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ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Local Variation and Age-Related Change in Atrial and Ventricular Myocardial Contiguity at the Atrioventricular Junction in Human Hearts

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Background: We explored the histologic patterns of and age-related changes in atrial and ventricular myocardial contiguity at the left and right atrioventricular (AV) junction that could be a target site for catheter ablation.

Methods and Results: Twenty-three structurally normal adult hearts obtained at autopsy were studied. The 2 AV annuli were divided into 13 clinically recognized portions in which we measured distance between the atrial and ventricular myocardium at the AV junction. Overall, measured distance was less on the right than left side (mean [±SD] 0.74±0.59 vs. 1.15±0.78 mm, respectively), and distance increased gradually with age. The gap was smallest at the anterolateral portion on the right side and posterolateral portion on the left side. Three specific features were noted, namely extension of the ventricular myocardium (coarse trabeculae) towards the atrium on the right side of the AV junction, extension of the atrial myocardium onto the AV valve leaflets, and a collection of small myocardial cells, perhaps including specialized cells, in the right anterolateral portion. No concealed AV muscular connections were found.

Conclusions: Contiguity and separation of the myocardium at the AV junction have specific patterns, and myocardial proximity is influenced by age. These histologic features of the AV junction may prove to be informative for catheter ablation of tachyarrhythmias related to the AV junction.

Key Words: Anatomy; Atrioventricular annulus; Atrioventricular junction; Catheter ablation; Histology

The atrioventricular (AV) junction is the critical site where the atrial myocardium and ventricular myocardium are contiguous with the attachments of AV valve leaflets.[1] The AV junction is well recognized as the target site for catheter ablation of arrhythmias, such as accessory pathway syndrome, that exist because of bridging between the atrial myocardium and ventricular myocardium,[2] as well as of atrial tachyarrhythmias related to the annular musculature.[3] Anatomical assessments are scarce and have described only the left AV junction with and without valvular degeneration,[4] and there have been no quantitative analyses that have revealed atrial and ventricular myocardial contiguity at the right and left AV junctions. Several reported histologic studies have revealed distinct atrial and ventricular myocardial connections in the hearts of patients with Wolff-Parkinson-White (WPW) syndrome.[5–9] However, information is lacking regarding the morphology of the AV junction on the right and left in structurally normal hearts not affected by paroxysmal supraventricular tachycardia or another significant atrial arrhythmia. Further, it is not known whether age-related changes in the morphology of the AV junction are implicated in such abnormal conduction. Thus, we conducted a study in which we examined contiguity between the ventricular myocardium and atrial myocardium at the right and left AV junction in adult human hearts. We also investigated age-related changes in the morphology of the AV junction pertinent to abnormal conduction.

Methods

Study Specimens

This study was performed in accordance with the principles outlined in the Declaration of Helsinki.

Twenty-three adult human hearts obtained at autopsy and of normal size were randomly selected for the study. No supraventricular tachyarrhythmia had been documented in any of the deceased patients. The autopsies were

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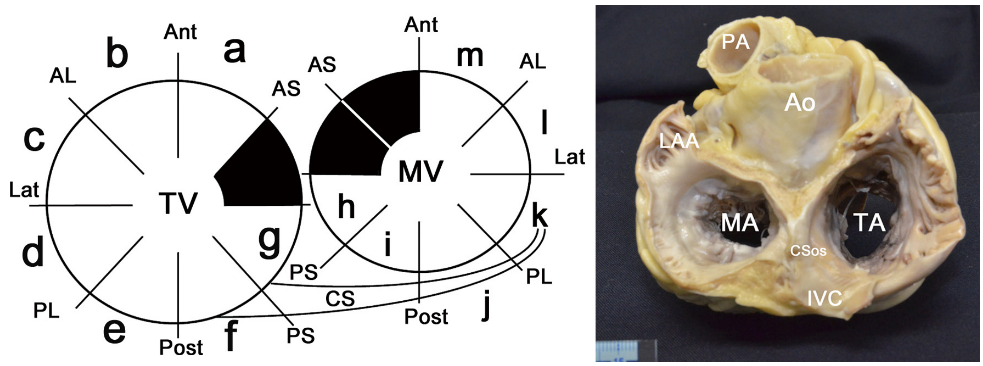

