Can an increase in the pulmonary vein volume measured by three dimensional computed tomography predict the presence of atrial fibrillation?

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Abstract
Background: Left atrial (LA) dilation is associated with morbidity of atrial fibrillation (AF). However, little is known about pulmonary vein (PV) dilation.

Purpose: We investigated the PV volume in the patients with AF.

Methods and results: We performed 3dimensional computed tomography (3DCT) in 155 patients and divided them into three groups: 19 patients without AF (non-AF group, mean age 66 ± 12 years), 50 with paroxysmal AF (PAF group, mean age 67 ± 8 years) and 24 with persistent AF (PeAF group, mean age 64 ± 10 years). The absence of AF was diagnosed in patients with a cardiac implantable electronic device for at least 1 year (mean: 59 ± 37 months). We determined the PV volume as the total volume from the orifice to the first branch of each PV. According to the echocardiographic data, the LA dimension (LAD) and LA volume index (LAVI) were largest in the PeAF group followed by the PAF and non-AF group. According to the morphometric data obtained on 3D-CT, the PV volume was similar in PeAF and PAF groups but significantly smaller in the non-AF group (median value: 24 vs 21 vs 14 mL, respectively). According to the receiver operating characteristic curve analysis, the area under the curve for the PV volume in the presence of AF was 0.80, and the optimum cut-off value was 17 mL (sensitivity 74%, specificity 80%).

Conclusion: The PV volume might be useful for predicting the presence of AF before increases in the LAD and LAVI on echocardiography.

Keywords
atrial fibrillation, computed tomography, left atrium, pulmonary vein, remodeling
1 | BACKGROUND

Atrial fibrillation (AF) is a common cardiac arrhythmia that is correlated with an increased risk of cerebral infarction, heart failure and all-cause mortality.1,2

Percutaneous catheter ablation has become an established therapy for AF.3 Most atrial triggers for paroxysmal AF (PAF) originate in the pulmonary veins (PVs); as such, pulmonary vein isolation (PVI) has become an effective therapy for patients with PAF.5–7

In patients with persistent AF (PeAF), a recently published study failed to demonstrate a superior outcome for the strategy of additional ablation of the left atrium (complex fractionated atriaelectrograms [CFAEs] or additional linear ablation) compared to the PVI-only strategy.8,9 We have thus focused on evaluating the PV structural changes in AF patients.

The PVs were the main source of ectopic beats initiating PAF.4 Stretching changed the electrophysiological properties that increased automaticity and triggered activity of the PVs. These changes induced ectopic firing from the PVs.10 Electrical and structural remodeling that occurred in the PVs subsequently contributed to the enlargement of the PVs.

The enlargement of the LA dimension (LAD) and LA volume index (LAVI) as measured by echocardiography is known to be associated with morbidity of AF.11–14 A long duration of AF leads to left atrial (LA) dilation,13,14 but little is known about the progressive enlargement of the PV volume. The aim of this study was to investigate the course of the PV volume in patients with AF.

2 | METHODS

2.1 | Patients

Patients between 40 and 80 years of age who were able to undergo contrast-enhanced cardiac computed tomography (CT) were enrolled into this study. A total of 155 patients treated at the Showa University Fujigaoka Hospital from January 2015 to December 2017 were initially included.

These patients were then divided into three groups: the Non-AF group (patients who had no episodes of AF); the PAF group (patients who had some episodes of AF lasting up to 1 week); and the PeAF group (patients who had some episodes of AF lasting more than 1 week).

The enrolled Non-AF group included patients fitted with cardiovascular implantable electronic devices (such as pacemaker, implantable cardioverter defibrillator and implantable cardiac monitor) and who had undergone contrast-enhanced cardiac CT due to suspicion of coronary artery disease. We checked that the patients had no history of AF after being fitted with an implantable electronic device for at least 1 year (mean period 59 ± 37 months). The enrolled PAF and PeAF groups included consecutive patients who underwent AF ablation and contrast-enhanced cardiac CT before AF ablation.

The exclusion criteria were a history of catheter ablation for AF, history of cardiac surgery, valvular disease, common PVs, and poor CT images. All patients provided oral informed consent for participation in the study, which was approved by the local Ethics Committee.

