Relationship Between Duration of Atrial Fibrillation and Right Heart Structure Remodeling as Assessed by 3-Dimensional Transesophageal Echocardiography

Izumi *et al.* AF Duration and Right Heart Remodeling

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Conflict of interest: None declared.

ABSTRACT

Background—Tricuspid valve (TV) remodeling occurs in patients with atrial fibrillation (AF); however, the affecting factor related to TV remodeling in AF remains to be elucidated. We sought to explore whether the AF persistence itself affects right heart remodeling.

Methods—A total of 372 lone AF patients (234 paroxysmal AF [paroxAF] and 138 persistent AF [persAF]) who underwent 3-dimensional transesophageal echocardiography (3D-TEE) was retrospectively reviewed. The duration from first-detected episode of AF to the TEE exam date was defined as AF duration.

Results—PersAF patients had a larger TV area index (625.4 vs 719.0 mm^2/m^2; P<0.001) and a higher right atrium area-to-right ventricle end-systolic area ratio (RA/RVESA ratio, 1.7 vs 1.9; P=0.005) than paroxAF patients. The prevalence of AF-tricuspid regurgitation was higher in persAF than in paroxAF patients (1.3 % vs 12.3 %; P<0.001). In persAF patients, AF duration was moderately correlated with TV diameter and 3D-TEE-derived TV annular area but not in paroxAF. On multivariable analysis, AF duration was independently associated with TV annular dilatation even after adjustment for RA/RVESA ratio and tricuspid regurgitation severity (β 0.37 [95% CI: 0.77-1.81]; P<0.001). Additionally, AF duration with cutoff values of 20 months for predicting TV annular dilatation and 37 months for predicting RA/RVESA ratio >2.1 had both high diagnostic accuracies among persAF patients (both P<0.01).

Conclusions—AF duration itself is independently associated with right heart remodeling in persAF but not in paroxAF, such as TV annular dilatation and predominant RA remodeling which may lead to subsequent TR progression and adverse outcomes.

Key Words: atrial fibrillation; right atrium; transesophageal echocardiography, 3-dimensional; tricuspid valve; tricuspid valve insufficiency.

1. Introduction

In the management of patients with atrial fibrillation (AF), there has been an increased focus on reducing adverse cardiovascular outcomes through early rhythm control rather than rate control.[1,2] This is also confirmed by the previous finding that restoration of sinus rhythm induces cardiac cavity reverse remodeling and reduces valvular regurgitation.[3] Long-standing AF by itself has been thought to be associated with the development of functional tricuspid regurgitation (TR) in patients with structurally normal valve leaflets and dilated tricuspid valve annulus (TVA), so called atrial functional TR (AF-TR).[4] In patients with AF-TR, TVA become larger, planar, rounder, and less contractile with small tethering angle. The prevalence of significant AF-TR was reportedly about 15% and increased in proportion to the duration of AF in lone AF cohort.[5] The most recent population-based cohort study demonstrated that one-third of the new-onset AF patients developing moderate or greater TR during 13.3 years follow-up and the incidence of significant AF-TR was associated with poor long-term survival.[6] Most previous studies have been focused on AF-TR, whereas recent study has been reported that right atrium (RA) and TVA remodeling is observed even in AF patients without significant AF-TR, which is considered as the effect of AF as the rhythm abnormality by itself.[7]

Due to nonplanar and dynamic complex geometry of tricuspid valve (TV) apparatus,[8] geometrical assumption or error in spatial orientation may occur using only 2-dimensional transthoracic echocardiography (2D-TTE). Real-time 3-dimensional transesophageal echocardiography (3D-TEE) allows the appreciation of leaflet deformation and the accurate quantification of annular area and of the complex annular dynamics during the cardiac cycle.[9] Since not all patients with AF develop significant right heart remodeling and AF-TR, addressing this issue may contribute to the precision medicine among patients with AF. Therefore, in the present study, we sought to investigate the prevalence of AF-TR in patients with AF, and the extent to which AF persistence itself affects the right heart remodeling especially focusing on AF patterns and AF duration using 3D-TEE.

2. Methods

2.1. Study population

This study was exempted from institutional review board approval owing to the use of publicly available deidentified data. The data that support the findings of this study are available from the corresponding author upon reasonable request. We retrospectively reviewed the echocardiographic and clinical data from the patients' clinical records of 643 consecutive patients with AF who underwent both 2D-TTE and 3D-TEE in Hiroshima University Hospital between January 2017 and December 2019 for clinical indications. 2D-TTE was performed within 3 months prior to 3D-TEE, and no patients underwent catheter ablation within the past one year from the date of TEE examination. Initial 3D TV screening using real time 3D-TEE was carefully performed, which can determine the primary TR with an anatomic abnormality in the TV leaflets. As a result of this screening, 57 patients were excluded from this study. Further exclusion criteria which were (1) patients with left-sided heart diseases such as significant mitral regurgitation (MR) including caused by AF, mitral stenosis, aortic stenosis, aortic regurgitation, and all kinds of cardiomyopathy (n = 195), (2) patients with pulmonary hypertension (n = 8), and (3) patients with right ventricle dysfunction (n = 11) left 372 patients (mean age, 67 ± 10 years; 71% men) included in this analysis. Hence, this cohort could be considered as having normal TV geometry and the exact lone AF population including AF-TR and comprised a group with paroxysmal AF (paroxAF) and persistent AF (persAF) (Figure S1). Biological variables such as plasma levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and human atrial natriuretic peptide (hANP) within 1 month before the TEE examination were collected from patients' clinical records.

2.2. Definition of AF patterns and duration

The duration from first-detected episode of AF to the date of TEE examination was defined as AF duration in this study (Figure 1). AF duration was retrospectively determined from the patients' clinical records such as medical history, electrocardiogram (ECG), Holter-ECG, echocardiography, and referral letters from family doctors. PersAF was defined as lasting for AF rhythm at least more than 7 days until the date of TEE examination and the rest of study population was defined as paroxAF according to the current definitions.[10] ParoxAF includes both of sinus and AF rhythm on the date of TEE (Figure 1A, 1B). PersAF includes those in which AF rhythm is sustained from the first-detected episode to the date of TEE (Figure 1C) and those in which paroxAF gradually shifts to persAF (Figure 1D).

2.3. 2D-TTE

Comprehensive 2D-TTE with a focus on the TV and the right ventricle (RV) was performed using a commercially available ultra-sound systems (S5-1 probe; EPIQ7, Philips Medical Systems, Andover, MA). Standard left-sided chamber volumes and left ventricular ejection fraction (LVEF) were measured according to the current recommendations.[11] The RV was imaged from multiple views, including an RV-focused apical four-chamber (A4C) view. Right-sided chamber size and function were measured according to the American Society of Echocardiography guidelines for the echocardiographic assessment of the right heart.[12] RA area-to-RV end-systolic area ratio (RA/RVESA ratio) was calculated from RA area divided by RV area at end-systolic frame. Systolic pulmonary artery pressure was calculated from the systolic RV pressure gradient and the RA pressure. RA pressure was estimated from the inferior vena cava diameter and respiratory changes.[12] Grading of TR severity was determined by using a multiparametric integrated approach.[13] Using the zoom mode focused on the TV, images were acquired in an A4C view and a parasternal RV-inflow view. Measurements of the TVA diameter was performed off-line by the first author and the echocardiography specialist (level III trained) in mid-diastole at the timing of the maximum TV opening and mid-systole at the timing of the minimum TV closing between the two hinge points at the junction between the TV leaflets and the TVA. In patients with AF, TVA diameter was determined as the average of three to five cardiac cycles.

2.4. 3D-TEE

3D-TEE was performed under sedation using intravenous injection of midazolam and pentazocine. EPIQ7 ultrasound imaging system equipped with a fully sampled matrix-array TEE transducer (X8-2t Live 3D TEE transducer; Philips) can display both 2D and 3D images. At first, the 2D TV images were clearly demonstrated in the mid esophageal oblique short-axis view and coronary sinus view. Volume datasets were obtained under breath-hold to avoid stitch artifacts using multi-beat 3D zoom mode focused on the TV (median frame rate = 90Hz) (Figure 2A) or using multi-beat full volume mode in the mid esophageal short-axis view focused on the right ventricle (median frame rate = 34Hz). In patients with AF, the live 3D zoom mode with one-beat volume acquisition was sometimes chosen to avoid stitch artifacts. The views were optimized for depth and gain setting before 3D acquisition and close attention was given to including the entire TV or RV in the sector boundaries.

