Optimized Mapping of Slow Pathway Ablation Guided by Subthreshold Stimulation: A Randomized Prospective Study in Patients With Recurrent Atrioventricular Nodal Re-entrant Tachycardia

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OBJECTIVES
This randomized prospective study sought to assess the value of slow pathway (SP) mapping and ablation guided by subthreshold stimulation (STS) in comparison with a strategy based on conventional criteria.

BACKGROUND
Previous studies have demonstrated that STS can be used as a highly specific and sensitive marker for successful SP ablation in the setting of atrioventricular nodal re-entrant tachycardia (AVNRT). Nonetheless, thus far this mapping strategy has not been investigated in contrast with the conventional approach.

METHODS
One hundred patients with sustained AVNRT were included. Fifty patients (group A) were randomly assigned to endocardial mapping and SP ablation using currently established criteria. In the other 50 patients (group B), SP ablation was guided by STS mapping. In group B patients, only radiofrequency current (RFC) was applied if additionally constant current STS (up to 5 mA) during AVNRT interrupted the tachycardia due to selective block within the SP.

RESULTS
Termination of AVNRT without apparent capture was observed during STS in 47 of 50 group B patients (94%). In all cases, this effect was indicative for successful subsequent SP ablation. The mean number of RFC pulses required for successful SP ablation was significantly lower in patients assigned to the STS-guided strategy (1.6 ± 1.3 vs. 3.9 ± 3.4; p = 0.0003). Similarly, the mean procedure duration was shorter in the STS group (156.9 ± 33.5 vs. 173.2 ± 49.7 min; p = 0.0221); the fluoroscopy time was comparable between both groups (14.1 ± 8.7 vs. 16.9 ± 10.6 min; p = 0.1278).

CONCLUSIONS
Subthreshold stimulation is an effective method for detection of target sites for selective SP ablation. This technique helps to minimize the number of RFC pulses without prolongation of the overall procedure and fluoroscopy time required for SP ablation. (J Am Coll Cardiol 2001;37:1645–50) © 2001 by the American College of Cardiology

Transcatheter radiofrequency current (RFC) ablation has evolved as the therapy of choice in patients with recurrent atrioventricular nodal re-entrant tachycardia (AVNRT). Catheter modulation of the atrioventricular (AV) node due to selective slow pathway (SP) ablation is a highly effective interventional method for curative treatment of this arrhythmia. Nonetheless, multiple RFC applications are necessary in most patients (1–9). Furthermore, this method still carries the risk of inadvertent fast pathway ablation (10) and induction of a complete AV block in approximately 2% of all cases (11,12). Therefore, the development of novel mapping strategies attempting to reduce the number of RFC pulses for SP ablation and, consequently, for the risk of AV-block induction is of clinical relevance.

Subthreshold stimulation (STS), defined as the delivery of noncaptured low energy pulses, has been shown to effectively terminate AVNRT due to selective block within the SP (13). In a previous study, it has been demonstrated that this technique can be a highly specific and sensitive marker for the detection of target site for successful SP ablation in the setting of AVNRT (14). However, the advantage of this method has not been investigated in a randomized fashion over conventional mapping for SP ablation. Thus, we conducted a randomized, prospective study to compare the effect of the currently established technique oriented on electrophysiologic and anatomic criteria with an STS-guided mapping and ablation approach.

METHODS
A total of 100 patients with reproducibly inducible AVNRT by programmed atrial stimulation were enrolled. The randomization was performed during the electrophysiologic study after the diagnosis of sustained AVNRT was established before starting the mapping procedure. These patients were obtained from a cohort of 157 consecutive patients with recurrent AVNRT referred for slow ablation (57 patients were not included due to the induction of nonsustained AVNRT only). Fifty patients (group A) were randomly assigned to endocardial mapping and ablation of...
the SP oriented on established criteria (1–9). The other 50 patients (group B) underwent endocardial mapping based on these criteria also, but ablation was guided by STS. Both groups were well-balanced with respect to demographic parameters (Table 1). There were no major differences regarding age, gender, the incidence of an underlying heart disease or the mean cycle length of induced AVNRT.

**Inclusion criteria.** All patients had recurrent episodes of AVNRT before the electrophysiologic study. In all cases, AVNRT of the slow anterograde-fast retrograde (common) type was reproducibly inducible in a sustained form without the need for additional pharmacological provocation. Patients were excluded from the study when spontaneous termination of the tachycardia or intermittent atrial fibrillation was observed.

