Clinical research

Heart rate is a predictor of success in the treatment of adults with symptomatic paroxysmal supraventricular tachycardia

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Aims To analyse whether heart rate may affect the efficacy of adenosine, verapamil and carotid sinus massage in terminating symptomatic episodes of paroxysmal supraventricular tachycardia (PSVT) in adults.

Methods and results The study population was selected among 175 adult patients, affected by symptomatic PSVT. One hundred and six of them were considered eligible for the study. Each subject received one of the following treatments: verapamil, 5 mg intravenously (IV) in 5–10 min, followed by 1–5 μg/kg/min; adenosine, 6 mg IV, followed by 12 mg IV after 2–3 min; carotid sinus massage. Adenosine and verapamil were similarly effective in terminating PSVT (74.4% vs 81.8%, \( P = 0.45 \)). The efficacy of carotid sinus massage was significantly lower in comparison with the other two groups (32.4%, \( P = 0.00032 \) vs adenosine and \( P = 0.00044 \) vs verapamil group). At logistic regression, PSVT rate showed a positive association with the percentage of sinus rhythm restoration in the group who received adenosine (\( P = 0.0004 \)). The probability of success in resolving the tachycardia following treatment with adenosine was >75% for heart rates over 166 beats per minute (bpm), but rapidly decreased at lower frequencies, reducing to 25% at 138 bpm. In the verapamil group, PSVT rate was negatively related to the percentage of sinus rhythm restoration (\( P = 0.018 \)). The probability of success in terminating PSVT following administration of verapamil was >75% for heart rates lower than 186 bpm, but tended to decrease at faster rates, reducing to 25% at 241 bpm. No significant effects of heart rate were observed in the carotid sinus massage group (\( P = 0.17 \)). The probability curves obtained in the adenosine and verapamil group crossed at a point corresponding to 173 bpm, which may represent a cut-off value to predict which treatment could ensure higher rate of success.

Conclusions Heart rate predicts restoration of sinus rhythm in adult subjects with symptomatic episodes of PSVT treated with adenosine and verapamil. Adenosine is highly effective in PSVT characterised by fast rates, whereas the efficacy of verapamil is increased in patients with low-frequency PSVT.

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KEYWORDS
Adenosine;
Verapamil;
Vagal manoeuvres;
Heart rate;
Supraventricular tachycardia

Introduction

Paroxysmal supraventricular tachycardia (PSVT) is a common arrhythmia which may be associated to a variety of electrophysiological abnormalities, including increased
Automaticity, triggered activity and re-entry circuits which develop in the atrial myocardium or in the atrioventricular (AV) junction.\textsuperscript{1,2} The general clinical approach to a subject with suspected PSVT includes a brief and targeted history and an accurate analysis of the electrocardiogram (ECG), in the attempt to differentiate PSVT from other narrow-complex tachycardias and to choose the most appropriate treatment.\textsuperscript{6,7} When no haemodynamic instability is present, vagal manoeuvres, adenosine and verapamil are usually considered as the first-line treatment of choice for PSVT,\textsuperscript{8,10} and the relative efficacy of each has been evaluated in many studies.\textsuperscript{11–16}

Both adenosine and verapamil are well known to have a frequency-dependent effect on functional AV-nodal properties,\textsuperscript{17–19} and the rate-dependence of depression in AV-nodal function has been reported to play a key role in the ability of interrupting experimental pacing-induced PSVT.\textsuperscript{20} These findings suggest that the rate of the tachycardia may potentially affect the anti-arrhythmic efficacy of both drugs in spontaneous PSVT. However, whether heart rate could be a predictor of success in the treatment of PSVT in clinical practice has never been analysed.

The aim of this study was to evaluate whether the rate of the tachycardia may predict the restoration of sinus rhythm in the treatment of adult subjects with symptomatic PSVT. The design of the study included two different pharmacological protocols (i.e., adenosine and verapamil) and one non-pharmacological approach (i.e., carotid sinus massage).

**Methods**

**Patient selection**

Male or female adult subjects, affected by symptomatic PSVT, seen at our Department between 11 September, 2000 and 5 February, 2004 were retrospectively enrolled for this study. Patients were considered eligible for the study if they had (1) age $\geq 16$ years, (2) sudden onset of symptoms due to the tachycardia (subjective awareness of palpitations or rhythm irregularity or arrhythmia-related dizziness, chest discomfort, dyspnoea, asthenia, anxiety) and (3) electrocardiographic evidence of PSVT. Exclusion criteria were: haemodynamic instability (which was considered an indication for immediate electrical cardioversion), bradycardia (<50 beats per minute (bpm)); high-grade sinoatrial or AV block, history of sick sinus syndrome or sinus node dysfunction, heart failure (New York Heart Association class III or IV), asthma, previous implantation of pacemaker or defibrillator, use of anti-arrhythmics or rate-limiting drugs within the previous 15 days, contraindications to carotid sinus massage (carotid bruit, history of previous adverse reaction to carotid sinus massage or cerebrovascular accidents in the last three months), hypersensitivity, intolerance or contraindications to verapamil or adenosine.

