Cardiovascular Topics

Echocardiographic multiparameter assessment for patients with heart failure with preserved ejection fraction and atrial fibrillation

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Abstract

We aimed to assess the echocardiographic parameters of cardiac structure and function in patients with heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation (AF). Thirty-seven HFpEF patients with AF were selected, while 38 patients with simple HFpEF in the same period were selected as controls. Three-dimensional speckle-tracking echocardiography was performed on both groups and the parameters were compared. The early diastolic longitudinal peak strain rates [early diastolic longitudinal strain rate (LSR_E), early diastolic circumferential strain rate (CSR_E), early diastolic radial strain rate (RSR_E) and early diastolic rotational strain rate ($RotR_E$)], late diastolic longitudinal peak strain rates (LSR_A, CSR_A, RSR_A and $RotR_A$) and untwisting parameters [untwisting rate during isovolumic relaxation time (UTR_{IVR}) and early peak untwisting rate (UTR_E)] were all negatively correlated with the ratio of early diastolic transmitral velocity to early diastolic mitral annular velocity (E/E′) ($p < 0.01$). The cardiac event-free survival rate of the simple HFpEF group (92.11%) was significantly higher than that of the HFpEF + AF group (81.08%) ($p < 0.0001$). UTR_{IVR} had a more significant correlation with E/E′ ratio than the other indicators and could serve as a sensitive indicator for evaluating the diastolic function of patients with HFpEF + AF.

Keywords: atrial fibrillation, heart failure, haemodynamics, myocardial ischaemia, preserved ejection fraction, pressure load

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Heart failure (HF) is associated with decreased cardiac output and increased cardiac pressure load.[1] As one of the diseases with a high mortality rate, HF causes millions of deaths worldwide each year. Based on left ventricular ejection fraction (LVEF), HF can be classified into HF with preserved ejection fraction (HFpEF) (LVEF ≥ 50%), HF with decreased ejection fraction (HFrEF) and HF with mid-range ejection fraction (HFmrEF).[2]

The global prevalence of HF in adults is about 1.0–3.0% and is increasing continuously, with an annual prevalence of about 2/103 in Europe and 3/103 in North America.[3,4] With aging populations and changes in lifestyle, the prevalence of HF in China is also increasing annually (1.3%, 4.5 million patients).[5] HFpEF is responsible for about half of the incidents of HF, with an annual increase in prevalence of 1.0%,[6,7] and significant differences among region, gender and correlation.[8]

Atrial fibrillation (AF) is defined as rapid and disorderly ventricular contractions caused by electrical signals in the atria due to an irregular heartbeat. AF can aggravate HF symptoms by damaging the diastolic function.[9] HFpEF with AF is a common heart disease characterised by the relative preservation of systolic function but impaired diastolic function, resulting in insufficient relaxation of the heart and affecting cardiac filling and output function.[10] Up to the present, treatment outcomes of HFpEF patients remain unsatisfactory, and the prognosis and quality of life need improvement. Besides, the detection rate of HFpEF (early stage) is low, so it is often ignored.

In clinical practice, HFpEF is refractory to therapy, and it brings great economic burden to patients and their families, so patients are prone to mental and emotional disorders.[11] In recent years, research into the pathogenesis, treatment methods and imaging of HFpEF have attracted widespread attention. In this study, therefore, the echocardiographic parameters of cardiac structure and function in patients with HFpEF + AF were explored, aiming to provide potential therapeutic regimens and to ameliorate their survival rate and quality of life.

Methods

This study complied with the medical research principles specified in the Declaration of Helsinki and was approved by the ethics committee of our hospital. Thirty-seven HFpEF patients with AF, admitted to our hospital from January 2020 to January 2023, were selected, while 38 patients with simple HFpEF in the same period were selected as controls. The diagnostic criteria for HFpEF and AF have been reported elsewhere.[12,13]

The inclusion criteria were as follows: (1) patients of any gender and aged ≥ 50 years and ≤ 75 years, (2) those meeting the

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Western medical diagnostic criteria for AF, HFpEF and HFpEF + AF, and undergoing cardiac resynchronisation therapy (CRT), (3) those with New York Heart Association (NYHA) functional class II–III, and (4) those who signed the informed consent form and had complete and valid baseline and clinical data. The exclusion criteria involved: (1) patients with severe cardiac insufficiency or NHYA functional class IV, (2) those complicated with serious diseases of the heart, kidney or liver, (3) those with mental, volitional and emotional disorders, (4) those with haematopoietic, coagulation, endocrine dysfunction or haematological diseases, or (5) pregnant or lactating women.