2.5. TVA quantitative analysis

Digitally stored 3D zoom mode of TV or full volume data focused on the RV was imported into the workstation (QLAB ver.13.0; Philips). We performed the volume rendering assessing of the entire TV displayed with the interatrial septum placed inferiorly in the 6 o'clock position. The mitral module of the QLAB mitral valve navigator (MVN) software (Philips) was used in an off-label fashion for semiautomated indirect measurement of 3D-TEE TVA diameter in the mid-diastole and the mid-systole. As previously described,[4] we used 20 landmarks to delineate the TVA and analyzed the TV leaflets using ≤ 22 intersections per patient. Anterior-posterior (A-P) and anterolateral-posteromedial (AL-PM) directions were determined based on the commissure between anterior and septal leaflets as an anterior direction (Figure 2B). TVA diameter: A-P and AL-PM diameters, TVA area, annular height, and TVA ellipticity (AL-PM/A-P ratio) were obtained in the mid-diastolic and mid-systolic frames. The closed leaflets were traced in mid-systole on successive equidistant of long-axis planes to obtain tenting volume. In patients with AF, three measurements from three different beats were averaged.

2.6. Statistical analysis

Categorical variables were expressed as numbers with relative percentages and were compared using the chi-square test or the Fisher's exact test. Continuous variables were expressed as mean ± standard deviation or median (inter-quartile range) and were compared using the student t-test or the Wilcoxon test. Clinical characteristics, 2D-TTE and 3D-TEE characteristics were included in univariate analysis. Correlation between AF duration and RA/RVESA ratio, TVA diameter measured by 2D-TTE and 3D-TEE, and 3D TVA area measured by 3D-TEE were examined using the Spearman rank correlation test. To identify the determinants of TVA dilatation, linear regression analyses were performed in persAF patients for multivariable analyses controlling for potential confounding variables based on their significance (p <0.2). Optimal cut-off values of AF duration in persAF patients for predicting TVA dilatation and increase of RA/RVESA ratio were determined using a receiver operating characteristic (ROC) analysis. Statistical significance was determined by a P value<0.05. Statistical analyses were performed using JMP pro 16 (SAS Institute, Cary, NC).

3. Results

3.1. Clinical characteristics

Of the 372 patients, 234 (63%) were categorized as paroxAF, and the rest of 138 (37%) were categorized as persAF. Clinical characteristics are listed in Table 1 and key parameters are also listed in Figure 3A. Patients with persAF had lower systolic blood pressure (p<0.001) and higher diastolic blood pressure (p <0.001) than patients with paroxAF. Heart rate was significantly higher in persAF than in paroxAF patients (p<0.001). There was no significant difference in AF duration between two groups (22 vs 29 months; p = 0.119). The frequency of more than moderate grade of AF-TR was significantly higher in persAF patients than in paroxAF patients (1.3 % vs 12.3 %; p <0.001) (Figure S2). Plasma levels of NT-ProBNP and hANP in persAF patients were significantly higher than in paroxAF patients (both p <0.001).

3.2. 2D-TTE parameters

2D-TTE characteristics are listed in Table 2 and key parameters are also listed in Figure 3B. Compared with paroxAF patients, persAF patients had a lower LVEF with larger left atrium volume index and RA area (all p <0.001). PersAF patients were generally associated with larger RV diameter and area than paroxAF patients, whereas there were no significant differences in end-diastolic longitudinal diameter between two groups (p = 0.928). PersAF patients had a lower tricuspid annular plane systolic excursion (TAPSE) and a higher tricuspid regurgitation pressure gradient and estimated RA pressure than paroxAF patients (all p <0.05). In the TVA analysis, 2D-TTE-derived TVA diameters measured in A4C and inflow views were significantly longer in persAF patients than in paroxAF patients both in mid-diastole and mid-systole frames (all $p < 0.05$). Notably, AF duration was mildly correlated with RA/RVESA ratio in persAF patients (r=0.32, $p < 0.001$), whereas there was no significant correlation in paroxAF patients (Figure 4). Additionally, there were no significant correlations between AF duration and 2D-TTE-derived TVA diameter measured in A4C view in mid-diastole both in paroxAF and persAF patients (Figure S3).

3.3. 3D-TEE TVA geometry

3D-TEE TVA geometry is also listed in Table 2. Compared with paroxAF patients, persAF patients had a longer TVA diameter both on AL-PM and A-P directions and a larger 3D TVA area index both (all $p < 0.001$). Also, persAF patients showed a lower ellipticity of TVA both in mid-diastole and mid-systole frames as compared with paroxAF (both $p < 0.05$), which means annulus becomes larger in A-P direction, as a result that annulus is getting closer to the circle. Annular contraction was significantly lower in persAF patients than in paroxAF patients ($p < 0.001$) and there was no significant difference in annular height between two groups. Notably, moderate correlations between AF duration and TVA diameters both on AL-PM and A-P directions and 3D TVA area in mid-diastole frame were observed in persAF patients (r = 0.35, 0.35, and 0.46, respectively, all $p < 0.001$), whereas there were no significant correlations between AF duration and TVA diameters and 3D TVA area in paroxAF patients (Figure 5).

3.4. Determinants of TVA dilatation

From the above findings, no correlation between AF duration and TVA dilatation in paroxAF patients, consequently we examined the determinants of TVA dilatation only in persAF patients. To explore the determinants of TVA dilatation such as TVA diameter measured by 2D-TTE and TVA area measured by 3D-TEE, multivariate linear regression analysis was performed with the following covariates: AF duration, RA/RVESA ratio, more than moderate grade of TR, and several demographic variables including age, sex, and body surface area. Higher grade of TR remained as the independent determinants of TVA diameter measured by 2D-TTE (β: 0.19 [95% CI: 0.21 to 3.04]; $p = 0.025$), whereas AF duration (per 1 month increase, β: 0.37 [95% CI: 0.77 to 1.81]; $p < 0.001$) as well as RA/RVESA ratio and more than moderate grade of TR were the independent determinants of TVA area measured by 3D-TEE (Table 3).

3.5. AF duration and right heart structure remodeling

ROC curve analysis was performed in persAF patients to determine the AF duration required for significant TVA dilatation and right heart remodeling. TVA dilatation was defined as TVA diameter more than 40 mm measured by 2D-TTE A4C view according to the current guideline[14] and as TVA area index more than 840 mm^2/m^2 measured by 3D-TEE which was calculated from the value of TVA area (mean + 2SD) in healthy volunteers in a previous paper.[8] As a result, AF duration with a cutoff value of 47 months is a low accurate parameter for predicting TVA diameter dilatation (AUC 0.58 [95% CI: 0.45 to 0.72], p = 0.031; Figure 6A). In contrast, AF duration with a cutoff value of 20 months to predict TVA area index dilatation measured by 3D-TEE had much larger AUC (AUC 0.73 [95% CI: 0.63 to 0.83], p = 0.002; Figure 6B). Regarding right-sided heart remodeling, a previous paper revealed that RA/RVESA ratio more than 2.1 was the cumulative event risk of AF-TR progression.[15] In this study, AF duration for predicting RA/RVESA ratio more than 2.1 was 37 months which was longer than the AF duration to predict TVA dilatation measured by 3D-TEE (AUC 0.76 [95% CI: 0.66 to 0.83], p <0.001; Figure 6C).

3.6. Reproducibility

Intraobserver and interobserver variabilities in the 3D measurements was as follows: TVA area in mid-systole frame, 22 ± 26 mm^2 and 35 ± 40 mm^2; TVA area in mid-diastole frame, 24 ± 24 mm^2 and 34 ± 38 mm^2, respectively. Intraclass correlations (95% CI) for each of the measurements were as follows: TVA area in mid-systole frame, 0.94 (0.92–0.96) and 0.92 (0.90–0.95); TVA area in mid-diastole frame, 0.94 (0.91–0.97) and 0.91 (0.89–0.94).

