Predictors of AVNRT Recurrence After Slow Pathway Modification
A Case Control Study

Felix K. Wegner,1 MD, Pia Habbel,1 MSc, Piet Schuppert,1 MSc, Gerrit Frommeyer,1 MD, Christian Ellermann,1 MD, Philipp S. Lange,1 MD, Patrick Leitz,1 MD, Julia Köbe,1 MD, Kristina Wasmer,1 MD, Lars Eckardt,1 MD and Dirk G. Dechering,1 MD

Summary
Atrioventricular nodal reentry tachycardia (AVNRT) is the most common regular supraventricular tachycardia (SVT). Slow pathway modification (SPM) is the accepted first line treatment with reported success rates around 95%. Information regarding possible predictors of AVNRT recurrence is scarce.

Out of 4170 consecutive patients with SPM in our department from 1993-2018, we identified 78 patients (1.9%) receiving > 1 SPM (69% female, median age 50 years) with a recurrence of AVNRT after a successful SPM. We matched these patients for age, gender and number of radiofrequency applications during first SPM with 78 patients who received one successful SPM in our center without AVNRT recurrence. Both groups were analyzed for possible predictors of a recurrence of AVNRT during long-term follow-up. The recurrence group contained a significantly lower proportion of patients with an occurrence of junctional beats during SPM (69% versus 89%, P = 0.006). Moreover, significantly more cases of previously diagnosed atrial fibrillation/tachycardia (AF/AT; 21% versus 5%, P = 0.007) and inducible AF/AT during electrophysiology study (23% versus 6%, P = 0.006) were present in the recurrence group. While more than half of patients had a recurrence within the first year, in 20% symptoms reappeared ≥ 4 years after ablation.

In a small percentage of patients, AVNRT recurs after an initially successful ablation. Interestingly, these patients had significantly fewer junctional beats during a blation and a higher rate of other (inducible) arrhythmias. AVNRT recurrence spanned a considerable timeframe and should remain a differential diagnosis, even years after ablation.

Key words: Electrophysiology, Supraventricular tachycardia, Catheter ablation, SPM

Atrioventricular nodal reentry tachycardia (AVNRT) is the most common regular supraventricular tachycardia (SVT) and is dependent on dual AV nodal pathway physiology (DNPP) for the propagation of its reentry circuit. When an AVNRT is successfully induced during electrophysiological study (EPS), the first-line therapy consists of slow pathway modification (SPM) of the AV node with radiofrequency energy (RF)1,2).

SPM has been the preferred method of interventional treatment since the mid-1990s with serious adverse effects such as complete AV-nodal block occurring in < 1% of cases.3) Since the introduction of SPM, research concentrated mainly on procedural endpoints and markers of a successful ablation. Most publications, albeit with small patient numbers, agree that slow pathway modification with the remainder of one AV nodal echo beat results in a similar success rate as slow pathway ablation with the abolition of DNPP and reduces the incidence of AV nodal block.4,6

Long-term success rates of slow pathway modification have been reported to be around 95% in case series.5,6 Most of these data were gathered in the 1990s in rather small patient groups and do not necessarily reflect potential contemporary advantages in clinical practice. Furthermore, the only recent study on this topic by Katritsis, et al. was a retrospective work analyzing 1084 patients, 24 of whom had an AVNRT recurrence.7) The authors were unable to show statistically significant differences between the recurrence group and controls, possibly due to the low number of patients with a recurrence. In addition, patients with inducible atrial fibrillation (AF) or flutter were excluded from the analysis. The purpose of the present study was, therefore, to analyze patients with a recurrence of AVNRT after an initially successful SPM and to elicit predictors of recurrence in a high-volume electrophysiology center with long-term follow-up.

Methods

Study design: The present report was designed as a case
control study. Recurrence was defined as both the presence of clinical symptoms indicative of AVNRT after a successful SPM as well as the induction of AVNRT on repeat EPS. We analyzed a population of 4170 consecutive patients who received at least one successful SPM in our department between 1993 and 2018 and identified 78 patients having received > 1 SPM. All patients included in this group met the following inclusion criteria: 1) First SPM because of AVNRT inducible during EPS, 2) Procedural success of the first SPM, 3) Recurrence of symptoms indicative of AVNRT, 4) Inducible AVNRT in the second EPS as proof of AVNRT recurrence.