In the simple HFpEF group (n = 38), there were 22 males and 16 females aged 50–75 (64.52 ± 4.76) years, with a course of disease of zero to six (4.05 ± 1.54) years, and 17 and 21 cases were in NHYA functional class II and III, respectively. In the HFpEF + AF group (n = 37), there were 21 males and 16 females aged 50–75 (64.33 ± 4.78) years, with a course of disease of zero to six (4.13 ± 1.47) years, and 18 and 19 cases were in NYHA functional class II and III, respectively. Age, gender, course of disease, NHYA functional classification and other routine data had no significant differences and were comparable between the two groups ($p > 0.05$).

In a resting state, all subjects (HFpEF + AF or simple HFpEF) were instructed to lie in a lateral decubitus position and given electrocardiography using vivid E9 ultrasound machine (GE, USA), and then routine three-dimensional speckle tracking echocardiography (3D-STE) with the transducer frequency adjusted to 3.5 MHz. Interventricular septum thickness, left ventricular posterior wall thickness, left ventricular end-diastolic dimension and left ventricular end-systolic dimension were obtained, and left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) were measured. LVEF was calculated:

$$LVEF = \frac{LVEDV - LVESV}{LVEDV} \times 100\%$$

Early diastolic transmitral velocity (E), early diastolic mitral annular velocity (E′), early mitral deceleration time (DT) and late diastolic transmitral velocity (A) were measured, and E/A and E/E′ (as the measurement criterion for left ventricular filling pressure[14]) ratios were calculated. All the above indicators were averaged in three cardiac cycles.

In addition, early diastolic longitudinal strain rate (LSR_E), late diastolic longitudinal strain rate (LSR_A), LSR_E/LSR_A, early peak untwisting rate (UTR_E) and untwisting rate during isovolumic relaxation time (UTR_{IVR}) were acquired and analysed using EchoPAC software. The variation in 3D-STE results among all examiners was evaluated by intraclass correlation coefficient,[15] and reliability > 0.75 indicated good reliability of repeatability.

Statistical analysis

An Excel database was established and all baseline and study data were processed using SPSS21.0 software (IBM Inc, USA). The count data were analysed with the chi-squared test and described as percentage. The measurement data were analysed with the t-test and described as mean ± SD.

The correlations of early diastolic longitudinal strain rate (LSR_E), early diastolic circumferential strain rate (CSR_E), early diastolic radial strain rate (RSR_E) and early diastolic rotational strain rate, and late diastolic longitudinal strain rates (LSR_A), late diastolic circumferential strain rate (CSR_A), late diastolic radial strain rate (RSR_A) and late diastolic rotational strain rate ($RotR_A$), and untwisting parameters [untwisting rate during isovolumic relaxation time (UTR_{IVR}) and early peak untwisting rate (UTR_E)] with the E/E′ ratio were explored by Pearson's analysis.

The receiver operating characteristic (ROC) curves of the correlations of early diastolic strain rates and untwisting parameters with CRT echocardiographic responsiveness were plotted, and the area under the curve (AUC) was calculated. A p-value < 0.05 was considered statistically significant.

Results

Echocardiographic diastolic function: LVEDV, LVESV, E/A ratio, E/E′ ratio, left atrial (LA) volume and $RotR_A$ of the HFpEF + AF group were significantly higher than those of the simple HFpEF group, while LVEF, deceleration time (DT), LSR_E, CSR_E, RSR_E, $RotR_E$ and UTR_{IVR} of the HFpEF + AF group were significantly lower than those of the simple HFpEF group ($p < 0.05$) (Table 1). Therefore, the two groups had significantly different echocardiographic diastolic function.

