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Topographical anatomy of the right atrial appendage vestibule and its isthmuses

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Abstract

Introduction: The right atrial appendage (RAA) vestibule is an area located in the right atrium between the RAA orifice and the right atrioventricular valve annulus and may be a target for invasive transcatheter procedures.

Methods and Results: We examined 200 autopsied human hearts. Three isthmuses (an inferior, a middle, and a superior isthmus) were detected. The average length of the vestibule was 67.4 ± 10.1 mm. Crevices and diverticula were observed within the vestibule in 15.3% of specimens. The isthmuses had varying heights: superior: 14.0 ± 3.4 mm, middle: 11.2 ± 3.1 mm, and inferior: 10.1 ± 2.7 mm ($p < .001$). The superior isthmus had the thickest atrial wall (at midlevel: 16.7 ± 5.6 mm), the middle isthmus had the second thickest wall (13.5 ± 4.2 mm), and the inferior isthmus had the thinnest wall (9.3 ± 3.0 mm; $p < .001$). This same pattern was observed when analyzing the thickness of the adipose layer (superior isthmus had a thickness of 15.4 ± 5.6 mm, middle: 11.7 ± 4.1 mm and inferior: 7.1 ± 3.1 mm; $p < .001$). The average myocardial thickness did not vary between isthmuses (superior isthmus: 1.3 ± 0.5 mm, middle isthmus: 1.8 ± 0.8 mm, inferior isthmus: 1.6 ± 0.5 mm; $p > .05$). Within each isthmus, there were variations in the thickness of the entire atrial wall and of the adipose layer. These were thickest near the valve annulus and thinnest near the RAA orifice ($p < .001$). The thickness of the myocardial layer followed an inverse trend ($p < .001$).

Conclusions: This study was the first to describe the detailed topographical anatomy of the RAA vestibule and that of its adjoining isthmuses. The substantial variability in the structure and dimensions of the RAA isthmuses may play a role in planning interventions within this anatomic region.

KEYWORDS
ablation, cardiac anatomy, right atrial appendage, right atrial appendage vestibule, right atrium, terminal crest

1 | INTRODUCTION

Catheter radiofrequency ablation is becoming an increasingly more popular procedure and has resulted in a renewed interest in the detailed anatomy of the right atrium. Within this cardiac chamber, the most common ablation target is the cavotricuspid isthmus,[1–4] although areas such as the interatrial septum and the right atrial appendage (RAA) have also been known to contain arrhythmogenic substrates.[5] As a result, the important morphological features of the cavotricuspid isthmus, Koch's triangle, and the interatrial septal region have been thoroughly studied.[4,6,7] However, little is known about the vestibule and the isthmuses of the RAA.

The RAA vestibule is a smooth area situated between the orifice of the RAA and the right atrioventricular valve annulus.[8–11] Although there are a few isolated studies about its anatomy, they do not provide a comprehensive outlook of its morphological features, since they were either conducted on a pediatric population[12] or had a relatively small sample size.[10] The RAA vestibule and its adjoining isthmuses are clinically important structures where right accessory pathways are predominantly distributed and thus may be used as targets for catheter ablation or as sites for device implantation during percutaneous right atrioventricular valve repairs.[13–16] Invasive transcatheter procedures are challenging and are associated with numerous complications. The most serious setbacks associated with these procedures include atrial wall rupture, cardiac tamponade, and local blood vessel injury.[17,18] These can be reduced if the clinician has a lot of experience or if he/she is knowledgeable about the area's anatomical properties. Therefore, accurate knowledge about the morphology of the targeted region is extremely valuable and may help avoid serious procedural complications.

Due to the lack of morphological data about the RAA vestibule and its clinical relevance, this study sought to evaluate the detailed topographical anatomy of the RAA vestibule and that of its isthmuses.

2 | METHODS

This study was approved by the Bioethical Committee of the Jagiellonian University in Cracow, Poland (No. 1072.6120.90.2020). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

2.1 | Study population

We examined 200 randomly selected human adult hearts. The specimens were collected during routine medical forensic autopsies and included Caucasian individuals (22.0% female) between the ages of 18 and 94 (the average age was 46.9 ± 17.9 years). The donors had a mean body mass index of 26.6 ± 4.5 kg/m^2 and an average body surface area of 1.9 ± 0.2 m^2. The primary causes of death included suicide, murder, traffic accidents, and home accidents. We excluded donors that had severe anatomical defects, heart trauma, heart grafts, severe macroscopic pathologies of the heart or vascular system, and those with signs of cadaveric decomposition. No chosen donors had a prior history of arrhythmias and none died of cardiac failure.

