Female preponderance in atrioventricular node reentrant tachycardia, but no sex related electrophysiological differences

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Abstract
The mechanism behind the female preponderance for atrioventricular node reentrant tachycardia (AVNRT) is not clear. We compared baseline electrophysiological measurements and clinical data in 141 consecutive patients (96 women) who underwent successful AVNRT ablation at their first therapeutic procedure. Women had on average 9% higher resting heart rate than men (p<0.05), but were similar in all measures of AV node function. Isoproterenol infusion was required for AVNRT induction in 69 cases (49%), and the need for isoproterenol was associated with lower resting heart rate and longer anterograde and retrograde AV node refractory periods (p<0.05 for comparisons), but not with sex. We conclude that the spectrum of baseline AV node physiology in AVNRT patients is wide, and is similar in men and women. The female preponderance for AVNRT cannot be explained from comparisons of baseline AV node electrophysiological properties.

Key words: atrio-ventricular node, supraventricular tachycardia, electrophysiology, sex, ablation

Introduction
Atrio-ventricular node reentrant tachycardia (AVNRT) is approximately twice as common in women, and the Wolff-Parkinson-White (WPW) syndrome twice as common in men.1-7 So far, no satisfactory mechanistic explanation for these sex related differences has been presented.3,6 Isoproterenol, a non-selective β-adrenergic agonist, is often effective in rendering AVNRT inducible,9,10 when it is not inducible in the baseline state, through differential effects on the different limbs of the reentry circuit.11-13 We sought to investigate differences in arrhythmia characteristics and electrophysiology between men and women, including the need for isoproterenol, which might shed light on the mechanisms behind the female predominance for AVNRT.

Methods
The records of 150 consecutive AVNRT cases referred and accepted for ablation therapy at one centre during a 2 year period were reviewed. Primary success, defined as non-inducibility of the tachycardia after posterior modification of the substrate, was achieved in 145 (97%). For 1 patient, the records (optical disk) could not be located. In 3 instances, the procedures were repeat attempts at AVNRT ablation, and these procedures were excluded. The study population, therefore, consists of 141 consecutive patients with AVNRT in whom the index procedure was the first and successful.

Patients were studied in the post-absorptive state, after antiarrhythmic drugs had been discontinued for at least 5 elimination half-lives. Light sedation and analgesia with midazolam and ketobemidone were used at the operating physician’s discretion.

With catheters placed in the right ventricle, coronary sinus, and at the His bundle, the anterograde and retrograde baseline properties of AV nodal conduction were determined through programmed atrial and ventricular stimulation. Atrial stimulation was performed from the coronary sinus catheter. The anterograde and retrograde Wenckebach cycle lengths (WbCL), i.e. the shortest cycle lengths allowing 1:1 atrio-ventricular (AV) and ventriculo-atrial (VA) conduction, were determined through incremental pacing to a cycle length no shorter than 300 ms, in steps of 10 ms. The anterograde and retrograde effective refractory period (ERP) was defined using single extra-beats
introduced after regular pacing at a basic cycle length of 500 or 600 ms, at coupling intervals no shorter than 200 ms. If arrhythmia had not been induced at this point in the protocol, induction was attempted by programmed atrial stimulation using 2 extra-beats coupled to a short train of regular atrial stimuli (S1-S2-S3).

If the arrhythmia was not inducible at baseline, isoproterenol infusion (30-180 μg/h) was started and programmed stimulation repeated until reproducible induction was achieved. Rarely, multiple atrial stimulation sites were used. In one case, atropine was added during continued isoproterenol infusion.

**Statistical analysis**

Median and range were used for descriptive statistics. The non-parametric Mann-Whitney test was used to compare continuous variables between men and women as well as between those who required isoproterenol for arrhythmia induction and those who did not because of skewed distribution of data. Chi-square analysis was used to compare baseline inducibility between men and women.

**Results**

Patient demographics, clinical and arrhythmia characteristics are shown in Table 1. The mean age (SD) was 53 (17) years and 96 patients (68%) were women. Altogether, 6 patients (4%) had more than one tachycardia substrate: WPW in 4 cases, of which 3 had previously undergone successful ablation, and atrial and ventricular tachycardia in 1 each. Most patients (94%) had no evidence of structural heart disease, but 5 patients (4 men) had ischemic heart disease, 2 had left ventricular hypertrophy (both men), and 2 valvular heart disease (both women).

Arrhythmia characteristics and baseline electrophysiologic measures are shown in Table 2. In 3 patients with previously documented AVNRT, arrhythmia could not be induced despite rigorous attempts. Female patients had a higher basic heart rate (median 70 vs. 64 bpm) (p < 0.05), while anterograde and retrograde AV node functional measures did not differ significantly. There was no sex related difference in AVNRT inducibility under baseline conditions (50% in women, 44% in men, NS).