It was found by Pearson correlation analysis that the early diastolic longitudinal peak strain rates (LSR_E, CSR_E, RSR_E and $RotR_E$) were negatively correlated with left ventricular diastolic function (E/E′ ratio) ($p < 0.01$) (Fig. 1). It was found by Pearson correlation analysis that the late diastolic longitudinal peak strain rates (LSR_A, CSR_A, RSR_A and $RotR_A$) were negatively correlated with left ventricular diastolic function (E/E′ ratio) ($p < 0.01$) (Fig. 2).

Pearson correlation analysis showed that the untwisting parameters (UTR_{IVR} and UTR_E) were negatively correlated with

Table 1. Echocardiographic diastolic function

Indicator	*Echocardiographic diastolic function* HFpEF + AF group (n = 37), mean ± SD	HFpEF group (n = 38), mean ± SD	t	p-value
LVEDV (ml)	235.45 ± 35.46	154.23 ± 35.68	9.887	< 0.001
LVESV (ml)	184.25 ± 11.58	114.35 ± 39.57	10.322	< 0.001
LVEF (%)	26.34 ± 2.41	37.26 ± 2.81	18.044	< 0.001
DT (ms)	199.54 ± 48.56	239.58 ± 36.45	4.046	< 0.001
E (cm/s)	76.24 ± 45.82	61.23 ± 12.35	1.948	0.055
E′ (cm/s)	6.21 ± 2.67	6.67 ± 1.34	0.947	0.346
E/A	1.21 ± 0.76	0.88 ± 0.51	2.214	0.030
E/E′	15.46 ± 3.28	11.35 ± 3.64	5.133	< 0.001
LA volume (ml)	78.51 ± 15.28	68.48 ± 15.68	2.805	0.007
LSR_E (s^{-1})	0.71 ± 0.23	0.88 ± 0.21	3.344	0.0013
LSR_A (s^{-1})	0.64 ± 0.22	0.64 ± 0.25	0.000	1.0000
CSR_E (s^{-1})	0.95 ± 0.23	1.23 ± 0.31	4.433	< 0.001
CSR_A (s^{-1})	0.78 ± 0.24	0.81 ± 0.22	0.565	0.574
RSR_E (s^{-1})	1.12 ± 0.45	1.62 ± 0.46	4.757	< 0.001
RSR_A (s^{-1})	1.26 ± 0.38	1.21 ± 0.44	0.526	0.600
$RotR_E$ (°/s)	37.15 ± 10.26	42.36 ± 9.10	2.328	0.023
$RotR_A$ (°/s)	39.59 ± 6.51	29.57 ± 6.58	6.628	< 0.001
UTR_{IVR} (°/s)	13.35 ± 2.25	15.23 ± 2.26	3.610	0.0006
UTR_E (°/s)	28.64 ± 12.36	30.52 ± 12.59	0.652	0.5162

A: late transmitral velocity; AF: atrial fibrillation; CSR: circumferential strain rate; DT: early mitral deceleration time; E: early transmitral velocity; E′: early mitral annular velocity; HFpEF: heart failure with preserved ejection fraction; LSR: longitudinal strain rate; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; RotR: rotational strain rate; RSR: radial strain rate; UTR: untwisting rate.

