Journal of the American Heart Association

VIEWPOINTS

The Specialized Atrioventricular Ring Tissues Participate in the Circuit of Atrioventricular Nodal Reentrant Tachycardia

Demosthenes G. Katritsis, MD, PhD; Hugh Calkins, MD; Robert H. Anderson, MD, PhD (Hon)

The exact location, let alone size, of the circuit of atrioventricular nodal reentrant tachycardia (AVNRT) is still among the mysteries of contemporary electrophysiology, despite advances in high-density mapping, tissue histochemistry, and connexin genotyping. This is most intriguing since AVNRT represents the most common regular arrhythmia in the human, and probably the second most often ablated arrhythmia after atrial fibrillation.[1,2] There has been evidence that the inferior extensions of the atrioventricular node are the substrates of the slow pathway, whereas the connections to the compact node through the working myocardium of the atrial septum serve as the fast pathway.[3,4] We also know that the circuit occupies an area of several centimeters.[5] The prominent variability of detected retrograde atrial activation, even in the same patient, suggests many possibilities, as described in a probabilistic model.[4] Although this conceptual model explains the electrophysiologic behaviour and activation patterns of the arrhythmia, it cannot provide quantitative data about the size of the involved pathways. More importantly, the described inferior and superior atrial inputs represent "dead ends," and not the entire circuit. Because of the problems in separating a large ventricular electrogram from the atrial tracing, high-resolution mapping of the atrial vestibules is inherently difficult.[6] Any mapping system will struggle to annotate a fused signal appropriately in the window and during tachycardia, although novel algorithms for this purpose do appear. It may also preferentially annotate the His bundle electrogram because of its high frequency (dv/dt). These limitations may also apply to animal models using micro-electrode mapping, thus making the tracing of the tachycardia circuit extremely difficult.

HYPOTHESIS

Recently, the study of patients with co-existent types of typical and atypical atrioventricular nodal re-entry has allowed the calculation of activation times of both slow and fast pathways.[7] Animal studies, and experimental studies using human hearts, have also provided data about the conduction velocity in the area of the atrioventricular node and its inferior extensions, and in working atrial myocardium.[8] Based on these data, we have proposed a method for the theoretical calculations of the dimensions of the slow pathway (Figure 1). In the context of measured conduction intervals during tachycardia, the calculated activation time of the slow and fast pathways were 268.8±32.4 and 101.9±23.5 ms, respectively.[8] Studies have provided evidence on the conduction velocity in the area of the atrioventricular node and its inferior extension, calculating it to between 0.069 to 0.162 m/s in perfused canine and rabbit hearts.[9–11] In the human heart, mathematical

Key Words: atrioventricular node ■ nodal extensions ■ ring tissues ■ tachycardia

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

Correspondence to: Demosthenes G. Katritsis MD, PhD, Hygeia Hospital, 4 Erythrou Stavrou Str, Athens 15123, Greece. E-mail: dkatrits@dgkatritsis.gr

For Disclosures, see page 3.

JAHA is available at: www.ahajournals.org/journal/jaha

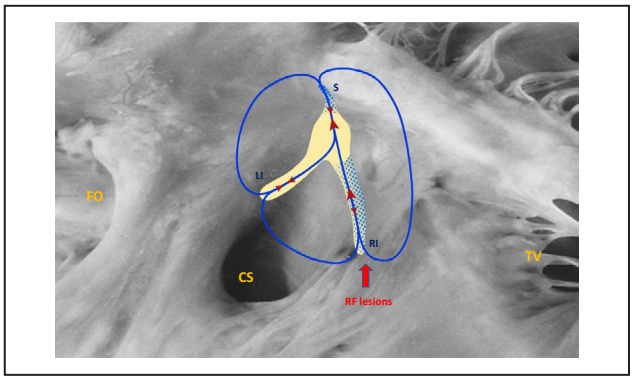

Figure 1. Theoretical model of the AVNRT circuit.
The left inferior extension is derived from the atrioventricular canal myocardium and is low in connexin 43 (C43) expression, thus being capable of only slow conduction. The right inferior extension could either be slowly or rapidly conducting, since it incorporates both the primary ring and the atrioventricular canal myocardium, and is an area of higher C43 expression. The site of successful ablation is indicated by the red arrow. CS indicates coronary sinus; FO, foramen ovale; LI, left inferior extension; RI, right inferior extension; S, superior "last" input; and TV, tricuspid valve. Reproduced with permission from Katritsis et al.[8] Copyright ©2021, Oxford University Press.