**Clinical examination and ECG**

All patients underwent an accurate clinical examination and a brief and targeted history. Systemic arterial pressure was determined using standard methods, with a cuff sphygmomanometer, after 3 min of supine position. Measurements were repeated every 3 min throughout the entire procedure. A 12-lead ECG was registered in each subject and electrocardiographic monitoring was maintained until completion of the therapeutic protocol. PSVT was defined as a regular tachycardia with sudden onset, QRS complexes of supraventricular origin (i.e., narrow complexes or wide complexes in the presence of aberrant conduction, previous conduction defects or suspected accessory pathways with no evidence of AV-dissociation) and abnormal non-sinus P waves.

**Study protocols**

On the basis of the general clinical evaluation, each participant in the study underwent one of the following treatments: (1) verapamil, 5 mg intravenously (IV) in 5–10 min, followed by 1–5 $\mu$g/kg/min, based on heart rate and blood pressure; (2) adenosine 6 mg IV, followed by a second dose of 12 mg IV after 2–3 min; (3) carotid sinus massage, applied twice for at least 5 s on each side. Any procedure was terminated in case of success of the treatment or if complications such as severe hypotension (systolic blood pressure <90 mmHg), bradycardia (<50 bpm), atrial fibrillation or flutter, high-degree AV-block or malignant ventricular arrhythmias occurred. Success of the treatment was defined as persistent sinus rhythm restoration, maintained for at least 3 min after the termination of PSVT.

**Statistical analysis**

Data are shown as mean values ± SD for continuous variables. The comparison of normal outcomes among the three study groups was assessed using one-way analysis of variance. Dichotomous variables (i.e., gender and success in terminating PSVT) were compared with use of the $\chi^2$ test. Logistic regression analysis was performed using the maximised log likelihood method, in order to evaluate the effect of PSVT rate on the success of the treatment in each group of study. Regression co-efficients, odds ratios, 95% confidence intervals (CI) and statistical significance were calculated for each treatment. The estimated probability of sinus rhythm restoration was expressed as a function of heart rate using the formula $p = 1 - 1/\left(\exp \left( a + b \cdot HR \right) + 1 \right)$, where $p$ is the probability of success, expressed as a decimal between 0 and 1, $a$ denotes the intercept and the slope of the logistic regression line in each group of study, and HR indicates heart rate. The heart rate values which corresponded to an estimated 25%, 50% and 75% probability of success were determined using the formula $HR = \left( \logit(p) - a \right)/b$, where the expression logit ($p$) indicates the log odds ratio, computed as the natural logarithm of $p/(1 - p)$. To obtain a direct and simplified quantification of changes in the probability of success for any unitary variation in heart rate, a linear approximation was assumed for the adenosine and verapamil curves in the interval between the values of heart rate corresponding to a 25% and 75% probability of success. Linearity in this range was tested by fitting data with use of linear regression analysis, based on the least square method. Parameter estimates, Pearson’s correlation co-efficients and levels of significance of the regression lines were determined in both groups. The significance level was set at 0.05. All statistical tests were two-tailed. The SPSS software (Statistical Package for Social Sciences, Chicago, Illinois, USA) for Windows Release 11.5.0 was used to generate the statistical analyses.

**Results**

**Study population**

One hundred and seventy-five patients met the inclusion criteria. One subject presented severe hypotension and was...
underwent successful DC-shock. In 23 cases, PSVT was associated with type 2 second-grade AV-block (19 with conduction ratio 2:1, one with conduction ratio 4:1 and three with variable ventricular response). Twenty-two subjects were under chronic anti-arrhythmic therapy (eight of which were assuming verapamil, six propafenone, five amiodarone, two sotalol and one diltiazem). Two previously untreated patients were also excluded because one of them had spontaneously taken 300 mg of propafenone and the other 160 mg of verapamil per os at the onset of symptoms. Twenty-one subjects experienced spontaneous termination of PSVT during electrocardiographic monitoring before the beginning of the treatment. One hundred and six patients were then admitted to the study group. Thirty-nine subjects received adenosine, 33 subjects were administered verapamil and 34 underwent carotid sinus massage.

