Coexistent Types of Atrioventricular Nodal Reentrant Tachycardia: 
Implications for the Tachycardia Circuit

Running title: Katritsis et al.: Typical and atypical AVNRT

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Abstract:

**Background** - There is evidence that atypical fast-slow and typical atrioventricular nodal re-entrant tachycardia (AVNRT) do not utilize the same limb for fast conduction, but no data exist on patients who have presented with both typical and atypical forms of this tachycardia. We compared conduction intervals during typical and atypical AVNRT that occurred in the same patient.

**Methods and Results** - In 20 out of 1299 patients with AVNRT, both typical and atypical AVNRT were induced at electrophysiology study by pacing maneuvers and autonomic stimulation or occurred spontaneously. The mean age of the patients was 47.6±10.9 years (range 32 to 75), and 11 patients (55%) were female. Tachycardia cycle lengths were 368.0±43.1 ms and 365.8±41.1 ms, and earliest retrograde activation was recorded at the coronary sinus ostium in 60% and 65% of patients with typical and atypical AVNRT, respectively. Thirteen patients (65%) displayed atypical AVNRT with fast-slow characteristics. By comparing conduction intervals during slow-fast and fast-slow AVNRT in the same patient, fast pathway conduction times during the two types of AVNRT were calculated. The mean difference between retrograde fast pathway conduction during slow-fast AVNRT, and anterograde fast pathway conduction during fast-slow AVNRT was 41.8 ± 39.7 ms, and significantly different compared to the estimated between measurements error (P=0.0055).

**Conclusions** - Our data provide further evidence that typical slow-fast and atypical fast-slow AVNRT utilize different anatomical pathways for fast conduction.

**Key words:** atrioventricular node, tachycardia, reentry, atypical, fast pathway
Introduction

The mechanism of atrioventricular nodal re-entrant tachycardia (AVNRT) remains elusive.\textsuperscript{1,2} Both anatomical and functional models have been proposed. There has been electrophysiologic evidence that the right and left inferior extensions of the human AV node and the atrio-nodal inputs they facilitate, which have been identified histologically, might provide the anatomic substrate for the slow pathway.\textsuperscript{3-6} Data indicating the potential anatomic site of the fast pathway are sparse. There is histologic evidence of multiple superior atrial inputs to the AV node,\textsuperscript{7-11} but the nature of fast pathway conduction, especially during atypical AVNRT of the fast-slow type, is poorly understood. We have previously reported data suggesting that atypical fast-slow and typical slow-fast AVNRT do not appear to utilize the same limb for fast conduction.\textsuperscript{12} This evidence, however, was derived by observations on typical and atypical tachycardias recorded in different patients. We are not aware of data on patients who have exhibited both typical and atypical tachycardia at the same study. We hypothesized that by comparing conduction intervals during typical and atypical forms that occur in the same patient at the same study, we could gain insight into the properties of the fast and slow pathways, and the mechanisms responsible for atypical AVNRT.

Methods

Patients

Data from adult patients with AVNRT undergoing catheter ablation at five centers, Beth Israel Deaconess Medical Center, and Rhode Island Hospital, Boston, MA, USA (2009-2013); Athens Euroclinic, Greece (2007-2014); the Johns Hopkins Hospital, Baltimore, MD, USA (2011-2014); and the University of Michigan Health System, Ann Arbor, MI, USA (2009-2014), were analyzed. The subjects of this study were the patients in whom both typical and atypical AVNRT
were induced in the same procedure and in whom tracings suitable for evaluation were available. All patients were studied in the post-absorptive state, under mild sedation, and after all antiarrhythmic agents had been discontinued for more than 5 half-lives. No patient had received amiodarone for the preceding three months. The study received approval from our institutional review boards.

Definitions
AVNRT was diagnosed by fulfillment of established criteria during detailed atrial and ventricular pacing maneuvers,1,2 and subsequent abolition of the tachycardia by anatomic ablation of the slow-pathway. Typical (slow-fast) AVNRT was defined by an atrial-His/His-atrial ratio (AH/HA) >1, and HA interval ≤70 ms. Atypical AVNRT was defined by delayed retrograde atrial activation with HA>70 ms. If the AH was <200 msec and the AH<HA, the atypical form was characterized as fast-slow. If AH>200 ms and AH>HA, the atypical form was considered slow-slow. Tachycardias with a prolonged AH interval >200 ms but AH<HA, or with AH<200 ms and AH>HA, or with variable intervals during the same or different episodes, were classified as indeterminate. Details of our methodology for measurements of intervals during tachycardia have been described elsewhere.12

Hypothesis
If the anatomical models are correct, AVNRT types that coexist in the same patient may utilize the same distinct limbs of the circuit regardless of the tachycardia type, and retrograde atrial and anterograde ventricular activation should utilize the same anatomic pathways in all forms of AVNRT. Therefore, conduction times such as the atrial-His (AH) and His-atrial (HA) intervals during types of tachycardia coexisting in the same patient can be calculated and used to provide data on the characteristics of the fast and slow circuit limbs.

