The impact of echocardiographic parameter ratio of E/E' on the late recurrence paroxysmal atrial fibrillation in patients accepted radiofrequency catheter ablation

A retrospective clinical study

Ke-Zeng Gong, MMed⁶, Qin-Dan Yan, MMed⁶, Rong-Da Huang, MMed⁶, Jian-Hua Chen, MMed⁶, Xue-Hai Chen, MD, Phd⁶, Wei-Wei Wang, MD, Phd⁶, Zhe Xu, MMed⁶, Liang-Long Chen, MD, Phd, FESC, FACC³, Lin Fan, MD, Phd³, Fei-Long Zhang, MD, Phd³,*

Abstract
This study aimed to evaluate the impact of the echocardiographic parameter ratio E/E' on the late recurrence of paroxysmal atrial fibrillation in patients after receiving radiofrequency catheter ablation.

We retrospectively examined total of 288 paroxysmal atrial fibrillation (PAF) patients that underwent a preliminary radiofrequency catheter ablation (RFCA) in our hospital. During the first phase in this study, the patients were divided into 2 groups upon AF recurrence after RFCA: Recurrent group, n=67 patients with rapid trial arrhythmia that lasted for more than 30 seconds at 3 months after RFCA and the Nonrecurrent group, n=221. The clinical conditions were compared between the 2 groups. During the second phase of this study, based on the results in the first phase, the patients were divided into another 2 groups according to whether the ratio of E/E' ≥ 13.45: Higher ratio of E/E' group, n=55 and Lower ratio of E/E' group n=233. The late AF recurrent rates were also compared between the 2 groups.

During the first phase, the univariate analysis indicated that the risk factors(p<.05) for PAF late recurrence included early recurrence, E', and the ratio E/E'. The Cox multivariate analysis showed that the ratio of E/E' and early recurrence were the independent predictors for late PAF recurrence. The ratio of E/E' that was cut off at 13.45 also predicted atrial tachyarrhythmia recurrence with 40.3% sensitivity and 87.3% specificity. In the second phase, after completing the 1:1 matching, the Kaplan–Meier analysis indicated that the ratio of E/E' ≥ 13.45 was associated with further recurrences after RFCA (log-rank P = .009), compared to the patients with a ratio of E/E' < 13.45. The univariate Cox analysis indicated that an elevated ratio of E/E' ≥ 13.45 was the independent predictor for late PAF recurrence (HR = 3.322, 95% CI: 1.560–7.075, P = .002). However, the ratio of E/E' cut off at 13.25 predicted atrial tachyarrhythmia recurrence with 75% sensitivity and 62.2% specificity.

The ratio of E/E' ≥ 13.25 is an important predictor of the late recurrence of paroxysmal atrial fibrillation (PAF) after radiofrequency catheter ablation (RFCA).

Abbreviations: BMI = body mass index, CAD = coronary artery disease, E = the mitral valve largest early diastolic blood flow velocity, E'/E = mitral value E velocity divided by mitral annular E' velocity, E' = early diastolic mitral annular velocity, ERAA = early recurrence of atrial arrhythmia, HDL-C = high-density lipoprotein cholesterol, HLP = hyperlipemia, HTHD = hypertensive heart
1. Introduction

Atrial fibrillation is one of the most frequent arrhythmias in the elderly population and the main risks of atrial fibrillation are heart failure and stroke.[1] The morbidity rate of this disease also tends to increase annually.[2,3] The success rate of radiofrequency catheter ablation for atrial fibrillation is 70% to 80%, but the recurrence of atrial fibrillation (AF) is frequent. Therefore, the predicting factors that affect the recurrence of AF after ablation would assist clinicians in selecting better surgical interventions for treatment and is important for improving surgical success rates and guiding clinical work.

