Paroxysmal reciprocating supraventricular tachycardia in infants: electrophysiologically guided medical treatment and long-term evolution of the re-entry circuit

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Aims The aim of this study is to evaluate the long-term prognosis in infants affected by paroxysmal reciprocating supraventricular tachycardia (SVT), to identify predictors of SVT disappearance, and to assess the efficacy of electrophysiologically guided drug therapy in preventing recurrences.

Methods and results A six step regimen of oral therapy was used in 55 infants with SVT: (i) propafenone (P); (ii) flecainide (F); (iii) flecainide plus propranolol (FP); (iv) amiodarone (A); (v) amiodarone plus propranolol (AP); (vi) amiodarone plus flecainide plus propranolol (AFP). If one step was not successful, the patient was passed on to the next treatment step and so on. Transesophageal atrial pacing (TAP) was used to evaluate treatment efficacy and the evolution of SVT at the end of the first, second, and third year. Propafenone was successful in 32.7% of the patients, F in 14.5%, FP in 23.6%, A alone in 5.4%, and AP in 18.1%; only 7.2% reached step 6. At month 12, after therapy wash out, SVT recurred spontaneously in 2 patients (3.6%) and remained inducible in 25 (45.5%). Inducibility was significantly higher in patients treated with A. At 24 months, SVT was inducible or spontaneous in 86% of the cases and at 36 months in 87%. There were no recurrences using the treatment confirmed by TAP. No further predictor of SVT inducibility was identified.

Conclusion Supraventricular tachycardia disappeared in ~50% of the patients during the first year of life and in another 20% thereafter. The necessity for A treatment is the only predictor of persistence of the re-entry circuit during the first year of life. Transesophageal atrial pacing is useful in guiding the medical treatment.

Introduction

Paroxysmal reciprocating supraventricular tachycardia (SVT) is the most common tachyarrhythmia during the first year of life. At this age, it can cause severe symptoms and heart failure.1–3

Transesophageal atrial pacing (TAP) is the easiest and most accurate method used to induce and show the presence and electrophysiological mechanism of SVT. In neonates and infants, TAP can be safely performed and repeated. Therefore, it may be useful in assessing the effectiveness of treatment used in the prevention of SVT recurrences or in evaluating the evolution of a re-entry circuit later on.4–6

Over the past 20 years, some authors have reported the electrophysiological development of SVT during the first year of life.7–12 Nevertheless, none of them analysed the electrophysiological development of re-entry circuits after the first year of life. Also, there are no reports of electrophysiological guided pharmacological therapy in infants affected by SVT.

The objectives of our study were to evaluate the long-term prognosis in neonates and infants affected by SVT, to analyse the development of the electrophysiological characteristics of the re-entry circuit, to identify the predictive factors regarding its disappearance during the first 3 years of life, and to assess the effectiveness of an electrophysiologically guided drug therapy in preventing SVT recurrences.
Methods

Study population

Between 1990 and 2004, 55 infants, without structural heart disease, were referred to our department for diagnosis and treatment of SVT. This latter was defined as tachycardia with a normal or aberrant QRS complex, 1:1 AV conduction in the absence of ECG features of atrial flutter/fibrillation, atrial tachycardia and junctional or ventricular tachycardia. Incipient reciprocating tachycardias, as permanent junctional reciprocating tachycardia, were excluded from the study. Normal heart anatomy was confirmed by physical examination, ECG, chest X-ray, and cardiac ultrasound.

Treatment protocol

An antiarrhythmic six step oral therapy was administered to all infants in order to prevent SVT recurrences.

The treatment steps were as follows: (i) propafenone (starting with 10 mg/kg/day and increasing the dose by 5 mg up to 20); (ii) flecainide (starting with 3 mg/kg/day and increasing the dose by 1 mg up to 5); (iii) flecainide plus propranolol (starting with 1 mg/kg/day and increasing the dose by 1 mg up to 3); (iv) amiodarone (loading dose for 7 days: 10–25 mg/kg/day, starting with 10 mg/kg/day and increasing the dose by 5 mg up to 25); (v) amiodarone plus propranolol; (vi) amiodarone plus flecainide plus propranolol.

After diagnosis, using transesophageal atrial pacing or recording, each patient was treated according to the above schedules. During each step, in the event of SVT recurrences or inducibility, the dosage of the drugs used was progressively increased as indicated above. However, if one step was not successful, even at the maximum dosage, the patient was passed on to the next treatment step and so on.