We matched the recruited patients 1:1 for 1) age at ablation, 2) gender and 3) number of RF applications during the first SPM with a control group of 78 patients. If matching criteria were fulfilled by more than one patient in our database of successful ablations, the control group patient was selected in a randomized fashion from this group. The number of RF applications was chosen as a matching criterion to control for technically challenging ablations, which require an increased number of RF impulse deliveries and have a higher likelihood of recurrence. All patients of the control group met the following inclusion criteria: 1) One SPM because of AVNRT inducible during EPS, 2) Procedural success of the SPM, 3) Freedom of symptoms as elicited by a follow-up telephone interview.

Procedural success was defined as the inability to induce a previously inducible AVNRT after the application of ≥ 1 RF impulse. Additionally, a maximum of one echo beat was allowed at the end of the first SPM, therefore including both patients with a slow pathway ablation and a slow pathway modification. Patients on an antiarrhythmic medication were excluded from the control group. The study was approved by the regional ethics committee. All patients gave informed consent to be included in the study.

Electrophysiological study: The EPS was conducted as previously reported. In short, venous access was gained through the left femoral vein, and three diagnostic catheters were placed: One in the high right atrium (alternatively in the coronary sinus in long RP tachycardias), one at the His bundle and one in the right ventricular apex. Programmed atrial stimulation up to a cycle length of 330 ms with up to two premature beats (S3) was performed. If AVNRT was not inducible, orciprenaline (0.25 mg bolus) was intravenously applied, and stimulation was repeated. When a SVT was induced, the diagnosis of typical AVNRT was established with a septal ventriculoatrial (VA) interval of < 70 ms and a VAV response after ventricular overdrive pacing. For atypical AVNRT, we demanded a concentric and low-to-high electric propagation with a corrected post pacing interval minus tachycardia cycle length of > 110 ms. Additional maneuvers were required in rare cases.

After the diagnosis of AVNRT was established, a 4 mm non-irrigated, steerable ablation catheter (Cerablate, Osypka, Rheinfelden, Germany) was used. For slow pathway modification the so-called integrated approach was used, combining anatomical landmarks and electrogram analysis. In short, the coronary sinus (CS) ostium was approached with the ablation catheter. From the ostium (large, sharp atrial electrogram), the ablation catheter was rotated out of the CS and an electrogram with an A:V ratio of 1:3 - 1:4 was sought (segment P1 or P2). In all patients, ablation was performed using RF energy with a maximum of 50 Watts and 60 °C. During RF delivery, our aim was to induce slow junctional beats. If no junctional rhythm was induced, the ablation catheter was rotated more towards the CS (A:V ratio 1:1) for subsequent RF delivery. In the few remaining cases without success, we moved to midseptal (M1) or ablated from the left side. After ablation, repeat diagnostic stimulation was performed to evaluate the inducibility of AVNRT. First before, then after the repeat administration of orciprenaline (0.25 mg bolus), even if AVNRT was inducible prior to RF application without orciprenaline. Our end point was the occurrence of no more than 1 AV-nodal echo beat and/or an AH jump.

For the purpose of our study, atrial fibrillation was defined as absolutely irregular R-R intervals without discernible P waves of > 30 seconds duration in the ECG. Atrial tachycardia was defined as a sustained (> 30 seconds) organized atrial tachycardia (> 100 bpm) from an origin remote from the sinus node spreading centrifugally over both atria. Micro-reentrant (entrainment possible) and focal AT were grouped as one in the context of our study.

Statistical analysis: We used Microsoft Excel© 2010 (Microsoft Corporation, Redmond, WA, USA) for data storage. SPSS Version 25 (IBM Corporation, Somers, NY, USA) was used for statistical analysis. Departure from a normal distribution was evaluated using Shapiro-Wilk’s test. To compare means, the Mann-Whitney U test was applied for paired or unpaired observations, as appropriate. Chi-Square or Fisher’s exact test was used for comparisons of proportions. Statistical significance was defined as a two-sided alpha level of 0.05 or less.