4. Discussion

In this study, we assessed the exact lone AF population considered as having normal TV geometry and having no left-sided heart disease including AF-MR, pulmonary hypertension, and RV dysfunction using TV screening by 3D-TEE. Therefore, the findings in the present study seems to be a consequence of AF itself as the rhythm abnormality. The main findings of this study can be summarized as follows; (1) The prevalence of significant AF-TR was higher in persAF patients than in paroxAF patients. (2) PersAF patients had larger RA area, RV dysfunctions, higher RA/RVESA ratio and larger TVA diameter and area than in paroxAF patients, nevertheless there was no significant difference in AF duration between two groups. (3) AF duration was correlated with TVA diameter and area measured by 3D-TEE in persAF patients, but not in paroxAF patients. (4) AF duration as well as RA/RVESA ratio and more than moderate grade of TR were the independent determinants of TVA area measured by 3D-TEE in persAF patients. (5) AF duration with a cutoff value of 20 months for predicting TVA area dilatation and AF duration with a cutoff value of 37 months for predicting RA/RVESA ratio more than 2.1 were both accurate parameters in persAF patients. To our knowledge, this is the first study to demonstrate the correlation between AF duration and TV geometry and right heart remodeling.

4.1. AF duration and TVA remodeling

Traditionally, AF has been thought to be associated with the development of AF-TR due to RA and TVA dilatation.[4] Another previous study demonstrated that AF itself and the associated RA dilation are the main cause of the TV remodeling in patients with intrinsically normal TV leaflets without severe TR.[16] However, not all patients with AF develop structural TV remodeling or AF-TR. Our study is unique due to focusing on AF patterns and AF duration to investigate this issue. In patients with persAF, AF duration was correlated with TVA area measured by 3D-TEE and AF duration was the independent determinant of TVA dilatation. These findings may indicate that TVA remodeling due to AF itself is depended on the extent of dividual exposure to AF as a rhythm abnormality. Consequently, the present study suggests that the early maintenance of sinus rhythm control in AF patients can prevent TVA remodeling and its adverse clinical effects, as described in previous studies.[1]

It has been shown that the measurements of the TVA diameter using 2D-TTE is systematically smaller than 3D-TEE measurements because of the TVA orientation and shape which are highly variable among individuals.[17] Utsunomiya et al.[18] reported that the TVA is likely to displaced posteriorly among AF-TR patients and AF-TR patients have higher posterior annular perimeter/total annular perimeter ratio than patients with ventricular functional TR. In our study, the ellipticity was lower in persAF patients due to the TVA enlargement in the A-P direction as in previous studies shown. Utsunomiya et al.[19] has also indicated that this direction of TVA dilatation among AF-TR patients contributes to more prominent bias of TVA diameter between 3D-TEE and 2D-TTE. With these findings, we used both 2D-TTE and 3D-TEE in the present study to clarify the difference between two parameters. Important findings are that among persAF patients, correlation between AF duration and TVA diameters and area measured by 3D-TEE were observed, whereas there was no significant correlation between AF duration and TVA diameters measured by 2D-TTE. Furthermore, ROC curve analysis showed that cutoff value of the AF duration was much shorter measured by 3D-TEE than 2D-TTE and the AUC was much larger measured by 3D-TEE than 2D-TTE. These results suggest that measurement of TVA by 2D-TTE may not detect early TVA remodeling due to the TVA dilatation in A-P direction.

4.2. AF duration and right heart structure remodeling

In considering the relationship between AF duration and TVA remodeling, it may also be important to consider the relationship between AF duration and right heart structure remodeling. The previous study showed that among AF-TR patients, RA volume was the determinant of TVA area and RA/RV end-systolic volume ratio was the determinant of TVA orientation.[20] Much attention has been focused on this remodeling balance between RA and RV, Kwak et al.[15] showed that larger RA area and RA/RVESA ratio were the independent predictors of AF-TR progression. In the present study, AF duration was mildly correlated with RA/RVESA ratio in persAF patients and multiple linear regression analyses revealed that RA/RVESA ratio was the one of the determinants of TVA area measured by 3D-TEE. Moreover, AF duration for predicting RA/RVESA ratio more than 2.1 was 37 months which could mean an increased risk of progression to AF-TR and it is longer than the AF duration for predicting TVA area dilatation. The present study has made it possible to consider the relationship between AF duration and right heart remodeling in the context of a time sequence only in persAF patients not in paroxAF patients (Figure 7).

4.3. Clinical implications

Previous studies have suggested that increasing TR severity is associated with worse survival regardless of LVEF or pulmonary artery pressure.[21] Therefore, it is important in the management of AF patients to prevent TV remodeling and progression of AF-TR to improve prognosis. Prospective randomized trials of rate-control versus rhythm-control therapy in patients with AF were conducted in 2000's, the rhythm-control strategy offers no survival advantage over the rate-control strategy.[22] In recent years, however, AF itself has been considered to be a cause of heart failure and valvular heart disease, a recent randomized control study demonstrated that early rhythm-control therapy was associated with a lower risk of adverse cardiovascular outcomes.[2] Looking at the current world guidelines of recommendations for catheter ablation in AF patients,[23,24] the indication for transcatheter treatment of longstanding persAF patients is still controversial and is often determined by the presence of symptoms or heart failure. The present study clarified that the clinical backgrounds of paroxAF and persAF are quite different, and that they may be considered as different pathologies especially in terms of right heart remodeling. This study also revealed that AF duration was associated with right heart remodeling such as TVA dilatation and predominant RA remodeling only in persAF patients, not in paroxAF patients. Therefore, these findings contribute to understand the precise disease severity in terms of structural heart remodeling which can lead to significant progression of AF-TR, and to determine the early intervention timing of rhythm control therapy. However, whether early rhythm-control therapy before right heart remodeling in this population translates into better outcomes remains to be addressed in prospective, randomized, and long-term studies.

4.4. Study limitations

Several limitations of our study needed to be considered. First, this was a retrospective single center study with a relatively small sample size. Second, it is quite difficult to know how long one patient has been exposed to AF rhythm in one's whole life, considering that quite a few patients have no symptoms while in AF rhythm. We evaluated AF duration which defined from the patients' record as much as possible in this study, but not all data of AF duration may reflect the accurate exposure period of AF rhythm. Third, to our knowledge, there is no exact cutoff value for TVA enlargement measured by 3D-TEE, so that we used TV area of the normal cohort +2 SD as TVA dilatation in this study. Prospective studies are needed to establish the definition for TVA enlargement measured by 3D echocardiography. Forth, we analyzed only TV not including mitral valve, this is because the present study cohort was exact lone AF patients which means all left-sided heart disease including AF-MR were excluded in this study protocol. Finally, the previous study showed that inflammasome activation in atrial cardiomyocytes is associated with the pathogenesis of AF;[25] however, pathophysiological complete mechanisms of AF remain to be elucidated. Further prospective studies are needed to resolve this issue.

5. Conclusions

The contributions of AF duration to TVA and right heart remodeling differs between paroxAF and persAF. In persAF patients, AF duration itself is one of the independent determinants of TVA dilatation. For management and treatment of AF, it is important to be aware of AF duration in terms of TVA and right heart remodeling, and to determine the appropriate timing of rhythm-control therapy to prevent the pathogenesis of AF-TR.