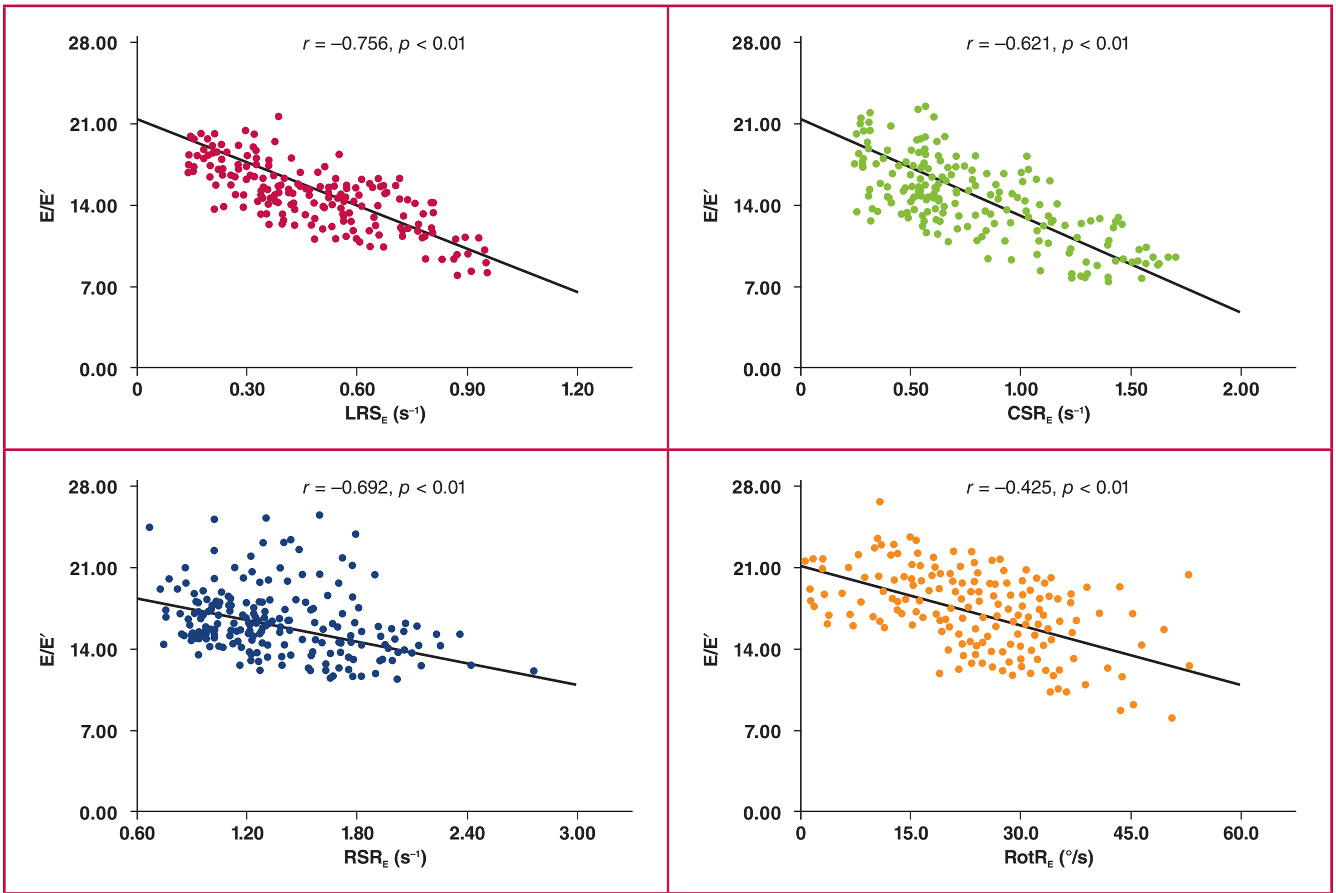

Fig. 1. Correlations of LSR_E, CSR_E, RSR_E and $RotR_E$ with E/E′ ratio detected by 3D-STE. CSR: circumferential strain rate; E: early transmitral velocity; E′: early mitral annular velocity; LSR: longitudinal strain rate; RotR: rotational strain rate; RSR: radial strain rate.

left ventricular diastolic function (E/E′ ratio) ($p < 0.01$) (Fig. 3). Collectively, UTR_{IVR} had a more significant correlation with the E/E′ ratio than other indicators.

Correlations of early diastolic strain rates and untwisting parameters with CRT echocardiographic responsiveness: ROC curves were plotted for the parameters with high correlations. It was found that UTR_{IVR} had the largest AUC (0.821), followed by UTR_E (0.717), LSR_E (0.624), $RotR_E$ (0.555), CSR_E (0.485) and RSR_E (0.247) (Table 2, Fig. 4). Therefore, UTR_{IVR} was the most sensitive indicator for evaluating diastolic function.