Results

Seventy-eight of all 4170 patients (1.9%) who received an initially successful SPM at our center subsequently had a repeat EPS with an inducible AVNRT. The baseline characteristics of this group are depicted in Table I.

Pre-ablation history: Three of 78 patients (4%) in the AVNRT recurrence group experienced AVNRT symptoms less than once per month. Thirty-two patients (41%) had symptoms once per month, 33 patients (42%) once per week, and ten patients (13%) had symptoms daily. Seven patients (9%) in the AVNRT recurrence group had a previous EPS before receiving their first SPM. Of those, one patient received an ablation of the cavotricuspid isthmus because of suspected typical atrial flutter. One further patient had inducible AVNRT, but did not receive a slow pathway modification. The five remaining patients had diagnostic EP studies without inducible tachycardia. Sixty-two patients (80%) had an ECG documentation consistent with AVNRT before the first SPM at our center. The group with AVNRT recurrence contained a significantly higher number of patients with previously diagnosed AF.
or atrial tachycardia (AT; 16 versus 4 patients, \( P = 0.007 \)) than the control group. There were no statistically significant differences in the occurrence of other cardiovascular risk factors or comorbidities (Table I).

**Procedural characteristics of EPS:** AVNRT was inducible during the first EPS in all 156 patients of both groups. The procedural characteristics of the recurrence and control groups are depicted in Table II. In the group with AVNRT recurrence, AF/AT was induced in a significantly higher number of patients (18 versus 5 patients, \( P = 0.006 \)) during the first EPS. Additionally, this group had a significantly lower number of patients with junctional beats/tachycardia during RF application in the slow pathway region (54 versus 69 patients, \( P = 0.006 \)). The presence of junctional beats during RF application therefore had a sensitivity of 89% and a specificity of 31% for long-term freedom from AVNRT recurrence in our highly selected patient population. Four patients (5%) in each group exhibited an atypical AVNRT. In the recurrence group, there was a trend toward a longer duration of the procedure (median time 105 versus 90 minutes, \( P = 0.10 \)) with a significantly longer fluoroscopy time (median time 853 versus 548 seconds, \( P = 0.04 \)) and a significantly higher cumulative radiation dose (median dose 721 versus 329 cGy/cm², \( P = 0.009 \)), respectively. There was no trend between the number of echo beats and long-term success, as both the recurrence and control groups contained the same number of patients with either one or zero echo beats (Table II). During the first EPS no serious complications such as AV block occurred.

**Follow-up:** After SPM, symptoms recurred in all patients in the AVNRT recurrence group. Nine patients (11.5%) reported an improvement in symptoms, 60 patients (77%) described no change in symptoms and nine patients (11.5%) had symptoms worse than before the initial EPS. The median time to repeat EPS in the AVNRT recurrence group was 276 days (Figure). Of note, 20% of patients had their repeat procedure ≥ 4 years after the initial SPM. There was no difference in age between these patients and patients with a recurrence < 4 years after initial SPM (\( P = 0.26 \)). Slow pathway modifications with resultant AVNRT recurrence occurred during the entire inclusion period with no clustering of AVNRT recurrences during the early years, i.e. there was no detectable learning curve (\( P = 0.42 \)). At the time of the repeat EPS, four patients (5%) were on antiarrhythmic medication (2 flecainide, 2 verapamil). Of the 4 patients with an initial atypical AVNRT, one patient exhibited an atypical AVNR during repeat EPS, and three patients exhibited a typical AVNRT.

All patients in the control group were reached for a follow-up telephone interview. The mean time of follow-up was 122 ± 77 months. All of the 78 patients in the control group were free of symptoms suggestive of recurrent AVNRT. None of the patients had a repeat EPS at another center. No patients in the control group were taking antiarrhythmic medication.