Left ventricular diastolic dysfunction is defined as normal or mildly reduced left ventricular systolic function and left ventricular muscle relaxation and compliance reduction leads to reduced left ventricular filling and increased filling pressure. This also results in increased left atrial pressure and pulmonary venous pressure, leading to the pulmonary circulation and systemic congestion. The gold standard for the diagnosis of left ventricular diastolic dysfunction includes the left atrial pressure that is more than 12 mm Hg, measured by a traumatic cardiac catheter at rest. The primary diastolic dysfunction (LVDD) are often related. But the association between the pre-ablation echocardiography index of LVDD and the recurrence of AF after radiofrequency catheter ablation (RFCA) is not yet clear. Quan et al reported that echocardiographic parameters such as the ratio of E/E′ (mitral value E velocity divided by mitral annular E′ velocity) have a good correlation with LAP in patients with atrial fibrillation, which is beneficial for the evaluation of LVDD patients with atrial fibrillation.[6] To address this challenge, we conducted a case-control study to examine the predictor value of the ratio E/E′ for AF recurrence after RFCA in patients with paroxysmal atrial fibrillation.

2. Materials and methods

2.1. Study participants

A total of 288 patients that underwent a preliminary Radio-frequency Catheter Ablation for symptomatic, drug-refractory PAF between May 2015 and May 2018 at the Fujian Medical University Union Hospital were enrolled in this study. PAF was defined according to the European Society of Cardiology(ESC), European Heart Rhythm Association(EHRA), and endorsed by the European Stroke Organization 2016 Guidelines for the management of atrial fibrillation that was established in collaboration.[1] All patients underwent transthoracic and transesophageal echocardiography 2 days before the arranged catheter ablation procedure was performed as a preoperative assessment. All the antiarrhythmic drugs were discontinued for at least 5 half-lives before the procedure. Patients were excluded from this study based on the following criteria:

1. Patients <18 or 80-years-old;
2. Patients with left atrium and/or left atrial appendage with thrombus;
3. Patients with moderate or severe mitral regurgitation, mitral stenosis is, and mitral valve calcification;
4. Patients with non-pulmonary venous origins of atrial fibrillation (AF);
5. Patients that could not adhere to 2 months of postoperative anticoagulant therapy; and
6. Patients with incomplete clinical data or failed to attend the follow-ups.

All patients signed informed consent before undergoing the treatment. The local Ethics Committee approved this study.

2.2. The procedure for measuring the ratio of E/E′

Echocardiography was performed on the patients once they were admitted to the hospital. The patients were placed in the left lateral decubitus position and practiced calm breathing while a full-digital color ultrasound Doppler diagnostic instrument (Philips Medical Systems, An Dover, MA), equipped with an S=1 endocardial probe and X3=1 matrix volume probe, were used for the echocardiographic test. The standard two-chamber view, long-axis view, and four-chamber view of the left ventricle in the cardiac apex position of continuous 3 to 5 cardiac cycles were attained. The frame rate of the images was greater than 110 frames/s. Then, these images were stored, and an electrocardiogram was recorded simultaneously. We then transformed the machines mode into a PW. A sampling container placed at the mitral valve apex to attain the peak blood flow velocity in early diastole. The additional sampling container was placed on the ventricular septal side of the mitral valve annulus. The sampling line was parallel to the direction of the long axis movement and then the early diastolic mitral annular velocity (E′) was obtained. The E/E′ ratio was calculated using the mean value of at least 3 cardiac cycles.

2.3. The patient follow-ups

All patients were assessed at the outpatient clinic during a mean follow up of 24.9 ± 15.9 months. Medications such as Warfarin were continued based on the physicians discretion and Antiarrhythmics were stopped at 3 months after the ablation. Patients were followed up once a month and asked about the recurrence of atrial fibrillation after surgery including symptoms such as palpitations, chest tightness, shortness of breath, fatigue, and other clinical indications. Electrocardiogram recordings were acquired during each visit every week and 24-hour Holter recordings were scheduled every 3 months during the follow-up. Notably, all patients were encouraged to immediately get an ECG recording when experiencing palpitations. A late recurrence of AF was defined as any recording of rapid trial arrhythmia on an ECG recording or an episode that lasted more than 30 seconds on the 24-hour Holter recording 3 months after the operation; early recurrence was considered to be within 3 months.

Keywords: catheter ablation, E/E′ ratio, late recurrence, paroxysmal atrial fibrillation.
considered statistically significant. Analysis was conducted using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA). A total of 288 paroxysmal atrial fibrillation (PAF) patients underwent an initial radiofrequency catheter ablation (RFCA) between May 2015 and May 2018. The results are shown in Table 1. Among these patients, 120(40%) were female, the mean age was 59.2 ± 10.2 years old, and the follow-up time was 24.90 ± 15.85 months. Also, 221(77%) patients had sinus rhythm without any atrial arrhythmia, 83(29%) of the patients had an early recurrence of atrial arrhythmia, and 67(23%) of the patients had a late recurrence of atrial arrhythmia.