2.2 | Dissection and measurements

The hearts and the proximal vessels (ascending aorta, pulmonary trunk, superior, and inferior vena cava along with the pulmonary veins) were dissected from the chest cavity. Before being immersed in a 10% paraformaldehyde solution, the hearts were weighed using a 0.5-g precision electronic laboratory scale.

The RAA vestibule (located between the ostium of the RAA and the annulus of the right atrioventricular valve) was labeled and assessed form the endocardial aspect (Figure 1). The length of the vestibule was measured along the right atrioventricular valve annulus. Three distinct isthmuses were observed within the vestibule (Figure 1):

(1) The inferior RAA isthmus—located within the RAA vestibule, at the inferior/terminal crest end of the RAA vestibule (demarcated by the distal end of the terminal crest)
(2) The superior RAA isthmus—located within the RAA vestibule, at the superior/septal end of the RAA vestibule (demarcated by superior end of RAA ostium)
(3) The middle RAA isthmus—located within the RAA vestibule, halfway between the inferior RAA isthmus and the superior RAA isthmus.

The height of each isthmus was measured (from the edge of the RAA orifice to the right atrioventricular valve annulus). Then, the isthmuses were cut longitudinally to obtain cross-sections (Figure 2). We measured the thickness of the entire atrial wall, the myocardial layer, and the adipose tissue layer at three different levels of the isthmus: the upper 1/3 (situated close to the RAA), the middle 1/3, and the lower 1/3 (situated close to the right atrioventricular valve annulus; Figure 2).

Linear measurements were obtained using 0.03-mm precision electronic calipers (YT-7201; YATO). All measurements were performed by two independent researchers to reduce human bias. If the results obtained by the two researchers differed by more than 10%, the sample was reassessed. The mean of the two new measurements was calculated and approximated to the tenth decimal place.

2.3 | Statistical analysis

The data is presented as a mean ± standard deviation with the median and interquartile ranges (Q1, Q3) for continuous variables, or percentages (%) for categorical variables. Shapiro–Wilk tests were used to determine if the quantitative data had normal distributions.

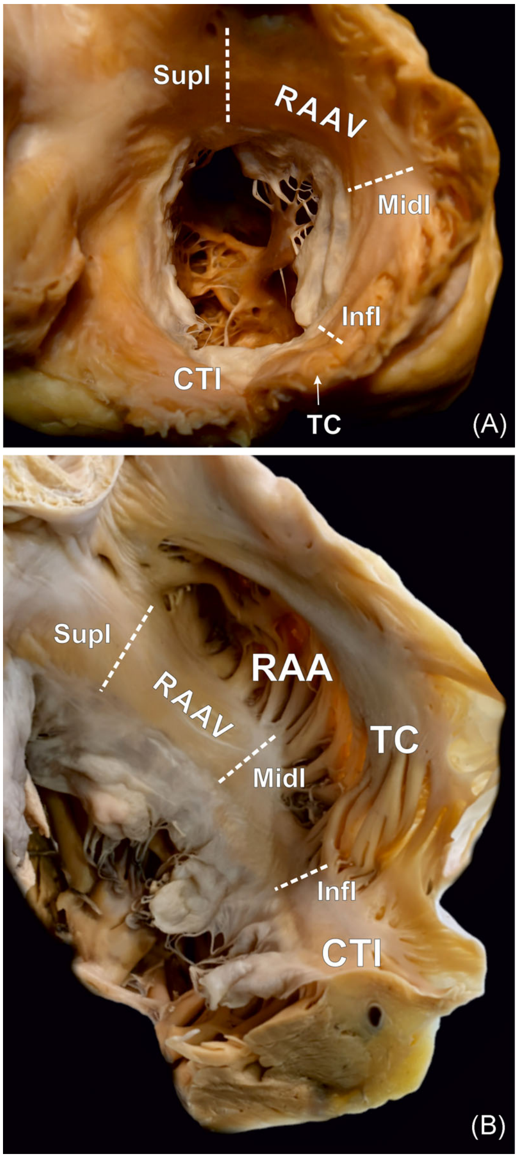


FIGURE 1 Photographs of cadaveric heart specimens showing the right atrial appendage vestibule (RAAV) with its isthmuses: superior isthmus (SupI), middle isthmus (MidI), and inferior isthmus (InfI). Dissection images of the formalin-fixed specimen as viewed (A) from the right atrium and (B) with the right atrioventricular valve annulus opened by an incision through the cavotricuspid isthmus (CTI). RAA, right atrial appendage; TC, terminal crest