To compare the cardiac event-free survival rate between the two groups, a 12-month follow-up survey was conducted. The results showed that there were three cases of cardiac event-induced re-admission in the simple HFpEF group and seven cases in the HFpEF + AF group. Among them, three patients underwent heart transplantation after re-admission (one case in the simple HFpEF group and two cases in the HFpEF + AF group), five patients were re-admitted for acute HF (one case in the simple HFpEF group and four cases in the HFpEF + AF group), and two patients were re-admitted for pacemaker lead dislocation or breakage (one case in the simple HFpEF group and one case in the HFpEF + AF group). The results of the Kaplan–Meier curve analysis showed that the cardiac event-free survival rate in the simple HFpEF group (92.11%) was higher than that in the HFpEF + AF group (81.08%) ($p < 0.0001$) (Fig. 5).

Table 2. Correlations of early diastolic strain rates and untwisting parameters with CRT echocardiographic responsiveness

		95% confidence interval		
Indicator	*AUC*	*Lower limit*	*Upper limit*	*p-value*
LSR_E	0.624	0.412	0.834	0.012
RSR_E	0.247	0.017	0.514	0.046
CSR_E	0.485	0.035	0.462	0.073
UTR_E	0.717	0.501	0.932	0.045
$RotR_E$	0.555	0.281	0.827	0.048
UTR_{IVR}	0.821	0.647	0.996	0.031

AUC: area under the curve; CRT: cardiac resynchronisation therapy; CSR: circumferential strain rate; LSR: longitudinal strain rate; RotR: rotational strain rate; RSR: radial strain rate; UTR: untwisting rate.

Discussion

The pathogenesis of HF is extremely complex and inextricably linked to AF. HF is a common causes of death in patients with AF and is responsible for about 14.50% of deaths in patients with AF.[16] AF is an independent predictor for the occurrence and progression of HF.[15] Up to 40.0% of patients in NYHA functional class IV suffer from AF.[17] AF and HF are intricately linked, interacting and influencing each other through common risks (age, neurohormonal changes, haemodynamics).[18-20]

Changes in cardiac structure and function have been found to be closely associated with AF, and AF can alter the heart and

