Association between left atrial size and atrial fibrillation recurrence after single circumferential pulmonary vein isolation: a systematic review and meta-analysis of observational studies

Jianhui Zhuang1†, Yi Wang2†, Kai Tang1, Xiankai Li1, Wenhui Peng1, Chun Liang2, and Yawei Xu1*

1Department of Cardiology, Shanghai Tenth People’s Hospital, Tongji University School of Medicine, 301 Middle Yanchang Road, Shanghai 200072, China; and 2Department of Cardiology, Shanghai Changzheng Hospital, Second Military Medical University, Shanghai, China

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Aims
Left atrial (LA) enlargement is associated with atrial fibrillation (AF). However, it is controversial whether dilated atrium can predict post-ablation AF recurrence. We undertook a systematic review and meta-analysis to analyse the association between LA diameter and AF recurrence after single circumferential pulmonary vein isolation (CPVI) and explore the potential mechanism.

Methods and results
Electronic databases and bibliographies of retrieved studies were searched. The anteroposterior diameters of LA were available in all included studies, which were measured at end-systole by M-mode transthoracic echocardiography. Subgroup analysis was conducted based on the duration of follow-up. Weighted mean difference (WMD) and 95% confidence interval (CI) were calculated using random-effect or fixed-effect model, depending on statistical heterogeneity. Twenty-two studies with a total of 3750 individuals met the inclusion criteria. The summary WMD of LA diameter between patients with and without recurrence was 1.87 mm (95% CI 1.26–2.48, \( P < 0.001 \)). Meta-regression analysis of the 22 studies indicated that study design, duration of follow-up, and measurement of asymptomatic recurrences were significant sources of heterogeneity. Sensitivity analysis suggested that the difference in LA diameter between patients with and without recurrences persisted regardless of the duration of follow-up.

Conclusion
Dilated LA significantly increases the risk of AF recurrence after single CPVI. This is especially applicable to the patients with long-term follow-up.

Keywords
Atrial fibrillation • Catheter ablation • Recurrence • Left atrial size • Meta-analysis

Introduction
Radiofrequent ablation has been shown to be more efficacious than drug therapy in restoring sinus rhythm in patients with atrial fibrillation (AF).1,2 ACCF/AHA/HRS practice guidelines in 2011 recommend catheter ablation as class I recommendation supported with level A evidence.3 Compared with other ablation strategies, circumferential pulmonary vein isolation (CPVI) is more popular in electrophysiology centres.4 Despite advances in the ablation technique, AF recurrences are common and significant number of patients require repeated procedures. It is uncertain what the risk of AF recurrence could be in a long term, because early and long-term success rates vary with studies, and the studies differ in AF type, ablation procedure, timing of follow-up, etc.

As a common consequence of AF, left atrial (LA) enlargement has proven to be associated with recurrent AF after spontaneous, chemical, or electrical cardioversion in AFFIRM study.5 Over the
last decade, a considerable number of studies have been performed to assess the relationship between LA diameter and AF recurrence after ablation. These studies showed inconsistent results. Thus, we performed a systematic review by means of a meta-analysis to assess the relationship between LA size and AF recurrence following single CPVI and explore the potential mechanism.

Methods

Search strategy
This meta-analysis was undertaken in accordance with the guidelines of the Meta-analysis of Observational Studies in Epidemiology.6 We searched MEDLINE (January 2000 to February 2011), EMBASE (January 2000 to February 2011), and the Cochrane Central Register of Controlled Trials (issue 1 of 4, January 2011) database, using the following search strings and terms: ‘atrial fibrillation’ and ‘catheter ablation’ and ‘recurrence’. Only articles in English were included in our study. Then we supplemented the database search by manually scanning bibliographies of retrieved studies. Two reviewers (Y.W. and J.Z.) independently performed the literature search.

Eligible studies
The included study should meet the following criteria: (i) observational study design; (ii) patients treated with initial CPVI; (iii) recurrences defined after the first procedure; (iv) over 6 months and completeness of follow-up; (v) means ± standard deviations of LA diameter reported on both non-recurrence and recurrence groups; and (vi) appropriate approaches to detecting asymptomatic recurrence. Studies meeting the following criteria were excluded: (i) enrolment of patients undergoing other ablation strategies; (ii) ablation history of AF at entry; (iii) recurrences documented after second sessions; and (iv) insufficient time period of follow-up. When data overlapped with other published reports, the latest publication was included.