In the infants who received combined treatments (flecainide plus propranolol, amiodarone plus flecainide, or amiodarone plus flecainide plus propranolol), the dosages of the drugs administered were initially reduced to the lowest level indicated above and then progressively increased to prevent toxic effects related to the drugs’ interactions.

Oral treatment was considered effective only if spontaneous episodes did not recur and if SVT was not inducible during TAP, after five half-lives of the drugs used or after the loading dose was complete.

Initial transesophageal studies

All transesophageal recordings or pacing were performed in all patients at the infant’s bedside and without sedation for initial evaluation of the electrophysiological characteristics of SVT and for the analysis of the effectiveness of the medical treatment.

Before the transesophageal study, infants were fasted for at least 2 h. Written informed consent was obtained from the parents of each infant. A silicone rubber-coated 6 Fr catheter with interelectrode spacing of 10 mm (Esokid-Fiab) was used for recording the pharyngeal electrogram.13

With the use of an ECG machine (HP pagewriter Xli), a bipolar esophageal electrogram was recorded during both sinus rhythm and tachycardia. Records were obtained at recording speeds of 25 and 50 mm/s. Low- and high-frequency filters were, respectively, 0.5 and 40 or 100 Hz.

A custom-made programmable stimulator (Sep 3, CB-Bioeletronica and then 8817, FIAB, Florence, Italy) that delivered constant-current square-wave pulses was used for the stimulation studies. Atrial pacing threshold was determined by the use of a stimulus duration of 10 ms. To ensure consistent atrial capture, subsequent stimulation was performed with a current of 25–50% higher than threshold.

Atrial overdrive pacing and atrial extrastimulation with single, double, and triple extrastimuli were performed for inducing SVT.

During tachycardia, five measurements each of cycle length, ventricular-atral (VA) interval (onset of ventricular depolarization to rapid deflection on the esophageal atrial waveform), were averaged and then a burst (two to eight stimuli) at cycle lengths of 10–80 ms shorter than the tachycardia cycle length was used to restore sinus rhythm.

Three-year follow-up

After an effective treatment was identified, each infant was discharged and monitored as an outpatient, with weekly clinical evaluations and surface ECGs. During these clinical checkups, the dose of the drugs was progressively increased according to the patients’ weight, except for amiodarone, whose loading dose was never changed but which decreased (‘maintenance dose’) due to the increasing weight of the patient treated until a stable dosage of 5–7 mg/kg/day was reached. A 24 h dynamic ECG was performed every 3 months up to the end of the first year of life.

At the end of the first year of life, drug therapy was discontinued in all patients. Then a TAP, in general anaesthesia, at a base-line condition and during isoproterenol iv infusion (infusion rates: 0.01–0.04 μg/kg/min), was performed to test inducibility of SVT after at least five half-lives of the drugs used or, in case of treatment with amiodarone, 45 days after its termination. In patients with non-inducible SVT, medical therapy was ceased, whereas in patients with spontaneous or still inducible SVT, drug therapy was resumed.

The same management was performed at the second and the third year of life.

Long-term follow-up

After the first 3-year follow-up period, all children with still inducible SVT were evaluated clinically and by ECG every 6 months. The dosage of the drugs was progressively increased according to patients’ weight and a 24 h ECG Holter monitoring was performed every year. All patients, who remained without therapy during the 3-year period, were contacted by phone on a yearly basis.

Statistical methods

Differences between means were tested using Student’s t-test after checking continuous variables for normality with the Kolmogorov-Smirnov test.

Comparisons among repeated measures were performed with appropriate one-way ANOVA, testing post hoc differences between paired observations with the Bonferroni test.

For categorical variables, Fisher’s exact test was performed. Disappearance was described with rates (event/person-time).

Persistence of arrhythmic events was depicted by the Kaplan-Meier curve, with the time to spontaneous recurrence or inducibility as the outcome variable; when SVT did not recur or was not inducible at the end of a 12-months interval, disappearance was estimated to have occurred at the midpoint.

The significance level was set at $P = 0.05$. STATA (version 7.0) software was used.

