg groups. We speculate that chronic persistent AF leads to irreversible, chronic structural and neurohormonal changes that could affect both LVEDP and the clinical outcomes.

This study has some limitations, the main one being the retrospective design without randomization. The number of patients was small and the follow-up period relatively short. Because it was a single-center study, it was difficult to collect an adequate number of patients with LV pressure wave data and recruit a relatively homogenous group with chronic persistent AF without valvular heart disease. Long-term clinical follow-up will be necessary after recruitment of more patients, particularly those with reduced LVEF. Even if we performed coronary angiography on the basis of its broad indications, LVEDP measurements were recorded for selective patients with symptoms such as unexplained chest discomfort, unexplained broad-spectrum dyspnoea, and typical and atypical chest pain. Further studies with long-term follow-up periods

are necessary after the recruitment of more patients for clarification of the relationship between diastolic dysfunction or elevated LVEDP and clinical outcomes. Furthermore, the number of patients treated with oral anticoagulants was very low in our study, primarily because our hospital is located in a rural area and the insurance system in Korea did not cover treatment with direct oral anticoagulants during the study period. Thus, the level of education and medical compliance were low, and the patients frequently refused warfarin treatment because of the inconvenience of blood sampling. Finally, LVEDP is affected by multiple factors such as dehydration and volume overload (e.g. combination of chronic kidney disease and anaemia), and elevated LVEDP cannot represent diastolic dysfunction, particularly in the setting of chronic AF.

CONCLUSION

Despite the study limitations, the findings are clinically meaningful because we investigated, for the first time, the relationship between elevated LVEDP and mid-term clinical outcomes along with the relationship between systolic dysfunction and clinical outcomes in patients with chronic AF. Also, this study proved that diastolic dysfunction itself does not appear to be a prognostic factor for hospitalization due to heart failure. Clinicians should apply these results during the treatment of patients with chronic AF, with careful evaluation of systolic function and prevention of risk factors that lead to LV systolic dysfunction.

CONTRIBUTORS

JH AHN conceptualized the study. JH AHN and HY YU cleansed the data. JH AHN and HY YU analyzed the data. JH AHN and HY YU reviewed the data analysis. JH AHN and HY YU wrote initial draft. JH AHN and HY YU reviewed the manuscript and interpreted the findings.

COMPETING INTERESTS

None declared

ETHIC APPROVAL

This study protocol was approved by the institutional review (IRB) board of the Soonchunhyang university hospital (IRB approval number: 2015-14).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. Camm AJ, Kirchhof P, Lip GY, *et al* . Guidelines for the management of atrial fibrillation: The task force for the management of atrial fibrillation of the european society of cardiology (esc). *Eur Heart J* 2010;31: 2369-429.
2. Siontis KC, Yao X, Noseworthy PA . Atrial fibrillation in heart failure syndromes: Does it matter more in some than in others? *Eur Heart J* 2018; 39: 4285–6.
3. Kim MH, Johnston SS, Chu BC, *et al* . Estimation of total incremental health care costs in patients with atrial fibrillation in the united states. *Circ Cardiovasc Qual Outcomes* 2011;4: 313-20.
4. Colilla S, Crow A, Petkun W, *et al* . X. Estimates of current and future incidence and prevalence of atrial fibrillation in the u.S. Adult population. *Am J Cardiol* 2013;112: 1142-7.
5. Kotecha D, Chudasama R, Lane DA, *et al* . Atrial fibrillation and heart failure due to reduced versus preserved ejection fraction: A systematic review and meta-analysis of death and adverse outcomes. *Int J Cardiol* 2016;203: 660-6.
6. Aljaroudi W, Alraies MC, Halley C, *et al* . Impact of progression of diastolic dysfunction on mortality in patients with normal ejection fraction. *Circulation* 2012;125: 782-8.
7. Halley CM, Houghtaling PL, Khalil MK, *et al* . Mortality rate in patients with diastolic dysfunction and normal systolic function. *Arch Intern Med* 2011;171: 1082-7.