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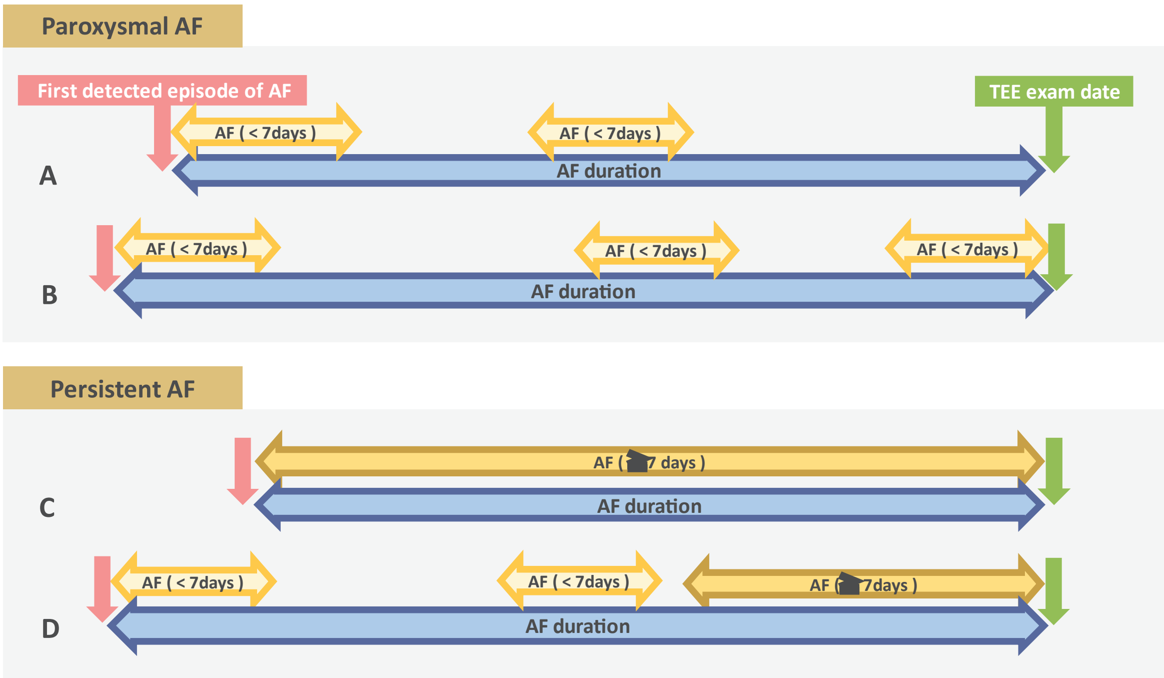
Supplemental Material

Figures S1–S3

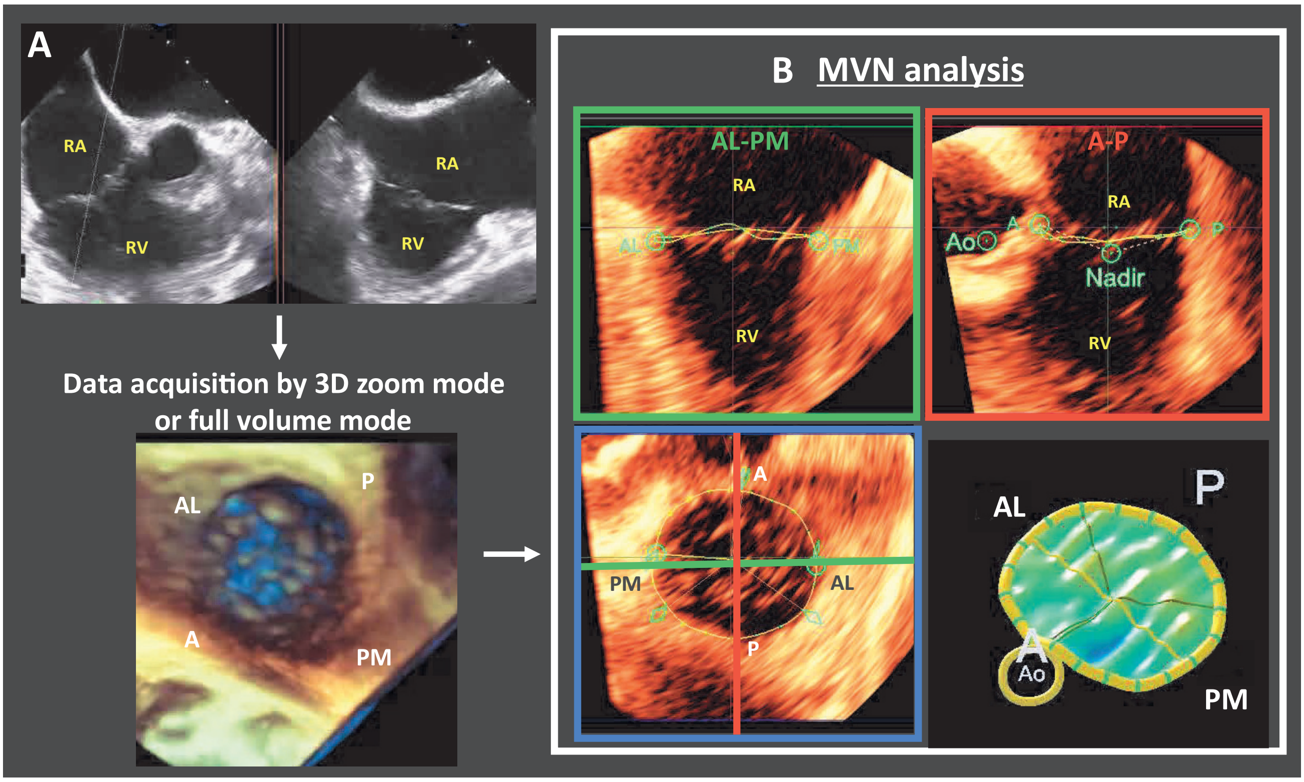
Figure Legends

Figure 1. Definition of AF patterns and duration



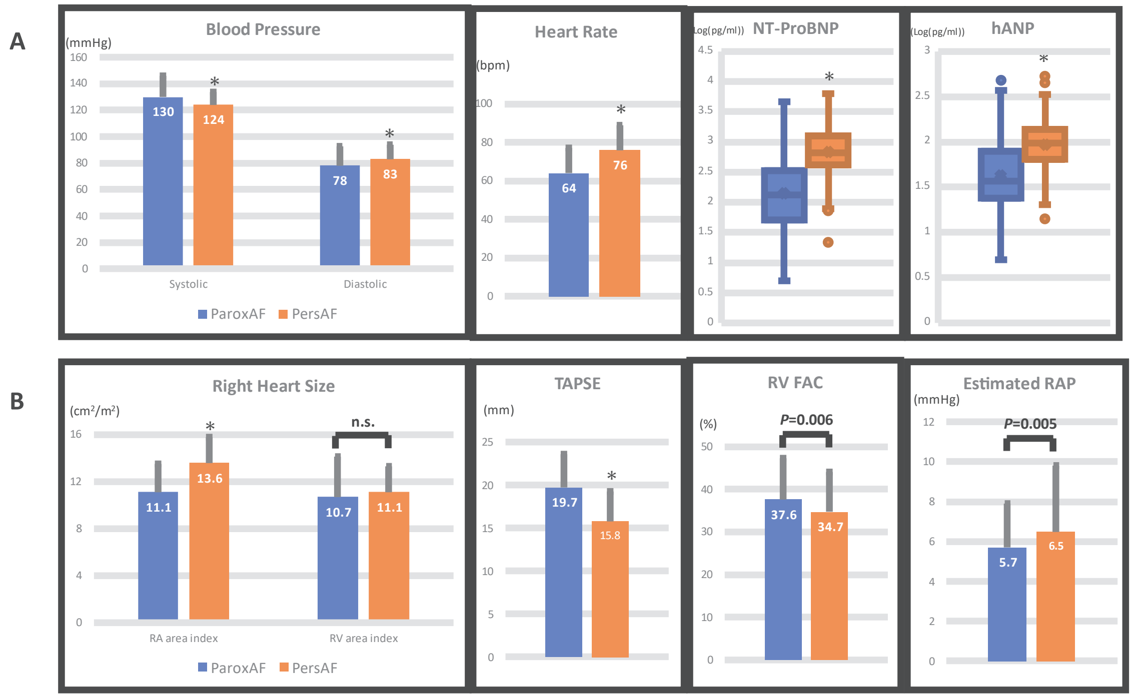
Duration from first-detected episode of AF to the date of TEE examination was defined as AF duration. ParoxAF was defined as lasting for AF rhythm less than 7 days and persAF was defined as at least more than 7 days. ParoxAF includes both of (**A**) sinus and (**B**) AF rhythm on the date of TEE. PersAF includes (**C**) AF rhythm is sustained from the first-detected episode to the date of TEE and (**D**) paroxAF gradually shifts to persAF. AF indicates atrial fibrillation, and TEE, transesophageal echocardiography.