Figure 1. (**Left**) Diagram of the 2 atrioventricular (AV) annuli from the left anterior caudal view. Tissue surrounding the tricuspid annulus ("a"–"g") and mitral annulus ("h"–"m") was divided into portions, as indicated. "a", anterior right ventricular (RV) region adjacent to the RV outflow tract; "b", anterolateral RV region; "c", anterior side of the acute margin; "d", posterior side of the acute margin; "e", posterolateral region and inferior vena cava (IVC); "f", posteroseptal region including the coronary sinus ostium (CSos); "g", posteroseptal region including the AV node; "h", posteroseptal region and AV node; "i", posterior region and proximal coronary sinus (CS); "j", posterior region and distal CS; "k", posterolateral region and great cardiac vein; "l", anterolateral region including the left atrial appendage (LAA); "m", anterior region adjacent to the mitral fibrous continuity. (**Right**) Photograph showing both AV annuli from the cranial aspect. Note that the diagram and specimen mirror each other. Shaded areas in the left-hand panel are those that were excluded because they contain no adjacent atrial-ventricular myocardium or the intervening membranous septum has no myocardial component. AL, anterolateral area; Ant, anterior area; Ao, aorta; AS, anteroseptal area; Lat, lateral area; MA, mitral annulus; MV, mitral valve; PA, pulmonary artery; PL, posterolateral area; Post, posterior area; PS, posteroseptal area; TA, tricuspid annulus; TV, tricuspid valve.

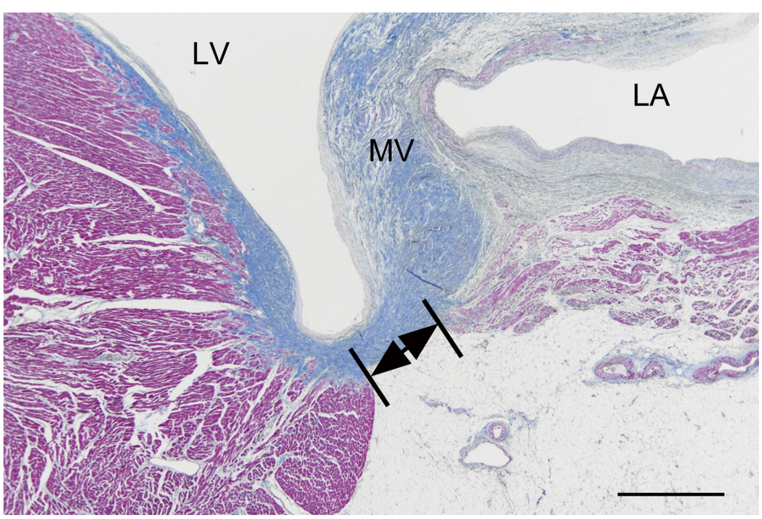

Figure 2. Masson's trichrome-stained section from the left atrioventricular (AV) junction illustrating measurement of the distance between the atrial myocardium and ventricular myocardium. Scale bar, 1 mm. LA, left atrium; LV, left ventricle; MV, mitral valve.

performed at Showa University Hospital between September 2014 and March 2020. None of the deceased patients, all Japanese, had signs of structural heart disease, and there was no remarkable concentric or dilated hypertrophy. The deaths were due to malignant disease (n=16), pneumonia (n=5), trauma (n=1), or carbon monoxide poisoning (n=1). The age and sex of the deceased patients, causes of death, the weights of the hearts, and various measurements are presented in the **Supplementary Table**. Fourteen of the deceased patients were men and 9 were women; age at the time of death ranged from 27 to 88 years (mean [±SD] 62.0±16.7 years). The hearts ranged in fresh weight from 215 to 390 g (mean [±SD] 314.6±49.6 g).

For the purposes of the study, the hearts were divided into 3 groups according to age at the time of death as follows: Group A, <50 years; Group B, 50–69 years; and Group C, ≥70 years.