Results

There were 37 males and 18 females. The mean age of SVT onset was 19.6 days (SD 28.5, median 10, range 1–145 days), whereas the mean age at the time of admission to our department was 33.3 days (SD 37.2, median 25, range 1–165 days). At the time of initial evaluation, 17 patients (30.9%) had congestive heart failure and 29 (52.7%) showed ECG evidence of ventricular pre-excitation.
Initial transesophageal study

**SVT rate**

In the 55 infants who underwent transesophageal recording during SVT, the mean heart rate was $280 \pm 32$ beats/min (median 280, range 200–350 beats/min). The SVT rate recorded was not significantly different between males and females, between patients with heart failure and without, and between patients with and without Wolff-Parkinson-White (WPW) syndrome (Table 1).

**VA interval**

During SVT, in the 55 infants examined, the mean VA interval was $104 \pm 30$ ms (median 100, range 35–185 ms). The VA interval was not significantly different between males and females, between patients with heart failure and without, and between patients with WPW and without (Table 1).

**Medical treatment**

Eighteen patients (33%) out of 55 were successfully treated with propafenone. Among the remaining 37 patients, only 8 (21%) responded to flecainide. In the other 29 patients, the combination of flecainide and propranolol was started and was successful in 13 (45%). In the other 16 refractory patients, amiodarone was attempted but was successful only in 2 (12%). The association of amiodarone and propranolol was administered to the remaining 14 patients and was successful in 10 (71%). The other 4, refractory to this association, reached step 6 of the therapy.

Before each baby could be discharged from hospital, it took an average of $23 \pm 10$ days.

**Follow-up study**

**Twelve months**

SVT recurrences were not detected at home during the first year of life, while the patients were receiving the therapy found to be effective by transesophageal stimulation protocol. After therapy wash out, SVT recurred spontaneously in 2 patients (3.6%) and remained inducible in 25 (45.5%). In 28 patients (50.9%), SVT could not be induced (Figure 1).

SVT rate at 12 months in inducible patients was $257 \pm 41$ vs. $283 \pm 32$ at presentation in the absence of therapy ($P = 0.001$), and VA was $100 \pm 20$ ms vs. $94 \pm 23$ ($P = 0.08$). Inducibility was significantly higher in patients treated with $\geq 3$ steps of therapy (33.4 vs. 78.6% in patients with $<3$ steps, $P = 0.01$).

**Twenty-four months**

During the second year of observation, one patient could no longer be followed up. Four additional patients could not be subjected to TAP due to lack of parent consent.

Among the remaining 22 patients, none of these had SVT recurrences detected at home but, after therapy wash out, SVT recurred spontaneously in 2 cases (9.1%), was still inducible in 17 (77.3%) and not inducible in 3 (13.6%) (Figure 1).

SVT rate in inducible patients was $245 \pm 35$ vs. $266 \pm 41$ of the preceding observation (NS), and VA was $102 \pm 33$ vs. $92 \pm 23$ (NS).

**Thirty-six months**

During the third year of observation, two patients could no longer be followed up and two could not undergo TAP due to lack of parent consent.

Among the remaining 15 patients, none had SVT recurrences detected at home and, after therapy wash out, no SVT recurred spontaneously, however it remained inducible in 13 (86.6%) and not inducible in 2 (13.4%) (Figure 1).

SVT rate in inducible patients was $247 \pm 28$ in comparison to $242 \pm 30$ (NS) observed at 24 months, and VA was $98 \pm 34$ vs. $98 \pm 33$ (NS).

**Analysis of short-term follow-up**

For each baby, an average of $3.5 \pm 2.4$ TAP was performed at presentation and 1 TAP at each yearly control. Only two hospital days for each baby were necessary for the evaluation at 12, 24, and 36 months of age.

The use of TAP did not cause side effects.

Gender, presence of heart failure or WPW during the initial evaluation did not correlate with SVT inducibility at 1, 2, and 3 years of follow-up.

SVT inducibility was significantly lower at 12 months (47.2%) than at 24 months (85%) and 36 months (86.6%—$P = 0.004$ and 0.008, respectively).

The analysis of disappearance of SVT (spontaneous or inducible) is represented in Figure 2.