8. Ahn J, Kim D, Kim T. Pulmonary arterial systolic pressure and e/e' in the evaluation of left ventricular filling pressure: Assessment of patients with atrial fibrillation. *Herz* 2015; 40: 298-303.
9. Mottram PM, Marwick TH. Assessment of diastolic function: What the general cardiologist needs to know. *Heart* 2005;91: 681-95.
10. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part i: Diagnosis, prognosis, and measurements of diastolic function. *Circulation* 2002; 105: 1387-93.
11. Schiller NB, Shah PM, Crawford M, *et al* . Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American society of echocardiography committee on standards, subcommittee on quantitation of two-dimensional echocardiograms. *J Am Soc Echocardiogr* 1989;2: 358-67.
12. Kern MJ, Christopher T. Hemodynamic rounds series ii: The lvedp. *Cathet Cardiovasc Diagn* 1998; 44: 70-4.
13. Badheka AO, Rathod A, Kizilbash MA, *et al* . Comparison of mortality and morbidity in patients with atrial fibrillation and heart failure with preserved versus decreased left ventricular ejection fraction. *Am J Cardiol* 2011;108: 1283-8.
14. Grigorian SL, Roman AV, Seara JG, *et al* . Atrial fibrillation in patients hospitalized for congestive heart failure: The same prognostic influence independently of left ventricular systolic function? *Int J Cardiol* 2006; 110: 366-72.
15. Pai RG, Varadarajan P. Prognostic significance of atrial fibrillation is a function of left ventricular ejection fraction. *Clin Cardiol* 2007;30: 349-54.
16. Anter E, Jessup M, Callans DJ. Atrial fibrillation and heart failure: Treatment considerations for a dual epidemic. *Circulation* 2009;119: 2516-25.
17. Kotecha D, Holmes J, Krum H, *et al* . Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: An individual-patient data meta-analysis. *Lancet* 2014;384: 2235-43.
18. Linssen GC, Rienstra M, Jaarsma T, *et al* . Clinical and prognostic effects of atrial fibrillation in heart failure patients with reduced and preserved left ventricular ejection fraction. *Eur J Heart Fail* 2011;13: 1111-20.
19. Zafir B, Lund LH, Laroche C, *et al* . Prognostic implications of atrial fibrillation in heart failure with reduced, mid-range, and preserved ejection fraction: A report from 14 964 patients in the european society of cardiology heart failure long-term registry. *Eur Heart J* 2018;39: 4277-84.
20. Hillis GS, Moller JE, Pellikka PA, *et al* . Noninvasive estimation of left ventricular filling pressure by e/e' is a powerful predictor of survival after acute myocardial infarction. *J Am Coll Cardiol* 2004;43: 360-7.
21. Mielniczuk LM, Lamas GA, Flaker GC, *et al* . Left ventricular end-diastolic pressure and risk of subsequent heart failure in patients following an acute myocardial infarction. *Congest Heart Fail* 2007;13: 209-14.
22. Planer D, Mehran R, Wittenbichler B, *et al* . Prognostic utility of left ventricular end-diastolic pressure in patients with st-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Am J Cardiol* 2011;108:1068-74.
23. Kosiuk J, Breithardt O, Bode K, *et al* . Left ventricular diastolic dysfunction and thromboembolic risk in atrial fibrillation: Diastolic dysfunction and thromboembolic risk in af. *Int J Cardiol* 2013;168: 547-8.
24. Lee SH, Choi S, Chung WJ, *et al* . Tissue doppler index, e/e' , and ischemic stroke in patients with atrial fibrillation and preserved left ventricular ejection fraction. *J Neurol Sci* 2008;271: 148-52.
25. Okura H, Takada Y, Kubo T, *et al* . Tissue doppler-derived index of left ventricular filling pressure, e/e' , predicts survival of patients with non-valvular atrial fibrillation. *Heart* 2006;92: 1248-52.
26. Sohn DW, Song JM, Zo JH, *et al* . Mitral annulus velocity in the evaluation of left ventricular diastolic function in atrial fibrillation. *J Am Soc Echocardiogr* 1999;12: 927-31.
27. Al-Omari MA, Finstuen J, Appleton CP, *et al* . Echocardiographic assessment of left ventricular diastolic function and filling pressure in atrial fibrillation. *Am J Cardiol* 2008;101: 1759-65.
28. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure—abnormalities in active relaxation and passive

- stiffness of the left ventricle. *N Engl J Med* 2004;350: 1953-9.
29. Flachskampf FA, Biering-Sorensen T, Solomon SD, *et al* . Cardiac imaging to evaluate left ventricular diastolic function. *JACC Cardiovasc Imaging* 2015;8: 1071-93.
30. Paulus WJ, Tschope C, Sanderson JE, *et al* . How to diagnose diastolic heart failure: A consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the heart failure and echocardiography associations of the european society of cardiology. *Eur Heart J* 2007;28: 2539-50.