### 2.4. Statistical analysis

The data were expressed as mean ± SD or median (interquartile range) for continuous variables and n (%) for categorical variables. The difference between groups was assessed using Chi-Squared statistics for categorical variables and group means for continuous variables with normal and non-normal distributions were compared using student t-tests and Mann–Whitney U tests, respectively. A Cox regression analysis was performed to examine the predictors of AF recurrence after RFCA. In the first phase, All variables (P < .05) mentioned in Table 1 were included in the multiple Cox regression analysis. A receiver operating characteristic (ROC) curve was generated to evaluate the ratio E'/E as a predictor of AF recurrence after RFCA. In the second phase, Propensity Score Mstching to eliminate the interference factors between another 2 groups according to whether the ratio of E/E' ≥ 13.45, the rate of PAF recurrence was assessed by Kaplan–Meier analysis with the log-rank test,different cut-off values for the ratio E'/E' were selected to evaluate the recurrence of AF. Analysis was conducted using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA). A P value of < .05 was considered statistically significant.

### 3. Results

#### 3.1. The baseline characteristics according to AF recurrence after the initial procedures

A total of 288 paroxysmal atrial fibrillation (PAF) patients underwent an initial radiofrequency catheter ablation (RFCA) between May 2015 and May 2018. The results are shown in Table 1. Among these patients, 120(40%) were female, the mean age was 59.2 ± 10.2 years old, and the follow-up time was 24.90 ± 15.85 months. Also, 221(77%) patients had sinus rhythm without any atrial arrhythmia, 83(29%) of the patients had an early recurrence of atrial arrhythmia, and 67(23%) of the patients had a late recurrence of atrial arrhythmia.

#### 3.2. The Univariate analysis

All patients were divided into two groups according to the time of recurrence of AF. The results of the univariate analysis are listed in Table 1. The univariate analysis revealed that the early recurrence of atrial arrhythmia (ERAA) (P = .000), E'/E (P = .026), and E/E' (P = .005) were risk factors that affected the late recurrence of AF (P < .05). Patients with a recurrence of AF had a higher ratio of E'/E' (11.68 ± 4.27 vs 10.49 ± 3.20 P = .005) and a lower ratio of E' (0.06(0.05–0.09) vs 0.08(0.06–0.09) (P = .026).

#### Table 2

Multivariate Cox regression analysis for the predictors of atrial fibrillation recurrence.

|     | HR(95%CI) | P value |
|-----|-----------|---------|
| ERAA | 4.719 (2.829–7.708) | .000* |
| E'/E' | 1.432 (0.000–4210) | .930 |
| E/E' | 1.080 (1.012–1.153) | .021* |

* P < .05. E'/E = mitral value E velocity divided by mitral annular E velocity, E' = early diastolic mitral annular velocity, E = the mitral valve largest early diastolic blood flow velocity, ERAA = early recurrence of atrial arrhythmia.
3.3. The multiple Cox regression analysis

All variables (P < .05) mentioned in Table 1 were included in the multiple Cox regression analysis. These results of this analysis are summarized in Table 2. The Cox regression analysis identified that the ratio of E/E' (HR = 1.080, 95% CI: 1.012–1.153, P = .021) and early recurrence (HR: 4.719, P = .000, 95% CI: 2.889–7.708) were independent predictors of AF recurrence. The area under the ROC curve shown in Figure 1 for the ratio of E/E' was 0.597(P = .016 95%, CI0.511–0.583) and the best discriminative cut-off value for E/E' was 13.45(sensitivity 40.3% and specificity 87.3%).