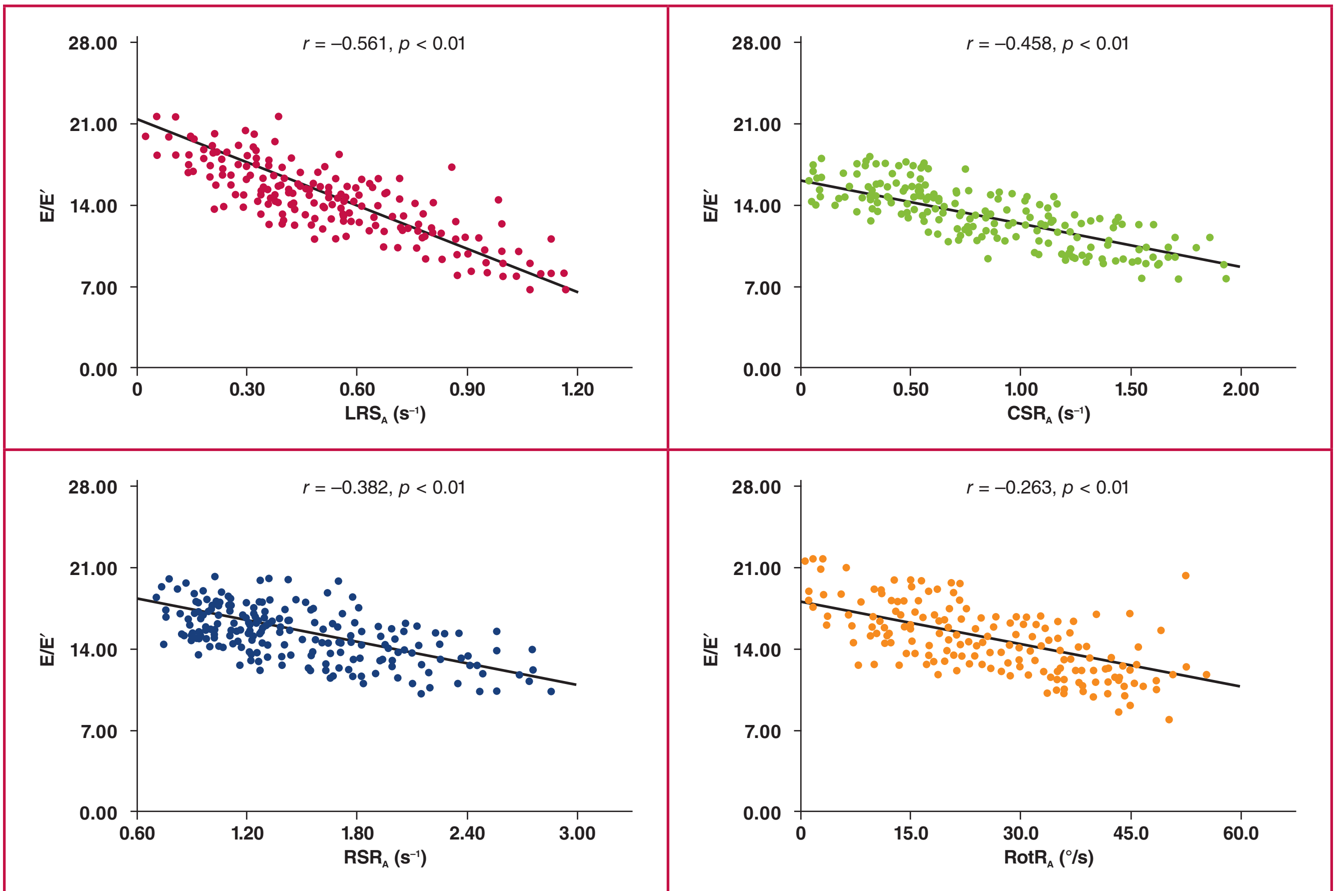

Fig. 2. Correlations of LSRA, CSRA, RSRA and RotRA with E/E′ ratio detected by 3D-STE. CSR: circumferential strain rate; E: early transmitral velocity; E′: early mitral annular velocity; LSR: longitudinal strain rate; RotR: rotational strain rate; RSR: radial strain rate.

its function through atrial enlargement, increased pulmonary circulatory pressure and atrioventricular valve regurgitation.[21] As shown in previous (univariate and multivariate) analysis of influencing factors, AF in patients with chronic heart failure is associated with abnormal brain natriuretic peptide levels [odds ratio (OR): 1.046], elevated thyroid-stimulating hormone (OR: 1.354), enlarged left atrial diameter (LAD) (OR: 1.596) and NYHA classification (OR: 12.291).[22]

The changes in cardiac configuration and function and the aggravation of valve injury in patients with CHF + AH are related to the TCM syndrome types (Qi deficiency and blood stasis, Qi yang deficiency and blood stasis, Qi yin deficiency and blood stasis – Chinese medicine), because LVEF gradually decreases and pulmonary artery systolic pressure increases in the three types. Both E and E/E′ ratio also have correlations with Qi deficiency and blood stasis, Qi yang deficiency and blood stasis,