Levene's test was performed to verify the relative homogeneity of variance. Student's *t*-tests and the Mann–Whitney *U* tests were used for statistical comparisons. The analysis of variance or nonparametric Kruskal–Wallis tests were used to compare values between different groups. Detailed comparisons were performed using Tukey's post hoc analyses. Qualitative variables were compared using χ^2 tests of proportions with Bonferroni corrections to account for the multiple comparisons. Correlation coefficients were also calculated. To detect a simple correlation ($r = .25$) with 80% power and a 5% significance level (two-tailed; $\alpha = .05$; $\beta = .2$), the minimal sample size was set at 123 cases. A p value of less than .05 was

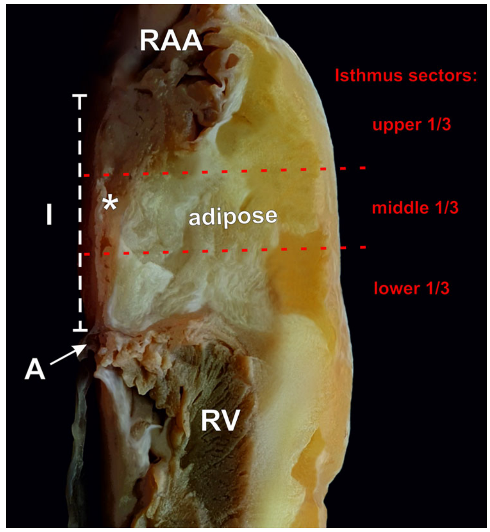


FIGURE 2 Photographs of cadaveric heart specimens showing longitudinal cross-sections of the inferior right atrial appendage (RAA) vestibule isthmus (I). The thickness of the whole atrial wall, myocardial layer (*), and adipose tissue layer were measured at three different levels: upper 1/3 (close to the RAA), middle 1/3, and lower 1/3 (close to the right atrioventricular valve annulus). A, right atrioventricular valve annulus; RV, right ventricle

considered statistically significant. Statistical analyses were performed using StatSoft STATISTICA 13.1 software (StatSoft Inc.).

3 | RESULTS

The RAA vestibule was identified in each examined heart. In 84.7% of specimens, the endocardial surface of the vestibule was completely smooth. The remaining hearts (15.3%) had noticeable crevices and diverticula (Figure 3).

The mean length of the RAA vestibule was 67.4 ± 10.1 mm (Table 1). The sex of the donor influenced the height of the vestibule (males: 67.9 ± 10.5 mm vs. females: 65.8 ± 8.1 mm; $p = .048$). Table 1 presents the heights of the three RAA isthmuses. The superior RAA isthmus was the highest (14.0 ± 3.4 mm), the middle RAA isthmus was second highest (11.2 ± 3.1 mm), and the inferior RAA isthmus was the shortest (10.1 ± 2.7 mm; $p < .001$). The height of all the isthmuses had a positive correlation with the donor's age and cardiac weight ($r > .25$; $p < .001$; Table S1).

Table 2 presents data about atrial wall thickness. Analysis of the thickness of the entire atrial wall showed that the superior RAA isthmus had the thickest wall, that the inferior isthmus had the thinnest wall and that the middle isthmus was in-between (Figure 4A; $p < .001$). Moreover, the atrial wall thickness varied based on the location of the measurement. Generally, it was thickest at the lower level of the isthmus (near the right atrioventricular valve annulus) and gradually thinned toward the upper level of the isthmus (toward RAA orifice) (Figure 4A; all $p < .001$). There was a positive correlation between the donor's age and wall

