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Original Contribution

A prognostic index for the successful use of adenosine in patients with paroxysmal supraventricular tachycardia in emergency settings: a retrospective study

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Abstract

Study Objectives: The use of adenosine on failure of vagal maneuvers in patients with paroxysmal supraventricular tachycardia (PSVT) is recommended. The aim of the present study was to identify a possible prognostic index for the efficacy of adenosine in PSVT.

Methods: This retrospective study included 321 patients with PSVT, in whom vagal maneuvers failed to restore normal sinus rhythm and who received 6 mg adenosine, followed by 12 mg adenosine (repeated if necessary). A 2-step clustering algorithm was used to reveal nonapparent groupings. Various patients' characteristics were inserted into the model.

Results: A straightforward index has been chosen that would aid the distinction of patients failing to respond to adenosine. The formula, (age / heart rate at admission) + number of past PSVT episodes, was chosen as the one that combined the highest sensitivity (96.2%) and specificity (71.2%).

Conclusions: This prognostic index constitutes a useful and reliable bedside diagnostic tool to identify patients with PSVT who were less likely to respond to adenosine administration in the emergency setting.

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1. Introduction

Paroxysmal supraventricular tachycardia (PSVT) is a distinct clinical syndrome. Most patients present with an abrupt onset of palpitations, dizziness, dyspnea, or chest pain. The electrocardiogram (ECG) demonstrates a fast heart rate (150-250 beats/min), a regular rhythm, and most often, a narrow QRS complex. Paroxysmal supraventricular tachycardia is caused by reentry, with the tachycardias being classified, electrophysiologically, according to the anatomic location of the reentry circuit. Atrioventricular (AV) nodal reentry is the most common form of PSVT. In AV nodal reentry, there are 2 conducting pathways located to the AV nodal and perinodal atrial tissue. The other common form of PSVT, termed AV reciprocating tachycardia, depends on an anatomically distinct or "accessory" pathway that may

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conduct impulses between the atria and the ventricles, while bypassing the AV node. The 2 forms of PSVT may be distinguished in many cases by examining the 12-lead ECG [1].

Several principles should guide the management of PSVT:

- Unstable patients require immediate electrical cardioversion.
- A 12-lead ECG should be obtained as soon as possible to confirm that the tachycardia has a narrow QRS complex.
- Vagal maneuvers may be attempted.
- In most patients, adenosine is the first-line agent to treat PSVT [3].

The purine nucleoside adenosine is a natural compound found in every cell of the human body. It was introduced into the American clinical setting in 1989 as an antiarrhythmic drug for the immediate management of reentrant supraventricular tachycardia involving the AV node [2]. In addition, adenosine has been used to differentiate wide QRS complex PSVT vs ventricular tachycardia, unmask the presence of a concealed bypass tract, and terminate catecholamine-dependent ventricular tachycardia [3].

By blocking the anterograde AV nodal limb of a reentrant circuit, adenosine converts almost all episodes of PSVT involving the AV node within 30 seconds of administration. Furthermore, if a dose of adenosine is ineffective, the exceptionally short plasma half-life of the adenyl nucleosides (<10 seconds) allows rapid upward dosage titration until PSVT is terminated. Noncardiac adverse effects (ie, flushing, dyspnea, and chest pain) may occur during acute arrhythmia termination or diagnosis with adenosine, and arrhythmias may develop; however, these effects are usually transient (lasting less than 1 minute) [4]. Potential users of adenosine should be aware of and be prepared for the rare cases of ventricular tachycardia and fibrillation observed in patients after its administration [2].

The aim of this study was to explore the characteristics of the patient groups and their relation with the therapeutic outcome, as well as to identify a sensitive, reliable, and yet specific prognostic index that may predict the restoration of sinus rhythm in the treatment of adult patients with PSVT in the emergency setting.

2. Materials and methods

2.1. Patient selection

This investigation is a retrospective, consecutive-case series, performed over a 3-year period (1999-2001), after approval was obtained from the university's ethics committee. A total of 321 adult male and female patients, aged 18 years or older, presenting to an emergency department (ED) with a diagnosis of PSVT, sustained and present at the time of evaluation, as evidenced by ECG, were included in this study. The population characteristics are depicted in Table 1. Patients were considered eligible for the study if they had sudden onset of symptoms due to the tachycardia (subjective awareness of palpitations or rhythm irregularity or arrhythmia-related dizziness, chest discomfort, dyspnea, anxiety).

