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Relationship Between Human Atrial Natriuretic Peptide and Tricuspid Valve Annular Dilatation in Patients With Atrial Fibrillation

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ABSTRACT

Background: Atrial fibrillation (AF) may cause right-sided heart remodeling such as tricuspid valve annular (TVA) dilatation, leading to atrial functional tricuspid regurgitation with prognostic impact. Not all AF patients develop TVA dilatation; therefore, predicting its occurrence is challenging. This study aimed to investigate human atrial natriuretic peptide (hANP) as a potential diagnostic marker of TVA dilatation in AF patients.

Methods: A total of 346 patients with lone AF (222 paroxysmal AF [paroxAF], 124 persistent AF [persAF]) who underwent 2-dimensional (2D) transthoracic and 3-dimensional (3D) transesophageal echocardiography (TEE) were retrospectively reviewed. This cohort was considered to have normal tricuspid valve geometry screening by 3D-TEE and having no left-side heart disease, pulmonary hypertension, and right ventricular dysfunction. We evaluated the association of plasma hANP concentration with AF-related right-sided heart remodeling including right atrial (RA) dilatation and TVA dilatation.

Results: Plasma hANP levels showed a correlation with RA area index in the paroAF group ($r = 0.27$, $p < 0.001$) but not in the persAF group. In contrast, as for association with 3D TVA area, plasma hANP levels demonstrated an inverse correlation with 3D TVA area ($r = -0.25$, $p = 0.005$) in the persAF group, especially with TVA diameter in the anterior-posterior direction, but not in the paroAF group. Multivariate analysis revealed that reduced hANP levels were independently associated with TVA dilatation (per 1 increase in Log_{10}hANP, β: −0.17 [95% CI: −306.7 to −7.59]; $p = 0.04$).

Conclusion: Declining plasma hANP levels may serve as a marker for diagnosing TVA dilatation in persAF patients, highlighting its potential role in assessing AF-related structural changes.

1 | Introduction

Long-standing persistent atrial fibrillation (AF) has been identified as a direct cause of tricuspid annular dilatation, and subsequently leads to tricuspid regurgitation (TR), also known as atrial functional TR (AF-TR) [1, 2]. A recent population-based cohort study revealed that, over a 13.3-year follow-up, one-third of patients with new-onset AF developed moderate or greater grades of TR, and the incidence of significant AF-TR has been associated with poor long-term survival [3]. In patients with AF-TR, the tricuspid valve annulus (TVA) becomes larger, more planar, rounder, and less contractile, accompanied by a smaller

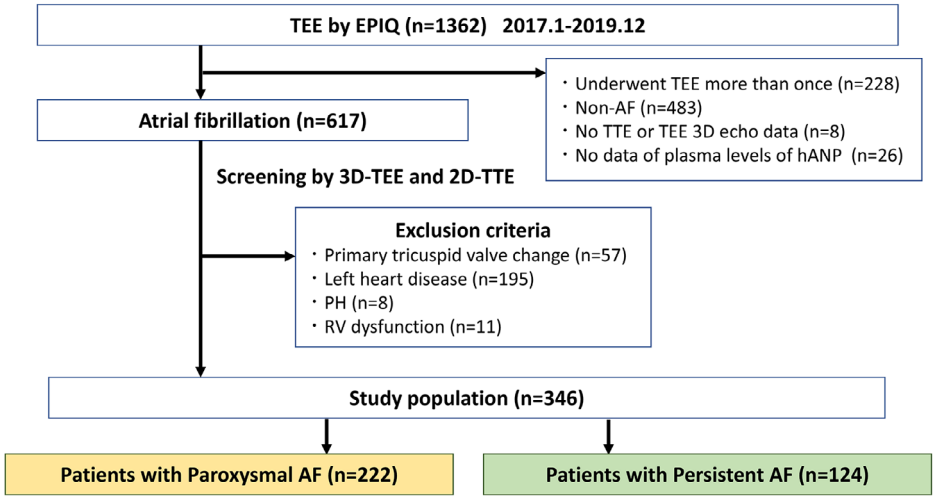

FIGURE 1 | Study population. We retrospectively reviewed the clinical records of 617 consecutive patients with AF who underwent both 3D-TEE and 2D-TTE. As a result of the initial 3D TV screening, 57 patients were excluded from this study. Further exclusion criteria are shown in this figure. This cohort can be considered to have normal TV geometry and represents the true lone AF population, including AF-TR. This patient population consisted of both paroxysmal and persistent AF groups. 3D-TEE, 3-dimensional transesophageal echocardiography; AF, atrial fibrillation; PH, pulmonary hypertension; RV, right ventricle; TTE, transthoracic echocardiography; TR, tricuspid regurgitation; TV, tricuspid valve.

tethering angle [1]. Predominant posterior annular dilatation of the TV is reportedly considered as the most important factor in the development of AF-TR [4]; however, not all patients with AF develop significant AF-TR with marked TVA dilatation, making it difficult to predict future TVA dilatation in AF patients.

Human atrial natriuretic peptide (hANP) is a 28-amino-acid carboxy-terminal fragment primarily produced in the cardiac atria and was first purified by Kangawa and Matsuo in 1984 [5]. Increased atrial wall tension, rather than pressure, is thought to be the primary stimulus for its release [6]. However, many aspects of its secretion mechanism and the significance of hANP as a biomarker remain to be elucidated in various underlying cardiac conditions. The aim of this study is to investigate the potential of hANP as a diagnostic marker of TVA dilatation in patients with AF using transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE).