Tissue Preparation

After the hearts had been weighed, they were fixed in 20% formalin, and the right and left AV annuli, along with ventricular myocardium at the AV junction, were excised. Photographs of each of the 2 annuli, as viewed from the atrial aspect of each of the 2 valves, were obtained, an incision was made at the posterolateral free wall, and both annuli were exposed. We then measured the circumference

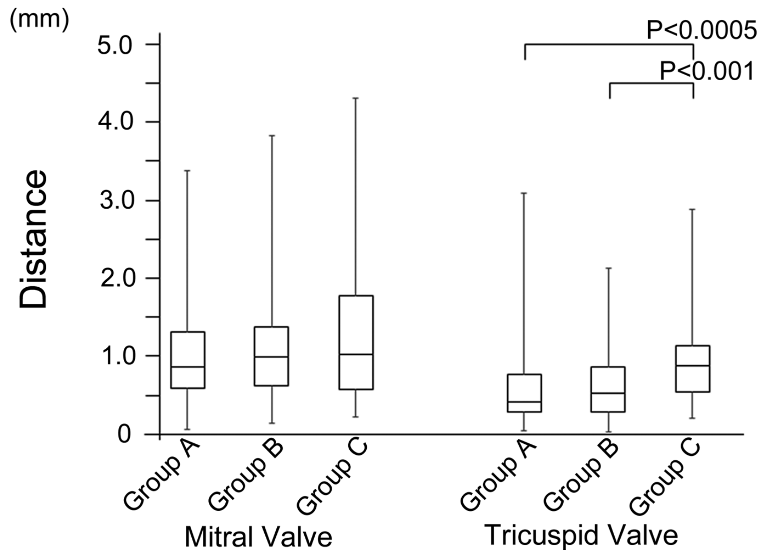

Figure 3. Box-and-whisker plots of distance between the atrial myocardium and ventricular myocardium in the tissue around the atrioventricular annuli per study group. Group A, hearts from people who died at ≤49 years of age; Group B, hearts from people who died at 50–69 years of age; Group C, hearts from people who died at age ≥70 years of age. The boxes show the interquartile range, with the median value indicated by the horizontal line; whiskers show the range.

of each annulus. The specimens including the AV junction were cut serially into 4-mm slices perpendicular to the AV ring and embedded in paraffin. Each cut sample was then sliced into thin (7 μm) sections with a rotary microtome and stained with Masson's trichrome.

Division of Tissues Adjacent to the AV Annuli for Analysis

For the purpose of analysis, we considered the 2 AV annuli, as viewed on typically obtained left caudal oblique projection images, to consist of 16 portions in total.[10,11] We then considered the portions of the surrounding tissue. As shown in **Figure 1**, the portions of the tricuspid annulus included the anterior right ventricular (RV) region adjacent to the RV outflow tract (labeled "a" in **Figure 1**), anterolateral RV region ("b"), anterior side of the acute margin ("c"), posterior side of the acute margin ("d"), posterolateral region and inferior vena cava ("e"), posteroseptal region including the coronary sinus (CS) ostium ("f"), and posteroseptal region including the AV node ("g"). The portions of the mitral annulus (also shown in **Figure 1**) included the posteroseptal region and AV node ("h"), posterior region and proximal CS ("i"), posterior region and distal CS ("j"), posterolateral region and great cardiac vein ("k"), anterolateral region including the left atrial appendage ("l"), and anterior region adjacent to the mitral fibrous continuity ("m"). We then selected specimens that corresponded to each of these 13 portions and examined them microscopically to identify myocardial contiguity or near contiguity across the valve attachments. We excluded the 3 anteroseptal portions (**Figure 1**, shaded areas) because those portions contain no atrial-ventricular myocardium or the intervening membranous septum has no myocardial component.

Measurement of the Distance Between the Atrial and Ventricular Myocardium on the Right and Left Sides of the AV Junction

To identify any myocardial contiguity, we measured the shortest distance between the atrial and ventricular myocardium at the attachment of the AV valve leaflets and examined the surrounding tissues histologically (**Figure 2**). The shortest distance between atrial and ventricular myocardium was taken as the measured distance between atrial and ventricular myocytes lying closest together. In addition, we investigated age-related histologic changes and other features of the tissue around the AV valve attachments. Images were captured using a digital microscope camera (DS-Ri2; Nikon Instruments, Tokyo, Japan) and the contiguity of the AV myocardium was evaluated using image analysis software (NIS-Elements; Nikon Instruments).

Statistical Analyses

Data are expressed as the mean±SD. The significance of differences in study variables between Groups A, B, and C between the 7 portions of tissue adjacent to the tricuspid valve and 6 portions of tissue adjacent to the mitral valve were assessed using the Kruskal-Wallis rank-sum test and Mann-Whitney U test, as appropriate. All statistical analyses were performed using R 3.2.4 (http://www.r-project.org). $P<0.05$ was considered significant.