Patients were specifically excluded if they demonstrated clinical signs of severe congestive heart failure (American Heart Association class III or IV), high-grade sinoatrial or AV block, history of sick sinus syndrome or sinus node dysfunction, unstable angina pectoris, ECG evidence of acute transmural myocardial infarction, or other signs of hemodynamic compromise (eg, systolic blood pressure of <90 mm Hg, altered mental status) during the tachyarrhythmia. Exclusion criteria included sinus tachycardia, atrial flutter, or atrial fibrillation, based on standard ECG criteria. Patients who were pregnant or receiving other antiarrhythmic agents were also excluded, as well as those with previous implantation of pacemaker or defibrillator and contraindications to carotid sinus massage (carotid bruit, history of previous adverse reaction to carotid sinus massage, or cerebrovascular accidents in the past 3 months).

2.2. Clinical examination and ECG

Before treatment, a clinical history was obtained, a physical examination was performed, and a standard 12-lead ECG and rhythm strip were recorded. Systemic arterial pressure was determined using standard methods, with a cuff sphygmomanometer, after 3 minutes of supine position. Measurements were repeated every 3 minutes throughout the entire procedure.

Paroxysmal supraventricular tachycardia was defined as a regular tachycardia with sudden-onset, narrow QRS complexes of supraventricular origin (ie, narrow complexes [QRS duration, <0.12 ms] or wide complexes in the presence of aberrant conduction, previous conduction defects, or suspected accessory pathways with no evidence of AV dissociation), with regular rates exceeding 140/min and abnormal nonsinus P waves.

2.3. Study protocol

Once PSVT was recognized, vagal maneuvers were attempted (Valsalva maneuver, carotid sinus massage), so

Table 1 General characteristics of the study group

Patients (men/women)	321 (178/143)
Age (y)	45.16 ± 7.86
Heart rate (beats/min)	175.37 ± 15.06
Systolic arterial pressure (mm Hg)	131.69 ± 9.04
Diastolic arterial pressure (mm Hg)	72.24 ± 6.13

as to increase parasympathetic tone and slow conduction through the AV node. When these nonpharmacologic interventions failed to terminate PSVT, adenosine was used. The first adenosine dose (6 mg) was administered as a rapid bolus (over 2-5 s) through a standard, free-flowing infusion set. The bolus was followed by a flush of 10 mL normal saline to clear the intravenous line. The intravenous catheter had previously been inserted into an arm vein in all patients. If PSVT persisted after the first dose of adenosine, a second (12 mg) and, if necessary, a third dose (12 mg), was administered at 2- to 3-minute intervals. Heart rate and rhythm were continuously monitored during and after each adenosine injection. Adverse reactions were recorded after each adenosine dose if reported by the patient or observed by the physician. If PSVT continued or recurred after adenosine treatment, other drugs known to be effective in managing this rhythm disturbance were administered at the discretion of the primary physician.

2.4. Clustering algorithm

A 2-step clustering algorithm was used to reveal nonapparent groupings (clusters). It is a multivariate procedure that enables the division of the population into subgroups, when the numbers of the groups and/or their participants are unknown. Clustering is mostly used as an effective exploratory tool in heterogeneous data, because it enables the detection of more homogenous subgroups [5,6].

The algorithm implemented uses a 2-step clustering approach similar to the BIRCH algorithm. The major advantages of this method are its ability to handle continuous as well as categoric data, automatic estimation of optimal number of clusters, and speed [7].

Age, sex, symptoms, past PSVT occurrences, heart rate, blood pressure, administered adenosine (mg), response to adenosine (binary), and personal medical history characteristics were inserted into the model. Schwarz Bayesian criterion (BIC) and log likelihood measure were selected as clustering criterion and distance measure, respectively.

2.5. Statistical analysis

Data are expressed as mean ± 1 SD for continuous variables and as percentages for categoric data. The Kolmogorov-Smirnov test was used to assess the normality of the distributions. Continuous variables were compared by using the unpaired t test and the nonparametric Mann-Whitney U test as appropriate. Repeated measures were compared with the paired t test or with the nonparametric Wilcoxon signed rank test. Categoric data were analyzed by using the χ^2 test or Fisher exact test as required. Analysis of variance was used for multiple comparisons between 3 or more groups. In cases of multiple comparisons, a reduced significance level (Bonferroni correction) was set. Receiver operator characteristic curves were used to determine the prognostic accuracy, the sensitivity, and specificity of the parameters and the derived indices. All performed tests were 2-sided and differences were considered statistically significant if the null hypothesis could be rejected with more than 95% confidence ($P < .05$).