2 | Methods

2.1 | Study Population

This study was exempt from institutional review board approval as it utilized publicly available, de-identified data. The data supporting the findings of this study can be obtained from the corresponding author upon reasonable request. We retrospectively reviewed the echocardiographic and clinical data from the medical records of 617 consecutive AF patients with available plasma hANP data who underwent both 2-dimensional (2D) and 3-dimensional (3D) echocardiography at Hiroshima University Hospital for clinical indications between January 2017 and December 2019. 2D-TTE was conducted within 3 months before 3D-TEE, and no patients had undergone catheter ablation in the year preceding the TEE examination. The initial 3D TV assessment using real-time 3D-TEE was meticulously conducted, allowing for the identification of primary TR associated with anatomical abnormalities in the tricuspid valve leaflets. As a result of this screening, 57 patients were omitted from the study. Additional exclusion criteria included patients with left-sided heart disease (n = 195), pulmonary hypertension (n = 8), and right ventricular dysfunction (n = 11), as determined using echocardiographic parameters and clinical information retrieved from medical records. Finally, 346 patients were enrolled in this study (mean age, 68 ± 10 years; 29% female). Therefore, this cohort can be regarded as having normal tricuspid valve geometry and representing a true lone AF population, including AF-TR, consisting of patients with paroxysmal AF (paroxAF) and persistent AF (persAF) (Figure 1).

2.2 | Type and Duration of AF and Laboratory Data

PersAF was defined as AF rhythm lasting for at least 7 days until the date of TEE examination, and the rest of the study population was defined as paroxAF according to the current definitions [7]. In this study, AF duration was defined as the time interval from the first documented episode of AF to the date of the TEE examination. This duration was retrospectively assessed based on information obtained from patients' clinical records, including medical history, electrocardiograms (ECG), holter monitoring, echocardiographic findings, and referral letters from primary care physicians. Biological parameters, including plasma levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and hANP, measured within 1 month prior to the TEE examination, were obtained from patients' medical records.

2.3 | Echocardiographic Measurements

A comprehensive 2D-TTE was performed using a commercially available ultrasound system (S5-1 probe; EPIQ7, Philips Medical Systems, Andover, MA), with a particular focus on the tricuspid valve (TV) and the right ventricle (RV). Standard left-sided

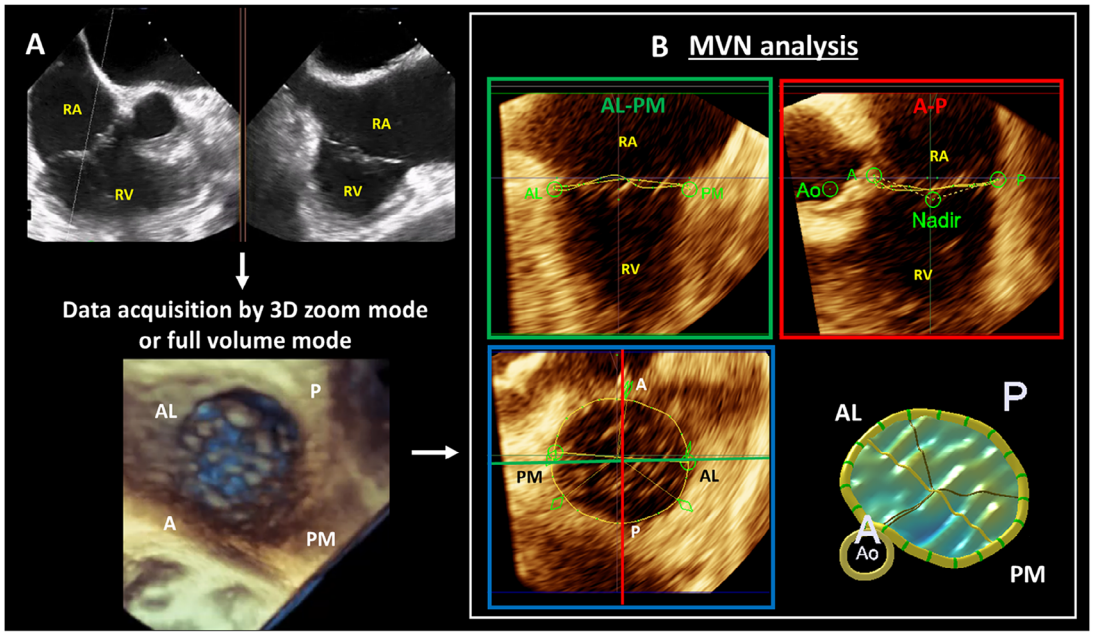

FIGURE 2 | 3D-TEE-based assessment of TV geometry. (A) Data acquisition and 3D TV demonstration. (B) MVN analysis. The A-P and AL-PM directions were determined based on the commissure between the anterior and septal leaflets, with the anterior direction being defined. A, anterior; AL, anterolateral; Ao, aortic valve; MVN, mitral valve navigator; P, posterior; PM, posteromedial; RA, right atrium.

chamber volumes and left ventricular ejection fraction (LVEF) were assessed in accordance with current guidelines [8]. The RV was evaluated using multiple imaging views, including an RV-focused apical four-chamber (A4C) view. Right-sided chamber size and function were evaluated following the American Society of Echocardiography guidelines for the assessment of the right heart [9]. Systolic pulmonary artery pressure was estimated using the systolic RV pressure gradient and right atrial pressure. Right atrium (RA) pressure was estimated based on the inferior vena cava diameter and its respiratory variations [9]. TR severity was graded using a comprehensive, multiparametric approach [10]. Images were obtained in an A4C view and a parasternal RV-inflow view using zoom mode focused on the TV. The TVA diameter was measured offline by the first author and an echocardiography specialist (Level III trained) during mid-diastole, at the point of maximum TV opening, and mid-systole, at the point of minimum TV closing, between the two hinge points where the TV leaflets meet the TVA. In patients with AF, the TVA diameter was calculated as the average of three to five cardiac cycles.