**General features and efficacy of treatment**

The three groups were similar as regards mean age, gender distribution, arterial systolic and diastolic pressures and heart rate (Table 1). The percentages of success in terminating PSVT were significantly different among the three groups ($P = 0.000029$). A similar efficacy of treatment was observed in the group treated with adenosine (74.4%) and among the subjects who received verapamil (81.8%, $P = 0.45$). The percentage of PSVT interruption in the group treated with the carotid sinus massage was consistently lower in comparison with the other two groups (32.4%, $P = 0.00032$ vs adenosine and $P = 0.000044$ vs verapamil group). No significant complications were observed in any subject.

**Effect of heart rate**

Logistic regression (Table 2) showed a significant positive association between heart rate and the probability of PSVT termination in the adenosine group (Fig. 1, top panel). The maximal effect of heart rate was observed in the central portion of the curve, where the slope of the relation assumed its highest values. The estimated probability of success for the treatment with adenosine was $>75$% for heart rates $>166$ bpm, but rapidly decreased at lower frequencies, reducing to 50% at 152 bpm — corresponding to the central inflection point of the curve — and to 25% at 138 bpm. In the range between 138 and 166 bpm, the sigmoidal curve was well approximated by a linear relation ($p = 0.0183 \; HR - 2.2754; \; r = 0.99, P < 0.0001$). This corresponded to an absolute 1.8% decrease in the probability of sinus rhythm restoration for any unitary decrease in heart rate — i.e., for any reduction by one beat per minute in PSVT frequency within that interval.

In the verapamil group, heart rate was negatively associated with the efficacy of the treatment in interrupting PSVT (Fig. 1, middle panel). The estimated probability of success was $>75$% for heart rates $<186$ bpm, but tended to decrease for higher values of frequency, reducing to 50% at 214 bpm and to 25% at a frequency of 241 bpm. Similarly to the adenosine curve, the S-shaped function was well fitted by a linear equation in the range between 186 and 241 bpm ($p = -0.0094 \; HR + 2.5232; \; r = 0.99, P < 0.0001$). This corresponded to an absolute 0.9% reduction in the probability of sinus rhythm restoration for any increase by one beat per minute in PSVT rate.

Although the efficacy of carotid sinus massage showed some tendency to decrease as PSVT frequency increased (Fig. 1, bottom panel), the relation to heart rate was not significant (Table 2). The comparison of the relations obtained in the adenosine and verapamil groups showed that the two curves crossed in a point which corresponded to 173.0 bpm. This represented the value of heart rate at which the two treatments would yield a similar percentage of success in PSVT termination.

### Table 1 General characteristics of the three study groups

<table>
<thead>
<tr>
<th></th>
<th>Adenosine</th>
<th>Verapamil</th>
<th>CSM</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (males/females)</td>
<td>39 (13/26)</td>
<td>33 (10/23)</td>
<td>34 (13/21)</td>
<td>0.78</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56.6 ± 19.0</td>
<td>57.9 ± 16.4</td>
<td>61.6 ± 14.0</td>
<td>0.43</td>
</tr>
<tr>
<td>Systolic arterial pressure (mmHg)</td>
<td>124.4 ± 16.6</td>
<td>132.3 ± 10.5</td>
<td>126.0 ± 21.9</td>
<td>0.13</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mmHg)</td>
<td>78.0 ± 10.5</td>
<td>81.7 ± 8.5</td>
<td>81.1 ± 12.8</td>
<td>0.30</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>172.0 ± 22.5</td>
<td>166.6 ± 29.8</td>
<td>170.6 ± 24.5</td>
<td>0.66</td>
</tr>
</tbody>
</table>

$p$ Values were calculated using analysis of variance or $\chi^2$ test. CSM, carotid sinus massage.

### Table 2 Effect of heart rate on the probability of sinus rhythm restoration in the three groups of study, as evaluated by logistic regression

<table>
<thead>
<tr>
<th></th>
<th>Intercept</th>
<th>$B$</th>
<th>SE</th>
<th>$p$ Value</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>Overall $p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine group</td>
<td>−11.698</td>
<td>0.077</td>
<td>0.028</td>
<td>0.006</td>
<td>1.081</td>
<td>1.023–1.141</td>
<td>0.0004</td>
</tr>
<tr>
<td>Verapamil group</td>
<td>8.546</td>
<td>−0.040</td>
<td>0.019</td>
<td>0.033</td>
<td>0.961</td>
<td>0.926–0.997</td>
<td>0.018</td>
</tr>
<tr>
<td>CSM group</td>
<td>3.087</td>
<td>−0.023</td>
<td>0.018</td>
<td>0.204</td>
<td>0.978</td>
<td>0.944–1.012</td>
<td>0.176</td>
</tr>
</tbody>
</table>

The co-efficients $B$ represent the slopes of the relations between heart rate and the log odds ratio for the probability of success of the treatment in each group of study. The standard error (SE) and the statistical significance of each slope are reported in the table. Odds ratio, 95% confidence intervals (CI) and overall model significance for each study group are also shown. CSM, carotid sinus massage.
Higher rates were then associated with better efficacy of adenosine, whereas lower rates were associated with better efficacy of verapamil (Fig. 2).