modelling of the conduction velocity in these areas has provided a value of 0.04 m/s.[12] Considering this conduction velocity, the length of the slow pathway is ≈10.8 mm. This is compatible with the length of the right nodal inferior extension as assessed in histologic specimens (Figure 2).[8] With a conduction velocity value of 0.162 m/s, however, the slow pathway could be as long as 43.5 mm. The conduction velocity in atrial myocardium has been estimated as 0.49 to 0.8 m/s,[11–13] with values less in the transverse than the longitudinal direction (0.49 versus 0.8 m/s), and less in the left than the right atrium (0.5 versus 0.8 m/s).[13] Mathematical modelling studies of human hearts have reported the conduction velocity of atrial tissue as 0.53 mm/ms.[12] Since the described "last connection" of the atrial septum to the node represents atrial working myocardium,[11] the conduction velocity of the fast pathway is likely within the range of 0.49 to 0.8 m/s. Considering an activation time of 101.9±23.5 ms, the length of the fast pathway ranges from 49.9 to 81.5 mm.

On this basis, we can assume that the dimensions of the slow and fast pathways have to be contained within the range of values derived by applying the boundaries of conduction velocity in the involved tissues. Do these numbers make sense? A circuit composed of a slow pathway of 1 cm, and a fast pathway of 5 cm, might well be contained within the triangle of Koch, as conventional wisdom dictates. Larger numbers, however,

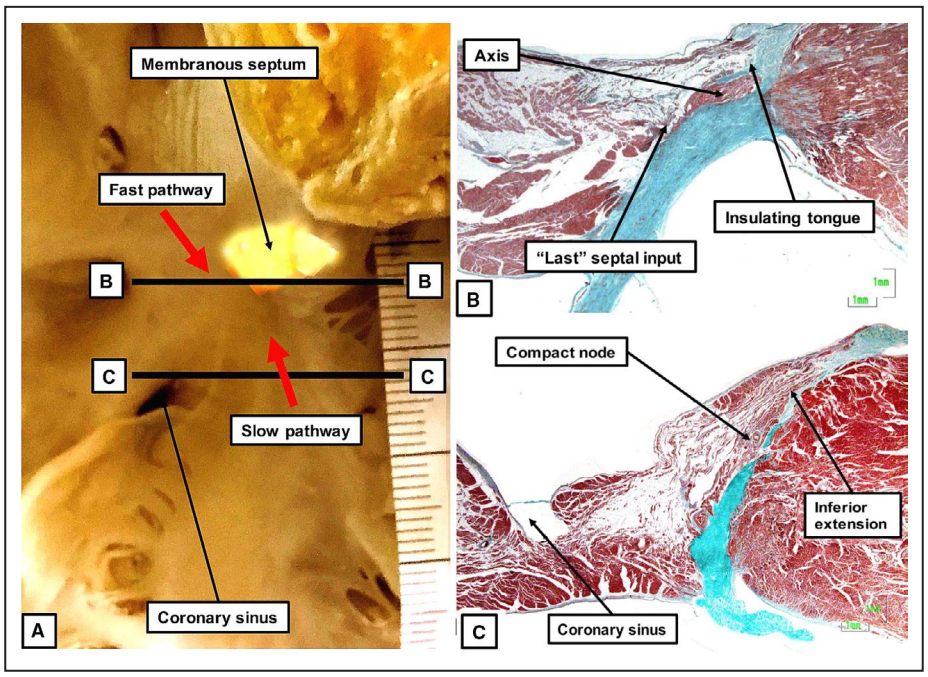

Figure 2. Calculation of the histological extent of the inferior extension of the atrioventricular node in serially sectioned human hearts.
The left panel shows the gross features of the triangle of Koch and the cavotricuspid isthmus, with arrows indicating the anticipated sites of the fast and slow pathways (**A**). Lines B-B and C-C show the corresponding histological sections as shown in (**B** and **C**). **B**, The last input to the conduction axis prior to its insulation by the fibrous tissues of the atrioventricular junctions. This is suggested to be the substrate of the fast pathway. **C**, The compact atrioventricular node and its inferior rightward extension. We tracked the inferior extension until it could no longer be distinguished histologically from the vestibular myocardium. Reproduced with permission from Katritsis et al.[8] Copyright ©2021, Oxford University Press.