2.4 | 3D-TEE

3D-TEE was conducted under sedation with intravenous midazolam and pentazocine. The EPIQ7 ultrasound imaging system, equipped with a fully sampled matrix-array TEE transducer (X8-2t Live 3D TEE transducer; Philips), was used to display both 2D and 3D images. Initially, clear 2D images of the TV were obtained in the mid-esophageal oblique short-axis view and the coronary sinus view. Volume datasets were acquired during breath-hold to minimize stitch artifacts, utilizing multi-beat 3D zoom mode focused on the TV (median frame rate = 90 Hz) (Figure 2A) or multi-beat full volume mode in the mid-esophageal short-axis view focused on the RV (median frame rate = 34 Hz). In patients with AF, the live 3D zoom mode with one-beat volume acquisition was sometimes used to prevent stitch artifacts. Prior to 3D acquisition, the views were optimized for depth and gain settings, ensuring that the entire TV or RV was included within the sector boundaries.

2.5 | 3D TVA Analysis

Digitally stored 3D zoom mode images of the TV or full-volume data focused on the RV were imported into the workstation (QLAB ver. 13.0; Philips). We performed volume rendering to assess the entire TV, with the interatrial septum positioned inferiorly at the 6 o'clock position. The mitral module of the QLAB Mitral Valve Navigator (MVN) software (Philips) was used off-label for semiautomated, indirect measurement of the 3D-TEE TVA diameter during mid-diastole and mid-systole (Figure 2B). As previously outlined [1], we identified 20 landmarks to define the TVA and analyzed the tricuspid valve leaflets using up to 22 intersections per patient. The anterior-posterior (A-P) and anterolateral-posteromedial (AL-PM) directions were established based on the commissure between the anterior and septal leaflets, with the anterior direction. The A-P and AL-PM diameters, TVA area, and TVA ellipticity (AL-PM/A-P ratio) were assessed at both the mid-diastolic and mid-systolic phases.

2.6 | Statistical Analysis

Categorical variables were presented as counts with corresponding percentages and were analyzed using either the chi-square test or Fisher's exact test for comparison. Continuous variables were presented as mean ± standard deviation or median (interquartile range) and were analyzed using the student's *t*-test or the Wilcoxon rank-sum test for comparisons. Clinical characteristics, as well as 2D-TTE and 3D-TEE parameters, were included in the univariate analysis. The relationships between

TABLE 1 | Clinical characteristics.

	Total cohort ($n = 346$)	Paroxysmal AF ($n = 222$)	Persistent AF ($n = 124$)	p value
Age (year)	68 ± 10	67 ± 11	66 ± 9	0.26
Female sex (%)	100 (28.9)	70 (31.5)	30 (24.2)	0.15
Body surface area (m^2)	1.7 ± 0.2	1.7 ± 0.2	1.7 ± 0.2	0.13
Systolic blood pressure (mmHg)	128 ± 16	130 ± 16	123 ± 15	<0.001
Diastolic blood pressure (mmHg)	80 ± 10	78 ± 10	83 ± 11	<0.001
Heart rate (bpm)	68 ±14	64 ± 13	76 ± 13	<0.001
AF duration (months)	24 (4–72)	24 (4–75)	27 (5–60)	0.76
TR grade ≥ moderate (%)	13 (3.8)	3 (1.4)	10 (8.1)	0.003
NT-proBNP (pg/mL)	271 (89–711)	132 (50–335)	651 (379–1214)	<0.001
hANP (pg/mL)	56 (29–109)	37 (24–79)	97 (64–139)	<0.001
Hypertension (%)	230 (66.5)	151 (68.0)	79 (63.7)	0.42
Diabetes mellitus (%)	59 (17.1)	35 (15.8)	24 (19.4)	0.39
Hyperlipidemia (%)	159 (46.0)	110 (49.6)	49 (39.5)	0.073
Chronic kidney disease (%)	111 (32.1)	69 (31.1)	42 (33.9)	0.59
Diuretics (%)	43 (12.4)	19 (8.6)	24 (19.4)	0.006
ACE inhibitor (%)	12 (3.5)	4 (1.8)	8 (6.5)	0.032
ARB (%)	128 (37.0)	84 (37.8)	44 (35.5)	0.66
β-blocker (%)	155 (44.8)	97 (43.7)	58 (46.8)	0.58
Anticoagulant agents (%)	336 (97.1)	216 (97.3)	120 (96.8)	0.78

Note: Values are presented as median (IQR), mean ± SD or *n* (%).
Abbreviations: ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; hANP, human atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TR, tricuspid regurgitation.