Figure 1 depicts one of the proposed fixed, anatomical models of slow-fast and fast-slow
AVNRT. According to this model, during AVNRT, the tachycardia circuit is confined within the AV node region, and activation of the atrium takes place following activation of the retrograde pathway. Thus, during typical, slow-fast AVNRT the HA interval represents the time difference between activation of the His bundle and activation of the atrium, this is HA=Fr+A-H, where Fr is the time the impulse travels retrogradely along the fast pathway, A is the time the impulse travels from the AV node to right atrium as recorded by the electrode positioned on the His bundle, and H is the time the impulse travels from the AV node to the His bundle. Similarly, the AH interval represents the time difference between activation of the right atrium as recorded by the catheter positioned on the His bundle, and the next activation of the His bundle. This is AH=Sa+H-A, where Sa is the anterograde conduction along the slow pathway, H is the time the impulse travels from the AV node to the His bundle, and A the time the impulse travels from the AV node to right atrium. During atypical, fast-slow AVNRT, HA=Sr+A-H, where Sr is the time required for the impulse to travel retrogradely along the slow pathway, A is the time the impulse travels from the AV node to right atrium, and H is the time the impulse travels from the AV node to the His bundle. AH=Fa+H-A, where Fa is the time required for anterograde conduction along the fast pathway, H is the time the impulse travels from the AV node to the His bundle, and A the time the impulse travels from the AV node to right atrium. Assuming that conduction velocity over the slow pathway is similar in the anterograde and retrograde direction (ie Sa=Sr), as happens in some types of accessory pathways,\textsuperscript{13} and retrograde atrial activation takes similar paths in all forms of AVNRT in the same patient, then HA (f-s) + AH (s-f) = (Sr+A-H) + (Sa+H-A) = 2S. Since TCL = AH+HA=S+F, by definition, derivation of the S interval can provide the value of F. If derived Fr values are significantly different than those for Fa, then the possibility of typical and atypical AVNRT utilizing the same anatomical limb for fast conduction is unlikely.
Statistical analysis

Data normality was assessed using the D’Agostino – Pearson test. Continuous, normally distributed variables were presented as mean ± standard deviation (SD). Categorical data were expressed as frequencies (percentages). Statistical analysis was performed to compare the measured difference between Fr and Fa (Fr-Fa) to the anticipated difference considering the variability between repeated measurements on the same subject. In order to determine the maximum difference that could be attributed to between measurements variability, we measured the AH interval, HA interval, and TCL during the typical form of AVNRT and computed Fr twice for each patient. The mean absolute value of the difference between these two measurements and its standard error (3.69ms±0.44ms) was used to estimate 95% confidence intervals (CI) for the between-measurement error (2.72 – 4.66ms). Accordingly, using one sample t-test, we compared the mean of the absolute values of Fr-Fa to the upper bound of the 95% CI (4.7ms). To further examine the relation of measured Fr-Fa values to an expected between-measurement error, we have plotted measured Fr-Fa values together with 95% CIs of between-measurement error, in a manner analogous to a Bland-Altman plot. Statistical analyses were performed using IBM SPSS Statistics v.22 (IBM Corp, Armonk, New York, USA). All tests were two-tailed, and P-values < 0.05 were considered significant.

Results

Patients

In total, 1299 patients with AVNRT were studied at Beth Israel Deaconess Medical Center, and Rhode Island Hospital, Boston, MA, USA (n=188); Athens Euroclinic, Greece (n=287); the Johns Hopkins Hospital, Baltimore, MD, USA (n=271); and the University of Michigan Health System, Ann Arbor, MI, USA (n=553). Using the criteria mentioned above, 20 patients, had both
typical and atypical AVNRT during the electrophysiology study. The mean age of all patients was 47.6±10.9 years (range 32 to 75), and 11 patients (55%) were female. Among these 20 patients, 13 patients (65%) displayed atypical AVNRT with characteristics compatible with the fast-slow type according to both the AH<HA and AH<200 ms, and 4 patients (20%) had slow-slow form of AVNRT. The remaining 3 patients (15%) could not be reliably classified due to inconsistent AH and HA/AH patterns or variable intervals. Conduction intervals during tachycardias are shown in Table 1. Typical anterograde conduction jumps during atrio-ventricular conduction curves were demonstrated in 11 out of 20 patients. Typical retrograde conduction jumps were not demonstrated in any patient.