Results

Circumferences of the AV Valve Annuli

The mean circumference of the tricuspid annulus was 11.0±1.1 cm, whereas that of the mitral annulus was 9.1±0.9 cm. Thus, the annuli were confirmed to be of normal size (not dilated).[12]

Distance Between the Atrial and Ventricular Myocardium at the AV Junction

Overall, the distance between the atrial and ventricular myocardium at the AV junction was 0.74±0.59 mm on the right side (between "a" and "g") and 1.15±0.78 mm on the left side (between "h" and "m"; $P<0.0001$). The difference was attributed to the thick collagenous fiber bundles that make up the mitral annulus and the thinner fiber bundles that make up the tricuspid annulus.

Distance Between the Atrial and Ventricular Myocardium at the AV Junction Per Group

The distance between the atrial and ventricular myocar-

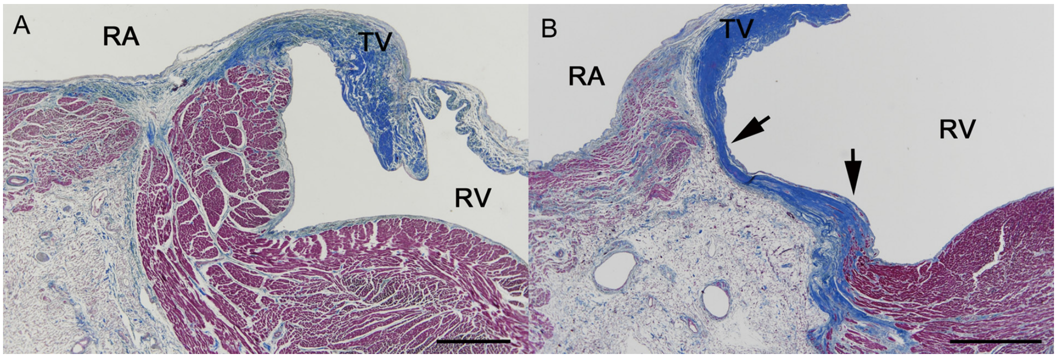

Figure 4. Microscopic images of Masson's trichrome-stained sections of area "g" tissue from (**A**) the heart of a woman who died at 34 years of age and (**B**) the heart of a man who died at 83 years of age. Note that in the heart of the younger person, the ventricular myocardium and atrial myocardium are quite close to each other (**A**), whereas in the heart of the older person the distance is much greater (arrows; **B**). The ventricular muscle layer beneath the valve attachment had thinned, and thus the gap between the atrial myocardium and ventricular myocardium was wide. RA, right atrium; RV, right ventricle; TV, tricuspid valve. Scale bars, 1 mm.