Of the 78 patients in the recurrence group, 74 (95%) could be reached for a follow-up telephone interview after a mean follow-up of 143 ± 88 months. Four patients could not be reached for an interview or were deceased. Forty-nine of the remaining 74 patients (66%) reported a freedom of symptoms after the second SPM. Seven pa-

### Table I. Baseline Characteristics of the Recurrence and Control Groups

|                     | Recurrence | Control | \( P \)-value |
|---------------------|------------|---------|---------------|
| Number of patients  | 78         | 78      | n/a           |
| Female              | 54 (69%)   | 54 (69%)| n/a           |
| Median age at SPM in years (IQR) | 50 (34-62) | 50 (35-61) | n/a         |
| ECG documentation before SPM | 62 (80%)  | 57 (73%) | 0.45       |
| Previously diagnosed AF/AT | 16 (21%)  | 4 (5%)  | 0.007        |
| Hypertension        | 27         | 25      | 0.87          |
| Diabetes            | 12         | 4       | 0.06          |
| Heart failure       | 1          | 2       | 1.0           |

AF indicates atrial fibrillation; AT, atrial tachycardia; IQR, interquartile range; n/a, not applicable; and SPM, slow pathway modification.

### Table II. EPS Procedural Characteristics of the Recurrence and Control Groups during EPS1

|                     | Recurrence | Control | \( P \)-value |
|---------------------|------------|---------|---------------|
| Length of EPS1 in min (IQR) | 105 (75-144) | 90 (70-125) | 0.10         |
| Fluoroscopy time in seconds (IQR) | 853 (351-1410) | 548 (268-1144) | 0.04        |
| Radiation dose in cGy*cm² (IQR) | 721 (190-2510) | 328 (129-944) | 0.009       |
| AVNRT induction without orciprenaline | 44 (56%) | 43 (55%) | 1.0          |
| Atypical AVNRT | 4 (5%) | 4 (5%) | n/a          |
| Induction of AF/AT | 18 (23%) | 5 (6%) | 0.006        |
| Median no. of RF impulses (IQR) | 3 (2-9) | 3.5 (2-9) | 0.98        |
| Median duration of RF application in min (IQR) | 3 (2-6) | 2 (2-5) | 0.72        |
| Abolition of DNPP | 25 (32%) | 25 (32%) | n/a          |
| Occurrence of junctional beats during ablation | 54 (69%) | 69 (89%) | 0.006       |

EPS indicates electrophysiological study; AF, atrial fibrillation; AT, atrial tachycardia; DNPP, dual AV-nodal pathway physiology; IQR, interquartile range; n/a, not applicable; and RF, radiofrequency.
Fig. Time to repeat EPS. Inverted Kaplan-Meier curve of time between EP study 1 (initial SPM) and EP study 2 (re-do procedure) in the AVNRT recurrence group in years. EP indicates electrophysiology.

patients (10%) described a significant improvement of symptoms without a wish for further therapy. Eighteen patients (24%) had no change in symptoms even after the second SPM. There was no statistically significant association between the predictors of AVNRT recurrence listed above and a persistence of symptoms after second SPM.

Of note, one patient experienced a permanent AV nodal block during the second SPM in the group with AVNRT recurrence and was subsequently implanted with a DDD pacemaker system.

Discussion

The present study reports on the largest group of patients with a recurrence of AVNRT after an initially successful slow pathway modification. Our main findings are 1) a significant association between the absence of junctional beats during SPM and AVNRT recurrence, 2) patients with AVNRT recurrence have other documented or inducible arrhythmias significantly more often and 3) AVNRT recurrence spans a considerable timeframe after an initially successful SPM.

The occurrence of junctional beats has been discussed as a sensitive but not specific predictor of ablation success. Jentzer, et al. in 1994 described a very high sensitivity of the occurrence of junctional rhythm for successful RF application in 52 patients albeit with a low specificity, as junctional beats frequently occurred during ineffective RF applications. Katritsis, et al. recently reported on a group of 1084 patients having received an initially successful SPM and identified 24 patients with a clinical recurrence of AVNRT after 3 months of follow-up. Although a trend toward a lower likelihood of junctional beats during SPM was identified in the recurrence group, statistical significance could not be reached, possibly due to sample size.