Data extraction
Reviewers extracted data on author, location, sample size, baseline characteristics of the patients, numbers of patients with sinus rhythm and recurrences, primary ablation procedure, methods used to detect asymptomatic AF recurrence, blanking period, and duration of follow-up. Paroxysmal AF was self-terminating in <7 days, usually within 48 h, as opposed to non-paroxysmal AF including persistent and permanent/long-standing persistent AF lasting beyond 7 days, or necessitating pharmacological or electrical cardioversion, which was defined as recurrent AF. LA diameter was defined as the anteroposterior diameter of LA before ablation, measured at end-systole on the M-mode image obtained from the parasternal long-axis view by trans-thoracic echocardiography. The CPVI procedure was described in detail elsewhere,16 and additional lines were targeted when necessary. Recurrence of AF was defined as an episode of AF, flutter, and tachycardia detected by monitoring during the follow-up if it lasted 30 s or more. Apart from conventional 12-lead electrocardiography (ECG), appropriate approaches to the detection of asymptomatic recurrent AF should include Holter, transtelephonic monitoring, and implanted device alone or in combination during follow-up.8

Data from eligible studies were extracted independently by two reviewers who used a standardized data extraction form and contacted study authors to obtain supplementary data via email. Disagreement was resolved by consensus and, by opinion of a third author if necessary (K.T.).

Statistical analysis
We used STATA 11.0 (StataCorp, TX, USA) to analyse the data. Weighted mean differences (WMD) and 95% confidence interval (CI) were calculated for each study. Statistical heterogeneity was evaluated with $\chi^2$ test and quantified by $I^2$ statistic, which assessed the appropriateness of pooling the individual study results.9 A value of $P < 0.1$ for $Q$ tests or $I^2 > 56\%$ indicated significant between-study heterogeneity.10 If no heterogeneity was present, fixed-effect estimates of WMD were calculated according to the inverse variance method. If heterogeneity was found, random-effect estimates of WMD were calculated with the approach by DerSimion and Laird.

Sensitivity analyses based on meta-regression and subgroup analysis were conducted to evaluate the robustness of our primary results and assess the source of heterogeneity. When available, outcomes were extracted for different subgroups, which included regions (Europe, the USA, or Asia), study designs (prospective or retrospective), sample sizes ($\geq 100$ patients or not), types of AF, ablation procedures (CPVI or CPVI plus), duration of follow-up (6 months or longer), and measurements to detect asymptomatic recurrences. The possibility of publication bias was assessed by the funnel plot and Egger test analysis.

Results
Our preliminary search yielded 1538 potential literature citations. Of these, 1401 were excluded after scanning titles and/or abstracts, leaving 137 citations for further evaluation. After this evaluation, 113 studies are excluded for the reasons shown in Figure 1. Of note, four of the excluded studies were of randomized controlled design, but re-ablations were conducted in these studies.1,2,11,12 Of the remaining 24 studies, 6 provided further data upon request. Finally, 22 publications involving 3750 patients were included in this meta-analysis.7,13–33

![Figure 1 Flowchart of study selection. LAD, left atrial diameter.](https://academic.oup.com/europace/article-abstract/14/5/638/473710/data supplemental)
Characteristics of included studies

Characteristics of the 22 studies included are shown in Table 1. Studies were widely carried out in the world (eight in Europe, five in the USA and nine in Asia). Eleven studies were prospective in design.15,16,19–22,24,26,31,33 The number of patients in each study ranged from 13 to 700. The average age of patients in the studies ranged from 52.9 to 89.9%.

Baseline characteristic of LA diameter in each study was 35–50 mm, partly beyond normal range. Of note, the mean LA diameters in three studies involving total non-paroxysmal individuals were >40 mm. Similar to former worldwide survey,4 the long-term success rate in these studies ranged from 52.9 to 89.9%.

The major processes of treatment and follow-up in each study are shown in Table 2. Additional ablations were reported in 91% studies. However, the difference in additional ablation strategies among individuals and studies made it difficult to stratify and pool the data. Besides ECG and Holter, 10 of the studies included were supplemented with transtelephonic ECGs and/or event monitors to record asymptomatic recurrences. Follow-up time of each study ranged from 6 to 29.9 ± 13.4 months after a single procedure.

Left atrial diameter and the risk of atrial fibrillation recurrence

Overall, the 22 studies involved 980 patients with recurrences and 2770 without recurrences. Patients with recurrences had a larger LA size than those without recurrences after single CPVI, with a significant increase in LA diameter of 1.87 mm (95% CI 1.26–2.48, P = 0.001). Statistical heterogeneity among the studies was present (I² = 47.4%, P = 0.008) (Figure 2). There was no evidence of publication bias by the funnel plot and Egger test analysis.