Mode of induction and earliest atrial retrograde activation

Typical tachycardia induction during atrial pacing was seen in 8 out of 20 patients, and in two of them only following isoproterenol infusion. Tachycardia induction with typical anterograde conduction jumps was seen in 9 patients. In two patients, typical AVNRT was induced with ventricular pacing and the use of three extrastimuli. Atypical AVNRT was induced by atrial pacing in 3 patients, and by ventricular pacing in 7 patients (in one patient with isoproterenol).

No typical retrograde conduction jumps were seen at induction; in one patient 2:1 retrograde conduction was noted at tachycardia induction. Atypical AVNRT was induced following atrial or ventricular ectopic beats in 2 patients. Earliest retrograde activation was variable and documented at the coronary sinus ostium in the majority of patients for both types of AVNRT.

In all patients, both tachycardias were abolished following anatomical slow pathway ablation.

Slow-fast vs fast-slow AVNRT

Using the strict criteria in this study, 13 patients had both slow-fast and fast-slow AVNRT according to our definitions. Patient characteristics and conduction intervals are presented in
Table 2. Conduction times over the fast pathway during slow-fast AVNRT (Fr) and during fast-slow AVNRT (Fa) are presented for each patient in Figure 2A. The mean difference between Fr and Fa was 41.8 ± 39.7 ms. This was significantly different compared to the estimated between-measurements error (P=0.0055)(Figure 2B).

Discussion

Our study represents the largest series of AVNRT cases with coexistence of both typical and atypical forms of which we are aware. Interestingly, in the majority of these patients, earliest retrograde atrial activation was detected at the coronary sinus ostium in both types of tachycardia. This is in keeping with previous observations on atypical AVNRT. 

Most patients with atypical AVNRT display the fast-slow variety. Our results argue against the conventional notion of a common anatomical fast pathway that supports both slow-fast and fast-slow AVNRT by conducting opposite directions. Derived Fr and Fa values were significantly different in our study, and this difference is unlikely to be due to a between-measurements error. Since CL=F+S, and according to the fixed anatomical model, both types of AVNRT utilize the same slow pathway, an indirect comparison of fast pathway conduction during typical and atypical AVNRT could be also derived by comparing tachycardia cycle lengths. However, changes in autonomic tone, either spontaneously or following isoprenaline infusion, do not make such a comparison legitimate. Our method of deriving slow pathway values by taking into account both tachycardias in the same patient represents an attempt to overcome this limitation.

Considering the anatomic models of the AVNRT circuit, our results provide further evidence in support of our proposed scheme of re-entry along the posterior nodal extension in all forms of atypical AVNRT. Attempts to provide a functional circuit model have also been made.
by reference to contextual considerations, such as the anisotropic conduction properties of the transitional area between the atria and the AV node,\textsuperscript{15-20} and variability in the space constant of tissue and poor gap junction connectivity, due to differential expression of connexin isoforms in the nodal area.\textsuperscript{21,22} Regardless of the nature of the reentry circuit in AVNRT, our results suggest that anterograde fast conduction during atypical AVNRT is distinct from retrograde fast conduction during typical AVNRT.

\textbf{Study Limitations}

The main limitation of our study is that we considered a hypothetical model based on theoretical assumptions such as similar anterograde and retrograde conduction velocities for the slow and fast pathways in both types of AVNRT. Although studies on orthodromic and antidromic conduction of lateral accessory pathways do not indicate fundamental differences in conduction velocity, whether this is true also for decremental AV nodal pathways is not known. The comparison of AV nodal conduction properties with that of bypass tracts is complex. It is likely that much of the difference between anterograde and retrograde conduction properties relates to impedance mismatch between ventricular or atrial muscle and that of the bypass tract. This does not directly parallel the situation in the AV node, and there are no data to allow any definitive conclusion in this respect. In addition, retrograde atrial activation, in particular, may not take similar paths in all forms of AVNRT as accepted in purely anatomical models. Finally, one could argue that using the same data and the same formula, an investigator who believes that there is a single fast pathway can 'prove' that there are discrete slow pathways. The fact that anatomic slow pathway ablation abolishes both typical and atypical AVNRT argues against such a hypothesis, although it cannot not exclude the possibility of anatomically close, but discrete, slow pathways affected by anatomical ablation.
Conclusion

Our data provide further evidence that slow-fast and fast-slow AVNRT that slow-fast and fast-slow AVNRT do not utilize the same anatomical pathway for fast conduction.