TABLE 1 Baseline clinical characteristics and Baseline laboratory, haemodynamic, and echocardiographic data of patients with chronic atrial fibrillation

Characteristic	REF group (n = 24)	PEF group (n = 90)	p
Age, years (mean $\pm$ standard deviation)	69.13 $\pm$ 10.7	69.11 $\pm$ 10.3	0.99
Sex, male; n (%)	15 (62.5)	48 (53.3)	0.42
Smokers, n (%)	8 (33.3)	24 (26.7)	0.52
NYHA class, n (%)			0.10
Class 1	7 (29.2)	38 (46.9)	
Class 2	9 (37.5)	25 (30.9)	
Class 3	4 (16.7)	15 (18.5)	
Class 4	4 (16.7)	3 (3.7)	
Diabetes mellitus, n (%)	4 (16.7)	23 (25.6)	0.36
Hypertension, n (%)	9 (37.5)	50 (55.6)	0.12
Myocardial infarction, n (%)	4 (16.7)	6 (6.7)	0.21
Hypercholesterolemia, n (%)	18 (75)	44 (50)	0.03
Coronary artery disease, n (%)	10 (41.7)	25 (28.1)	0.20
Aspirin, n (%)	16 (66.7)	46 (51.1)	0.17
Clopidogrel, n (%)	7 (29.2)	23 (25.6)	0.72
Warfarin, n (%)	13 (54.2)	54 (60.0)	0.61
Angiotensin-converting enzyme inhibitor, n (%)	2 (8.3)	3 (3.4)	0.29
Angiotensin receptor blocker, n (%)	12 (50.0)	33 (36.7)	0.24
Diuretics, n (%)	17 (70.8)	47 (52.2)	0.10
Digitalis, n (%)	12 (50.0)	36 (40.0)	0.38
Beta-blocker, n (%)	15 (62.5)	49 (54.4)	0.48
Calcium channel blocker, n (%)	10 (41.7)	33 (36.7)	0.65
Heart rate (beats/minute)	89.0 $\pm$ 22.1	82.7 $\pm$ 22.8	0.23
Systolic blood pressure (mmHg)	122.8 $\pm$ 21.0	123.4 $\pm$ 18.6	0.90
Diastolic blood pressure (mmHg)	76.4 $\pm$ 12.4	76.8 $\pm$ 12.4	0.90
CHA ₂ DS ₂ -VASc score	2.18 $\pm$ 0.15	2.35 $\pm$ 0.11	0.12
High-sensitivity CRP level (mg/dl)	1.0 $\pm$ 1.4	1.0 $\pm$ 2.3	0.96
Creatinine level (mg/dl)	1.2 $\pm$ 1.1	1.1 $\pm$ 1.0	0.30
BNP level (pg/ml)	1170.3 $\pm$ 393.0	393.0 $\pm$ 547.0	0.04*
Minimal left ventricular pressure (mmHg)	12.0 $\pm$ 5.0	10.5 $\pm$ 4.7	0.17
LVEDP (mmHg)	17.3 $\pm$ 7.9	14.9 $\pm$ 4.6	0.17
Echocardiographic data			
EF (%)	37.8 $\pm$ 9.2	60.9 $\pm$ 5.2	<0.01**
E	92.6 $\pm$ 21.1	95.0 $\pm$ 24.6	0.67
DT (m/sec)	151.1 $\pm$ 41.2	167.9 $\pm$ 33.9	0.04*
e'	5.4 $\pm$ 1.5	7.0 $\pm$ 1.9	<0.01**
E/e'	18.3 $\pm$ 5.8	14.3 $\pm$ 5.4	<0.01**
Vp (m/s)	39.3 $\pm$ 7.8	58.2 $\pm$ 15.7	<0.01**
E/Vp	2.4 $\pm$ 0.4	1.8 $\pm$ 0.8	<0.01**
LAVI (ml/m ²)	49.0 $\pm$ 24.1	43.2 $\pm$ 16.9	0.18

Characteristic	REF group (n = 24)	PEF group (n = 90)	p
LVMl (gm/m ²)	125.2 ± 49.8	96.2 ± 28.9	0.01*
RWT	0.3 ± 0.1	0.3 ± 0.1	0.39
PAP (mmHg)	39.2 ± 14.1	34.0 ± 11.1	0.11
LVEDD (mm)	56.9 ± 7.7	51.2 ± 5.0	<0.01**
LVESD (mm)	46.5 ± 8.1	34.4 ± 4.3	<0.01**
IVS (mm)	9.1 ± 2.1	8.6 ± 2.0	0.29
LVPW (mm)	8.7 ± 2.2	8.6 ± 1.5	0.73