Log_{10} hANP and the RA area index, TVA diameter assessed by 2D-TTE and 3D-TEE, and 3D TVA area measured by 3D-TEE were evaluated using the Spearman rank correlation test. To identify the determinants of TVA dilatation, linear regression analyses were performed in persAF patients, with multivariable models adjusting for potential confounders selected based on statistical significance ($p < 0.1$). Statistical significance was considered at a p value <0.05. All statistical analyses were conducted using JMP Pro 18 (SAS Institute, Cary, NC).

3 | Result

3.1 | Clinical Characteristics

Among the 346 patients, 222 (64%) were classified as paroxAF, while the remaining 124 (36%) were classified as persAF. The clinical characteristics are presented in Table 1. Patients with persAF had significantly lower systolic blood pressure ($p < 0.001$) and higher diastolic blood pressure ($p < 0.001$) compared with those with paroxAF. Additionally, the heart rate was notably higher in persAF patients than in paroxAF patients ($p < 0.001$). The incidence of AF-TR greater than moderate grade was significantly higher in persAF patients compared to paroxAF patients (1.4% vs. 8.1%; $p < 0.001$). Plasma concentrations of NT-ProBNP and hANP were significantly elevated in persAF patients compared to paroxAF patients (both $p < 0.001$).

3.2 | Echocardiographic Data

The 2D-TTE characteristics are shown in Table 2. Compared to paroxAF patients, persAF patients demonstrated a lower LVEF, as well as a greater left atrial volume index and RA area index (all $p < 0.001$). In the TVA analysis, TVA diameters measured by 2D-TTE in the A4C and inflow views were significantly larger in persAF patients than in paroxAF patients, both at mid-diastole and mid-systole (all $p < 0.05$).

The 3D-TEE TVA geometry is also presented in Table 2. Patients with persAF had larger TVA diameters in both the AL-PM and A-P directions and a greater 3D TVA area index compared to those with paroxAF (all $p < 0.001$). Furthermore, patients with persAF demonstrated reduced TVA ellipticity in both mid-diastole and mid-systole (both $p < 0.05$) compared to those with paroxAF, suggesting that the annulus expanded in the A-P direction, resulting in a more circular shape.

3.3 | Association of Plasma hANP Concentration With RA and TVA Areas

Notably, a moderate correlation between Log_{10} hANP and the RA area index was observed in patients with paroxAF ($r = 0.27$, $p < 0.001$), whereas no significant correlation was found in those with persAF (Figure 3). Further analysis of the correlation

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

	Total cohort (n = 346)	Paroxysmal AF (n = 222)	Persistent AF (n = 124)	p value
2D-TTE characteristics				
LV ejection fraction (%)	60.5 ± 6.2	62.4 ± 4.5	57.1 ± 7.3	<0.001
LA volume index (mL/m^2)	41.2 ± 12.0	37.3 ± 9.9	48.3 ± 12.2	<0.001
RA area index (cm^2/m^2)	11.8 ± 2.7	11.0 ± 2.4	13.2 ± 2.7	<0.001
RV parameters				
RV end-diastolic area index (cm^2/m^2)	10.7 ± 2.2	10.6 ± 2.2	10.9 ± 2.2	0.24
End-systolic area index (cm^2/m^2)	6.8 ± 1.7	6.6 ± 1.6	7.1 ± 1.7	0.007
RV end-diastolic basal diameter (mm)	37.3 ± 5.7	36.7 ± 5.6	38.5 ± 5.8	0.005
Mid diameter (mm)	31.0 ± 5.8	30.4 ± 5.9	31.9 ± 5.5	0.026
Longitudinal diameter (mm)	74.0 ± 8.1	74.1± 8.2	74.0 ± 8.1	0.93
RV fractional area change (%)	36.5 ± 9.7	37.6 ± 9.8	34.7 ± 9.2	0.008
TAPSE (mm)	18.3 ± 4.2	19.8 ± 3.9	15.7 ± 3.5	<0.001
TRPG (mmHg)	20.4 ± 9.3	19.8 ± 10.1	21.4 ± 7.7	0.14
Estimated RAP (mmHg)	5.9 ± 2.5	5.7 ± 2.1	6.3 ± 3.1	0.025
TVA in mid-diastole				
A4C view (mm)	32.5 ± 5.0	31.6 ± 4.6	34.1 ± 5.3	<0.001
Inflow view (mm)	33.5 ± 6.2	32.9 ± 6.2	34.5 ± 6.2	0.021
TVA in mid-systole				
A4C view (mm)	26.9 ± 4.7	25.8 ± 4.2	29.0 ± 4.9	<0.001
Inflow view (mm)	27.9 ± 5.7	26.9 ± 5.3	29.8 ± 5.8	<0.001
3D-TEE characteristics				
TVA in mid-diastole				
AL-PM (mm)	39.9 ± 4.3	39.2 ± 4.1	41.1 ± 4.5	<0.001
A-P (mm)	34.3 ± 5.8	33.0 ± 5.3	36.7 ± 6.0	<0.001
3D Annulus area (mm^2)	1115.3 ± 238.5	1057.1 ± 205.6	1219.5 ± 258.0	<0.001
Ellipticity (AL-PM/A-P) (%)	119.2 ± 23.1	121.8 ± 23.4	114.7 ± 22.0	0.006
TVA in mid-systole				
AL-PM (mm)	36.5 ± 4.4	35.7 ± 4.2	38.1 ± 4.3	<0.001
A-P (mm)	30.9 ± 5.7	29.4 ± 5.1	33.5 ± 5.7	<0.001
3D Annulus area (mm^2/m^2)	938.0 ± 218.0	872.2 ± 188.1	1055.6 ± 218.9	<0.001
Ellipticity (AL-PM/A-P) (%)	122.0 ± 25.9	125.0 ± 26.3	116.7 ± 24.2	0.004

Note: Values are presented as mean ± SD.