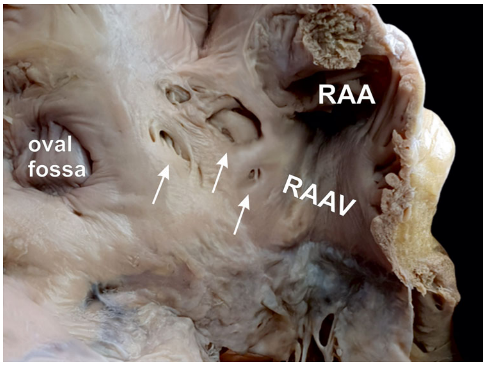


FIGURE 3 Photographs of cadaveric heart specimens showing the endocardial surface of the right atrial appendage vestibule (RAAV) with crevices and diverticula (solid arrows). RAA, right atrial appendage

thickness for the superior RAA isthmus (at all levels) and for the inferior RAA isthmus (at the upper and middle levels; $r > .25$; $p < .05$). Conversely, this correlation, albeit small, was negative for the middle RAA isthmus (at all levels; $r < -.10$; $p < .05$; Table S1). The heart weight also positively correlated with the thickness of the superior isthmus (at all levels) and with the thickness of the inferior isthmus (at the upper and middle levels; Table S1).

The thickness of the myocardial layer did not vary between the three RAA isthmuses ($p > .05$), although there were variations within each isthmus (Figure 4B). The myocardial layer was always thinnest at the lower level of the isthmus and thickest at the upper level (near the RAA orifice; Figure 4B; all $p < .001$). There were no recorded anthropometric parameters that influenced the thickness of the myocardial layer (Table S1). A myocardial layer less than 0.5 mm was rare—it was seen in 1% of superior RAA isthmuses and 1.5% of inferior RAA isthmuses.

The adipose tissue layer was thickest at the superior RAA isthmus and thinnest at the inferior RAA isthmus (Figure 4C; $p < .001$). Within each isthmus, the adipose tissue layer was thickest at the lower level and thinnest at the upper level (Figure 4C; all $p < .001$). Significant and strong correlations were found between the donor's age as well as heart weight and adipose tissue layer at all levels of the superior RAA isthmus ($r \geq .25$; $p < .001$). These correlations were less pronounced in the inferior RAA isthmus (upper and middle level) (Table S1).

The sex of the donor had no influence on thickness measurements ($p > .05$). The thickness of the entire atrial wall and the thickness of the adipose layer of the superior RAA isthmus (at all levels) correlated with the length of the superior isthmus (all $r > .25$; $p < .005$). No significant correlations were found between the myocardial layer of the superior RAA isthmus and the length of the superior isthmus. Similarly, no correlations were observed between the measured thicknesses of the middle and inferior RAA isthmuses and their respective lengths ($p > .05$).

4 | DISCUSSION

The morphology of the RAA vestibule has not been studied enough. It has often been considered as a component of the broader area of the right atrium which surrounds the annulus of the right atrioventricular valve—the right atrial vestibule.[19] When observed from the inferior aspect, the vestibule of the RAA is separated from the cavotricuspid isthmus by the final ramifications of the terminal crest.[4] From the superomedial aspect, it extends freely into the anteroinferior region of the interatrial septum and into the area of Koch's triangle.[6,7,20]

To date, the most complex macroscopic study of this structure has been performed by Ueda et al.,[10] which analyzed 39 normal human hearts. Although their study examined the composition of the RAA vestibule at the three main isthmuses, they did not measure their heights. There was a need to fill that gap since the height of the isthmuses could have important clinical implications. It has been demonstrated that the length of an ablation line is negatively correlated with the ablation success rates.[21] In other words, a high isthmus could be associated with a worse ablation outcome. However, on the other hand, higher isthmuses could allow more room for maneuvers within the right atrioventricular annulus, which could be beneficial for complicated surgeries. In this study, we found that the RAA inferior isthmus had the lowest height (10.1 ± 2.7 mm), which could make it a good site for ablations. The RAA superior isthmus was the highest (14.0 ± 3.4 mm), which could make it a good access site for complex invasive procedures. Finally, since it was demonstrated that the height of all the isthmuses correlated with the donor's age and cardiac weight (Table S1), clinicians should expect more challenges during ablation procedures in older and larger/heavier patients.