Abbreviations: REF=reduced ejection fraction (ejection fraction < 50%); PEF=preserved ejection fraction (ejection fraction [?] 50%), NYHA=New York Heart Association; CRP=C-reactive protein; BNP=brain natriuretic peptide; LVEDP=left ventricular end-diastolic filling pressure; EF=ejection fraction; DT=deceleration time; E=early diastolic mitral inflow; e'= early diastolic mitral annular tissue velocity; Vp=propagation velocity; LAVI= left atrial volume index; LVMl=left ventricular mass index; RWT=relative wall thickness; PAP=pulmonary arterial systolic pressure; LVEDD=left ventricular end-diastolic diameter; LVESD=left ventricular end-systolic diameter; IVS=interventricular septum; LVPW=left ventricular posterior free wall.

* p<0.05; **p<0.01

TABLE 2 Baseline clinical characteristics and Baseline laboratory, haemodynamic, and echocardiographic data of patients with chronic atrial fibrillation and a preserved ejection fraction

Characteristics	Characteristics	LVEDP [?] 15 mmHg g
Age, years (mean ± standard deviation)	Age, years (mean ± standard deviation)	69.6 ± 9.5
Sex, male; n (%)	Sex, male; n (%)	33 (63.5)
Smokers, n (%)	Smokers, n (%)	13 (25.0)
NYHA class, n (%)	NYHA class, n (%)	
Class 1	Class 1	22 (46.8)
Class 2	Class 2	13 (27.7)
Class 3	Class 3	9 (19.1)
Class 4	Class 4	3 (6.4)
Diabetes mellitus, n (%)	Diabetes mellitus, n (%)	14 (26.9)
Hypertension, n (%)	Hypertension, n (%)	26 (50.0)
Myocardial infarction, n (%)	Myocardial infarction, n (%)	3 (5.8)
Hypercholesterolemia, n (%)	Hypercholesterolemia, n (%)	26 (51.0)
Coronary artery disease, n (%)	Coronary artery disease, n (%)	15 (29.4)
Aspirin, n (%)	Aspirin, n (%)	26 (50.0)
Clopidogrel, n (%)	Clopidogrel, n (%)	9 (17.3)
Warfarin, n (%)	Warfarin, n (%)	35 (67.3)
Angiotensin-converting enzyme inhibitor, n (%)	Angiotensin-converting enzyme inhibitor, n (%)	1 (1.9)
Angiotensin receptor blocker, n (%)	Angiotensin receptor blocker, n (%)	15 (28.8)
Diuretics, n (%)	Diuretics, n (%)	26 (50.0)
Digitalis, n (%)	Digitalis, n (%)	22 (42.3)
Beta-blocker, n (%)	Beta-blocker, n (%)	28 (53.8)
Calcium channel blocker, n (%)	Calcium channel blocker, n (%)	22 (42.3)
Heart rate (beats/minute)	82.5 ± 18.5	82.5 ± 18.5
Systolic blood pressure (mmHg)	125.2 ± 18.9	125.2 ± 18.9
Diastolic blood pressure (mmHg)	78.1 ± 11.9	78.1 ± 11.9
CHA ₂ DS-VASc score	2.38 ± 0.11	2.38 ± 0.11
High-sensitivity CRP level (mg/dl)	0.7 ± 1.6	0.7 ± 1.6

Characteristics	Characteristics	LVEDP [?] 15 mmHg g
Creatinine level (mg/dl)	1.0 ± 0.9	1.0 ± 0.9
BNP level (pg/ml)	380.9 ± 676.9	380.9 ± 676.9
Minimal left ventricular pressure (mmHg)	8.0 ± 2.7	8.0 ± 2.7
LVEDP (mmHg)	11.7 ± 2.4	11.7 ± 2.4
Echocardiographic findings		
EF (%)	61.4 ± 4.5	61.4 ± 4.5
E	86.4 ± 18.6	86.4 ± 18.6
DT (m/sec)	169.8 ± 32.4	169.8 ± 32.4
e'	7.3 ± 2.2	7.3 ± 2.2
E/e'	12.5 ± 4.5	12.5 ± 4.5
Vp (m/s)	62.2 ± 15.5	62.2 ± 15.5
E/Vp	1.5 ± 0.05	1.5 ± 0.05
LAVI (ml/m ²)	38.3 ± 12.0	38.3 ± 12.0
LVMl (gm/m ²)	92.0 ± 25.5	92.0 ± 25.5
RWT	0.3 ± 0.1	0.3 ± 0.1
PAP (mmHg)	31.6 ± 9.2	31.6 ± 9.2
LVEDD (mm)	50.4 ± 4.6	50.4 ± 4.6
LVESD (mm)	33.7 ± 3.6	33.7 ± 3.6
IVS (mm)	8.6 ± 1.8	8.6 ± 1.8
LVPW (mm)	8.4 ± 1.2	8.4 ± 1.2