Abbreviations: 2D, 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; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TEE, transesophageal echocardiography; TRPG, tricuspid regurgitation pressure gradient; TTE, transthoracic echocardiography; TVA, tricuspid valve annulus.

between TV area measured by 3D-TEE and Log_{10} hANP revealed an inverse correlation between the two parameters in patients with persAF (r = 0.25, p = 0.005), whereas no such correlation was observed in those with paroxAF (Figure 4). Subsequently, the correlation between TV diameters in two directions and Log_{10} hANP was analyzed. An inverse correlation between the A-P annular diameter and Log_{10} hANP was observed in patients with persAF (r = 0.27, p = 0.002) (Figure 5A), whereas no correlation was found in those with paroxAF. Meanwhile, the AL-PM annular diameter showed no correlation with Log_{10} hANP in either paroxAF or persAF patients (Figure 5B).

3.4 | Factors Associated With TVA Dilatation

To investigate the factors contributing to TVA dilatation, such as TVA area measured by 3D-TEE, a multivariate linear regression analysis was conducted, including the following covariates: Log_{10} hANP, RA area, RV area, tricuspid annular plane systolic excursion (TAPSE), AF duration and various demographic variables such as age, sex, and body surface area. RA dilatation remained an independent determinant of TVA area measured by 3D-TEE (per 10 cm^2 increase, β: 0.45 [95% CI: 153.3 to 347.7]; $p < 0.001$), whereas Log_{10} hANP was also recognized as an independent determinant

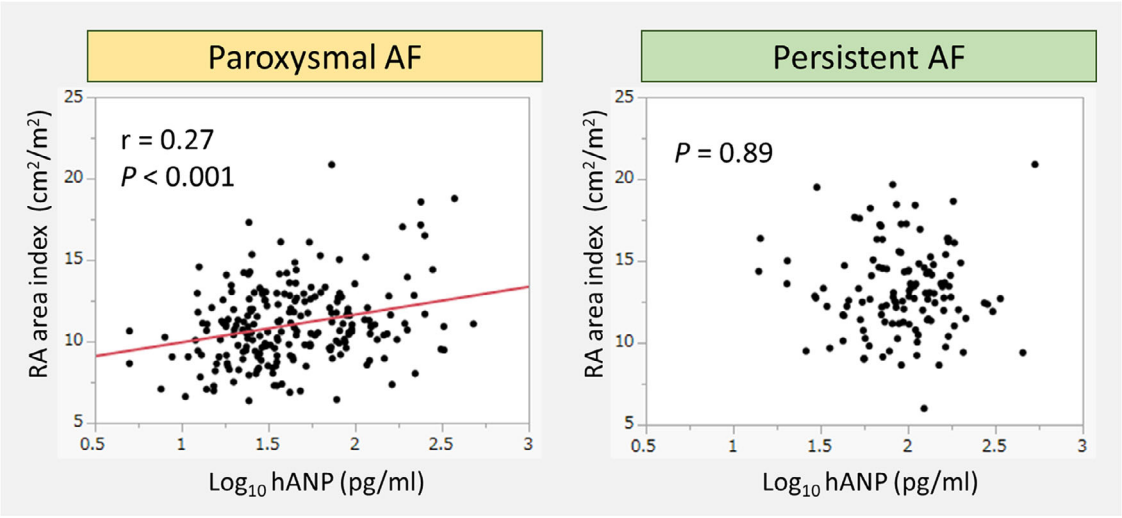

FIGURE 3 | Correlations between Log_{10} hANP and RA area index. Log_{10} hANP showed a mild correlation with the RA area index in patients with paroxysmal AF ($p < 0.001$), while no significant correlation was observed between Log_{10} hANP and the RA area index in patients with persistent AF. AF, atrial fibrillation; hANP, human atrial natriuretic peptide; RA, right atrium.