Conflict of Interest Disclosures: None.

References:


Table 1: Conduction intervals during typical and atypical AVNRT of all types.

<table>
<thead>
<tr>
<th>AVNRT type</th>
<th>CL (ms)</th>
<th>AHtachy (His)* (ms)</th>
<th>HA tachy (His)* (ms)</th>
<th>HAtachy (pCS)* (ms)</th>
<th>Earliest retrograde atrial activation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical AVNRT</td>
<td>368.0±43.1</td>
<td>281.6±47.1</td>
<td>67.3±14.6</td>
<td>62.0±13.7</td>
<td>pCS (60%)</td>
</tr>
<tr>
<td>Atypical AVNR</td>
<td>365.8±41.1</td>
<td>128.2±58.0</td>
<td>217.4±66.2</td>
<td>202.3±70.1</td>
<td>pCS (65%)</td>
</tr>
</tbody>
</table>

*: in 7 patients, the HRA electrogram was used for measurements, due to overlap of the atrial and ventricular electrograms on His.
+ : measured in 17 patients.
CL: tachycardia cycle length, AH tachy: atrial to His interval during tachycardia, HA tachy: His to right atrium interval during tachycardia.
Table 2. Patients with typical (slow-fast) and atypical AVNRT of the fast-slow type.

<table>
<thead>
<tr>
<th>Pt No</th>
<th>Age</th>
<th>Sex</th>
<th>CL</th>
<th>AH tachy</th>
<th>HA tachy</th>
<th>CL</th>
<th>AH tachy</th>
<th>HA tachy</th>
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<tbody>
<tr>
<td>1</td>
<td>57</td>
<td>M</td>
<td>410</td>
<td>320</td>
<td>62</td>
<td>394</td>
<td>154</td>
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<td>2</td>
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<td>F</td>
<td>395</td>
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<td>60</td>
<td>275</td>
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<td>187</td>
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<tr>
<td>3</td>
<td>36</td>
<td>F</td>
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<td>248*</td>
<td>77*</td>
<td>450</td>
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<td>300</td>
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</tr>
<tr>
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<td>53</td>
<td>M</td>
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<td>95*</td>
<td>400</td>
<td>35</td>
<td>325</td>
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<td>60</td>
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</tbody>
</table>

*: due to overlap of ventricular and atrial electrograms, the HRA electrogram was used for measurements.

CL: tachycardia cycle length, AH tachy: atrial to His interval during tachycardia on the His-recording electrogram, HA tachy: His to right atrium interval during tachycardia on the His-recording electrogram.
Figure Legends:

**Figure 1**: Depiction of conduction and resultant AH and HA during typical and atypical AVNRT types. Please see text for details.

Fr: retrograde conduction over the fast pathway; Fa: anterograde conduction over the fast pathway that is utilized by the fast-slow form; S: conduction over the slow pathway (anterogradely or retrogradely); A: conduction from the AVN node to right atrium as recorded by the electrode positioned on the His bundle; H: conduction from the AVN to His bundle; HA: time difference between activation of the His bundle and right atrium; AH: time difference between activation of right atrium and the next His.

**Figure 2**: A: Conduction times over the fast pathway during slow-fast AVNRT (Fr) and during fast-slow AVNRT (Fa) for each patient. Corresponding values for each patient are connected with lines. B: Scatterplot of the difference in conduction times over the fast pathway during slow-fast AVNRT (Fr) and during fast-slow AVNRT (Fa)(Fr-Fa) against mean conduction time over the fast pathway for each patient. The 95% confidence intervals of the estimated between-measurements error are superimposed (dotted lines) for comparison.
Slow-fast (s-f) AVNRT

\[ HA = F_r + A - H \]
\[ AH = S_a + H - A \]

Fast-slow (f-s) AVNRT

\[ HA = S_r + A - H \]
\[ AH = F_a + H - A \]

\[ HA \text{ (f-s)} + AH \text{ (s-f)} = (S_r + A - H) + (S_a + H - A) = 2S \]
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