Patients with inducible arrhythmia at baseline had a higher basic heart rate and shorter refractory periods and anterograde and retrograde WbCL in each. Most patients (94%) had no evidence of structural heart disease, but 5 patients (4 men) had ischemic heart disease, 2 had left ventricular hypertrophy (both men), and 2 valvular heart disease (both women).

**Discussion**

We found that the only statistically significant sex related difference in baseline electrophysiologic measurements in patients undergoing AVNRT ablation was a higher resting heart rate in women. The magnitude of the heart rate difference is similar to that observed in previous series of subjects with and without AVNRT, and may partly be attributable to differences in autonomic tone partly to intrinsic properties. The spectrum of baseline AV node physiology in AVNRT patients was wide, and similar in men and women. The female preponderance for AVNRT could therefore not be explained from comparisons of baseline AV node electrophysiologic properties.

The data distribution for several electrophysiologic measures was in our study markedly skewed. Partly, this was because the true AV node functional measures could not be precisely determined at baseline. The true AV node functional measures could not be precisely determined from comparisons of baseline AV node electrophysiologic properties. The female preponderance for AVNRT cannot be explained from comparisons of baseline AV node electrophysiological properties.

![Table 1: Clinical characteristics. All data are presented as median and range. Proportions are presented as percentages within brackets.](image-url)
determined in approximately 30% of patients, since we limited extra-beat coupling intervals to no less than 200 ms, and incremental pacing for WbCL assessment to no less than 300 ms cycle lengths to avoid provocation of atrial fibrillation and flutter. The utility of baseline electrophysiological measures for predicting the need for isoproterenol for AVNRT induction has been explored in previous studies. In 103 patients with proven AVNRT, Strickberger et al. found no correlation between baseline measures and the need for isoproterenol. Their stricter definition of inducibility (induction in 7 of 10 consecutive attempts) may explain the discrepancy with our results. Our results are in this regard similar to those of Liuba et al, who found several measures of AV nodal function predictive of baseline inducibility, although only in female patients. In contrast to their study, however, we found that larger measures of retrograde conduction associated with the need for isoproterenol in both sexes. The discrepancy may stem from the larger number of men in our study who required isoproterenol, or be related to the higher prevalence of structural heart disease (25%) among males in their cohort. Liuba et al. suggested that sex related differences in AV node physiology in AVNRT patients could contribute to explaining the female propensity, through a postulated “wider tachycardia window” in females with AVNRT. The “tachycardia window” (difference between anterograde slow and fast pathway refractoriness), however, was not determined for individual patients, but deduced from differences in group means of fast and slow pathway refractoriness. In contrast, Suenari et al. found similar “windows” in men and women in the largest study of AVNRT patients published so far (64.4± 54.5 vs. 60.8± 51.7 ms, p=0.25). Baseline electrophysiological measures in patients with AVNRT vary within a wide range, and overlap in men and women as exemplified in Fig 1. We conclude that there were no significant differences in baseline measures between the sexes, which may explain the similar results in both groups.

Table 2: Electrophysiological characteristics in the entire study group and specified subgroups presented as median (range) and for the entire study group also as mean (SD).

<table>
<thead>
<tr>
<th>Measure</th>
<th>All</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>n=141</td>
<td>n=96</td>
<td>n=45</td>
</tr>
<tr>
<td>BHR (basic heart rate) (n=141)</td>
<td>70 (44-110)</td>
<td>70 (44-110)</td>
<td>64 (45-110)*</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>70 (14)</td>
<td>72 (14)</td>
<td>66 (14)*</td>
</tr>
<tr>
<td>AV node anterograde measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AH (n=141)</td>
<td>75 (40-159)</td>
<td>75 (40-159)</td>
<td>81 (49-159)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>82 (25)</td>
<td>80 (22)</td>
<td>89 (29)</td>
</tr>
<tr>
<td>Anterograde WbCL (n=115)</td>
<td>354 (290-840)</td>
<td>344 (290-610)</td>
<td>371 (290-840)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>384 (93)</td>
<td>371 (71)</td>
<td>410 (125)</td>
</tr>
<tr>
<td>AVN-ERP (n=140)</td>
<td>300 (210-600)</td>
<td>290 (210-600)</td>
<td>310 (220-600)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>319 (91)</td>
<td>320 (78)</td>
<td>318 (114)</td>
</tr>
<tr>
<td>AV node retrograde measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrograde WbCL (n=126)</td>
<td>341 (280-660)</td>
<td>350 (280-640)</td>
<td>330 (300-660)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>367 (77)</td>
<td>372 (77)</td>
<td>358 (77)</td>
</tr>
<tr>
<td>Shortest VA-interval (n=121)</td>
<td>260 (190-530)</td>
<td>260 (190-490)</td>
<td>260 (200-530)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>281 (69)</td>
<td>278 (64)</td>
<td>287 (78)</td>
</tr>
</tbody>
</table>