Figure 2. 3D-TEE-based assessment of TV geometry



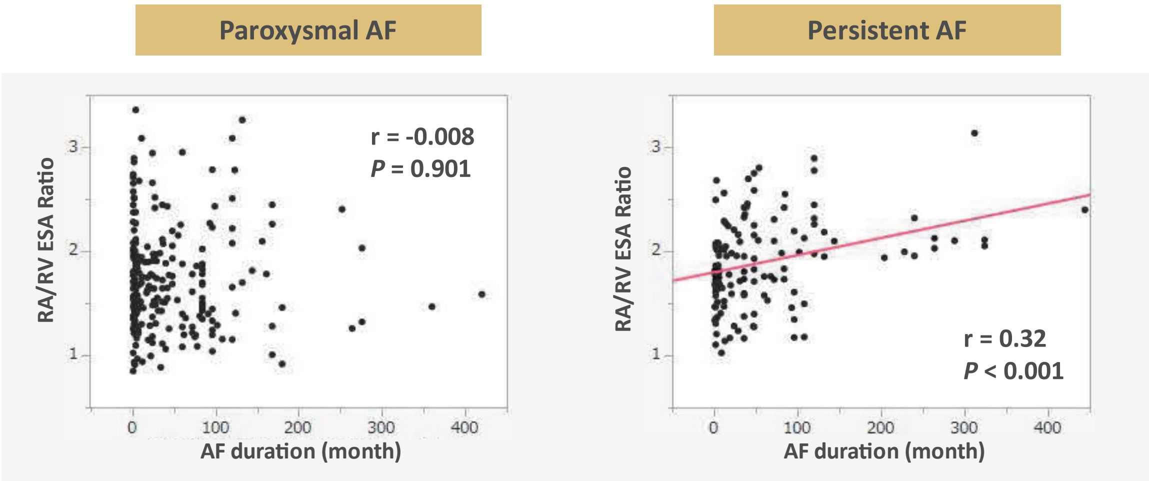
(**A**) Data acquisition and 3D TV demonstration. (**B**) MVN analysis. A-P and AL-PM directions were determined based on the commissure between anterior and septal leaflets as an anterior direction. A indicates anterior; AL, anterolateral; Ao, aortic valve; MVN, mitral valve navigator; P, posterior; PM, posteromedial; RA, right atrium; and RV, right ventricle.

Figure 3. Differences in clinical and echocardiographic characteristics between paroxAF and persAF patients



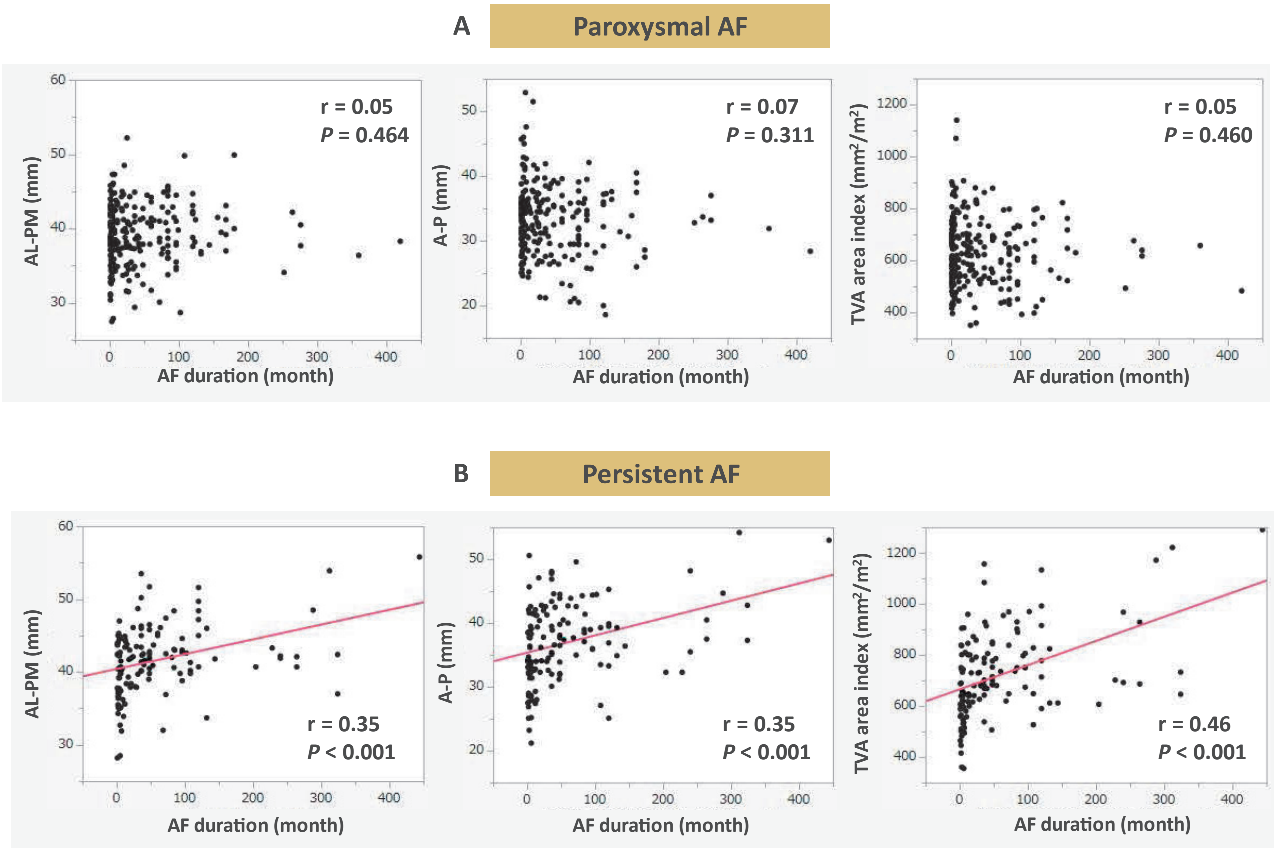
(A) Differences in blood pressure, heart rate, NT-proBNP and hANP between paroxAF and persAF. (B) Differences in right heart size, TAPSE, RV FAC and estimated RAP between paroxAF and persAF. **p*< 0.001 (paroxAF vs persAF), The errors bars are standard deviation of the values. FAC indicates fractional area change; hANP, human atrial natriuretic peptide; NT-pro BNP, N-terminal pro-B-type natriuretic peptide; RAP, right atrial pressure; and TAPSE, tricuspid annular plane systolic excursion. Other abbreviations as in Figures 1 and 2.