2.2 | Detection of AF

We detected AF episodes lasting for more than 30 seconds using 12-lead electrocardiography, 24-hour Holter monitoring or ambulatory electrocardiographic monitoring. We determined no history of AF when they were found to have no electrocardiographic AF burden at all or only episodes within 30 seconds duration.

2.3 | Echocardiographic examinations

Standard echocardiographic examinations were performed using an Artida 4D (Toshiba Medical Systems, Tochigi, Japan) before contrast-enhanced cardiac CT. The left ventricular ejection fraction (LVEF) was calculated using the modified Simpson’s method. The LAVI was measured using the modified biplane area-length method from biplane twodimensional (2D) apical views.15 All echocardiographic measurements were performed at endventricular systole at the maximum left atrium size.

2.4 | Cardiac Multi Detector row Computed Tomography (MDCT) and imaging analyses

Contrast-enhanced cardiac CT was performed using a 64-slice MDCT system (Discovery™ CT750HD; GE Healthcare, Waukesha, WI, USA). The dosage of oral metoprolol, which was administered 2 hours before CT, was adjusted so that the patient’s heart rate did not exceed 65 beats/min.16

A bolus of 0.7 mL/kg of nonionic contrast material (iopromide 370; Bayer Healthcare, Tokyo, Japan) was injected into the right antecubital vein at a flow rate of 3.5-5 mL/s for 12 seconds, followed by a 35-mL salinechasing bolus at 3.5-5 mL/s for all patients.16 The start delay was defined as a test injection in the ascending aorta, and the scan was initiated manually. Scanning was performed using the following parameters: retrospective electrocardiogram (ECG)gated acquisitions, 100-120 kVp, 250-800 mA depending on the patient size, and 64 × 0.625-mm slice collimation. Scanning was performed from the tracheal bifurcation to the diaphragm.

The field of view was adjusted according to the size of the heart. Cardiac CT scans were reconstructed at the end-systolic and mid-diastolic phases using a slice thickness of 0.625 mm and an increment interval of 0.625 mm. One cardiologist who was blinded to any clinical information calculated the PV and LA volumes from threedimensional (3D)-CT images using an imaging software program (Volume analyzer SYNAPS VINCENT; Fujifilm, Tokyo, Japan).

The volume, including that of the PVs and LA, was obtained by segmentation of the LA, which the software automatically calculated. Threedimensional models including these volumes were constructed to exclude the surrounding structures.
The volume of the PVs was defined as the total volume from the orifice to the first branch of each PV in the 3D configuration (Figure 1). The PV orifice was defined by the intersection of tangents extending from the surface of the main trunk of the PV and adjacent LA wall, as the point of maximal inflection between the PV wall and the LA wall. The end of the first branch of each PV was defined by the intersection of the tangents at the branching point (green line). PV, pulmonary vein; LA, left atrium.

The volume of the PVs was defined as the total volume from the orifice to the first branch of each PV in the 3D configuration (Figure 1). The PV orifice was defined by the intersection of tangents extending from the surface of the main trunk of the PV and adjacent LA wall, as the point of maximal inflection between the PV wall and the LA wall. The end of the first branch of each PV was defined by the intersection of the tangents at the branching point. The orifice diameter of the PV was defined as the longest distance between two points of the orifice.

2.5 Statistical analyses

Categorical data were expressed as n (%). Comparisons of categorical data were tested using the Chi-square test. Continuous variables with a normal distribution were expressed as the mean ± standard deviation (SD), and continuous variables without a normal distribution were expressed as the median with 25th and 75th percentiles. The Shapiro-Wilk test was used to check for normality of data distribution. Comparisons of variables with a normal distribution were tested by an analysis of variance followed by a Tukey-Kramer post hoc analysis. Comparisons of variables with a nonnormal distribution were tested using the Kruskal-Wallis test followed by a Steel-Dwass post hoc analysis. A receiver operating characteristic (ROC) curve analysis was performed to determine the optimum cut-off value of the PV volume that gave the best sensitivity and specificity. The JMP 12 software program (SAS institute, Cary, NC, USA) was used for the statistical analyses. A P value of <0.05 was considered statistically significant.