Discussion

PSVT is a common clinical condition which may be explained by various pathophysiological mechanisms. Enhanced automaticity, triggered activity or re-entry circuits which develop in the atrial myocardium or in the AV-junction may be responsible for different types of PSVT, although recent observations have suggested that other unknown mechanisms could be involved in some cases with peculiar electropharmacological responses. The most common arrhythmia mechanisms in PSVT are AV-intranodal re-entry, which leads to AV-nodal reciprocating tachycardia, and re-entry by an accessory AV-connection, which produces AV-reciprocating tachycardia. Atrial tachycardia is a less frequent type of PSVT which may be underlied by focal or macro re-entrant mechanisms in different regions of the atrial tissue, whereas other PSVT types are rare. Despite heterogeneity of pathogenesis, contemporary management of PSVT usually follows a general algorithm which initially includes vagal manoeuvres and administration of adenosine or verapamil. Diltiazem, β-blockers, anti-arrhythmics of class Ic and III, pharmacological associations, new selective A1 adenosine receptor agonists currently under clinical investigation, and transoesophageal atrial pacing may also be useful in the treatment or prevention of episodes of PSVT in adults, and immediate electrical cardioversion with DC-shock is recommended in case of haemodynamically compromised patients. Digoxin is the drug of choice for supraventricular tachycardias occurring in foetuses and may be effective in the prophylaxis of recurrences in infants and children, but has a limited role in adults. Transoesophageal and/or endocardiac electrophysiology are often required to determine the exact mechanism of the arrhythmia and radiofrequency catheter ablation is generally indicated in subjects with drug-refractory arrhythmias.

Adenosine and verapamil have been reported to have similar high efficacy in terminating PSVT, with a rate of success ranging from 59% to 100% for adenosine and from 73% to 98.8% for verapamil, according to the dose and mode of administration. Vagal manoeuvres present the advantage of being relatively simple and non-invasive, but their efficacy seems to be quite lower in comparison with pharmacological interventions, with
percentages of PSVT termination ranging from 6% to 22% following carotid sinus massage.16,70–72,75 Our results confirm the evidence that adenosine and verapamil are similarly highly effective in terminating spontaneous episodes of PSVT in adults, whereas carotid sinus massage is able to interrupt tachycardia in a relatively low percentage of cases. However, our data also suggest that the efficacy of both adenosine and verapamil is affected by the frequency of the arrhythmia. Increasing PSVT rates were significantly associated to higher percentages of sinus rhythm restoration following treatment with adenosine (Fig. 1, top panel). In contrast, the efficacy of verapamil in restoring sinus rhythm was inversely related to the frequency of PSVT (Fig. 1, middle panel), and no significant effect of heart rate was observed in the group which had undergone carotid sinus massage (Fig. 1, bottom panel). Of note, the effect of heart rate on the efficacy of verapamil was less in comparison with that observed for adenosine, as shown by the milder steepness of the curve in the plots. However, the comparison of the relations obtained in the adenosine and verapamil groups suggested that 173 bpm could be used as the best cut-off value to predict which treatment may ensure a higher probability of success in restoring sinus rhythm (Fig. 2). Heart rates over this cut-off value may be associated to percentages of PSVT interruption by administration of adenosine, whereas slower frequencies may be associated to better efficacy of verapamil.