**Electrophysiologic studies.** Antiarrhythmic agents were discontinued before the study for at least five half-lives. Electrophysiologic studies were performed in a fasting, lightly sedated state after a written informed consent had been obtained. Multipolar electrode catheters were positioned into high-right atrium, His-bundle region and right-ventricular apex via the femoral veins. A coronary sinus catheter was inserted through the left subclavian vein. The investigations followed a conventional protocol of intracardiac recording and stimulation. Retrograde and anterograde AV nodal conduction capabilities, including effective refractory periods of SP and fast pathway and the inducibility of AVNRT, were investigated at baseline. The protocol included incremental atrial and ventricular stimulation as well as programmed atrial and ventricular stimulation with a basic drive cycle length of 510, 440 and 370 ms using a single extrastimulus (9). Isoproterenol infusion was not required to induce AVNRT before ablation in all patients. The protocol was repeated after ablation in the same fashion as described in the preceding text. Continuous anticoagulation was maintained throughout the procedure.

**Endocardial mapping.** A conventional 7F deflectable electrode catheter (Dr. P. Osypka, Grenzach-Whylen, Germany or Cordis Webster, Diamond Bar, California) was guided by anatomic landmarks (5) and local electrograms (4,5,8,9) in both groups. The mapping procedure began posteroseptally close to the ostium of the coronary sinus where the most suitable local electrogram recording was detected and continued to more midseptal sites, if needed. Electrograms obtained during sinus rhythm were considered as target sites if the previously described criteria were met (4,5,8,9). These included the detection of fractionated and long-duration atrial electrograms with an amplitude of half or less of the ventricular signal and recording of a presumable SP potential (4,5). When a target site was selected and the catheter position remained in a stable position, RFC ablation was performed in group A, and STS was performed in group B.

Electrogram characteristics of the first selected target site were analyzed in both groups according to previously published methods (9). The analysis was performed at the first selected target site in order to avoid a potential bias due to the modification of the electrograms caused by subsequent RFC application. Measurements were based on the onset of local electrograms with the exception of a few cases where the onset of a local electrogram could not be reliably determined, where the first rapid deflection-crossing baseline was used. Likewise, the duration of a local atrial electrogram was measured by determining the interval from its onset to the beginning of an isoelectric line located preceding the ventricular electrogram or at the beginning of the earliest ventricular activity if such isoelectric line was not present. Any possible SP potential was included to the duration of the atrial electrogram.

An independent, with respect to the mode of randomization blinded individual (R.R.), was involved into the selection of the first target sites after the first 60 patients in order to avoid a potential bias. This person guided the selection of target sites according to the anatomic and electrophysiologic criteria mentioned earlier in the text whenever the operator indicated that a stable catheter position was achieved.

**STS.** Subthreshold stimulation was applied at selected target sites after induction of AVNRT with direct current pulses of 5 s duration as previously described (14). Pulses were delivered in a unipolar mode via the distal electrode of the ablation catheter using a commercially available stimulator (Dr. Rissel, Datteln, Germany). Each application had a constant power output level starting with 1.0 mA. From one pulse to the next pulse, current strength was increased in stepwise fashion with increments of 1.0 mA. The stimulation protocol was stopped at one selected target site when a power output of 5.0 mA was applied or catheter dislocation was noted. The protocol was also interrupted when AVNRT was terminated and in case of junctional escape rhythms or atrial or ventricular ectopic beats (14). After STS, local electrogram recordings and the surface electrocardiogram were carefully investigated with respect to any evidence for inadvertent capture. A maximum of seven

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**Table 1.** Distribution of Demographic Parameters and Tachycardia Cycle Length

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 50)</th>
<th>Group B (n = 50)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>52.6 ± 15.2</td>
<td>52.3 ± 14.0</td>
<td>0.7884</td>
</tr>
<tr>
<td>Women (n)</td>
<td>42</td>
<td>41</td>
<td>NS</td>
</tr>
<tr>
<td>Heart disease (n)</td>
<td>3</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>AVNRT cycle length (ms)</td>
<td>361.2 ± 60.7</td>
<td>370.1 ± 63.7</td>
<td>0.1881</td>
</tr>
</tbody>
</table>

AVNRT = atrioventricular nodal re-entrant tachycardia.
selected target sites were investigated with STS. Radiofrequency current was only applied when a selective block of the SP was observed or when the tachycardia did not terminate despite the mapping of seven different posteroseptal to midseptal sites.