3 RESULTS

The patient distribution is summarized in Figure 2. All 155 patients (42 without AF, 66 with PAF and 47 with PeAF) who underwent 3D-CT were included. In the Non-AF group (n = 42), 23 patients were excluded due to common PVs (n = 1) and poor CT images (n = 22). In the PAF group (n = 66), 16 patients were excluded due to a history of catheter ablation for AF (n = 3), common PVs (n = 6) and poor CT images (n = 7). In the PeAF group (n = 47), 23 patients were excluded due to a history of catheter ablation for AF (n = 9), a history of cardiac operation (n = 1), common PVs (n = 5) and poor CT images (n = 8).

Accordingly, the final analysis included 372 PVs in 19 patients in the Non-AF group, 50 patients in the PAF group and 24 patients in the PeAF group.

3.1 Clinical characteristics

The clinical characteristics of the patients in the three groups in this study are presented in Table 1. There were no significant differences in the age, sex, body weight, body surface area or the prevalence of hypertension or diabetes mellitus among the three groups. However, the PeAF group was taller (median [interquartile range (IQR)]: 158 [151, 169] cm vs 163 [155, 170] cm vs 165 [161, 174] cm, P < 0.001) and had a higher BNP (median [IQR]: 43 [20, 113] cm vs 62 [34, 91] cm vs 138 [75, 175] cm, P < 0.001) than the Non-AF and PAF groups. The prevalence of chronic heart failure (CHF) was greatest in the PeAF group followed by the PAF group and Non-AF group (n [%]: 12 [50%] vs 8 [16%] vs 1 [5%], respectively), and a majority were cases of heart failure with a preserved ejection fraction (HFpEF).

3.2 A comparison of echocardiographic data

Table 2 shows the echocardiographic data. Overall, both the Non-AF and PAF groups showed comparable echocardiographic features including the LAD, LAVI, left ventricular enddiastolic dimension (LVDd), LVEF and left ventricular filling pressure (E/e’). The PeAF group had a significantly larger LAD (median value [IQR] 38 [34, 45] mm vs 39 [35, 41] mm, 43 [40, 47] mm, P < 0.001) and had a higher BNP (median [IQR]: 43 [20, 113] cm vs 62 [34, 91] cm vs 138 [75, 175] cm, P < 0.001) than the Non-AF and PAF groups. The prevalence of chronic heart failure (CHF) was greatest in the PeAF group followed by the PAF group and Non-AF group (n [%]: 12 [50%] vs 8 [16%] vs 1 [5%], respectively), and a majority were cases of heart failure with a preserved ejection fraction (HFpEF).

3.3 A comparison of morphometric data obtained on CT

Table 3 shows the morphometric data obtained by CT. The PV volume was similar in the PeAF and PAF groups but significantly smaller in the Non-AF group (median: 24 vs 21 vs 14 mL). After correcting for the body surface area (BSA), the result was similar (median value: 14 vs 13 vs 9 mL). The orifice diameter of both the left superior PV (LSPV) and right superior PV (RSPV) showed similar trends (LSPV: median: 22 vs 20 vs 18, RSPV: median: 23 vs 23 vs 18 cm) with reference to the PV volume.
TABLE 1  Patients’ clinical characteristics

|                  | Non-AF (n = 19) | PAF (n = 50) | PeAF (n = 24) | P value |
|------------------|----------------|--------------|--------------|---------|
| Age, years       | 66 ± 12        | 67 ± 8       | 64 ± 10      | N.S     |
| Male gender, n (%) | 9 (47)        | 31 (62)      | 18 (75)      | N.S     |
| Height, cm       | 158 (151, 169) | 163 (155, 170) | 165 (161, 174) | 0.0237 |
| Body weight, kg  | 59 (53, 77)    | 66 (54, 78)  | 62 (55, 78)  | N.S     |
| BSA, m²          | 1.6 (1.5, 1.8) | 1.7 (1.5, 1.8) | 1.7 (1.5, 1.9) | N.S     |
| Hypertension, n (%) | 6 (32)       | 21 (42)      | 8 (33)       | N.S     |
| DM, n (%)        | 5 (26)         | 8 (16)       | 4 (19)       | N.S     |
| Dyslipidemia, n (%) | 6 (32)      | 16 (32)      | 6 (25)       | N.S     |
| CHF, n (%)       | 1 (5)          | 8 (16)       | 12 (50)      | 0.0008  |
| HFpEF, n(%)      | 0 (0)          | 8 (16)       | 10 (42)      | <0.001  |
| BNP, pg/mL       | 43 (20, 113)   | 62 (34, 91)  | 138 (75, 175) | 0.001   |

AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; BSA, body surface area; DM, diabetes mellitus; CHF, chronic heart failure; HFpEF, heart failure with preserved ejection fraction; BNP, brain natriuretic peptide; N.S, not significant.