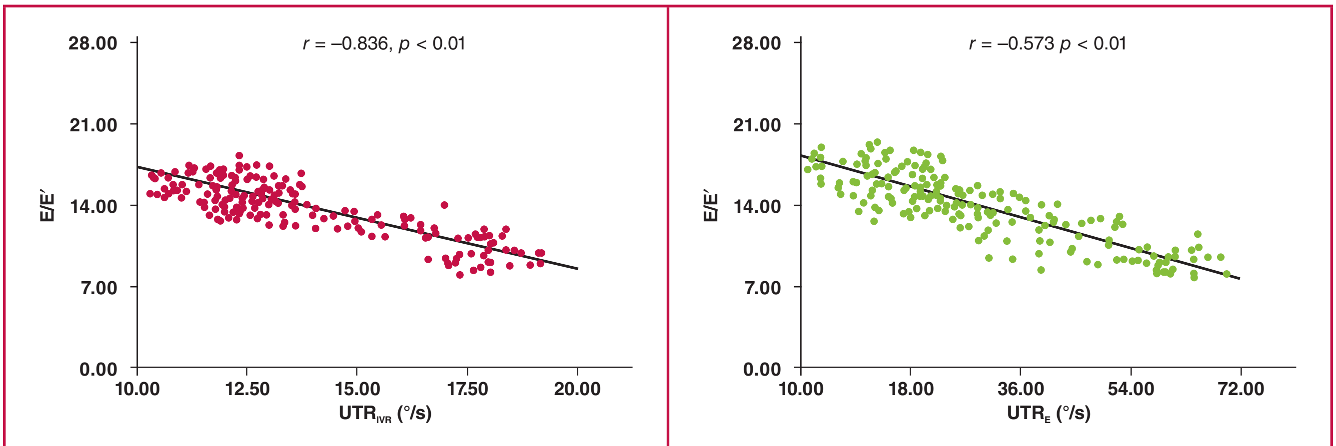

Fig. 3. Correlations between untwisting parameters and left ventricular diastolic function.

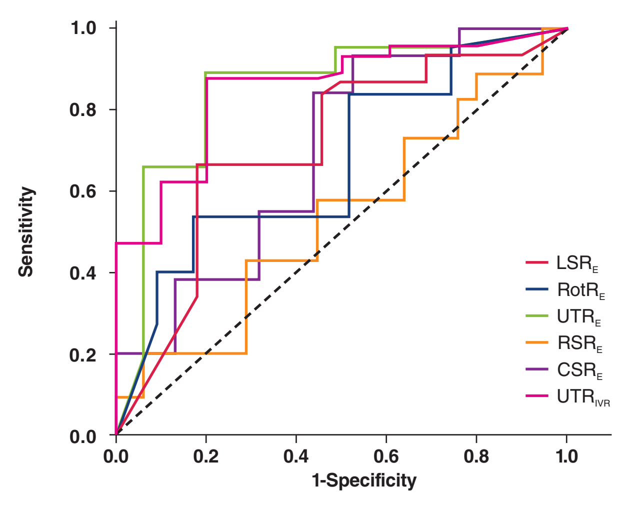

Fig. 4. ROC curves of early diastolic strain rates and untwisting parameters for predicting echocardiographic responsiveness.

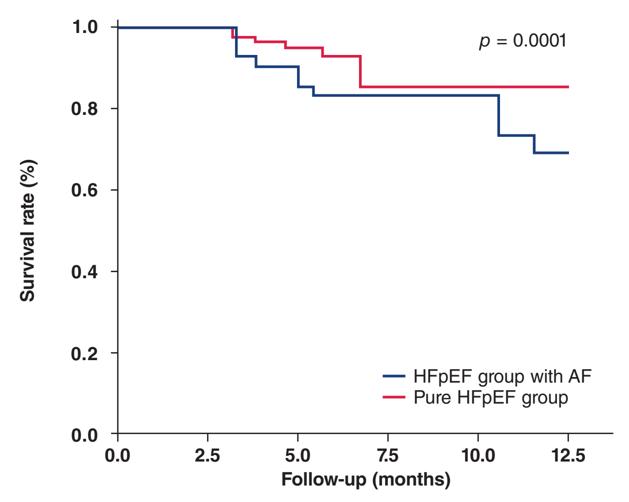

Fig. 5. Kaplan–Meier cardiac event-free survival curves.

and Qi yin deficiency and blood stasis. HFpEF + hypertension and HFpEF are correlated with AF.

In this study, LVEDV, LVESV, E/A ratio, E/E′ ratio, LA volume and RotR$_A$ in the HFpEF + AF group were significantly higher than those in the simple HFpEF group, while LVEF, DT, LSR$_E$, CSR$_E$, RSR$_E$, RotR$_E$ and UTR$_{IVR}$ in the HFpEF + AF group were significantly lower than those in the simple HFpEF group ($p < 0.05$). Therefore, it is necessary to study and evaluate the echocardiographic parameters of patients with HFpEF + AF.