Many patients were free of inducibility or did not have spontaneous SVT recurrences at the end of the first year

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### Table 1 Heart rate (beats/min) and VA (ms) gender and clinical characteristics comparison

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
<th>Heart rate (mean ± SD)</th>
<th>P</th>
<th>VA (mean ± SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>37 (67.3)</td>
<td>278.8 (29.8)</td>
<td>NS</td>
<td>109 (27.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Females</td>
<td>18 (32.7)</td>
<td>282.2 (93.3)</td>
<td></td>
<td>93.3 (33.5)</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17 (30.9)</td>
<td>281.5 (27.7)</td>
<td>NS</td>
<td>103.8 (22.2)</td>
<td>NS</td>
</tr>
<tr>
<td>No</td>
<td>38 (69.1)</td>
<td>279.2 (33.7)</td>
<td></td>
<td>103.8 (33.3)</td>
<td></td>
</tr>
<tr>
<td>WPW</td>
<td></td>
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<tr>
<td>Yes</td>
<td>29 (52.7)</td>
<td>283.7 (24.2)</td>
<td>NS</td>
<td>107.7 (26)</td>
<td>NS</td>
</tr>
<tr>
<td>No</td>
<td>26 (47.3)</td>
<td>276.6 (37.8)</td>
<td></td>
<td>100.2 (33.4)</td>
<td></td>
</tr>
</tbody>
</table>

SD, standard deviation; NS, not significant.
(time of disappearance was attributed at half period) (Figure 2); the rate of disappearance was 0.28 × year (95% CI 0.20–0.39). This analysis was restricted to the first 3 years after birth, because most events (disappearance of abnormality) occurred in this period, but recurrence is a possibility in the long term.

Analysing the 13 patients in whom SVT was inducible during the 3-year follow-up, no significant difference among VA intervals was observed (ANOVA, $P = 0.9$), whereas RR intervals varied significantly during the follow-up period (ANOVA, $P = 0.005$), particularly between 24 months and presentation and between 36 months and presentation ($P = 0.02$ and 0.008, respectively), but not between presentation and the first point of follow-up at 12 months ($P = 0.2$) (Figure 3).

**Clinical long-term follow-up**

During long-term follow-up (mean duration: 104.3 months; SD: ± 40.7; median 101) of patients in whom SVT disappeared during the first 3 years of life, only in one patient, who showed signs of ventricular pre-excitation during the first observation, but which disappeared together with SVT during the first year, ventricular pre-excitation reappeared on an ECG at 9 years of age. A TAP, performed at that time, showed reinducibility of SVT.

All patients, except one, in whom SVT remained inducible at the end of the 3 years of electrophysiologically guided treatment protocol, did not discontinue therapy. The medical treatment, judged effective during the initial evaluation, was never changed in all patients and SVT was never detected at home. At the present, nine patients underwent radiofrequency transcatheter ablation (RFTA) at an average age of 7 ± 2 years. All RFTA were successful.

**Discussion**

SVT is the most common tachyarrhythmia in neonates and infants. It may disappear during the follow-up period and

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**Figure 1** Flow chart of patients with reciprocating SVT (FU, follow-up).
predictors of recurrences are masculine sex, WPW syndrome, or first episode at <4 months.1,3

The variations in frequency of spontaneous episodes of SVT may be due to observed developmental changes in the electrophysiologic properties of accessory connections8 and it may relate to chronological variations in frequency and type of initiating events.6 Therefore, the documented decrease in the spontaneous occurrence of atrial extrasystoles14 during the first year of life may play a role in the reported decrease in SVT recurrence after this period.7

Benson et al.8 reported that, using TAP, SVT could be reinitated at 12 months of age in 68% of the patients in whom SVT, using an accessory AV connection, had been previously evaluated by TAP during the first 2 months of life and that changes in anterograde conduction and retrograde conduction (an increase of the VA interval) of the accessory AV connection can be observed. Moreover, the persistence of a delta wave was correlated with the persistence of SVT. This finding was confirmed by Tortoriello et al.12 Only Etheridge and Judd11 suggested that, at this moment, there are no data observed at presentation or detected during the initial esophageal study that can effectively predict the clinical course of an SVT.

Our study is the first one where patients with SVT were studied with TAP during the first 3 years of life. This technique was used to guide medical treatment and to evaluate
the development of the electrophysiological characteristics of the re-entry circuit. In our study population, similarly to the Benson study, SVT (spontaneous or inducible) recurred in ~50% of the patients at 12 months of age with a significant reduction of the heart rate. Because previous reports have shown that a negative TAP may have an excellent predictive value,15,16 contrarily to other studies, we can also claim that the re-entry circuit can disappear further, at least electrophysiologically, in ~20% of patients during the second year of life and in another 10% of cases in the third year of age.