Abbreviations: LVEDP=left ventricular end-diastolic filling pressure; NYHA=New York Heart Association

CRP=C-reactive protein; BNP=brain natriuretic peptide; LVEDP=left ventricular end-diastolic filling pressure; EF=ejection fraction; DT=deceleration time; E=early diastolic mitral inflow; e'=early diastolic mitral annular tissue velocity; Vp=propagation velocity; LAVI=left atrial volume index; LVMl=left ventricular mass index; RWT=relative wall thickness; PAP=pulmonary arterial systolic pressure; LVEDD=left ventricular end-diastolic diameter; LVESD=left ventricular end-systolic diameter; IVS=interventricular septum; LVPW=left ventricular posterior free wall.

* p<0.05; **p<0.01

TABLE 3 Three-year clinical outcomes of patients with chronic atrial fibrillation

Characteristics	REF group (n = 24)	PEF group (n = 90)	p
All-cause mortality, n (%)	1 (4.2)	1 (1.1)	0.38
Stroke, n (%)	0 (0.0)	3 (3.3)	0.49
Hospitalisation, n (%)	7 (29.2)	16 (17.8)	0.25
AF with RVR, n (%)	5 (20.8)	3 (3.3)	0.01*
Major bleeding, n (%)	1 (4.2)	2 (2.2)	0.51
HF hospitalisation, n (%)	7 (29.2)	8 (8.9)	0.02*

Abbreviations: AF=atrial fibrillation; RVR=rapid ventricular rhythm; HF=heart failure

* p<0.05

TABLE 4 Predictors of 3-year clinical outcomes for patients with chronic atrial fibrillation

Characteristics	Unadjusted (univariate analysis)	Unadjusted (univariate analysis)	Unadjusted (univariate analysis)
HR	95% CI	p	

Characteristics	Unadjusted (univariate analysis)	Unadjusted (univariate analysis)	Unadjusted (univariate analysis)
Age	0.975	0.931–1.012	0.286
Diabetes mellitus	1.685	0.576–4.930	0.341
BNP level	1.000	1.000–1.000	0.185
Hypertension	0.817	0.296–2.253	0.696
LVEDP > 15 mmHg	1.155	0.419–3.186	0.781
LVEF < 50%	3.666	1.319–10.114	0.012

Abbreviations: BNP=brain natriuretic peptide; LVEF=left ventricular ejection fraction; HR=hazard ratio; CI=confidence interval; LVEDP=left ventricular end-diastolic filling pressure

* $p < 0.05$

TABLE 5 Three-year clinical outcomes of patients with chronic atrial fibrillation and a preserved ejection fraction

Characteristics	LVEDP [?] 15 mmHg (n = 52)	LVEDP > 15 mmHg (n = 38)	<i>p</i>
All-cause mortality	1 (1.9)	0 (0.0)	0.58
Stroke	0 (0.0)	3 (7.9)	0.07
Hospitalisation	8 (15.4)	8 (21.1)	0.58
AF with RVR	3 (5.8)	0 (0.0)	0.26
Major bleeding	1 (1.9)	1 (2.6)	0.67
HF hospitalisation	5 (9.6)	3 (7.9)	0.54

Abbreviations: AF=Atrial fibrillation; RVR=rapid ventricular rhythm; HF=heart failure; LVEDP=left ventricular end-diastolic filling pressure

Figure 1

Figure 1 Kaplan–Meier survival curves for patients with chronic atrial fibrillation

a Event-free rate of heart failure hospitalisation for patients with REF (LVEF < 50%) and those with PEF (LVEF [?] 50%). **b** Event-free rate of heart failure hospitalisation for patients with LVEDP [?] 15 mmHg and those with LVEDP > 15 mmHg. LVEDP=left ventricular end-diastolic filling pressure, LVEF=left ventricular ejection fraction; PEF=preserved ejection fraction; REF=reduced ejection fraction.