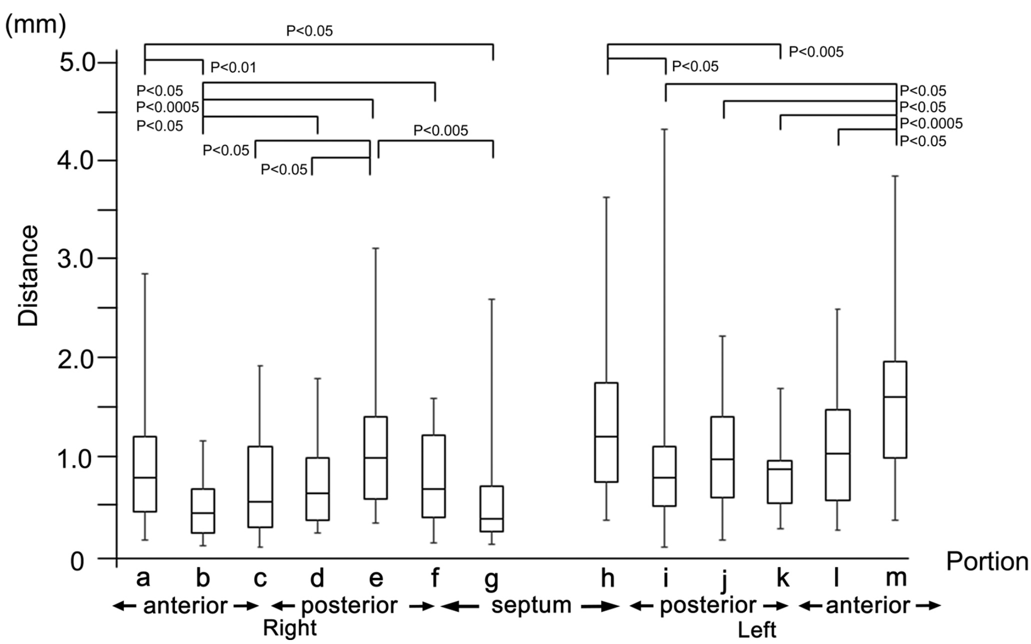

Figure 5. Box-and-whisker plots of distance between the atrial myocardium and ventricular myocardium in each of the 7 portions on the right side and 6 portions on the left side of the atrioventricular junction. At the tricuspid annulus, the distance between the atrial myocardium and ventricular myocardium in the anterolateral region (portion "b") is shorter than that in portions "a", "d", and "e". However, in portion "e" myocardium in the posterolateral region, the distance is significantly greater than many portions of the tricuspid annulus. At the mitral annulus, the myocardium in portion "k" in the posterolateral region is significantly more proximate. At the septal portion "h" and anterior portion "m", the gap is especially wide. The boxes show the interquartile range, with the median value indicated by the horizontal line; whiskers show the range.

dium at the tricuspid valve in Groups A, B, and C was 0.56±0.54, 0.64±0.48, and 1.01±0.69 mm, respectively, with the difference between Groups A and C and that between Groups B and C being significant ($P<0.0005$ and $P<0.001$, respectively). However, the distance between the atrial and ventricular myocardium on the left side in Groups A, B, and C (0.99±0.67, 1.09±0.68, and 1.34±0.93 mm, respectively) did not differ significantly (**Figure 3**). Microscopic images of tissues at the attachment of the tricuspid valve from a woman who died at 34 years of age and those from a man who died at 83 years of age are shown in **Figure 4**. These images are representative of their respective groups (i.e., Groups A and C, respectively). The myocardium beneath the valve attachment appears to have to thinned

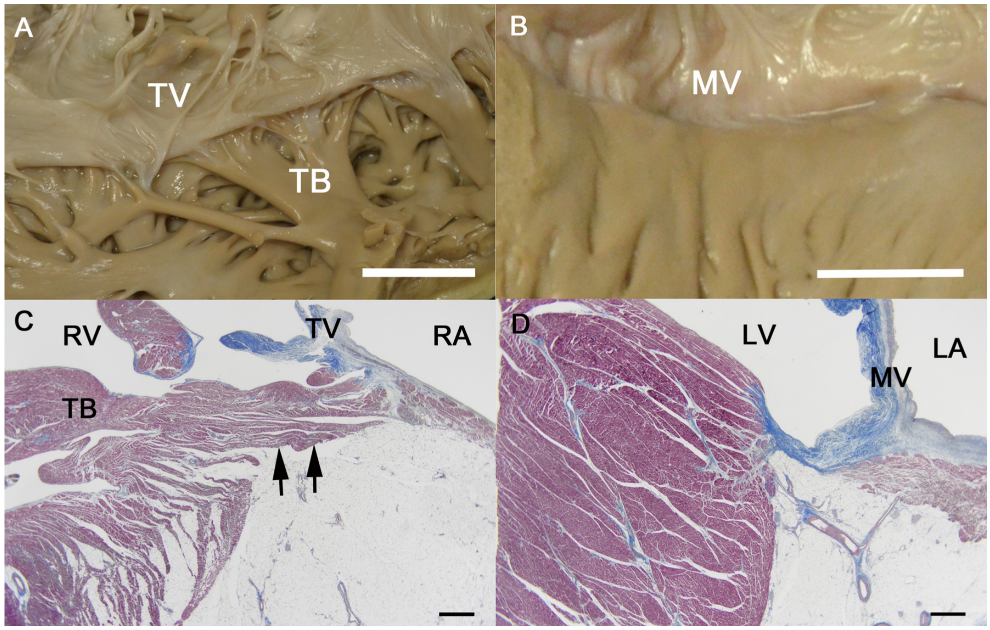

Figure 6. Macroscopic and histologic findings of trabeculations (TB) below the atrioventricular (AV) annuli. (**A**,**C**) Most of the endocardial muscular layer derived from the trabeculae extended upward from the ventricular summit and towards the atrial myocardium (arrows). RA, right atrium; RV, right ventricle; TV, tricuspid valve. (**B**,**D**) A similar structure is seen at the left AV annulus. However, the trabeculations there are thinner, and extension of the muscle towards the atrium is not pronounced due to the thick, fibrous AV annulus. LA, left atrium; LV, left ventricle; MV, mitral valve. Scale bars, 10 mm (**A**,**B**); 1 mm (**C**,**D**).

with age, and the gap between the atrial and ventricular myocardium appears to have widened.