TABLE 2  A comparison of the echocardiographic data

|                  | Non-AF (n = 19) | P value<sup>a</sup> | PAF (n = 50) | P value<sup>b</sup> | PeAF (n = 24) |
|------------------|----------------|----------------------|--------------|----------------------|---------------|
| LAD, mm          | 38 (34, 45)    | N.S                  | 39 (35, 41)  | <0.001               | 43 (40, 47)   |
| LAVI, mL/m²      | 32 (26, 39)    | N.S                  | 34 (25, 40)  | 0.008                | 42 (34, 45)   |
| LVDd, mm         | 49 (46, 52)    | N.S                  | 46 (42, 51)  | N.S                  | 48 (45, 52)   |
| LVEF, %          | 60 (54, 66)    | N.S                  | 63 (58, 65)  | N.S                  | 61 (48, 65)   |
| E/e’(sep)        | 11 (8, 13)     | N.S                  | 9 (8, 13)    | N.S                  | 8.6 (7.1 12)  |
| E/e’(lat)        | 9 (7, 13)      | N.S                  | 9 (6, 11)    | N.S                  | 9 (6, 11)     |

AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; LAD, left atrial dimension; LAVI, left atrial volume index; LVDd, left ventricular enddiastolic dimension; LVEF, left ventricular ejection fraction.

<sup>a</sup>P-value of Non-AF groups vs PAF groups.

<sup>b</sup>P-value of PAF groups vs PeAF groups.
In contrast, the LA volume was largest in the PeAF group followed by the PAF and Non-AF groups (median: 117 vs 95 vs 72 mL). There were significant differences among the groups, suggesting a step-by-step increase in the LA volume, depending on the disease severity. After correcting for the BSA, the results were similar (median: 69 vs 59 vs 44 mL).

As shown in Figure 3, the receiver operating characteristic (ROC) curve analysis revealed that the area under the curve (AUC) for the PV volume in the presence of AF between the Non-AF group and PAF group was 0.80. The optimum cut-off value for the PV volume in the presence of AF was determined to be 17 mL (sensitivity 74%, specificity 80%).

Figure 4 shows the distribution of PV volume/BSA and LA volume/BSA in each group. Non-AF group patients tended to locate in lower left while PeAF group patients tended to locate in upper right, which was in-between but upper in PAF group.

4 | DISCUSSION

The main finding of this study was that the PV volume increased when PAF occurred. However, the volume did not change when AF was sustained. This was the first study to evaluate the course of the PV volume by 3D-CT in patients with AF. The PV volume by

![Diagram of ROC curve](image)

**FIGURE 3** An ROC curve analysis for the PV volume in the presence of AF. The ROC curve analysis reveals that the AUC for the PV volume in the presence of AF between the Non-AF and PAF groups is 0.80, with the optimum cut-off value for PV volume being 17 mL (sensitivity 74%, specificity 80%). ROC, receiver operating characteristic; AUC, area under the curve

![Diagram of distribution](image)

**FIGURE 4** The distribution of the PV volume/BSA and LA volume/BSA in each group. The blue circles are the Non-AF patients, the red triangles are the PAF patients, and the green squares are the PeAF patients. PV, pulmonary vein; BSA, body surface area; LA, left atrium
3D-CT increased before that of the LAD or LAVI as measured by echocardiography.

A previous study revealed the significant dilation of the superior PV orifice in AF patients compared to patients with a normal sinus rhythm. In the present study, the significant dilation of the LSPV and RSPV orifice was observed in the PAF group compared to the Non-AF group. However, the PV orifice did not change when AF was sustained. The PV volume was also significantly increased in the PAF group compared to the Non-AF group but was unchanged when AF was sustained. The AUC for the PV volume in the presence of AF was higher than that for LSPV and RSPV orifice (0.80 vs 0.75 vs 0.69, respectively; Fig. S1).