Sensitivity analyses

Meta-regression analysis of the 22 studies indicated that study design (coefficient: −0.91, P = 0.02), duration of follow-up (coefficient: 2.21, P = 0.02), and measurement of asymptomatic recurrences (coefficient: 0.80, P = 0.03) were significant sources of heterogeneity (Table 3).

Our literature search yielded only three studies including 143 patients in the setting of non-paroxysmal AF. The small sample size did not allow us to perform a further sensitivity analysis. On the other hand, we stratified studies by mean duration of follow-up (6 months, 12 months and >12 months) (Figure 3). There was a significant difference in mean LA diameter between patients with recurrence vs. non-recurrence in studies with 6 months of follow-up (WMD 1.23 mm, P = 0.023), similar to what were observed in...
studies with 12 months and >12 months of follow-up (WMD 1.12 and 2.39, respectively). Only the subgroup with >12 months of follow-up presented significant between-study heterogeneity ($I^2 = 60.6\%, P = 0.003$).

**Discussion**

The result suggests that enlarged LA increase the risk of AF recurrence after single CPVI. Measurement of LA diameter provides a window into the status of structural remodelling of LA, commonly used in clinical practice. The pathophysiological mechanism tying dilated LA to post-ablation AF recurrence remains under debate; however, several theories have been postulated. First, chronic LA dilation strongly induces structural remodelling and vice versa. More recently, some experts indicate that patients with modest LA dilation in the absence of reduced LA compliance respond to reversal of LA remodelling after ablation, whereas a more advanced remodelling of the LA may not be ameliorated. Although the mechanisms underlying the structural remodelling are extremely complicated, the principal changes in atrium manifest as a reduction in myocardium and an increase in atrial fibrosis. Atrial fibrosis is a hallmark of atrial structural remodelling and leads to trigger and persistence of AF through changes in substrate of LA and subsequent electrical remodelling. Second, it is conceivable that patients with larger LA require more energy and longer lesions to complete the ablation. Some studies demonstrate that severe LA scarring after ablation predispose patients to AF recurrences, which seems to result from re-conduction between LA to pulmonary veins (PVs). Simultaneously, pre-existent LA scarring concomitant with dilated LA has unfavourable implications on atrial fibrosis and may reduce success rate after ablation. These may explain why enlarged extent of ablation and re-ablation do not appreciably increase the success rate of patients with large LA scar and perhaps
second sessions should not be routinely required in patients with either severe LA enlargement or scarring. Moreover, evidence shows that inflammation disorder is well correlated with LA size, involving in-structure remodelling.\(^{28}\) Lastly, angiotensin-converting enzyme overexpression have exhibited that angiotensin II indirectly involve in electrical remodelling through effects on ion channels of atrium and PVs—all of which are factors in the initiation and perpetuation of AF.\(^{39}\)

The previous meta-analysis regarding predictors of AF recurrence after ablation concludes that non-paroxysmal AF is the only independent predictor of recurrent AF.\(^{40}\) Nonetheless, a notable limitation of evaluating the predictors of AF in the previous meta-analysis is the fact that many studies are performed in patients with re-ablations and complicated ablation procedures including segmental pulmonary vein isolation and CPVI. As noted in Figure 1, 16 studies with other ablation strategies and 23 studies with re-ablations were excluded in our meta-analysis due to lack of evaluable data.

Meta-regression analysis reveals that the duration of follow-up and measurements of asymptomatic recurrences are the key

### Table 3 Meta-regression analysis

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>SE</th>
<th>95% CI</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region (Europe, the USA, Asia)</td>
<td>0.33</td>
<td>0.24</td>
<td>-0.20 to 0.87</td>
<td>0.20</td>
</tr>
<tr>
<td>Sample size (≥ 100 patients or less)</td>
<td>-1.32</td>
<td>0.61</td>
<td>-2.66 to 0.03</td>
<td>0.05</td>
</tr>
<tr>
<td>Study design (prospective or retrospective)</td>
<td>-0.91</td>
<td>0.34</td>
<td>-1.66 to -0.15</td>
<td>0.02</td>
</tr>
<tr>
<td>Ablation procedure (CPVI or CPVI plus)</td>
<td>0.93</td>
<td>0.70</td>
<td>-0.60 to 2.46</td>
<td>0.21</td>
</tr>
<tr>
<td>Duration of follow-up (6 months or longer)</td>
<td>2.21</td>
<td>0.82</td>
<td>0.40 to 4.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Measurement of asymptomatic recurrences*</td>
<td>0.80</td>
<td>0.33</td>
<td>0.08 to 1.52</td>
<td>0.03</td>
</tr>
</tbody>
</table>

CI, confidence interval; SE, standard error.
*Studies are grouped according to whether a combination of Holter and transtelephonic electrocardiography/event monitor is adopted to detect asymptomatic recurrences during follow-up or not.