Separation of the Myocardium in Each of the 13 Portions

The distance between the ventricular and atrial myocardium in each of the portions on the right and left sides is shown in **Figure 5**. On the right side, the distance between the ventricular and atrial myocardium was 0.96±0.73 mm in portion "a", 0.46±0.28 mm in portion "b", 0.64±0.47 mm in portion "c", 0.68±0.39 mm in portion "d", 1.15±0.83 mm in portion "e", 0.76±0.49 mm in portion "f", and 0.51±0.51 mm in portion "g". Thus, on the right side, the ventricular myocardium and atrial myocardium were relatively far apart in the posterior region and tended to be close together in the anterior region. On the left side, the distance between ventricular and atrial myocardium was 1.48±0.95 mm in portion "h", 1.01±0.90 mm in portion "i", 0.99±0.57 mm in portion "j", 0.78±0.37 mm in portion "k", 1.07±0.58 mm in portion "l", and 1.56±0.90 mm in portion "m". Thus, on the left side, the atrial myocardium and ventricular myocardium were fairly close together in the posterolateral region and far apart in the anterior region.

Specific Findings Related to Myocardial Contiguity

The 3 features appeared to be associated with the spatial proximity between the atrial and ventricular myocardium observed at the AV junction: (1) muscular trabeculations beneath the right AV junction and left AV junction; (2) extension of the atrial myocardium onto the AV valve leaflets; and (3) small, round cardiomyocytes at the end of atrial muscular layer on the right side of the AV junction.

Muscular Trabeculations Beneath the Right and Left AV Junction At the summit of the ventricular septum in the region of the AV junction, there were trabecular muscle bundles below the attachment of the valve leaflets. The bundles on the right side were particularly coarse and thick, and many terminated at the attachment of the valve leaflets. Histologically, these trabeculae extended towards the atrium in areas where the atrial and ventricular myocardium were in close proximity (**Figure 6A**,**C**). Similarly, trabeculae were noted below the left AV junction, but these trabeculae were thinner, and the myocardium did not extend towards the atrium due to the thick fibrous AV annulus (**Figure 6B**,**D**). We measured the trabecular protrusions that extended towards the valve attachment beyond the ventricular summit. Of the 161 histologic sections of tissues taken from all 7 portions next to the tricuspid annulus, 38 contained myocardial protrusions. These protrusions measured 3.2±1.2 mm and extended towards the atrium. The distance between the atrial myocardium and ventricular myocardium in 38 sections was 0.54±0.36 mm, whereas the distance in the other 123 sections was significantly greater (0.80±0.63 mm; $P<0.05$).

Extension of the Atrial Myocardium Onto the AV Valve Leaflets The atrial myocardium extended beyond the fibrous annulus and onto the valve leaflets on the right side of the AV junction in 15 hearts and on the left side of the AV junction in 5 hearts (**Figure 7A**).

Small, Round Cardiomyocytes at the End of Atrial Muscular Layer On the Right Side of the AV Junction A collection of small, round myocytes set in a fibrous background was noted at the end of the atrial myocardial layer in all hearts. This collection of cells may include the so-called specialized cells. Such a collection of cells was commonly observed in