demand larger structures to be involved. We know that we are able successfully to ablate the tachycardia circuit by applying radiofrequency lesions at the septal isthmus between the hinge of the tricuspid valve and the mouth of the coronary sinus.[8] This site is beyond the histologically identifiable inferior extensions of the node, which most probably, represent the anatomic substrate of the slow pathway. There is additional evidence in animal studies that the right inferior extension continues within the vestibule of the tricuspid valve as "ring tissue." This is a remnant of the so-called "primary ring" found during development. The leftward ring encircles the vestibule of the mitral valve, and is derived from the initial atrioventricular canal of the developing heart.[14] It could well be that, in humans, the extent of these structures varies in such a way that some subjects are susceptible to atrioventricular nodal re-entry, whereas others are not. Thus, part of the tricuspid or the mitral vestibule contribute to the re-entry circuit, at least in some atypical forms with prolonged His-atrial intervals. The circumference of the right atrioventricular orifice has been measured at between 9 and 11 cm in patients aged <65 years,[15,16] whereas that of the mitral orifice is from 7 to 9 cm.[17,18] The possibility of the vestibules being involved in the circuit, therefore, cannot theoretically be excluded, especially in atypical cases of AVNRT with prolonged HA intervals.

We propose that the "ring" tissues are part of the circuit of AVNRT. Depending on their length in different individuals, they may contribute to the development of typical or atypical AVNRT forms. In this regard, we also emphasise the likely marked variation in the pathways between different individuals. We can speculate that, in patients with typical slow-fast AVNRT, the remnants of these structures are short. The complete circuit, therefore, requires capture and excitation of the very close atrial or transitional tissue that is capable of conduction fast enough to support the tachycardia. In the majority of cases, however, the ring tissues extend to at least the septal isthmus between the hinge of the tricuspid valve and the mouth of the coronary sinus, a site where successful and safe ablation is usually implemented. In atypical forms of the arrhythmia with prolonged HA intervals, which suggest involved pathways with only slow conduction properties, the involved atrioventricular ring tissues are likely to be more developed and longer, thus participating in the circuit as a component with slow conduction properties. This possibility is compatible with the low expression of connexin 43, and thus slower conduction, in these tissues.[14] This could also explain the significant variability in retrograde atrial activation during tachycardia, that may simulate even atrioventricular reentry due to a left lateral accessory pathway.[1,2] In persons without discernible ring tissues, no AVNRT is developed. A schematic representation of our model is depicted in Figure 3.

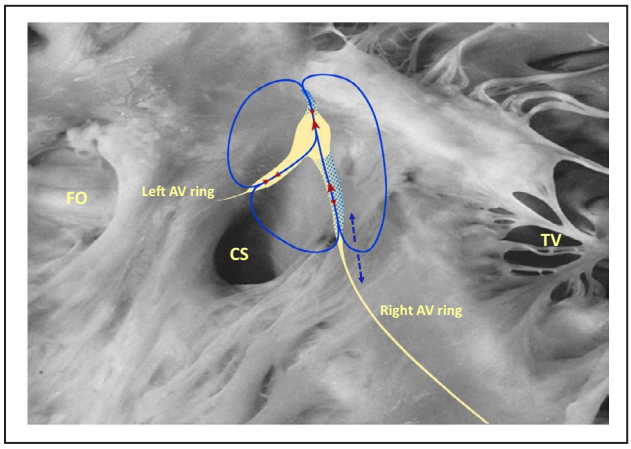

Figure 3. A new proposal for the circuit of AVNRT. Depending on the development and length of the atrioventricular ring tissues the potential circuits (blue lines) may be contained within the triangle of Koch (typical, slow-fast AVNRT) or extend toward the left and, especially, the right vestibule (atypical forms).

ARTICLE INFORMATION

Affiliations

Hygeia Hospital, Athens, Greece (D.G.K.); Johns Hopkins Hospital, Baltimore, MD (D.G.K., H.C.); and Biosciences Institute, Newcastle University, Newcastle upon Tyne, United Kingdom (R.H.A.).

Disclosures

None.