Moreover, our data demonstrate that the SVT rate and VA interval during the initial evaluation, as well as SVT recurrences, spontaneous or induced, during the first three years of age, were not significantly different between males and females, among patients with or without heart failure, and among those with or without WPW at the moment of the initial evaluation. The only significant factor found to predict the persistence of a re-entry circuit after the first year of age was an SVT which was refractory to I C class antiarrhythmic drugs, alone or associated with propranolol. In fact, SVT inducibility was significantly higher in patients treated with ≥4 steps of therapy. This finding could depend on the presence of a larger and consequently more malignant accessory pathways, resistant to apoptosis, that are inactivated only by a medical treatment, effective on several electrophysiological mechanisms.

This hypothesis could be further validated by two previous studies, which assessed the risk of SVT recurrences in pediatric patients with WPW syndrome.9,12 One study showed that patients requiring ≥2 medications to maintain sinus rhythm were at an increased risk of SVT recurrences.7 Torriello’s study12 showed an increased risk of recurrences in infants who were on antiarrhythmics, in addition to digoxin and/or propranolol when compared with those who were on digoxin and/or propranolol only.

In our study, the electrophysiologically guided follow-up of the 13 patients in whom SVT was always inducible showed that in those patients, during the 3-year follow-up, there were significant changes in tachycardia cycle length but not in VA interval. This lead us to conclude that in patients in whom the electrophysiologic properties of the anomalous pathways do not change with time, the susceptibility to both inducible and/or spontaneous SVT remains the same. This is also in accordance with the data reported by Benson et al.8 Moreover, our data showed that nearly 3% (1/33) of patients with an SVT, which was no longer inducible by the end of the first year of life, showed a tachycardia that may recur during the long-term follow-up and in particular at the end of the first decade of life. This finding signifies that, in a few cases, the accessory pathway may become only electrophysiologically silent in the first years of life. This pathway may then become active again when important changes in the electrophysiologic properties of the growing heart take place.

Medical therapy appears to be effective and safe in infants with SVT and radiofrequency ablation has been reserved for infants who failed to respond to aggressive medical regimens or in particular situations such as ventricular dysfunction, severe symptoms, or complex congenital heart disease.8,10,12,17–19

In our study, the electrophysiologically guided medical treatment was always effective in preserving patients from SVT recurrences. Using our treatment protocol, SVT never recurred at home during the first 3 years of life, when symptoms tend to be more difficult to recognise by parents. Propafenone was the first-step drug in our protocol because of its safety and efficacy as was demonstrated in one of our previous experiences. Digoxin was excluded, on the other hand, for its already demonstrated failure in the treatment of SVT in infants.10,21 Beta blockers were not used alone as first choice treatment because we prefer to change conduction and refractoriness of the anomalous pathway, especially if manifest, rather than change conduction and refractoriness of the AV node.

If we analyse the results of our treatment protocol, it is very difficult to establish which is the most effective treatment. However, it appears reasonable to initiate treatment with flecainide and, in case of failure, to then add propranolol. This treatment, in fact, was effective in 56% of our patients refractory to propafenone.

Radiofrequency transcatheter ablation, in the long-term follow-up, was used in nine patients (~16% of the study population). In all these cases, the indication was the parents’ choice. This further confirms the long-term effectiveness of the treatment selected as the most successful after the initial episode.

Limitations of the study

This study has several limitations. First, it is not a controlled study. Therefore, it is a single arm study with no placebo comparison. Secondly, we did not determine the serum concentrations of the drugs used. Therefore, even if the drugs were used at increasing doses in case of failure, we were unable to determine if the drugs had reached the therapeutic range.

Thirdly, our comparisons may suffer from limited power, due to the small number of patients, and ‘negative’ conclusions based on a 0.05 significance level can be questioned.

Conclusion

In conclusion, SVT, occurred in neonatal age or in infancy, disappears, at least electrophysiologically, in half of the cases during the first year of life and can disappear altogether thereafter. Only in very few cases, SVT, no longer inducible in the first 3 years of life, can recur in the long-term follow-up. The necessity of the use of amiodarone, alone or in combination with other antiarrhythmic drugs, is the only factor able to predict the persistence of the re-entry circuit in the first year of life. Moreover, during this period, the cycle length of the re-entry circuit significantly increases due to the increase in AV nodal conduction time and the lack of developmental changes in the electrophysiologic properties of the accessory pathway can determine the susceptibility to SVT recurrences. The electrophysiologically guided drug therapy is very safe and effective in preventing SVT recurrences in the short- and long-term follow-up.

Conflict of interest: none declared.
References