TABLE 1 The morphometric characteristic of the right atrial appendage (RAA) vestibule ($n = 200$)

Parameter	Mean	*SD*	Min	Max	Median	Q1	Q3
RAA vestibule length	67.9	10.6	9.2	88.2	68.6	62.5	75.2
Superior RAA isthmus height (mm)	14.0	3.4	5.8	24.4	13.8	11.8	16.0
Middle RAA isthmus height (mm)	11.2	3.1	5.4	19.2	11.0	8.8	13.3
Inferior RAA isthmus height (mm)	10.1	2.7	4.3	18.5	9.8	8.2	11.8

TABLE 2 Atrial wall thickness of the cross-sections of the right atrial appendage (RAA) isthmuses ($n = 200$)

Isthmus	Parameter	Mean	*SD*	Min	Max	Median	Q1	Q3
Superior RAA isthmus	Whole atrial wall thickness at upper level[a]	8.9	4.7	1.6	32.8	8.2	5.7	11.2
	Whole atrial wall thickness at middle level	16.7	5.6	6.5	43.4	15.6	12.8	19.7
	Whole atrial wall thickness at lower level[b]	23.5	6.2	10.2	45.5	23.5	18.9	27.6
	Myocardial layer thickness at upper level	2.0	0.6	0.6	4.5	1.9	1.5	2.3
	Myocardial layer thickness at middle level	1.3	0.5	0.5	2.7	1.3	1.0	1.6
	Myocardial layer thickness at lower level	0.9	0.3	0.1	2.2	0.9	0.7	1.1
	Adipose tissue layer thickness at upper level	7.0	4.6	0.4	30.5	6.1	3.8	9.0
	Adipose tissue layer thickness at middle level	15.4	5.6	5.4	42.9	14.4	11.4	18.4
	Adipose tissue layer thickness at lower level	22.6	6.1	8.8	45.0	22.6	18.1	26.7
Middle RAA isthmus	Whole atrial wall thickness at upper level	11.0	3.7	3.4	22	10.8	8.3	13.6
	Whole atrial wall thickness at middle level	13.5	4.2	4.5	27.8	13.3	10.6	15.8
	Whole atrial wall thickness at lower level	14.9	4.6	5.2	32.3	14.8	11.7	17.7
	Myocardial layer thickness at upper level	2.4	0.9	0.7	7.7	2.2	1.8	2.7
	Myocardial layer thickness at middle level	1.8	0.8	0.6	7.8	1.7	1.4	2.0
	Myocardial layer thickness at lower level	1.4	0.7	0.5	6.3	1.3	1.1	1.5
	Adipose tissue layer thickness at upper level	9.2	3.7	1.6	18.7	9.0	6.4	11.7
	Adipose tissue layer thickness at middle level	11.7	4.1	3.3	26	11.4	8.8	14.3
	Adipose tissue layer thickness at lower level	13.1	4.6	3.8	30.5	12.9	10	15.7
Inferior RAA isthmus	Whole atrial wall thickness at upper level	7.1	2.6	1.9	17.7	6.6	5.3	8.6
	Whole atrial wall thickness at middle level	9.3	3.0	3.4	19.9	8.6	7.1	11.2
	Whole atrial wall thickness at lower level	11.0	3.4	3.0	22.1	10.4	8.2	12.7
	Myocardial layer thickness at upper level	2.1	0.7	0.7	4.4	1.9	1.5	2.5
	Myocardial layer thickness at middle level	1.6	0.5	0.7	4.0	1.5	1.2	1.8
	Myocardial layer thickness at lower level	1.2	0.4	0.3	3.1	1.2	0.9	1.3
	Adipose tissue layer thickness at upper level	5.1	2.8	0.2	15.2	4.5	3.0	6.8
	Adipose tissue layer thickness at middle level	7.1	3.1	1.5	18.4	7.1	5.3	9.8
	Adipose tissue layer thickness at lower level	9.9	3.5	2.3	21.4	9.3	7.5	11.7

[a]Upper level—Close to the right atrial appendage.