REFERENCES

1. Katritsis DG, Josephson ME. Classification, electrophysiological features and therapy of atrioventricular nodal reentrant tachycardia. *Arrhythm Electrophysiol Rev*. 2016;5:130–135. doi: 10.15420/AER.2016.18.2
2. Katritsis DG, Josephson ME. Classification of electrophysiological types of atrioventricular nodal re-entrant tachycardia: a reappraisal. *Europace*. 2013;15:1231–1240. doi: 10.1093/europace/eut100
3. Anderson RH, Sanchez-Quintana D, Mori S, Cabrera JA, Back SE. Re-evaluation of the structure of the atrioventricular node and its connections with the atrium. *Europace*. 2020;22:821–830. doi: 10.1093/europace/euaa031
4. Katritsis DG. A unified theory for the circuit of atrioventricular nodal re-entrant tachycardia. *Europace*. 2020;22:1763–1767. doi: 10.1093/europace/euaa196
5. Keim S, Werner P, Jazayeri M, Akhtar M, Tchou P. Localization of the fast and slow pathways in atrioventricular nodal reentrant tachycardia by intraoperative ice mapping. *Circulation*. 1992;86:919–925. doi: 10.1161/01.CIR.86.3.919
6. Chua K, Upadhyay GA, Lee E, Aziz Z, Beaser AD, Ozcan C, Broman M, Nayak HM, Tung R. High-resolution mapping of the triangle of Koch: spatial heterogeneity of fast pathway atrionodal connections. *Heart Rhythm*. 2018;15:421–429. doi: 10.1016/j.hrthm.2017.10.030
7. Katritsis DG, Marine JE, Latchamsetty R, Zografos T, Tanawuttiwat T, Sheldon SH, Buxton AE, Calkins H, Morady F, Josephson ME. Coexistent types of atrioventricular nodal re-entrant tachycardia: implications for the tachycardia circuit. *Circ Arrhythm Electrophysiol*. 2015;8:1189–1193. doi: 10.1161/CIRCEP.115.002971
8. Katritsis DG, Marine JE, Katritsis G, Latchamsetty R, Zografos T, Zimetbaum P, Buxton AE, Calkins H, Morady F, Sánchez-Quintana D, et al. Spatial characterization of the tachycardia circuit of atrioventricular nodal re-entrant tachycardia. *Europace*. 2021:euab130. [epub ahead of print]. doi: 10.1093/europace/euab130

9. Efimov IR, Nikolski VP, Rothenberg F, Greener ID, Li J, Dobrzynski H, Boyett M. Structure-function relationship in the AV junction. *Anat Rec A Discov Mol Cell Evol Biol*. 2004;280:952–965. doi: 10.1002/ar.a.20108
10. Choi BR, Salama G. Optical mapping of atrioventricular node reveals a conduction barrier between atrial and nodal cells. *Am J Physiol*. 1998;274:H829–H845. doi: 10.1152/ajpheart.1998.274.3.H829
11. Temple IP, Inada S, Dobrzynski H, Boyett MR. Connexins and the atrioventricular node. *Heart Rhythm*. 2013;10:297–304. doi: 10.1016/j.hrthm.2012.10.020
12. Greener ID, Monfredi O, Inada S, Chandler NJ, Tellez JO, Atkinson A, Taube M-A, Billeter R, Anderson RH, Efimov IR, et al. Molecular architecture of the human specialised atrioventricular conduction axis. *J Mol Cell Cardiol*. 2011;50:642–651. doi: 10.1016/j.yjmcc.2010.12.017
13. Zheng Y, Xia Y, Carlson J, Kongstad O, Yuan S. Atrial average conduction velocity in patients with and without paroxysmal atrial fibrillation. *Clin Physiol Funct Imaging*. 2017;37:596–601. doi: 10.1111/cpf.12342
14. Yanni J, Boyett MR, Anderson RH, Dobrzynski H. The extent of the specialized atrioventricular ring tissues. *Heart Rhythm*. 2009;6:672–680. doi: 10.1016/j.hrthm.2009.01.021
15. Kalyani R, Thej MJ, Prabhakar K, Venkatesh TK, Thomas AK, Kiran J. Morphometric analysis of tricuspid valve: an Indian perspective. *J Nat Sci Biol Med*. 2012;3:147–151. doi: 10.4103/0976-9668.101892
16. Tei C, Pilgrim JP, Shah PM, Ormiston JA, Wong M. The tricuspid valve annulus: study of size and motion in normal subjects and in patients with tricuspid regurgitation. *Circulation*. 1982;66:665–671. doi: 10.1161/01.CIR.66.3.665
17. Ormiston JA, Shah PM, Tei C, Wong M. Size and motion of the mitral valve annulus in man. I. A two-dimensional echocardiographic method and findings in normal subjects. *Circulation*. 1981;64:113–120. doi: 10.1161/01.CIR.64.1.113
18. Okamoto H, Itoh Y, Nara Y. Geometric analysis of the anterior mitral leaflet and mitral valve orifice in cadaveric hearts. *Circ J*. 2007;71:1794–1799. doi: 10.1253/circj.71.1794