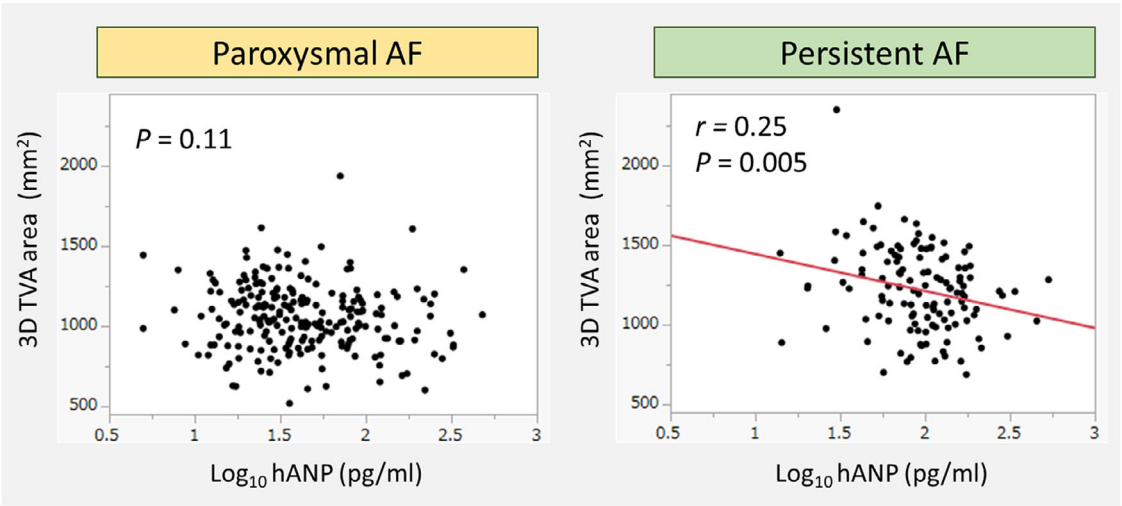

FIGURE 4 | Correlations between Log_{10} hANP and 3D TVA area. No significant correlation was found between Log_{10} hANP and the 3D TVA area in paroxysmal AF patients. In contrast, a mild negative correlation was observed between Log_{10} hANP and the 3D TVA area in persistent AF patients ($p = 0.005$). AF, atrial fibrillation; hANP, human atrial natriuretic peptide; TVA, tricuspid valve annulus.

of TVA area (per 1 increase, β: −0.17 [95% CI: −306.7 to −7.59]; $p = 0.04$) (Table 3).

4 | Discussion

To the best of our knowledge, this study is the first to investigate the potential role of reduced hANP as a marker for diagnosing TV dilatation using both 2D-TTE and 3D-TEE. The main findings of this study can be summarized as follows: (1) In patients with paroxAF, a moderate correlation was observed between hANP and the RA area index, whereas no significant correlation was seen in those with persAF. (2) In persAF patients, an inverse correlation was observed between TV area and hANP, and multivariate regression analysis also revealed that reduced hANP is independently associated with annular dilatation. (3) In persAF patients, a negative correlation was noted between the A-P direction of the TVA diameter and hANP, while no correlation was observed in the AL-PM direction.

The primary trigger for hANP release is thought to be the increase in atrial transmural pressure with associated atrial stretch [6, 11]. hANP levels have long been recognized as being elevated in patients with AF [12, 13]. The most recent report also indicated that, in paroxAF patients, the irregularity of heart rhythm independently contributes to the elevation of hANP levels, beyond other factors [14]. On the other hand, it has been reported that in patients with persAF, hANP levels decrease as the duration of AF increases [15]. In another study, it has been stated that, as the duration of AF increases, the amount of atrial collagen, a marker of atrial remodeling, also increases, and the secretion of hANP decreases as the amount of atrial collagen increases [16].