Inducible at baseline, n (%)  
68 (48)  
48 (50)  
20 (44)

Inducible with isoproterenol  
70 (50)  
47 (49)  
23 (52)

Non-inducible  
3 (2)  
1 (1)  
2 (4)

AVNRT, uncommon type  
8  
5  
3

* p < 0.05

Table 3: Comparison between electrophysiological measures and the inducibility at baseline vs. with isoproterenol presented as mean (SD).

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>Isoproterenol</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline heart rate (bpm)</td>
<td>73 (15)</td>
<td>68 (13)</td>
<td>0.016</td>
</tr>
<tr>
<td>AH interval (ms)</td>
<td>79 (23)</td>
<td>86 (26)</td>
<td>0.089</td>
</tr>
<tr>
<td>Anterograde WbCL</td>
<td>351 (58)</td>
<td>413 (108)</td>
<td>0.0003</td>
</tr>
<tr>
<td>AVN-ERP</td>
<td>298 (71)</td>
<td>341 (102)</td>
<td>0.004</td>
</tr>
<tr>
<td>Retrograde WbCL</td>
<td>340 (51)</td>
<td>395 (89)</td>
<td>0.00005</td>
</tr>
<tr>
<td>Shortest VA-interval (n=4)</td>
<td>265 (58)</td>
<td>298 (76)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Table 4: Sensitivity, specificity, and positive predictive values for the cut-off level = median of electrophysiological measures with a significant relation to the need for isoproterenol infusion for AVNRT induction (n=69; 49%). Proportions are presented as percentages with 95% confidence intervals within brackets. See also table 3.

<table>
<thead>
<tr>
<th>Cut-off level</th>
<th>Sensitivity [%]</th>
<th>Specificity [%]</th>
<th>Positive Predictive Value [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic heart rate ≤ median = 70 bpm; n=83</td>
<td>61 (49-73)</td>
<td>41 (29-54)</td>
<td>52 (41-63)</td>
</tr>
<tr>
<td>Anterograde WbCL &gt; median = 354 ms; n=56</td>
<td>63 (50-75)</td>
<td>67 (53-79)</td>
<td>68 (54-80)</td>
</tr>
<tr>
<td>AVN-ERP &gt; median = 300 ms; n=62</td>
<td>56 (44-68)</td>
<td>66 (53-77)</td>
<td>63 (50-75)</td>
</tr>
<tr>
<td>Retrograde WbCL &gt; median = 341 ms; n=70 (incl. 8 VA-block)</td>
<td>68 (56-79)</td>
<td>62 (49-73)</td>
<td>64 (52-75)</td>
</tr>
<tr>
<td>Shortest VA-interval &gt; median = 260 ms; n=58 (incl. 8 VA-block)</td>
<td>57 (44-70)</td>
<td>69 (56-79)</td>
<td>63 (49-76)</td>
</tr>
</tbody>
</table>

For abbreviations please refer to the text.
sex related differences in baseline AV node characteristics in this series of AVNRT patients undergoing ablation. In addition, neither among patients with nor without AVNRT Suenari et al. and Liu et al. found any significant sex related difference in the proportion of patients with dual AV node physiology defined as a jump in the baseline conduction curve.6,14

Limitations
A minor fraction (6%) of the patients had the uncommon type of AVNRT, but this did not seem to affect the overall results, and actually reflects the clinical reality, which was part of the purpose of the present study of a consecutive series of patients. In 14 patients the physician responsible for the procedure decided to start isoproterenol infusion without trying S1S2S3 at baseline. Not surprisingly, most of these patients as well as most of the 8 patients with the uncommon type of AVNRT (fast-slow) had anterograde AV node functional measures greater than the median. Fast pathway refractoriness was not consistently recorded. In our experience, the absence of a distinct “jump” (conventionally a prolongation of A2H2 ≥ 50 ms for a decrement in A1A2 or S1S2 of 10 ms) is not unusual in adult AVNRT patients, in line with previous observations in adults as well as in children.6,16

Conclusions
The female preponderance for AVNRT cannot be explained from comparisons of AV node electrophysiological properties in women vs. men with and without AVNRT according to the results of this and previous studies.

Acknowledgement
Elisabeth Berg and Thomas Karlsson provided valuable statistical advice. There are no relevant disclosures to be made in relation to this study for any of the authors.

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References