**RFC ablation.** The RFC-generator HAT 300 (Dr. P. Osypka, Grenzach-Whylen, Germany) was used for ablation. The catheter tip temperature was preselected at 60°C to 65°C with a power output of up to 50 W for 60 s. Radiofrequency current application was initiated during sinus rhythm and continued when junctional escape beats were observed. The applications were discontinued automatically in case of sudden rises in impedance. Furthermore, the energy delivery was interrupted immediately when catheter dislocation, AV block or retrograde ventricular atrial block during junctional rhythms was observed. Non-inducibility of AVNRT during programmed atrial stimulation was defined as the end point of the ablation session. Isoproterenol was not required for the induction of AVNRT in any patient before ablation and was, therefore, also not used after the procedure.

**Data analysis.** Continuous data are expressed as mean ± SD or as median. Variables were compared by the Wilcoxon signed-rank test. A p value < 0.05 was considered significant. Statistical analysis was performed using commercially available computer software (SPSS, SPSS Inc., Chicago, Illinois).

**RESULTS**

Before ablation, the mean tachycardia cycle length of induced AVNRT of the common type was not different between patients of group A (361.2 ± 60.7 ms) and group B (370.1 ± 63.7 ms) (Table 1).

**Local electrogram characteristics.** The local electrogram characteristics at the first selected target site for STS or RFC ablation of both groups are depicted in Table 2. No significant differences were observed with respect to the duration (66.7 ms ± 14.9 ms vs. 68.9 ms ± 12.0 ms) and amplitude of the atrial signal (6.1 mV ± 3.5 mV vs. 6.0 mV ± 3.4 mV). Similarly, the amplitude of the ventricular electrogram (32.5 mV ± 14.6 mV vs. 32.9 mV ± 17.3 mV) and the AV ratio (0.23 mV ± 0.18 mV vs. 0.23 mV ± 0.15 mV) were not different between the two groups.

Presumable SP potentials according to the criteria mentioned in the preceding text were observed in the majority of initial target sites in both groups (66% group A vs. 70% group B).

**STS mapping.** Long-duration direct current pulses of STS were applied at a mean number of 2.57 ± 1.88 posteroseptal to midseptal target sites. Termination of AVNRT attributed to selective block of the SP was observed after 1.96 s ± 1.37 s of STS in 47 of 50 patients (94%). Subthreshold stimulation with mean current strength of 2.80 mA ± 1.06 mA was delivered at the time of tachycardia termination. A discrete prolongation of the tachycardia cycle length (20 to 50 ms) due to an increase of the A-to-H interval occurred before the termination in 16 patients (Fig. 1). Additionally, a block within the retrograde conducting fast pathway during STS without prior cycle length alteration was noted in two patients (one midseptal and one posteroseptal localization). In these two patients, endocardial mapping, including STS, was continued until selective block of the SP was obtained. In three patients, AVNRT could not be terminated by STS despite mapping of seven posteroseptal to midseptal target sites.

**RFC ablation.** The parameters of the ablation procedure are summarized in Table 3. After RFC ablation, AVNRT was rendered noninducible due to SP ablation in all patients of both groups. A significantly lower number of 1.6 ± 1.3 pulses was required in group B as compared with 3.9 ± 3.4 applications in group A (p = 0.0003). Single RFC applications were delivered for ablation of AVNRT in 35 of 50 group B patients (70%) but only 10 of 50 patients of group A (20%). Successful RFC applications were always accompanied by the induction of junctional escape beats. Termination of AVNRT by STS-induced block of the SP was also indicative of the successful ablation site in patients requiring multiple applications. In these 15 patients, the initial application was always interrupted prematurely due to catheter dislocation induced by junctional escape beats. A subsequent application of one or more RFC pulses at the same site resulted in successful abolition of AVNRT in all cases. Distribution of successful posteroseptal to midseptal sites was well-balanced between both groups (Fig. 2).

No inadvertent fast pathway interruption or permanent high-degree AV block was induced in any patient of this cohort. Four patients experienced a transient high-degree AV block (two in group A and two in group B). In three patients, this effect persisted for less than 30 s but was sustained for 4 h in one patient in group A.

Despite the additional STS mapping in group B, the mean procedure duration of this group was shorter than those observed in group A (156.9 min ± 33.5 min vs. 173.2 min ± 49.7 min, p = 0.0221) (Table 3). However, there was no statistically significant difference with respect to the mean fluoroscopy duration.