Heart rate is known to influence the pharmacodynamic effect of both adenosine and verapamil on the AV-node. It has been shown that the negative dromotropic effect of adenosine tends to increase when the atrial pacing cycle is progressively reduced during experimental PSVT,17 and the rate-dependent conduction slowing seems to be more pronounced for adenosine than for verapamil.19 Adenosine has been demonstrated to increase AV-nodal fatigue — i.e., the AV-nodal delay which slowly develops at fast rates — and to attenuate facilitation — i.e., the tendency of short cycles to improve subsequent nodal recovery — without directly altering AV-nodal recovery, and this may result in frequency-dependent increases in the AV-nodal conduction time and effective refractory period. The substrate of this phenomenon remains to be clarified, although complex interaction among different electrophysiological and molecular mechanisms is likely to be involved. These include a direct effect on the activation of the inward rectifier potassium current I(K, Ado), which produces hyperpolarization and depression in AV-conduction,76 and an indirect effect of antagonism on catecholamine-stimulated adenylate cyclase activity, which occurs through coupling with guanosine triphosphate-binding inhibitory proteins.77,78 A possible alternative ionic mechanism has also recently been proposed, involving a different adenosine-activated, time- and voltage-dependent potassium current defined Ado-I(Kr), which could play a key role in determining nodal depression at lower concentrations of the nucleoside and particularly at fast heart rate.79 Regardless of the exact mechanism underlying these phenomena, our hypothesis is that the enhancement in the negative dromotropic effect and the increase in the effective refractory period of the AV-node which occurs at fast heart rates may play a key role in determining a higher efficacy of adenosine in terminating PSVT characterised by relatively high frequencies.

The efficacy of verapamil in the treatment and prophylaxis of supraventricular tachycardias is due to its ability to produce an inhibition of the inward calcium current I(Ca, L), secondary to the blockage of type L calcium channels, resulting in a rate-dependent prolongation in AV-nodal conduction time and effective refractory period and yielding a decrease in the atrial pacing rate at which AV-Wenckebach occurs.80–85 An adjunctive anti-arrhythmic mechanism of verapamil may be due to the inhibition of the rapid component of the delayed rectifier potassium current I(Kr), which produces a delay in the myocyte repolarisation process and leads to a prolongation of the action potential and effective refractory period.86,88 The rate-dependency of the pharmacological effect of verapamil is probably the result of an interaction among various factors, which may include differential effects on calcium or potassium channels, a large constant time of adaptation due to slow drug-specific association and dissociation kinetic to the calcium channel,18,84,89,90 and a modulating action by the autonomic tone.91,92 A recent study has shown that administration of verapamil in healthy adults leads to a prolongation of the atrial effective refractory period at low frequencies and to a shortening at high frequencies, suggesting a predominant effect on I(Ca, L) at fast rates and a predominant effect on I(Kr) at slow rates.93 The report that I(Kr) may play an important role in the electrophysiological properties of the AV-node94 may suggest the intriguing hypothesis that a predominant effect on the potassium channels, with subsequent increase in the effective refractory period, could exist at slow rates in the AV-nodal tissue and play some role in determining a higher efficacy of verapamil in low-frequency PSVT. The relation among rate-dependent and slowly adaptive pharmacodynamic interaction with calcium channels, differential effects on calcium and potassium channels, and potentially higher efficacy in terminating PSVT in patients with low heart frequencies in comparison with those with high frequencies should be evaluated in further studies.

Limitations of the study

The major limitation of this study is that the design did not include either electrophysiological study or electrocardiographic determination of PSVT types, so that the effect of different electrical patterns in affecting the relationship between heart rate and success of treatment could have not been evaluated. It is well known that different subtypes of PSVT may show unequal responsiveness to anti-arrhythmics, particularly in the case of atrial tachycardia, which does not directly involve the AV-node and tends to show variable sensitivity to nodal blocking agents such as adenosine and verapamil.95,96 However, atrial tachycardia has been reported to be relatively infrequent, accounting for only 5–15% of all PSVTs.97–100 Accordingly, an a posteriori analysis in our
study population revealed electrographic findings suggestive for AV-nodal reciprocant tachycardia in 66 cases (62.3%), for AV-reciprocant tachycardia in 32 cases (30.2%) and for atrial tachycardia in only eight cases (7.5%). Also, the protocol of the study was designed taking into account that: (1) PSVT subtype identification by surface ECG is often difficult to perform, particularly when the tachycardia presents high frequencies, (2) electrophysiological tests are not routinely performed in clinical practice, (3) although various electrocardiographic criteria have been proposed in the attempt to distinguish different types of PSVT, about 20% of PSVT may be incorrectly classified on the basis of the surface ECG. The possibility that some cases of regular PSVT may be incorrectly classified on the basis of the electrocardiogram.

Conclusions

In the treatment of symptomatic episodes of PSVT in adult subjects, both adenosine and verapamil demonstrated a high rate of success in terminating the tachycardia, whereas a poor response to carotid sinus massage was observed. The rate of the tachycardia may predict the success of pharmacological treatment. The efficacy of adenosine was directly related to the frequency of the arrhythmia, so it should be considered the treatment of choice in patients with PSVT characterised by high heart rates. Conversely, the efficacy of verapamil seems to be increased in patients with low-frequency PSVT, so that it could be appropriately used as the first-line treatment in these subjects.

References


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