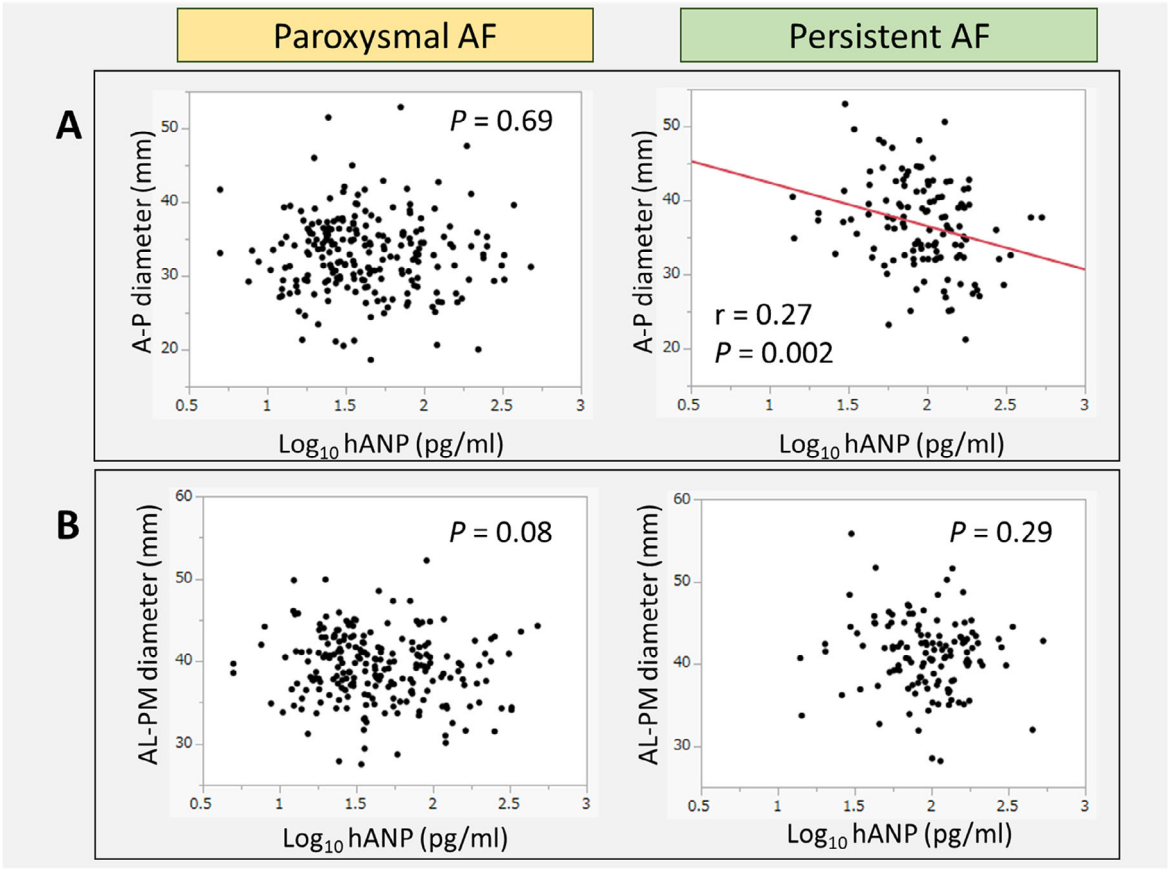

FIGURE 5 | Correlations between Log_{10} hANP and TVA diameter in the A-P and AL-PM directions. (A) No significant correlation was observed between Log_{10} hANP and the TVA diameter in the A-P direction in paroxysmal AF patients. However, a mild negative correlation was found between Log_{10} hANP and the TVA diameter in the A-P direction in persistent AF patients ($p = 0.002$). (B) The AL-PM annular diameter did not show any correlation with Log_{10} hANP in either paroxysmal AF or persistent AF patients. AF, atrial fibrillation; hANP, human atrial natriuretic peptide; PM, posteromedial; TVA, tricuspid valve annulus.

TABLE 3 | Linear regression analyses to predict TVA dilatation in patients with persistent AF.

	Univariable	Multivariable[a]			
	***p* value**	***β***	**95% CI**	***p* value**	**VIF**
Log_{10}hANP (per 1 increase)	0.004	−0.17	−306.7 to −7.59	0.04	1.12
RA area (per 10 cm^2 increase)	<0.001	0.45	153.3 to 347.7	<0.001	1.31
RV area (per 10 cm^2 increase)	0.003	−0.01	−123.0 to 105.8	0.88	1.60
TAPSE (per 1 mm increase)	0.07	0.05	−8.15 to 16.3	0.51	1.13
AF duration (per 1 month increase)	0.01	0.14	−0.08 to 1.18	0.09	1.10

Abbreviations: AF, atrial fibrillation; hANP, human atrial natriuretic peptide; RA, right atrial; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion.
[a]Age-, sex-, and BSA-adjusted.

There have been several reports on the relationship between atrial size and hANP, and this study found a correlation between left atrial volume and hANP in sinus rhythm, but no such correlation was observed in the persAF group [17]. In this study, a correlation between right atrial size and hANP was observed in patients with paroxAF, while no such correlation was found in persAF. This may be because the study included patients with long-term persAF, and as mentioned earlier, some cases may have experienced a decrease in hANP production.

To the best of our knowledge, no previous reports have examined the relationship between annular size and hANP. In this study, for the first time, we demonstrated a negative correlation between hANP and both the 3D TV area and the TV diameter in the A-P direction. A case of persAF in which multiple hANP measurements were performed is shown in Graphical abstract. According to previous reports [16], hANP in persAF tends to increase to a certain level before decreasing as atrial remodeling progresses. In AF patients, the atrium enlarges first, leading to subsequent

annular dilatation. [18]. The negative correlation between hANP and annular size observed in this study suggests that annular dilatation may progress when hANP begins to decline. Additionally, the fact that a negative correlation with hANP was observed only in the A-P annular diameter is consistent with previous reports indicating that annular dilatation in AF patients occurs predominantly in the A-P direction [19].

4.1 | Limitations

This study has some limitations. First, it was a single-center retrospective study with a limited sample size, which may have led to inadequate adjustment for confounding factors. Second, the timing of hANP measurement is considered the most significant limitation of this study. We included patients whose hANP levels were measured within 1 month before 3D-TEE. While all samples from persAF patients were collected during AF episodes, those from paroxAF patients included both samples taken during AF episodes and those taken in sinus rhythm. It has been shown that hANP levels differ between AF episodes and sinus rhythm in the same patient [14]. Third, in this study, it was suggested that hANP exhibits a biphasic pattern over the course of AF; however, we were unable to determine the threshold of hANP for diagnosing annular dilatation. Future prospective studies may allow for the determination of an optimal cutoff value for hANP and may further elucidate its potential utility not only as a diagnostic marker but also as a predictor of future annular dilatation. Fourth, while this study suggested that hANP may serve as a biomarker for TVA dilatation, the pathogenesis underlying the relationship between hANP and annular dilatation was not investigated. Fifth, as this was a retrospective study, it was challenging to comprehensively exclude all potential causes of myocardial involvement that could lead to secondary tricuspid annular dilatation. Finally, we aimed to examine the longitudinal decline of hANP in persAF patients. However, the number of cases with multiple hANP measurements at our institution was extremely limited, making it difficult to perform this analysis.

5 | Conclusions

In patients with persAF, hANP reduction showed a negative correlation with the 3D TV area, particularly with the TV diameter in the A-P direction. Moreover, hANP reduction was independently associated with TVA dilatation, regardless of other factors. In patients with persAF, decreased plasma hANP levels may serve as a potential marker for tricuspid annular dilatation.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. H. Utsunomiya, Y. Itabashi, H. Mihara, et al., "Functional Tricuspid Regurgitation Caused by Chronic Atrial Fibrillation: A Real-Time 3-Dimensional Transesophageal Echocardiography Study," *Circulation: Cardiovascular Imaging* 10 (2017): e004897.