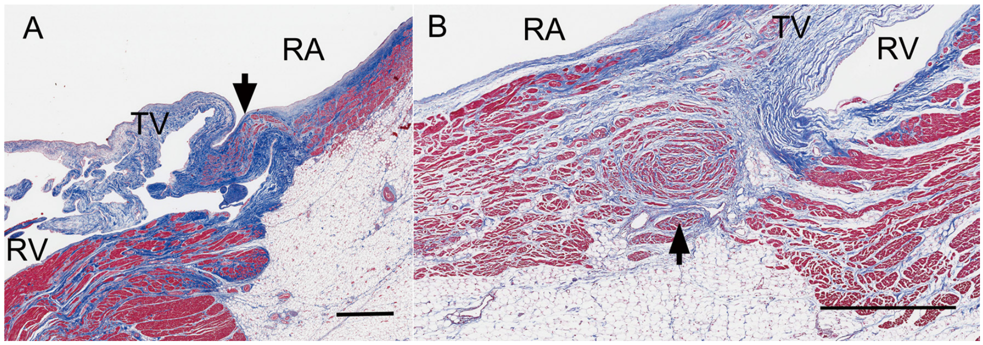

Figure 7. Specific findings regulating myocardial contiguity. (**A**) Representative microscopic view (Masson's trichrome-stained section) showing extension of the atrial myocardium onto the leaflet. Scale bar, 1 mm. RA, right atrium; RV, right ventricle; TV, tricuspid valve. (**B**) Representative microscopic view of cell aggregates (small, round cardiomyocytes) thought to be remnants of specialized cardiac muscle. Scale bar, 500 μm.

portions "a" and "b" on the right side of the AV junction (**Figure 7B**).

Discussion

In this study we focused on area differences and age-related changes at the AV junction in structurally normal hearts in which no electrocardiogram (ECG) abnormalities suggestive of an accessory pathway had been documented, with the aim of documenting myocardial contiguity vs. separation as an explanation for an abnormal connection between the atrial myocardium and ventricular myocardium near the AV annulus. The AV junction has been described both macroscopically and schematically,[7,13] but, to the best of our knowledge, myocardial contiguity on the right and left sides of the AV junction has not been described microscopically or quantitatively. We did not find AV myocardial connections that can work as accessory pathways, but, at the tricuspid valve attachment, we found that the distance between the atrial myocardium and ventricular myocardium was 0.41 mm less than that at the mitral valve attachment, and this shorter distance was associated with a lesser degree of annular fibrosity. Moreover, the gap between the atrial myocardium and ventricular myocardium tended to widen with age. We think this change may be associated with age-related physiological factors, such as volume overload in the ventricular cavities, and may thus explain, at least in part, the reduced frequency of palpitations after middle age in individuals with WPW syndrome.[14,15]

With regard to differences in the 13 portions of the right and left AV annuli according to the orientation used for electrophysiological studies, the distance between the atrial myocardium and ventricular myocardium was relatively short in areas between the anterior and lateral regions of the right AV annulus, as well as between the lateral and posterior regions of the left AV annulus, and short distance areas are all in the free wall part of the annulus (**Figure 5**). The local variation in myocardial contiguity at the AV junction may have technical implications, especially with respect to radiofrequency catheter ablation for AV reentrant tachycardia and tachyarrhythmias arising from the AV junction. On the right side especially, the coarse ventricular trabeculae reaching the AV junction may affect the ease with which the electrode catheter can be placed at the target site. In addition, an increased distance between the atrial myocardium and ventricular myocardium was observed in the posterior region on the right side and in the anterior region on the left side. These increases may be due to the supraostial lamina, which creates a gap between the atrial and ventricular myocardium on the right posterior wall.[16] In 1988, Angelini et al described mitral annulus "disjunction", having observed separation between the mitral annulus and left atrial wall,[4] and recent attention has been given to the effect of this structural abnormality on catheter ablation.[17]