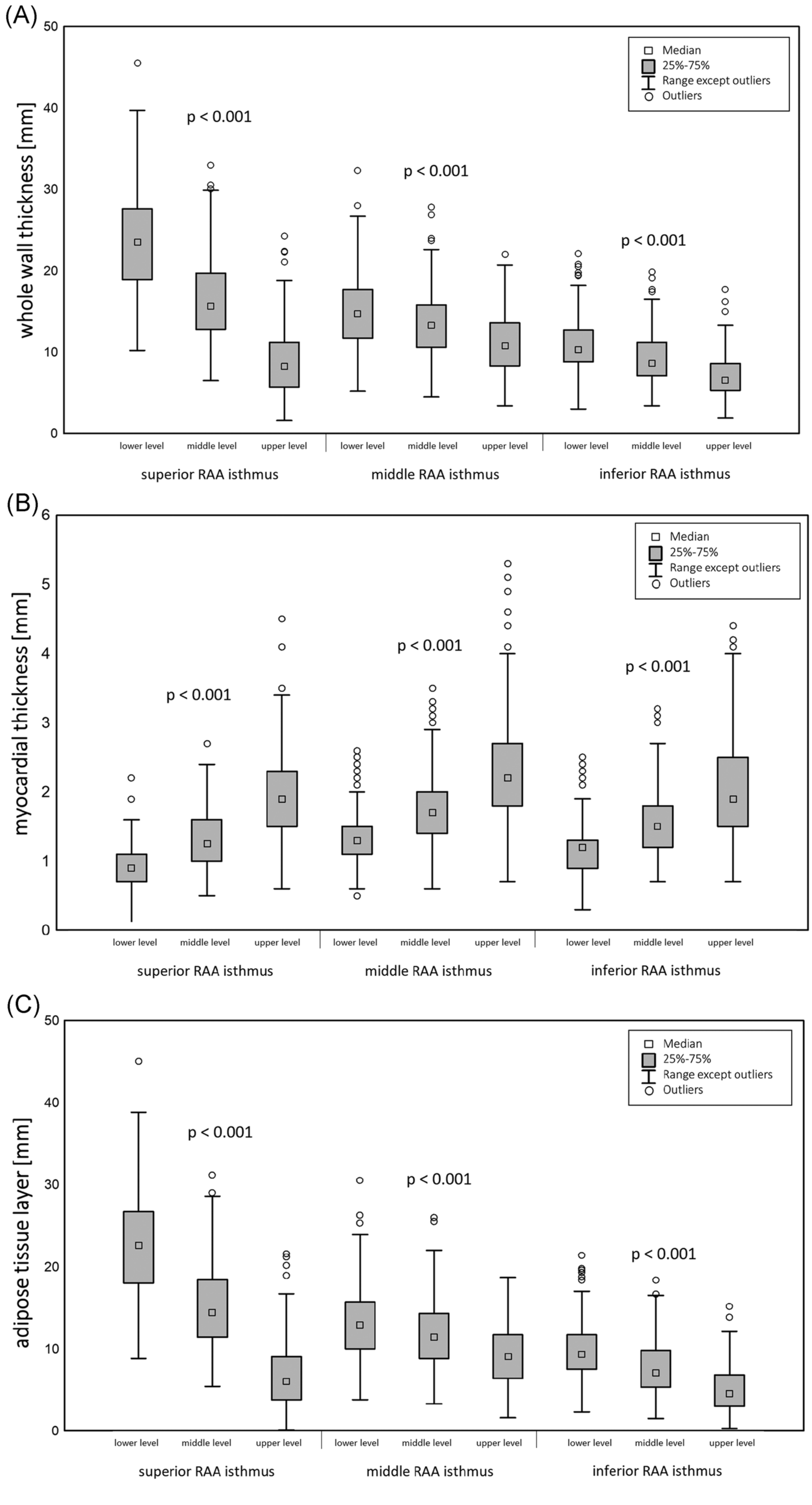
[b]Lower level—Close to the right atrioventricular valve annulus.

The current study has shown that the endocardial surface of the RAA vestibule is not as smooth as previously thought. In 15.3% of all studied specimens, the region of the vestibule was dotted with small crevices, diverticula, recesses, or even tissue bridges (Figure 3). The presence of these extra structures can be explained by one of two theories: either these are embryological remnants of the pectinate muscles that extended from the RAA body or they are outlet points of anterior cardiac veins. Regardless of their origin, these additional structures disturb tissue anisotropy within the area of the vestibule and may create and maintain arrhythmogenic foci.[22] Their presence can also negatively influence ablation procedures. They can hinder catheter support, force clinicians to use higher energy levels, or extend the length of the intervention.[23]

Previously, the study by Ueda et al.[10] demonstrated that the thickness of the vestibule of the RAA isthmus was influenced by the amount of adipose tissue. Our study confirmed this finding. There was significant heterogeneity between the different isthmuses. The adipose layer was thickest at the superior RAA isthmus and thinnest at the inferior isthmus. There were also variations within each isthmus—the adipose layer was thickest near the valve annulus and thinnest near the RAA orifice. Since the epicardial adipose tissue produces numerous mediators that may promote atrial fibrillation, its distribution within the vestibule may be important for locating arrhythmogenic substrates.[24] Moreover, it is highly probable that abundant epicardial adipose tissue, that is located at the superior isthmus area could allow the muscle bundles of accessory nonannulus pathways to cross the annulus at a greater distance than anticipated (more epicardially), thus hindering their destruction via endocardial access.[10,25]