In this context, we were able to document a similar incidence of recurrence as reported by Katritsis, et al. in a quadrupled patient population during a much longer median follow-up time of more than 10 years. The occurrence of junctional beats was significantly associated with freedom from AVNRT recurrence in our patient population. Furthermore, our results affirm the high sensitivity of the occurrence of junctional beats for an effective RF application, as 89% of patients in our control group exhibited junctional beats during SPM. Of note, junctional beats were present in more than 2/3 of patients with an AVNRT recurrence, resulting in a very low specificity for freedom from AVNRT recurrence. Therefore, the presence of junctional beats should only be one of several factors informing the electrophysiologist’s decision whether to conclude the SPM or continue with the ablation procedure. Our data further support the hypothesis that slow pathway modification is as effective as complete ablation of the slow pathway, as both groups exhibited an equal proportion of patients with and without DNPP after RF application.

Patients with an inducible AVNRT on repeat EPS had a significantly higher likelihood of AF or AT. We cannot fully exclude the possibility that these arrhythmias were a confounder in the present study, as an ECG documentation of the recurrence was not always obtainable. However, all patients in the recurrence group had an inducible AVNRT on repeat EPS. In theory, a diagnosis of AF/AT is an indicator of more atrial premature beats (APB) or bursts. More APB in turn increase the likelihood of AVNRT recurrence in a patient with persistent conduction properties allowing for the propagation of the AVNRT circuit. The AVNRT recurrence group furthermore exhibited a statistically significantly higher cumulative radiation dose and fluoroscopy time, possibly indicating technically more challenging ablations.

Pathophysiologically, multiple aspects may help to explain why an AVNRT not inducible at the end of SPM may recur in the long term. Basic research conducted in the early 1990s was able to show that slowly heating car-
diac tissue leads to increased depolarization, decreased depolarization and irreversible damage in a sequential order. While junctional beats most likely represent a moderate increase in tissue temperature, it is conceivable that cardiac tissue directly adjacent to the ablation catheter may immediately be heated to a state of decreased excitability, therefore not exhibiting junctional beats. However, if the temperature threshold for permanent damage is not reached, this tissue may re-gain the ability to maintain an AVNRT reentrant circuit in the long-term. Additionally, reversible ablation-associated tissue edema with slow pathway compression may explain a return of conduction properties after ablation.

The present study gives an important insight into the course of AVNRT after interventional treatment in a large cohort. Most research on the topic had a rather small sample size and was based on data collected in the 1990s. In comparison, we were able to report a lower recurrence rate during a much longer follow-up time with no serious complications occurring during first SPM. However, since only patients with both a symptomatic recurrence and an inducible AVNRT on repeat EPS were included, the total number of AVNRT recurrences might be higher than documented.

Interestingly and previously unreported, our data show that 50% of patients experience a recurrence of symptoms within the first year, while 20% had a symptom-free survival of ≥4 years. Consequently, recurrence of AVNRT should remain a differential diagnosis in a patient with symptomatic paroxysms even years after a procedurally successful SPM and a follow-up interview 3 months after SPM might fail to identify most patients with an AVNRT recurrence. As the first study to comment on the long-term course of patients with an AVNRT recurrence, we were able to document that these patients have a much lower chance of symptom-free survival, even after a re-do procedure.

Clinical implications: The results of the present study should reinforce interventional electrophysiologists to aim for the induction of junctional ectopy during slow pathway modification next to non-inducibility as a procedural end point. Importantly, inducibility of AVNRT should be re-assessed after each RF delivery. One inducible AVN echo can be tolerated at the end of the ablation, as it is not associated with a higher likelihood of recurrence during long-term follow-up. If patients present with recurrent symptoms during follow-up, an AVNRT recurrence should remain a differential diagnosis even in the long term.

Limitations: The present study reports on a heterogeneous collective of patients having been interventionaltreated over the course of two decades. The usual limitations for single center and retrospective analyses apply. The proportion of 12-lead ECG documentation of symptomatic recurrences was not able to be reported, as a re-do procedure was conducted without requiring a repeat 12-lead documentation in individual cases to avoid a delay in treatment. Facilitation of AVNRT reinduction after ablation by orciprenaline administration was not systematically recorded. However, orciprenaline administration did not change reinduction rates in a controlled trial. By recruiting a propensity matched control group we aimed to reduce possible bias. Additionally, the broad inclusion time allowed us to reach follow-up times much longer than previously reported with interesting clinical implications as presented above. Furthermore, since AVNRT recurrence is a rare event, prospective trials or those analyzing only short timeframes have a high likelihood of being underpowered.