We noticed 3 additional features that seem to be associated with muscular contiguity at the AV junction. First, trabecular ventricular myocardium was directly attached to the valve leaflets on the right side in many of the hearts due to its rough, coarse texture.[9] This direct attachment was assumed to arise from the protrusion of the myocardium in the right AV junction towards the atrium. Moreover, also on the right side, the myocardium at the ventricular summit extended towards the atrium, most likely because of a difference in the manner of growth during embryo development. These histologic features may explain the close proximity of the atrial and ventricular myocardium at the AV junction.[18] Second, extension of the atrial myocardium onto the valve leaflets was found on the right side in 15 (65%) cases and on the left side in 5 (22%). Contiguity of the AV myocardium was more pronounced in these cases and suggests a difference in histologic development between the 2 AV annuli. Becker[13] reported this anatomical feature at the mitral annulus, suggesting that it may be one of the causes of recurrence of atrial arrhythmia after ablation, but, in terms of accessory pathway formation, if the valve leaflet attachments are displaced towards the ventricle, it is likely that the atrial myocardium extending onto the valve leaflets would be relatively close to ventricular myocardium. Ebstein's malformation at the right AV junction typically arises from this pathophysiology.[19] Third, there was an aggregation of small, round myocardial cells, making up so-called "ring tissue",[20] in all hearts studied. Although there was no connection between these small, round cardiomyocytes and the AV node, the cells may be involved in the pre-excitation phenomenon. Davies et al[21] described a case in which specialized cells had descended into the muscularized portion of the anterior leaflet of the dysplastic tricuspid valve and suggested that Ebstein's malformation played a role in WPW syndrome.[19] Similar small, round muscle cells within a rich fibrous background were found in all hearts in our study, but there was no continuity between these cells and the AV junction, including the AV node. Myocardial proximity was noted only in the sections that included such small, round muscle cells. This specific structure is, of course, not related morphologically to the normal AV conduction system, but it may affect circuit conduction and may be a cause of the recently reported unusual re-entrant tachycardia around the superior side of AV nodal tissue or ATP-sensitive characteristics in atrial tachycardia.[22,23] This structure was found in all the hearts we studied and for which no arrhythmia had been documented; this may mean that such node-like structures are more common than previously documented.[24] Recent animal studies have also revealed the existence of similar specialized cells around the AV junction and suggested they generate pacemaker activity,[20,25] but the mechanism in human hearts is still not understood.

These 3 specific histologic features and differences in the size of the gaps between the myocardium on both the right and left sides of the AV junction (**Figure 5**) are related to normal development of the heart. Wessels et al[18] demonstrated in the human embryo that the originally contiguous myocardium in the estimated atrial and ventricular field separated over the course of AV valve leaflet formation, with the separation being dependent on interruption by sulcus and cushion tissue. Interestingly, this AV muscular interruption does not occur simultaneously on the left and right sides, and there is a time difference in the formation of the 2 AV annuli.

Finally, although the right-side septal area is a relatively common site of accessory pathways and of unusual clinical electrophysiological features, such as Mahaim fibers, which make up the so-called nodo-ventricular pathway, its morphology is complex and still debated,[26] including that of the AV annuli and original AV conduction system that penetrates them. In this region, the tricuspid annulus is usually more apically displaced than the mitral annulus, and this valvular offset is one of the reasons for myocardial proximity. Indeed, we showed a short gap in areas "f" and "g". This structural characteristic becomes the source of septal accessory pathways and may be subclinical in patients with WPW syndrome, especially those with multiple accessory pathways.[27]

Study Limitations

Our study was limited in several respects. First, the sample size was small and the sample consisted of normal hearts. A study of hearts with an accessory electrical AV connection is needed. However, few, if any, such hearts are available. Second, all hearts examined in this study were from Japanese patients (i.e., from what can be considered a genetically homogeneous population). An ideal study would involve the examination of hearts from a genetically diverse population. Third, although no clinical supraventricular tachyarrhythmia had been documented in any of the autopsied patients, ECGs were not typically recorded, so we cannot completely rule out the possibly of an electrical AV connection in any of the hearts examined. Fourth, because hearts obtained at autopsy were used for the study, the orientation of the annuli may have differed slightly from the in situ orientation, as seen clinically on the left anterior oblique view. However, each portion was defined as a broad area and was noted to be approximate. Fifth, the histologic sections examined were not serial sections. However, the study was not conducted to identify direct connections between muscle bundles. We believe that the 4-mm sections we used were sufficient to assess the distance between myocardial cells. Lastly, formalin fixation tends to shrink tissue specimens, so the measured distances between cells may have differed slightly from distances in vivo.

Conclusions

This study revealed histologic features of and age-related changes in the myocardium on the right and left sides of the AV junction in the normal adult human heart. The age-related changes may contribute to the decreased prevalence of pre-excitation syndrome seen among elderly patients with WPW. The variation observed in myocardial contiguity without distinct myocardial connection at either the right or left AV junction suggests that atypical histologic features, especially of the right AV annulus, will be informative in terms of planning electrophysiological interventions in cases of an accessory pathway.

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Disclosures

None.

IRB Information

The study was approved by the Ethics Committees of the Showa University School of Medicine (Reference no. 3142).

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Supplementary Files

Please find supplementary file(s);
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