Figure 4. Correlations between AF duration and RA/RVESA ratio



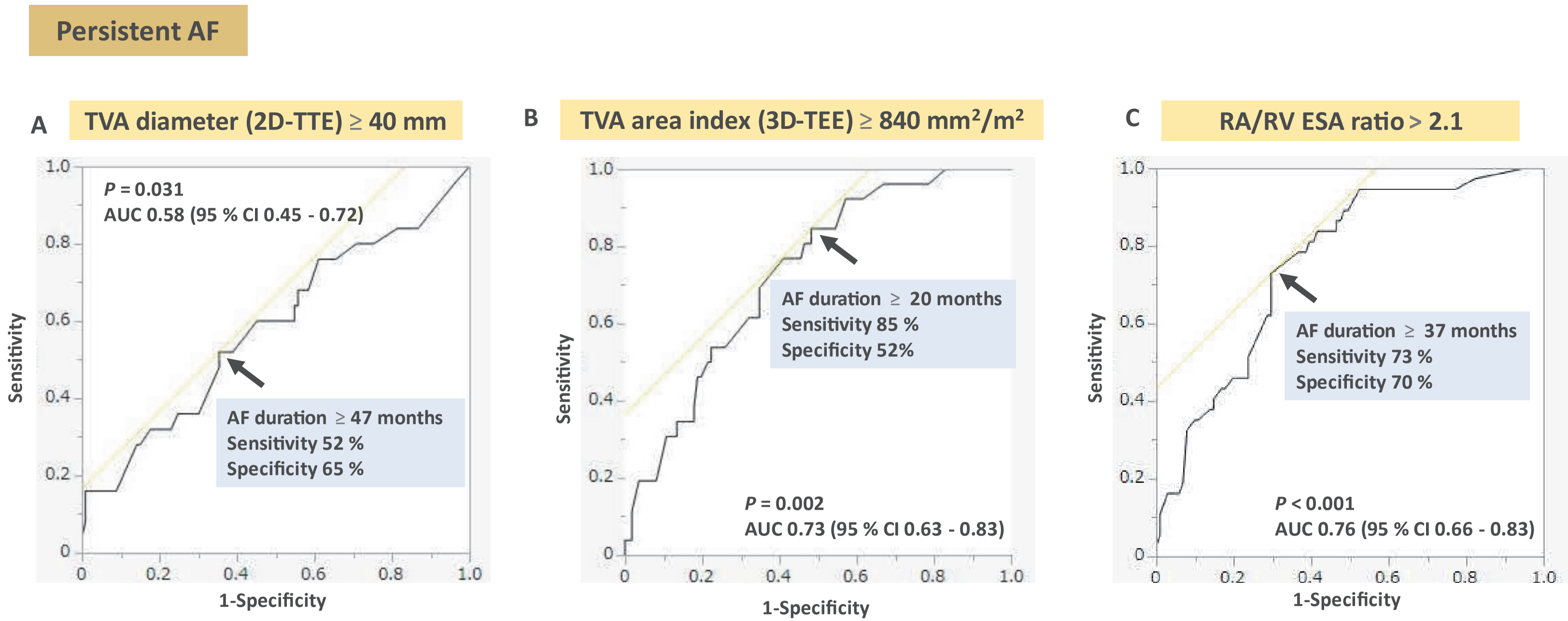
(**A**) There was no significant correlation between AF duration and RA/RVESA ratio in paroxAF patients, whereas (**B**) AF duration was moderately correlated with RA/RVESA ratio in persAF patients (P<0.001). RA/RVESA ratio indicates right atrium area-to-right ventricle end-systolic area ratio.

Figure 5. Correlations between AF duration and TVA measured by 3D-TEE



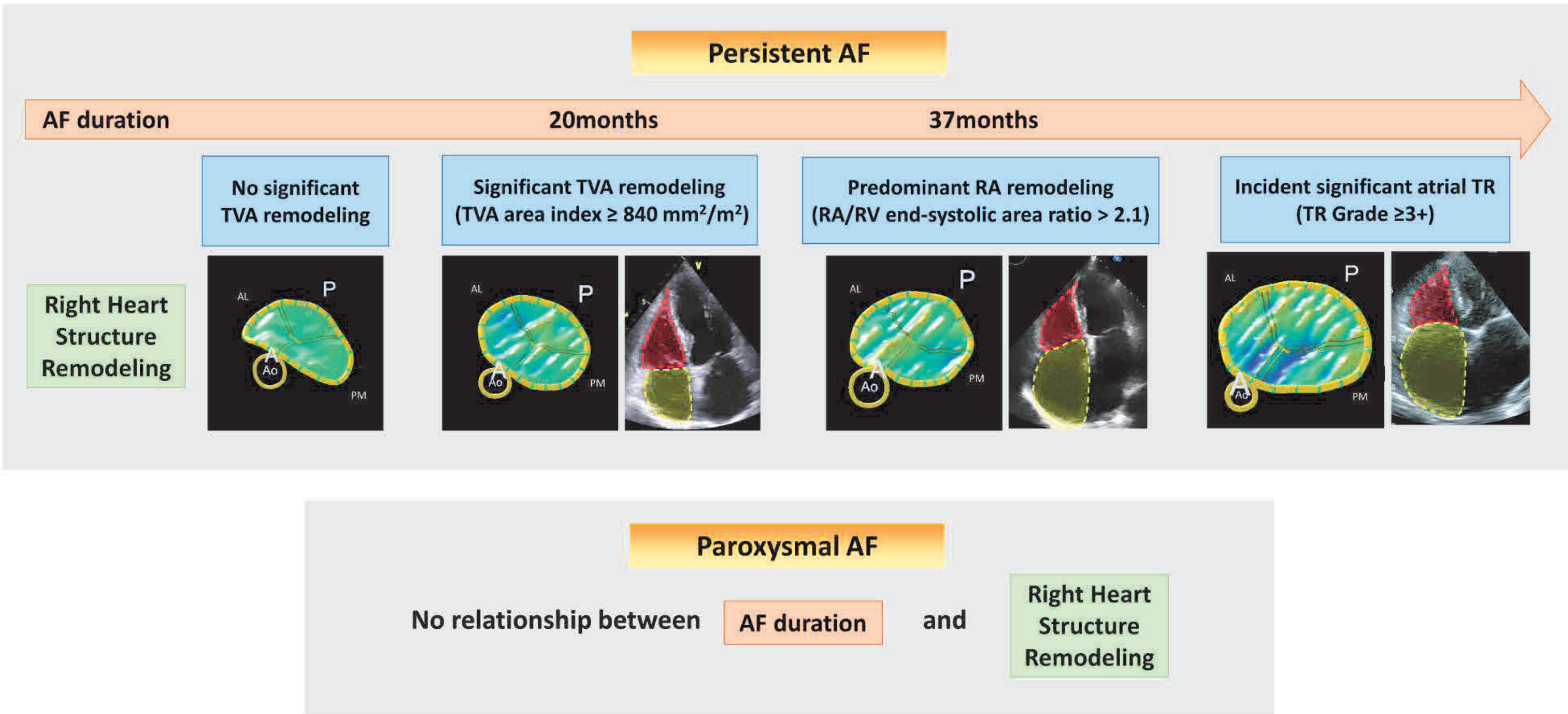
(**A**) There was no significant correlation between AF duration and TVA diameters both on AL-PM and A-P directions and 3D TVA area in paroxAF patients, whereas (**B**) moderate correlation of all these parameters were observed in persAF patients. TVA indicates tricuspid valve annulus.

Figure 6. ROC curve analysis showing the cutoff level of AF duration.



(**A**) AF duration with a cutoff value of 47 months is a low accurate parameter for predicting TVA diameter more than 40 mm measured by 2D-TTE. (**B**) AF duration with a cutoff value of 20 months to predict TVA area more than 840 mm^2 measured by 3D-TEE had larger AUC than TVA measured by 2D-TTE. (**C**) AF duration with a cutoff value of 37 months is a moderately accurate parameter for predicting RA/RVESA ratio >2.1. AUC indicates area under the curve; ROC, receiver operating characteristic; and TTE, transthoracic echocardiography. Other abbreviations as in Figures 1, 3 and 4.

Figure 7. Relationship between AF duration and right heart structure remodeling



The relationship between AF duration and right heart remodeling were shown to progress along the time sequence only in persAF patients, not in paroxAF patients. AF duration predicting TVA area index ≥ 840 mm^2/m^2 was 20 months and AF duration predicting RA/RVESA ratio >2.1 was 37 months. Further prolong AF duration may lead to the incidence of AF-TR. TR indicates tricuspid regurgitation.

Table 1. Clinical characteristics

	Total Cohort (n=372)	Paroxysmal AF (n=234)	Persistent AF (n=138)	*p*
Age, y	67 ± 10	67 ± 11	67 ± 9	0.686
Female sex, %	107 (28.7)	74 (31.6)	33 (23.9)	0.113
Body surface area, m^2	1.7 ± 0.2	1.7 ± 0.2	1.7 ± 0.2	0.093
Systolic blood pressure, mmHg	128 ± 16	130 ± 16	124 ± 15	< 0.001
Diastolic blood pressure, mmHg	80 ± 11	78 ± 10	83 ± 11	< 0.001
Heart rate, bpm	68 ± 14	64 ± 13	76 ± 13	< 0.001
AF duration, months	24 (4 - 72)	22 (3 - 72)	29 (5 - 74)	0.119
TR grade -none, %	20 (5.4)	17 (7.3)	3 (2.2)	0.036
-trivial, %	142 (38.2)	108 (46.2)	34 (24.6)	< 0.001
-mild, %	151 (40.6)	89 (38.0)	62 (44.9)	0.191
-mild-moderate, %	39 (10.5)	17 (7.3)	22 (15.9)	0.008
-moderate, %	16 (4.3)	3 (1.3)	13 (9.4)	< 0.001
-severe, %	4 (1.1)	0 (0)	4 (2.9)	0.018
NT-proBNP (pg/ml)	289 (94 - 769)	132 (51 - 340)	675 (426 - 1313)	< 0.001
hANP (pg/ml)	56 (29 - 109)	37 (24 - 79)	97 (64 - 139)	< 0.001
Hypertension, %	246 (66.1)	157 (67.1)	89 (64.5)	0.609
Diabetes mellitus, %	61 (16.4)	36 (15.4)	25 (18.1)	0.492
Hyperlipidemia, %	168 (45.1)	116 (49.6)	52 (37.7)	0.026
Chronic kidney disease, %	125 (33.6)	75 (32.1)	50 (36.2)	0.410
Diuretics, %	50 (13.4)	20 (8.6)	30 (21.7)	< 0.001
β-blocker, %	166 (44.6)	101 (43.2)	65 (47.1)	0.460
Anticoagulant agents, %	356 (95.7)	225 (96.2)	131 (95.0)	0.573

Values are median (IQR), mean ± SD or n (%). AF indicates atrial fibrillation; hANP, human atrial natriuretic peptide; NT-pro BNP, N-terminal pro-B-type natriuretic peptide; and TR, tricuspid regurgitation.