Conclusion

In this large long-term case-control study, we were able to show that AVNRT recurrence seldom occurs, but is associated with a prolonged symptomatic course. The absence of junctional beats during ablation and the co-occurrence of other supraventricular arrhythmias emerged as significant predictors of AVNRT recurrence. A considerable proportion of patients had their AVNRT recurrence several years after the initial slow pathway modification.

Acknowledgment

This study contains data from the doctoral thesis of P.H.

Disclosure

Conflicts of interest: There are no conflicts of interest.

References

1. Brugada J, Katritsis DG, Arbelo E, et al. 2019 ESC Guidelines for the management of patients with supraventricular tachycardia. The Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC). Eur Heart J 2020; 41: 655-720.
2. Page RL, Joglar JA, Caldwell MA, et al. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2016; 67: e27-115.
3. Wann S, Decherini DG, Köbe J, et al. Patients’ and procedural characteristics of AV-block during slow pathway modulation for AVNRT-single center 10 year experience. Int J Cardiol 2017; 244: 158-62.
4. Chrispin J, Misra S, Marine JE, et al. Current management and clinical outcomes for catheter ablation of atrioventricular nodal re-entrant tachycardia. Europace 2018; 20: e51-9.
5. Hummel JD, Strickberger SA, Williamson BD, et al. Effect of residual slow pathway function on the time course of recurrences of atrioventricular nodal reentrant tachycardia after radiofrequency ablation of the slow pathway. Am J Cardiol 1995; 75: 628-30.
6. Estner H, Ndreppea G, Dong J, et al. Acute and long-term results of slow pathway ablation in patients with atrioventricular nodal reentrant tachycardia—an analysis of the predictive factors for arrhythmia recurrence. Pacing Clin Electrophysiol 2005; 28: 102-10.
7. Clague JR, Dagres N, Kottkamp H, Breithardt G, Borggreve M. Targeting the slow pathway for atrioventricular nodal reentrant tachycardia: initial results and long-term follow-up in 379 consecutive patients. Eur Heart J 2001; 22: 82-8.
8. Chen SA, Wu TJ, Chiang CE, et al. Recurrent tachycardia after selective ablation of slow pathway in patients with atrioventricu-
lar nodal reentrant tachycardia. Am J Cardiol 1995; 76: 131-7.
9. Scheinman MM, Huang S. The 1998 NASPE prospective catheter ablation registry. Pacing Clin Electrophysiol 2000; 23: 1020-8.
10. Katritsis DG, Zografos T, Siontis KC, et al. Endpoints for successful slow pathway catheter ablation in typical and atypical atrioventricular nodal re-entrant tachycardia: A contemporary, multicenter study. JACC Clin Electrophysiol 2019; 5: 113-9.
11. Wegner FK, Silvano M, Bögeholz N, et al. Slow pathway modification in patients presenting with only two consecutive AV nodal echo beats. J Cardiol 2017; 69: 471-5.
12. Kalbfleisch SJ, Strickberger SA, Williamson B, et al. Randomized comparison of anatomic and electrogram mapping approaches to ablation of the slow pathway of atrioventricular node reentrant tachycardia. J Am Coll Cardiol 1994; 23: 716-23.
13. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016; 37: 2893-962.
14. Hsieh MH, Chen SA, Tai CT, Yu WC, Chen YJ, Chang MS. Absence of junctional rhythm during successful slow-pathway ablation in patients with atrioventricular nodal reentrant tachycardia. Circulation 1998; 98: 2296-300.
15. Jentzer JH, Goyal R, Williamson BD, et al. Analysis of junctional ectopy during radiofrequency ablation of the slow pathway in patients with atrioventricular nodal reentrant tachycardia. Circulation 1994; 90: 2820-6.
16. Simmers TA, De Bakker JM, Wittkampf FH, Hauer RN. Effects of heating on impulse propagation in superfused canine myocardium. J Am Coll Cardiol 1995; 25: 1457-64.
17. Heydari A, Tayyebi M, Jani RD, Amiri A. Role of isoproterenol in predicting the success of catheter ablation in patients with reproducibly inducible atrioventricular nodal reentrant tachycardia. Tex Heart Inst J 2014; 41: 280-5.