One of the most important factors necessary to achieve successful ablation procedures is proper energy selection. Recent reports have shown that the myocardial layer thickness plays an important role in this process. Myocardial layers which are thicker seem to be safer, although they are also associated with higher failure rates and may require increased levels of energy.[26] Our study showed that the thickness of the myocardial layer did not differ between the different RAA isthmuses, although there was significant intra-isthmus variability is observed (Figure 4B). The myocardial layer was thinnest near the valve annulus and thickest near the RAA orifice. Therefore, clinicians should exercise more

FIGURE 4 Box and Whiskers plots showing thickness of the tissue located within different right atrial appendage (RAA) isthmuses. (A) Whole atrial wall thickness. (B) Myocardial layer thickness. (C) Adipose tissue layer thickness



caution during ablation procedures near the ring valve to avoid undesired complications.[2]

There are also coronary vessels that travel near the area of the vestibule of the RAA. The right coronary artery is the main vessel found within the wall of the vestibule.[10] However, there are possibly other vessels which course through this region, like the branches of the right coronary artery or coronary veins. Currently, there is no data about the spatial relationships between the coronary vessels and the atrial wall components in the area of the vestibule of the RAA. Understanding if and where there are blood vessels inside the vestibule may greatly influence our approach to interventions. For instance, the right coronary artery may become damaged during ablation procedures (thermal injury, thrombosis) or during procedures that repair the right atrioventricular valve (direct injury, compression).[27,28] On the other hand, it is also possible that the blood flow within the coronary vasculature may act as a heat sink and account for the local cooling of the right atrial myocardium, which in turn can reduce the effectiveness of ablation procedures.

A quick comparison between the morphology of the RAA isthmuses and the cavotricuspid isthmus reveals some major differences. First, the RAA vestibule is significantly longer than the cavotricuspid isthmus (67.4 ± 10.1 vs. 21.5 ± 4.9 mm; $p < .001$).[4] Second, all the isthmuses of the RAA vestibule (superior: 14.0 ± 3.4 mm, middle: 11.2 ± 3.1 mm, and inferior 10.1 ± 2.7 mm) are lower than those within the cavotricuspid region (paraseptal: 18.5 ± 4.0 mm, central: 24.0 ± 4.2 mm, and inferolateral: 29.3 ± 4.9 mm).[4] Furthermore, the RAA vestibule is characterized by a simpler morphology than that of the cavotricuspid region. Most of the time, the endocardial surface of the vestibule is entirely smooth (this was observed in almost 85% of our examined specimens), whereas the cavotricuspid region has three different sectors: a smooth anterior sector (proper part of the right atrial vestibule), a richly trabeculated middle sector and an almost paper-thin posterior (membranous) sector.[4] These considerable differences should be remembered when planning and performing interventions within the inferolateral region of the right atrial vestibule.

The current study has some limitations. First, all the observations and measurements were performed on hearts which were fixed in a 10% paraformaldehyde solution. This could have potentially altered the size and shape of the tissues, although a previous study showed that the use of formaldehyde for the preservation of cardiac samples did not significantly affect atrial tissue dimensions.[29] Second, the measurements were done on autopsied material and may not accurately represent the in vivo morphology. Moreover, this study did not take into account the natural dimensional changes that occur within the cardiac cycle. Nonetheless, we consider that these limitations do not significantly impede our morphological analysis of the RAA vestibule and its isthmuses.

5 | CONCLUSIONS

This study is the first to describe the detailed topographical anatomy of the RAA vestibule and its isthmuses. A significant difference could be found in the isthmuses' structure. The superior isthmus was found to be the highest of all the isthmuses. It also had the largest overall atrial thickness and adipose layer thickness (followed by the middle and the inferior isthmuses). Moreover, within the isthmuses, there was considerable intraheterogeneity in the thickness of the entire atrial wall and in the thickness of the adipose layer. These were greatest near the valve annulus and thinnest near the RAA orifice; and the inverse trend was observed for myocardial layer thickness. Age and heart weight affected the dimensions of the vestibule of the RAA, including the height of all the RAA isthmuses, the thickness of the entire atrial wall, and the thickness within the adipose tissue layer at the superior and inferior RAA isthmuses. The substantial variability in the structure and dimensions of the RAA isthmuses may play a role in planning interventions within this anatomic region.

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