3.4. The baseline characteristics according to the ratio of E/E' ≥ 13.45

The patients clinical characteristics vs the ratio of E/E' ≥ 13.45 are listed in Table 3. After matched, while creating the Kaplan–Meier curve for the analysis of incidence for AF recurrence according to a cut-off for the ratio of E/E' ≥ 13.45, patients with the ratio of E/E' ≥ 13.45 had a significantly lower AF-free survival rate after the initial procedure than those with the ratio of E/E' < 13.45(P = .001)(Fig. 2). The univariate Cox regression analysis (Table 4) identified E/E' ≥ 13.45 as an independent predictor of AF recurrence (HR = 3.322, 95% CI:1.560–7.07). This means that patients with E/E' ≥ 13.45 had a 3.322-fold increased chance of experiencing recurrent AF. The area under the ROC curve (Fig. 3) for the ratio of E/E' was 0.654(95% CI: 0.547–0.761) and the best discriminative cut-off value for the E/E' was 13.25(sensitivity 75% and specificity 62.2%) after being matched.

4. Discussion

4.1. The Left ventricular diastolic dysfunction (LVDD) and E/E' ratio

Diastolic dysfunction is an important risk factor for cardiovascular disease. Previous studies have shown that increased left
atrial pressure can lead to atrial remodeling and promote the development of atrial fibrillation.\textsuperscript{7,8} The diagnostic criterion of left ventricular diastolic function is used to measure left atrial pressure (LAP) $\geq$ 12 mm Hg. Previous studies had also used invasive LAP measures using pressure transducer-tipped catheter through transseptal puncture as an independent predictor of AF recurrence after pulmonary vein isolation.\textsuperscript{9} But the atrial septum puncture is problematic and has a high risk.\textsuperscript{10,11} Therefore, echocardiography is often used in clinical practice to indirectly reflect left atrial pressure. In 2016, the American Society for Echocardiography (ASE) updated its guidelines for assessing left ventricular diastolic function in patients with atrial fibrillation using echocardiography. The ratio of $E/E'$ (the mitral valve largest early diastolic blood flow velocity ($E$) and the early diastolic mitral annular velocity ($E'$)) and other indicators are also recommended to evaluate cardiac diastolic function.\textsuperscript{12} Quan et al demonstrated that the $E/E'$ ratio correlated well with LAP ($r=0.397, P=.006$).\textsuperscript{13} Our study confirmed that the ratio of $E/E'$

\begin{table}[h]
\centering
\caption{Univariate Cox regression analysis for the predictors of atrial fibrillation recurrence.}
\begin{tabular}{lll}
\hline
                  & $P$ value & HR (95\%CI)  \\
\hline
$E/E' \geq 13.45$ & .002      & 3.322 (1.560–7.07)  \\
\hline
\end{tabular}
\label{tab:univariate}
\end{table}

\textbf{Table 4}

Univariate Cox regression analysis for the predictors of atrial fibrillation recurrence.

- $E/E'$ = mitral valve $E$ velocity divided by mitral annular $E'$ velocity.
- $E'$ = early diastolic mitral annular velocity.
- $E$ = the mitral valve largest early diastolic blood flow velocity.
- ERAA = early recurrence of atrial arrhythmia.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{roc_curve.png}
\caption{Kaplan–Meier event-free analysis for patients with the ratio of $E/E' \geq 13.45$ compared with patients with $E/E' < 13.45$.}
\end{figure}
may operates as a noninvasive, easy, and useful tool in predicting AF recurrence after ablation (RFCA).

The mechanism of left ventricular diastolic dysfunction (LVDD) increasing the risk of AF recurrence could be because LVDD leads to increased left atrial pressure (LAP) and pulmonary vein (PV) stretching and enlargement. Increased LAP leads to left atrial volume increase compensation and the progressive compensation of left atrial tissue while electrophysiological remodeling leads to pulmonary vein dilatation. The increased left atrial/left ventricular pressure also leads to pulmonary vein congestion, which then leads to atrial fibrillation. Furthermore, the abnormal left ventricular diastolic function can easily lead to the abnormal autonomic nervous system, leading to the occurrence of atrial fibrillation. At the same time, atrial fibrillation induces atrial/ventricular electrophysiology and anatomy, which then leads to left ventricular diastolic dysfunction, representing a vicious circle.