In the early period of AF, measuring the PV volume might be a better method of evaluating the remodeling closely connected with arrhythmogenic characteristics than the measurement of the orifice of PVs. The high pressure of the LA may stretch the PVs at the proximal portion beyond the visceral pericardium. Due to the lack of time series data in our study, it is difficult to fully clarify the cause-effect relationship between PV dilation and LA stretches. In the PV, the myocardial sleeve is directly extended from the LA myocardium and has arrhythmogenic characteristics. The mean lengths of the myocardial sleeves of the LSPV and RSPV were 14.3 ± 7.5 and 12.6 ± 6.6, respectively. The most distal area of the myocardial sleeves showed increasing fibrosis. Furthermore, pericardial reflection is located on the proximal portion of the PVs. The average distance of pericardial reflection from the PV orifice in the LSPV is 13.7 mm, while that in the RSPV is 9.2 mm. The visceral pericardium is made up of collagen fibers that resist dilation, so the portion of the PVs covered by the visceral pericardium shows difficulty in being sufficiently dilated. The proximal portion beyond the visceral pericardium is thus more easily affected by stretching and dilation than the PV orifice. The measurement of PV volume may thus be better than that of the PV orifice.

Enlargement of the LAD and LAVI associated with electrical and structural remodeling is important for the initiation and maintenance of AF. Previous studies have suggested that certain LA structures, including the LAD and LAVI, increase in size with a lengthy burden of AF. However, a study in an AF population found that there were some patients with a normal LA size but an abnormal LA function.

We also showed that despite the normal LAD and LAVI in the PAF group, a significantly increased PV volume was observed. In contrast, the PeAF group had a significantly increased LAD and LAVI as well as PV volume. Progressive LA dilation is associated with asymmetrical structure remodeling and adoption of shapes such as trapezoidal. The largest LA surface in AF patients is frequently situated just under the upper PVs. Therefore, in the early period of AF, we underestimated the LA volume when using echocardiography with the ellipsoid formula. According to our data, it is also important to note that the volume assessment of the LAVI showed some discrepancy between CT and echocardiography. The LAVI was larger on CT than on echocardiography, with the difference the greatest in the PeAF (mean LAVI [mL/m²]: 69 on CT vs 42 on echocardiography) group followed by the PAF (59 vs 34) group and non-AF group (44 vs 32).

After initiating AF, electrical and structural remodeling occurred in the PVs and LA. These changes contributed to the enlargement of the LA and the maintenance of AF. Our data showed that a long duration of AF leads to LA dilation as demonstrated by echocardiography, suggesting that the PV volume was increased before the significant enlargement of the LAD or LAVI on echocardiography (Figure 5). PV dilation without LA enlargement may suggest that the patient is in the early period of AF.

When measuring the PV volume, it is important to confirm the lack of an AF episode. A previous study showed that the definition of no AF episode was a normal sinus rhythm as assessed by ambulatory electrocardiographic monitoring or no history of documented AF. However, the evaluation of
AF episodes by these methods was shown to be insufficient. Remodeling occurs both before and during early AF. We therefore evaluated the duration of the electrocardiographic AF burden with cardiovascular implantable electronic devices used for more than 1 year.

### 4.1 Limitations
Several limitations associated with the present study warrant mention. First, this study included a relatively small number of patients in a highly selected population. Second, we determined patients to have no history of AF using cardiovascular implantable electronic devices. This method was the best way to evaluate the presence of AF episodes, but there was a selection bias for patients with cardiovascular implantable electronic devices. However, most characteristics and echocardiographic features were similar between the Non-AF group and the other groups. Third, 22 out of 42 patients (52%) in Non-AF group were excluded from this study due to ‘poor image.’ In these excluded patients, the PV was partially out of scan range because the images were obtained for suspicion of coronary artery disease.

Fourth, we evaluated the structural remodeling but not the electrical remodeling.

### 5 Conclusion
Enlargement of the PV develops before enlargement of the LAD and LAVI as measured by echocardiography, suggesting that the PV volume, particularly that over 17 mL, might be useful for predicting the presence of AF.

### Conflict of Interest
The authors declare no conflicts of interest for this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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