**Figure 2** Comparison of left atrial diameter between recurrence and non-recurrence groups in included studies. Note that results are expressed as weighted mean difference and 95% CI. CI, confidence interval.
sources of between-study heterogeneity. AF is often associated with typical symptoms such as palpitations, dizziness, and dyspnea, but a certain proportion of patients remain asymptomatic. Notably, conventional approaches to documenting asymptomatic recurrences are prone to underestimate the overall recurrence rate during follow-up. This is the major reason that anticoagulation, aiming at prevention of thrombus formation, is maintained even after successful ablation. Currently, none of the non-invasive devices available for detecting asymptomatic AF provides comprehensive accurate estimates, the best one being a combination of Holter and transtelephonic ECG, which was adopted in only seven of all the included studies. Given the infeasibility of the widespread use of implanted devices, which may reveal otherwise harbouring episodes of AF, optimization of the protocol for detecting asymptomatic AF appears to be practical and cost-effective.

Study limitations

While it is generally accepted that CPVI offers advantages of increasing acute success rate and low incidence of complications, there is no agreement among worldwide electrophysiology centres regarding a preferred ablation strategy. Despite the exclusion of studies treated with other ablation strategies, the CPVI remains a varying ablation method, ranging from stepwise approach to very extensive substrate ablation. In this meta-analysis, we are unable to distinguish whether diverse additional ablation lines have influence on the association between LA size and AF recurrence for the fact that few patients with diverse additional lines for CPVI were reported with enough details. Hence, we acknowledge that the evidence in favour of enlarged LA for predicting AF recurrences after ablation is less robust and not conclusively proven.

The meta-analysis itself poses limits to determine whether the LA diameter–AF recurrence relationship is linear or not. However, one of the included studies has demonstrated that the risk of AF recurrence after ablation has a 7.3% increase for every 1 mm increase in LA diameter. Patients with mild-to-moderate LA enlargement show a varying response to catheter ablation while patients with a severely enlarged LA may be accurately identified as ‘high risk’ for relapse. Additionally, when LA dilation inclines to asymmetry, LA volume prioritizes to LA diameter. On the other hand, although transthoracic echocardiography is an established and economic accessory examination, foreseeable multiple imaging platforms like delayed-enhancement magnetic resonance imaging are in the interest of clinical practice because

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<thead>
<tr>
<th>Study ID</th>
<th>WMD (95% CI)</th>
<th>% Weight</th>
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<tbody>
<tr>
<td>Delgado (2008)</td>
<td>2.00 (-2.59, 6.59)</td>
<td>1.55</td>
</tr>
<tr>
<td>Husser (2010)</td>
<td>0.00 (-3.06, 3.06)</td>
<td>2.96</td>
</tr>
<tr>
<td>Naskazawa (2009)</td>
<td>1.00 (-1.51, 3.51)</td>
<td>3.9</td>
</tr>
<tr>
<td>Shin (2011)</td>
<td>2.00 (0.46, 3.54)</td>
<td>6.53</td>
</tr>
<tr>
<td>Verma (2004)</td>
<td>0.00 (-2.54, 2.54)</td>
<td>3.84</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, P = 0.623)</td>
<td>1.23 (0.17, 2.29)</td>
<td>18.79</td>
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Figure 3 Subgroup analysis based on different durations of follow-up. Group 1 represents the studies with 6-month follow-up; Group 2 represents the studies with 12-month follow-up; Group 3 represents the studies with over 12-month follow-up. AF, atrial fibrillation.
of their possibility to more accurately quantify LA myocardium injuries and provide insight into the progress of the disease. 38,41 Therefore, pre-procedural measurement of LA size, coupled with quantification of LA fibrosis by advanced image technologies, would be more comprehensive in guiding physicians to manage AF patients with mild-to-moderate LA dilation.

Conclusions

Dilated LA is expected to increase the risk of AF recurrence after single CPVI. This is especially applicable to the patients with long-term follow-up. Further studies are required to explore the mechanism underlying AF recurrences.

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