4.2. Early recurrence

Although early recurrence of atrial fibrillation does not equate to the failure of radiofrequency ablation or late recurrence. It may be a temporary reversible phenomenon, associated with a temporary reversible injury response of the atrial muscle tissue induced by catheter ablation, the release of inflammatory factors, the increase of sympathetic nerve tension, the decrease of parasympathetic nerve tension, PV reconnection, and delayed self-healing related to atrial structural remodeling and electrical remodeling. However, relevant studies have revealed that patients with early recurrence are more likely to have a late recurrence and early recurrence is an independent predictor for late recurrence. Predictors of early recurrences, such as age, type of atrial fibrillation, surgical procedure, and P-wave dispersion, were similar to the signs of late recurrence. This implies that the mechanism of early recurrence is not only the transient inflammatory response caused by catheter ablation but also the frequent pathological basis for the occurrence and maintenance of atrial fibrillation. Therefore, the management of early recurrent AF patients and effective intervention (early re-ablation or drug therapy) are beneficial to promoting efficient structural and electrical remodeling and improving the prognosis in patients.

4.3. The early diastolic mitral annular velocity (E')

Our study revealed that E’ was not an independent risk factor for the recurrence of AF. The probable reasons are as follows: E’ was continuously used for assessing diastolic dysfunction in normal people, but not in patients with AF. The delay in annular E’ velocity occurs in the circumstance of impaired left ventricular (LV) relaxation, so, we should combine E’ with other echocardiographic parameters to predict LV filling pressures.

In our research, we investigated a noninvasive and easily applicable predictor for AF recurrence after RFCA. From our results, we found that there was a significant difference between patients with recurrence and patients without recurrence regarding early recurrence and the ratio of E/E’. To further explore the value of the E/E’ ratio in predicting the late recurrence of PAF, we divided patients into 2 groups according to whether patients with the E/E’ ratio ≥ 13.45, with several confounders such as age, hypertension, and postoperative Amiodarone therapy and postoperative Propafenone therapy were a coordinated propensity score matching (PSM). The Kaplan–Meier analysis indicated that the ratio of E/E’ ≥ 13.45 was associated with more late recurrence after PAF ablation (log-rank P = .009), compared to those with the E/E’ ratio < 13.45. The univariate Cox analysis indicated that the E/E’ ratio ≥ 13.45 was the independent predictor for the late recurrence of PAF (HR = 3.322, 95% CI: 1.241–8.799, P = .018).
95%CI: 1.560–7.075, P=.002). This means that patients with E'/E' ≥ 13.45 had a 3.322-fold increased chance of experiencing recurrent AF, the cut-off value for the ratio of E/E' was 13.25 (sensitivity 75.1% and specificity 62.2%) after being matched. Our study is unique in the following points: Firstly, all patients included in this study received echocardiography 1 week before RFCA, which ensured that the parameters were stable and reliable. Secondly, though E'/E' ≥ 11 were suggested to evaluate left ventricular diastolic dysfunction (LVDD) for patients with AF according to the guideline, a more suitable ratio of E'/E' to predict the late recurrence of PAF is unknown. We took the E'/E' ratio as the continuous variable and both the univariate and multivariate Cox analyses suggested that a higher E'/E' ratio was the independent predictor for the late recurrence of PAF. Thirdly, to further confirm the predictive value of the E'/E' ratio for the late recurrence of PAF, our study specifically conducted a case-control analysis to explain the predictive value of the E'/E' ratio for the late recurrence of PAF. To our knowledge, no such case-control study has been completed before.

5. Conclusions
Patients with a higher E'/E' ratio had significantly higher AF recurrence compared to patients with a lower E'/E' ratio. The cut-off value for the ratio of E'/E' predicting AF recurrence was 13.25 (sensitivity 75.1% and specificity 62.2%). Preventing paroxysmal atrial fibrillation (PAF) with a higher E'/E' ratio (≥13.25) in radiofrequency catheter ablation (RFCA) was important for improving surgical success rates and guiding clinical work.

Author contributions
Ke-zeng Gong: data collection and analysis, data interpretation, drafting manuscript, final critical revision of the manuscript and final approval.
Rong-da Huang: data collection and analysis, data interpretation, drafting manuscript, final critical revision of the manuscript and final approval.
Qin-dan Yan: drafting manuscript, final critical revision of the manuscript and final approval.
Jian-hua Chen and Xue-hai Chen and Wei-wei Wang and Zhe Xu and Liang-long Chen: The Surgeons of Radiofrequency Catheter Ablation.
Fei-long Zhang and Lin Fan: designer of the study, data analysis, data interpretation, drafting manuscript, final critical revision of the manuscript and final approval.

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