Additionally, in the second phase of the study (after the first 60 patients), the mean number of RFC pulses required for successful SP ablation was significantly lower in group B (1.4 ± 0.85) than in group A (4.1 ± 2.8; p = 0.0254), whereas procedure duration (group A: 151.2 ± 33.3; group

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Table 2. Local Electrogram Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 50)</th>
<th>Group B (n = 50)</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Duration A (ms)</td>
<td>66.7 ± 14.9</td>
<td>68.9 ± 12.0</td>
<td>0.5997</td>
</tr>
<tr>
<td>Amplitude A (mV)</td>
<td>6.1 ± 3.5</td>
<td>6.0 ± 3.4</td>
<td>0.8307</td>
</tr>
<tr>
<td>Amplitude V (mV)</td>
<td>32.5 ± 14.6</td>
<td>32.9 ± 17.3</td>
<td>0.9601</td>
</tr>
<tr>
<td>AV ratio</td>
<td>0.23 ± 0.18</td>
<td>0.23 ± 0.15</td>
<td>0.8611</td>
</tr>
</tbody>
</table>

A = atrium; V = ventricle.
B: 138.6 ± 23.7) and fluoroscopy time (group A: 13.4 ± 7.7; group B: 11.1 ± 4.5) tended to be lower in group B without reaching statistical significance.

Follow-up. Recurrence of AVNRT was observed in one patient of each study group. Both patients underwent repeat successful ablation in a second procedure. The other patients (98%) remained free of AVNRT episodes during a follow-up period of 16.5 ± 6.3 months.

DISCUSSION

Main findings. In this study, the conventional approach for SP ablation has been compared for the first time in a randomized fashion to a novel mapping strategy using STS. The STS-guided mapping technique led to a significant reduction of RFC-pulses required for abolition of recurrent AVNRT without prolongation of the X-ray exposure time. The average procedure duration tended to be shorter in patients assigned to the ablation strategy oriented on STS. These main findings were similar in the second phase of the study when an individual blinded with respect to the randomization protocol was involved in the decision about the first target site. Additionally, the characteristics of local electrograms recorded at these sites were comparable between both groups. A sustained high-degree AV block was not observed in any of the patients irrespective of the mode of mapping. The results indicate that the introduction of the STS maneuver may help to further improve the efficacy of the conventional technique for SP ablation.

Table 3. Parameters of the Ablation Procedure

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 50)</th>
<th>Group B (n = 50)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFC pulses</td>
<td>3.9 ± 3.4</td>
<td>1.6 ± 1.3</td>
<td>0.0003</td>
</tr>
<tr>
<td>X-ray duration (min)</td>
<td>16.9 ± 10.6</td>
<td>14.1 ± 8.7</td>
<td>0.1278</td>
</tr>
<tr>
<td>Procedure duration (min)</td>
<td>173.2 ± 49.7</td>
<td>156.9 ± 33.5</td>
<td>0.0221</td>
</tr>
<tr>
<td>Transient AV block (n)</td>
<td>2</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Permanent AV block (n)</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>

AV = atrioventricular; RFC = radiofrequency current.

The STS-guided mapping technique led to a significant reduction of RFC-pulses required for abolition of recurrent AVNRT without prolongation of the X-ray exposure time. The average procedure duration tended to be shorter in patients assigned to the ablation strategy oriented on STS. These main findings were similar in the second phase of the study when an individual blinded with respect to the randomization protocol was involved in the decision about the first target site. Additionally, the characteristics of local electrograms recorded at these sites were comparable between both groups. A sustained high-degree AV block was not observed in any of the patients irrespective of the mode of mapping. The results indicate that the introduction of the STS maneuver may help to further improve the efficacy of the conventional technique for SP ablation.

Although SP ablation has been established as the method of choice for transcatheter RFC-ablation of AVNRT, this treatment still carries a low, but definite, risk of major complications (1–9). Complete interruption of the AV node is the most severe undesirable adverse effect of this procedure. The incidence of inadvertent permanent AV block varies between 1% and 2% according to large retrospective (11) and recent prospective multicenter studies (12). Cath-