Table 2. Echocardiographic characteristics measured by 2D-TTE and 3D-TEE

	Total Cohort (n=372)	Paroxysmal AF (n=234)	Persistent AF (n=138)	*p*
2D-TTE parameters				
LV ejection fraction, %	60.5 ± 6.3	62.4 ± 4.7	57.3 ± 7.2	< 0.001
LA volume index, ml/m^2	42.1 ± 13.1	37.6 ± 10.1	50.0 ± 14.1	< 0.001
RA area index, cm^2/m^2	12.0 ± 3.0	11.1 ± 2.4	13.6 ± 3.4	< 0.001
RA/LA area ratio	0.87 ± 0.2	0.87 ± 0.2	0.89 ± 0.2	0.219
RV parameters				
RV end-diastolic area index, cm^2/m^2	10.8 ± 2.2	10.7 ± 2.2	11.1 ± 2.2	0.091
RV end-systolic area index, cm^2/m^2	6.9 ± 1.7	6.6 ± 1.6	7.2 ± 1.7	0.002
RV end-diastolic basal diameter, mm	37.4 ± 5.9	36.7 ± 5.6	38.8 ± 6.0	< 0.001
RV end-diastolic mid diameter, mm	31.0 ± 5.9	30.4 ± 5.9	32.1 ± 5.7	0.007
RV end-diastolic longitudinal diameter, mm	74.0 ± 8.1	74.1± 8.0	74.0 ± 8.2	0.928
RV fractional area change, %	36.5 ± 9.7	37.6 ± 9.7	34.7 ± 9.4	0.006
RA/RVESA ratio	1.8 ± 0.5	1.7 ± 0.5	1.9 ± 0.4	0.005
TAPSE, mm	18.3 ± 4.2	19.7 ± 3.9	15.8 ± 3.5	< 0.001
TRPG, mmHg	20.7 ± 9.4	19.9± 10.2	21.9 ± 7.7	0.043
Estimated RAP, mmHg	6.0 ± 2.7	5.7 ± 2.2	6.5 ± 3.3	0.005
TVA in mid-diastole				
A4C view, mm	32.7 ± 5.2	31.6 ± 4.7	34.6 ± 5.5	< 0.001
Inflow view, mm	33.5 ± 6.3	32.9 ± 6.1	34.6 ± 6.5	0.016
TVA in mid-systole				
A4C view, mm	27.1 ± 4.9	25.8 ± 4.2	29.3 ± 5.1	< 0.001

Inflow view, mm	28.1 ± 5.8	27.0 ± 5.4	29.9 ± 6.0	< 0.001
3D-TEE parameters				
TVA in mid-diastole				
AL-PM, mm	40.0 ± 4.4	39.1 ± 4.1	41.6 ± 4.7	< 0.001
A-P, mm	34.5 ± 5.9	33.0 ± 5.3	36.9 ± 6.1	< 0.001
3D Annulus area, mm^2/m^2	660.2 ± 147.8	625.4 ± 125.6	719.0 ± 163.7	< 0.001
Ellipticity (AL-PM/A-P), %	119.1 ± 22.9	124.5 ± 26.4	117.2 ± 24.1	0.008
Annular height, mm	4.6 ± 1.4	4.5 ± 1.3	4.7 ± 1.6	0.350
TVA in mid-systole				
AL-PM, mm	36.7 ± 4.6	35.6 ± 4.2	38.6 ± 4.6	< 0.001
A-P, mm	31.1 ± 5.9	29.4 ± 5.2	33.8 ± 5.9	< 0.001
3D Annulus area, mm^2/m^2	556.4 ± 136.3	515.3 ± 111.6	626.1 ± 146.1	< 0.001
Ellipticity (AL-PM/A-P), %	121.8 ± 25.8	121.3 ± 23.5	115.3 ± 21.4	0.016
Annular height, mm	5.5 ± 1.6	5.5 ± 1.6	5.6 ± 1.6	0.477
Tenting volume, ml	0.7 ± 0.5	0.6 ±0.4	0.8 ± 0.5	0.019
Tenting height, mm	3.6 ± 1.2	3.6 ± 1.3	3.7 ± 1.2	0.476
Annular contraction, %	19.6 ± 10.5	22.2 ± 10.9	15.2 ± 8.0	< 0.001
AL-PM contraction, %	9.3 ± 5.1	10.2 ± 5.4	7.9 ± 4.3	< 0.001
A-P contraction, %	11.5 ± 7.0	12.8 ± 7.5	9.3 ± 5.5	< 0.001

Values are mean ± SD. 2D indicates 2-dimensional; 3D, 3-dimensional; A4C, apical four-chamber; AL-PM, anterolateral-posteromedial; A-P, anterior-posterior; LA, left atrium; LV, left ventricle; RA, right atrium; RAP, right atrial pressure; RA/RVESA ratio, right atrium area-to-right ventricle end-systolic area ratio; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TEE, transesophageal echocardiography; TRPG, tricuspid regurgitation pressure gradient; TTE, transthoracic echocardiography; and TVA, tricuspid valve annulus.

Table 3. Linear regression analyses to predict TVA dilatation

	Univariable	Multivariable*			
	p	β	95% CI	*p*	VIF
TVA diameter measured by 2D-TTE					
AF duration, per 1 month increase	0.178	0.067	-0.007 to 0.016	0.428	1.121
RA/RVESA ratio, per 0.1 increase	0.047	0.142	-0.037 to 0.414	0.100	1.205
TR severity ≥ moderate	0.014	0.195	0.211 to 3.035	0.025	1.200
TVA area measured by 3D-TEE					
AF duration, per 1 month increase	< 0.001	0.369	0.774 to 1.806	< 0.001	1.121
RA/RVESA ratio, per 0.1 increase	< 0.001	0.218	4.303 to 24.730	0.006	1.205
TR severity ≥ moderate	0.021	0.201	20.154 to 148.203	0.010	1.200

*Age-, sex-, and body surface area-adjusted. Abbreviations as in Tables 1 and 2.