2. K. Izumi, H. Utsunomiya, M. Takeuchi, et al., "Relationship Between Duration of Atrial Fibrillation and Right Heart Structure Remodeling as Assessed by 3-Dimensional Transesophageal Echocardiography," *International Journal of Cardiology* 399 (2024): 131667.

3. S. H. Patlolla, H. V. Schaff, R. A. Nishimura, et al., "Incidence and Burden of Tricuspid Regurgitation in Patients With Atrial Fibrillation," *Journal of the American College of Cardiology* 80 (2022): 2289–2298.

4. H. Utsunomiya, J. Yoshida, K. Izumi, et al., "Predominant Posterior Annular Dilatation Is Associated With Vena Contracta Morphology in Atrial Functional Tricuspid Regurgitation," *Journal of the American Society of Echocardiography* 35 (2022): 588–599.

5. K. Kangawa and H. Matsuo, "Purification and Complete Amino Acid Sequence of Alpha-Human Atrial Natriuretic Polypeptide (alpha-hANP)," *Biochemical and Biophysical Research Communications* 118 (1984): 131–139.

6. B. S. Edwards, R. S. Zimmerman, T. R. Schwab, et al., "Atrial Stretch, Not Pressure, Is the Principal Determinant Controlling the Acute Release of Atrial Natriuretic Factor," *Circulation Research* 62 (1988): 191–195.

7. J. A. Joglar, M. K. Chung, A. L. Armbruster, et al., "2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines," *Circulation* 149 (2024): e1–e156.

8. R. M. Lang, L. P. Badano, V. Mor-Avi, et al., "Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update From the American Society of Echocardiography and the European Association of Cardiovascular Imaging," *Journal of the American Society of Echocardiography* 28 (2015): 1–39.

9. L. G. Rudski, W. W. Lai, J. Afilalo, et al., "Guidelines for the Echocardiographic Assessment of the Right Heart in Adults: A Report From the American Society of Echocardiography Endorsed by the European Association of Echocardiography, a Registered Branch of the European Society of Cardiology, and the Canadian Society of Echocardiography," *Journal of the American Society of Echocardiography* 23 (2010): 685–713.

10. W. A. Zoghbi, D. Adams, R. O. Bonow, et al., "Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report From the American Society of Echocardiography Developed in Collaboration With the Society for Cardiovascular Magnetic Resonance," *Journal of the American Society of Echocardiography* 30 (2017): 303–371.

11. M. Sramko, D. Wichterle, V. Melenovsky, et al., "Independent Effect of Atrial Fibrillation on Natriuretic Peptide Release," *Clinical Research in Cardiology* 108 (2019): 142–149.

12. D. Roy, F. Paillard, D. Cassidy, et al., "Atrial Natriuretic Factor During Atrial Fibrillation and Supraventricular Tachycardia," *Journal of the American College of Cardiology* 9 (1987): 509–514.

13. A. Rossi, M. Enriquez-Sarano, J. C. Burnett Jr., et al., "Natriuretic Peptide Levels in Atrial Fibrillation: A Prospective Hormonal and Doppler-Echocardiographic Study," *Journal of the American College of Cardiology* 35 (2000): 1256–1262.

14. P. Stojadinovic, D. Wichterle, M. Fukunaga, et al., "Acute Effect of Atrial Fibrillation on Circulating Natriuretic Peptides: The Influence of Heart Rate, Rhythm Irregularity, and Left Atrial Pressure Overload," *American Journal of Cardiology* 208 (2023): 156–163.

15. M. P. van den Berg, G. Tjeerdsma, P. Jan de Kam, et al., "Longstanding Atrial Fibrillation Causes Depletion of Atrial Natriuretic Peptide in Patients With Advanced Congestive Heart Failure," *European Journal of Heart Failure* 4 (2002): 255–262.

16. F. Yoshihara, T. Nishikimi, Y. Sasako, et al., "Plasma Atrial Natriuretic Peptide Concentration Inversely Correlates With Left Atrial Collagen Volume Fraction in Patients With Atrial Fibrillation: Plasma ANP as a Possible Biochemical Marker to Predict the Outcome of the Maze Procedure," *Journal of the American College of Cardiology* 39 (2002): 288–294.

17. B. Wozakowska-Kaplon and G. Opolski, "No Correlation Between Atrial Natriuretic Peptide Concentrations and Echocardiographic Measurements of Left Atrial Size or Left Ventricular Size and Function in Patients With Persistent Atrial Fibrillation," *Pacing and Clinical Electrophysiology* 28, Suppl no. 1 (2005): S110–114.

18. D. Muraru, K. Addetia, A. C. Guta, et al., "Right Atrial Volume Is a Major Determinant of Tricuspid Annulus Area in Functional Tricuspid Regurgitation: A Three-Dimensional Echocardiographic Study," *European Heart Journal – Cardiovascular Imaging* 22 (2021): 660–669.

19. H. Utsunomiya, Y. Itabashi, S. Kobayashi, et al., "Clinical Impact of Size, Shape, and Orientation of the Tricuspid Annulus in Tricuspid Regurgitation as Assessed by Three-Dimensional Echocardiography," *Journal of the American Society of Echocardiography* 33 (2020): 191–200.