Figure 1. Subthreshold stimulation (STS) during atrioventricular nodal re-entrant tachycardia at a posteroseptal mapping position. After induction of sustained atrioventricular nodal re-entrant tachycardia (cycle length: 395 ms), STS is applied for 5 s (see arrows). The tachycardia is interrupted due to selective block within the slow anterograde pathway after 1.5 s, and normal sinus rhythm is established. Please note that no apparent capture is visible at surface electrocardiogram or intracardiac recordings. The termination of the tachycardia is preceded by discrete prolongation of the cycle length from 395 to 430 ms. This is suggestive of the slowing of conduction within the slow pathway because the A-to-H interval, but not the H-to-A interval, is prolonged. CSdis = coronary sinus, distal; CSprox = coronary sinus, proximal; HBE = His bundle electrocardiogram; HRA = high right atrium; MAP = mapping catheter; RVA = right ventricular apex.
Mechanism of STS-induced tachycardia termination. The effect of STS on cardiac conduction properties has been investigated in several previous studies. Nevertheless, the exact underlying mechanism of this phenomenon has not been completely elucidated thus far. Experimental studies have shown that cellular refractoriness and excitability can be modulated by local application of low-level direct-current pulses (16–18). Studies in isolated neural tissue suggested that the effects of STS are mediated by electronic impulse propagation (18). Interruption of ventricular tachycardia due to STS applied to critical components of the re-entrant circuit was demonstrated in an experimental model including dogs with remote myocardial infarction (19). Endocardial mapping showed that slowing of conduction velocity and local conduction block were responsible for this phenomenon. Prolongation of the conduction time within the SP is also a potential mechanism for termination of AVNRT. This is underlined by a discrete increase of the atrium (A) to His (H) interval before the termination, while the HA interval remains stable. In 16 patients of this study, this phenomenon was observed. This finding reflects that the conduction capacity of the SP can be selectively modulated by STS without influencing fast pathway conduction. STS-guided mapping in AVNRT. The ability of STS to induce tachycardia termination to ventricular and supraventricular re-entrant tachycardias has been previously demonstrated in the clinical setting. This includes ventricular tachycardia after myocardial infarction (20) as well as orthodromic tachycardia (21,22) involving accessory pathways and AVNRT (13). Fromer and Shenasa (13) initially showed that trains of STS delivered to various right atrial sites were able to interrupt AVNRT. This was mainly attributed to conduction block within the slow antegrade pathway, but interruption of the fast retrograde pathway has also been observed (13). Nonetheless, no detailed analysis and characterization of these effects was possible because no endocardial mapping was performed. Encouraging attempts to introduce this method as an additional tool to guide endocardial mapping of accessory pathways (22) and AVNRT (14) followed these studies. The effects of STS applied to target sites chosen for SP ablation were correlated with the results of subsequent RFC application in a recent study (14). Atriointerventricular nodal re-entrant tachycardia was terminated due to selective block within the SP in 15 of 18 patients. It could be demonstrated that STS-induced tachycardia termination is a highly predictive and sensitive marker for successful SP ablation in patients with AVNRT. In this study, AVNRT was terminated due to STS applied to the region of the SP in 94% of all patients. Furthermore, the presumed benefit with respect to a reduction of RFC pulses could be demonstrated in patients assigned to the STS-guided approach. Previous studies have shown that fast pathway conduction can also be modified by STS. In two cases in this study, AVNRT was interrupted by STS-induced block within the retrograde fast pathway despite application to the postero-septal region of the presumed SP. Mapping was continued until STS produced block within the SP, and RFC subsequently abolished AVNRT due to selective SP ablation at these sites. Thus, in these cases, inadvertent fast pathway ablation or induction of a high-degree AV block may have been avoided by STS mapping. However, due to the expected low incidence of inadvertent high-degree AV block, no benefit of the STS-guided approach could be demonstrated with respect to this parameter in this study. Study limitations. Not all patients with recurrent AVNRT are amenable to the STS-guided strategy because sustained and reproducible inducibility is a prerequisite for this approach. Fortuitous termination of AVNRT may have
been occasionally present and cannot be completely ruled out. However, this is not likely to be the general rule because all patients had sustained AVNRT without previously observed spontaneous termination. Furthermore, this effect of STS applied to the region of the SP has been well-described in previous studies (13,14,22). An unintended bias during the selection of target sites favoring the STS method may have been present in the initial phase of the study. However, a third person performed the randomization, and the main results, such as the number of required RFC-pulses, were consistent in the second phase of the study. Furthermore, the local electrogram characteristics at the first target site were similar between both groups.

Conclusions. Subthreshold stimulation-guided mapping is a novel tool for the detection of target sites for SP ablation in patients with reproducibly inducible and sustained AVNRT. The technique helps to reduce the number of RFC pulses required for SP ablation without an increase of fluoroscopy time or procedure duration. Thus, this method can be used as an adjunctive criterion during endocardial mapping before SP ablation in order to further improve the efficacy of this approach.

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REFERENCES