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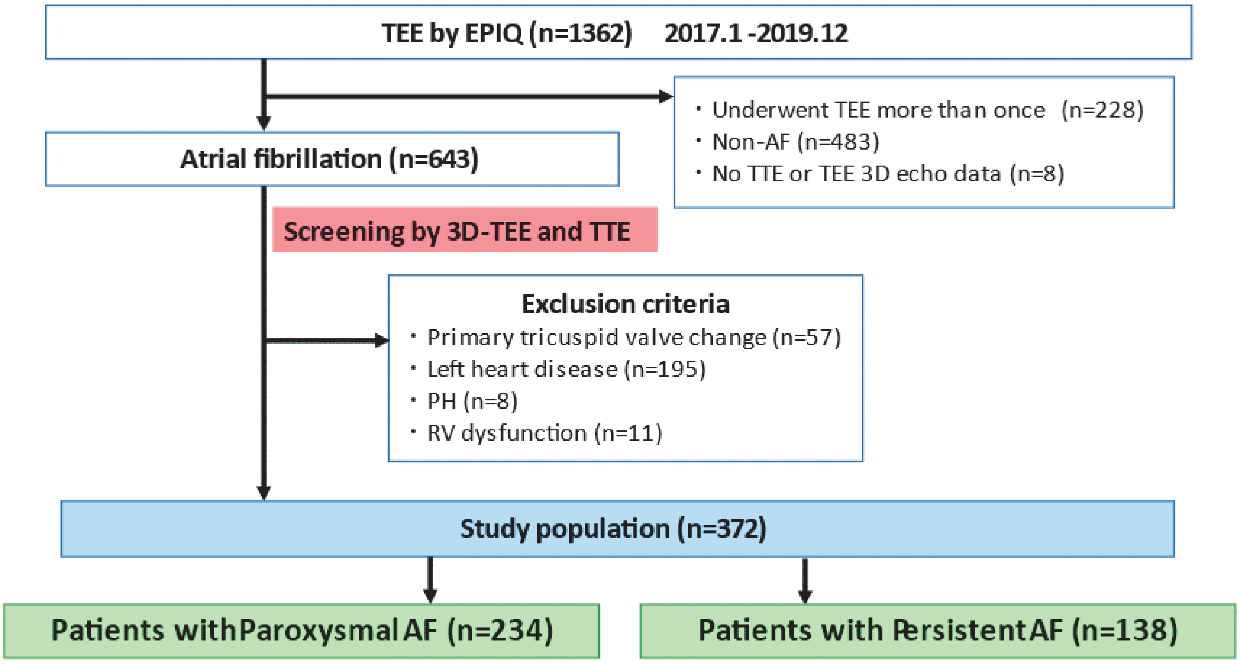
Supplemental Material

Figure S1. Study Population

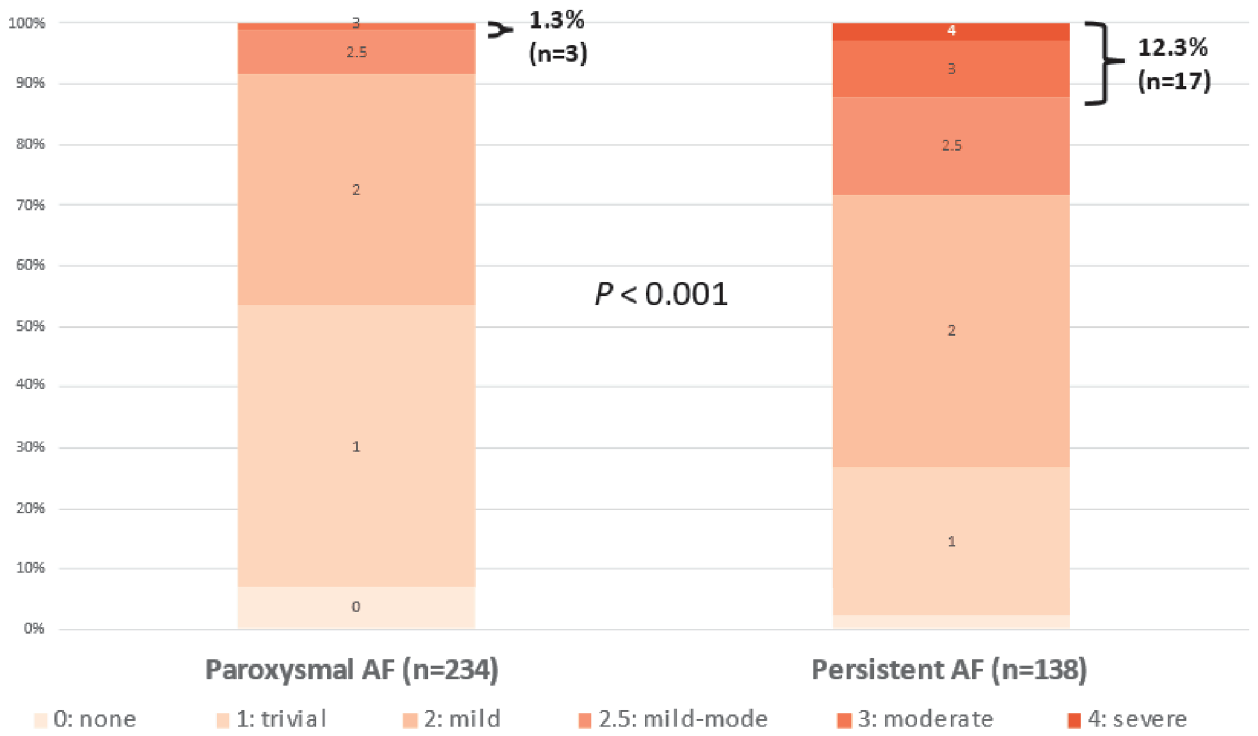
We retrospectively reviewed patients' clinical records of 643 consecutive patients with AF who underwent both 3D-TEE and 2D-TTE. As a result of initial 3D TV screening, 57 patients were excluded from this study. Further exclusion criteria are shown in this Figure. This cohort could be considered as having normal TV geometry and the exact lone AF population including AF-TR. This patient population comprised a group with paroxysmal and persistent AF.



3D-TEE = 3-dimensional transesophageal echocardiography; AF = atrial fibrillation; PH = pulmonary hypertension; RV = right ventricle; TTE = transthoracic echocardiography; TR = tricuspid regurgitation; TV = tricuspid valve.

Figure S2. Prevalence of AF-TR

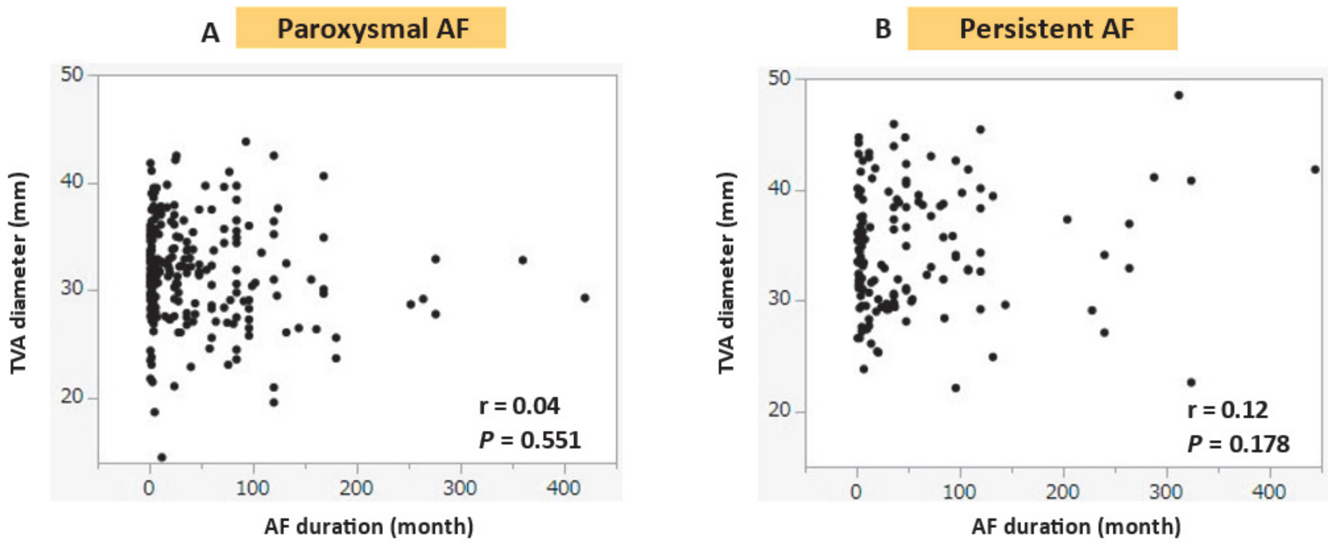
The frequency of more than moderate grade of AF-TR was significantly higher in persAF patients than in paroxAF patients.



Abbreviations as in Supplemental Figure 1.

Figure S3. Correlation between AF duration and TVA diameter measured by 2D-TTE

There was no significant correlation between AF duration and TVA diameter measured by 2D-TTE both in (A) paroxAF and (B) persAF patients.



TVA = tricuspid valve annulus; other abbreviations as in Supplemental Figure 1.