CRT can significantly reduce mortality and improve the quality of life of HF patients.[15] However, the effect of CRT on left ventricular diastolic function in patients with HFpEF, especially HFpEF + AF, has been less explored and remains controversial. In a follow-up study, Waggoner *et al.* found that up to 56.0% (28/50) of HF patients responded to CRT with an increase in LVEF > 5.0%, and had a higher E/E′ ratio than CRT non-responders, but E′ showed no significant difference between CRT responders and non-responders,[22] suggesting that CRT is beneficial to left ventricular filling pressure of HFpEF patients. Furthermore, Jansen *et al.* reported that diastolic function indicators such as the E′ and E/E′ ratio of those with improved left ventricular systolic function were significantly ameliorated because of the correlations of left ventricular filling pressure and left ventricular relaxation with improvement of left ventricular systolic function.[22]

Based on the above studies, Pearson correlation analysis was performed on the echocardiographic parameters of patients with HFpEF + AF in this study, with the E/E′ ratio as the main reference. The results showed that the early diastolic longitudinal peak strain rates (LSR$_E$, CSR$_E$, RSR$_E$, RotR$_E$) and late diastolic longitudinal peak strain rates (LSR$_A$, CSR$_A$, RSR$_A$ and RotR$_A$) were negatively correlated with the E/E′ ratio ($p < 0.01$). Lai *et al.* demonstrated that early and late diastolic strain rates were independent predictors for E/A.[6]

Our study has proven the correlation between diastolic strain rates and E/A and E/E′ ratios in patients with HFpEF on one hand, but there are limitations. In this study, the E/E′ ratio was used as an assessment criterion for left ventricular filling in patients with HFpEF + AF, and correlation analysis was carried out. The results revealed that early diastolic longitudinal peak strain rates (especially LSR$_E$, $r = –0.756$) had a higher correlation with E/E′ ratio than did late diastolic longitudinal peak strain rates.

End-diastolic load is not associated with UTR$_{IVR}$, which is important in patients with HFpEF + AF. Isovolumic relaxation is a critical point at which most ventricular elastic recoil occurs. It has been verified that subendocardial loosening (right-hand screw rule) results in an adequate filling gradient towards the apex from epicardial contractions (left-hand screw rule) to untwisting. The potential energy in early diastole comes from the energy reserve in the subendocardial systole. In a study by Mordi *et al.*, left ventricular untwisting rate correlated with global left ventricular diastolic function in patients with non-ischaemic HF, which is a determinant for diastolic dysfunction.[15] Due to significant diffuse fibrosis of the myocardium in HF patients, the untwisting rate is lower than that in patients with myocardial infarction.

In this study, untwisting parameters (UTR$_{IVR}$ and UTR$_E$) were negatively correlated with the E/E′ ratio ($p < 0.01$). UTR$_{IVR}$ in patients with HFpEF + AF was significantly lower than that in patients with simple HFpEF, and it had the strongest correlation with E/E′ ratio ($r = –0.836$). It can be seen that apical rotation and torsion are weaker in patients with HFpEF + AF than that in patients with simple HFpEF, and apical rotation plays a leading role in diastolic function. Rapid apical rotation reduces wall load, and thus lowers left ventricular pressure, creating a pressure gradient from the base to the apex, so blood flows to the apex. It is difficult to create a pressure gradient in the case of decreased apical rotation.

As proved previously, the untwisting rate was correlated with the E/E′ ratio and relaxation time constant (tau). In our study, UTR$_{IVR}$ was negatively correlated with the E/E′ ratio ($p < 0.01$) and had the largest AUC (0.821), followed by LSR$_E$ (0.624), which is similar to the findings of Jansen *et al.*[22] Therefore, diastolic functional parameters may be superior to systolic functional parameters in assessing cardiac structural and functional responsiveness in patients with HFpEF + AF. Besides, the cardiac event-free survival rate in the simple HFpEF group (92.11%) was higher than that in the HFpEF + AF group (81.08%) ($p < 0.0001$).

This study had some limitations. The sample size was small, and the results are from only two hospitals. Further multicentre studies with larger sample sizes are needed to confirm the findings.

Conclusions

Patients with HFpEF + AF had significantly higher LVEDV, LVESV, E/A ratio, E/E′ ratio, LA volume and $RotR_A$ values, but significantly lower LVEF, DT, LSR_E, CSR_E, RSR_E, $RotR_E$ and UTR_{IVR} values than those with simple HFpEF. UTR_{IVR} had a more significant correlation with the E/E′ ratio than the other indicators, and could serve as a sensitive indicator for evaluating the diastolic function of patients with HFpEF + AF.

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