3. Results

A total of 321 patients met the inclusion criteria to receive adenosine. Of this total, 138 (42.99%) patients required a single dose of adenosine (6 mg) to restore sinus rhythm, 110 (34.26%) received a second dose of 12 mg, and 73 (22.74%) required an additional dose of 12 mg. Only 26 (8.09%) patients failed to respond to the aforementioned regimen. Systolic and diastolic blood pressure decreased significantly after restoration of sinus rhythm (Fig. 1). Eleven (3.42%) patients described shortness of breath, but only 2 female patients had clinically evident bronchospasm. Only 49 (15.26%) patients complained of restrictive and throbbing chest pain and 26 (8.09%) patients experienced loss of consciousness and dizziness, accompanied by an ECG pause, of various duration.

Patients with past PSVT episodes showed higher incidence and twice the risk of ECG pauses (nonprevious PSVT episodes, 6.8%; PSVT episodes, 14.9%; odds ratio, 2.42; 95% confidence interval, 1.14-5.11; $P < .05$). Patients who had a history of PSVT also exhibited a significantly more frequent inability to convert to sinus rhythm with adenosine administration. These patients had more than 57 times the risk of requiring assistance of other methods to restore sinus rhythm (required assistance: nonprevious PSVT episodes, 0.5%; PSVT episodes, 21.9%; odds ratio, 57.87; 95% confidence interval, 7.72-433.69; $P < .001$).

The 2-step cluster analysis revealed 4 groups: I (n = 72, 22.4%), II (n = 121, 37.7%), III (n = 83, 25.9%), IV (n = 45, 14.0%). The significant characteristics for the formation of

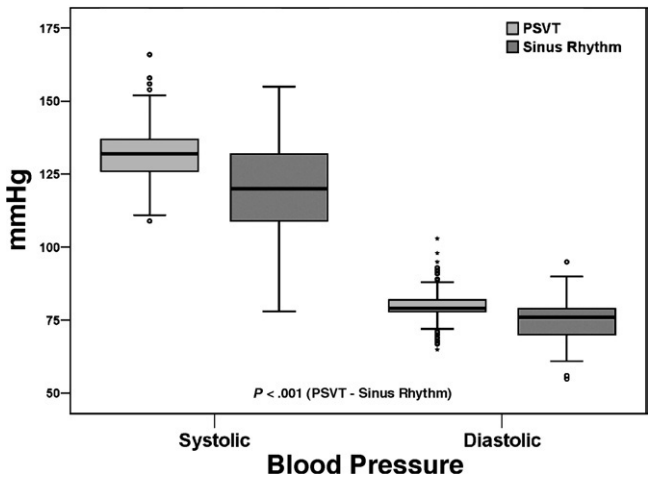

Fig. 1 Systolic and diastolic blood pressure before treatment and after sinus rhythm restoration.

Table 2 Subgroup (cluster) characteristics

Parameters	Groups				Comparisons					
	I (n = 72)	II (n = 121)	III (n = 83)	IV (45)	I and II	I and III	I and IV	II and III	II and IV	III and IV
Age	49.1 ± 6.1	48.6 ± 6.6	38.5 ± 5.3	41.8 ± 7.9	NS	*	*	*	*	**
PSVT episodes	1.4 ± 0.6	0	0	1.5 ± 0.8	*	*	NS	NS	*	*
% PSVT episodes	71 (98.6%)	0%	0%	43 (95.6%)	*	*	NS	NS	*	*
Adenosine (mg)	8.7 ± 3.9	4.6 ± 2.0	4.3 ± 1.9	8.9 ± 3.7	*	*	NS	NS	*	*
Admission heart rate	174.1 ± 15.7	173.1 ± 13.9	177.5 ± 14.8	179.6 ± 16.7	NS	NS	NS	NS	NS	NS
Age/heart rate	0.29 ± 0.04	0.28 ± 0.04	0.22 ± 0.04	0.24 ± 0.05	NS	*	*	*	*	NS
Female sex	28 (38.9%)	51 (42.1%)	42 (50.6%)	22 (48.9%)	NS	NS	NS	NS	NS	NS
Not responded	17 (23.6%)	0%	0%	9 (20.0%)	*	*	NS	NS	*	*
Free past medical history	0%	0%	83 (100%)	45 (100%)	NS	*	*	*	*	NS

NS indicates nonsignificant.
* $P < 0.001$.
** $P < 0.05$.

the clusters were as follows: adenosine administration, past PSVT episodes, personal medical history, age, and failure to convert to sinus rhythm with adenosine administration. The first cluster (I) was characterized by older patients with past PSVT episodes who received higher adenosine doses. The second cluster (II) included older patients with no past PSVT episodes who received lower adenosine doses. The third cluster (III) comprised younger patients with free medical history (PSVT and other major illnesses) who responded to low adenosine administration. The last cluster (IV) is composed of younger patients with past PSVT episodes who received higher adenosine doses. The reported differences between the clusters are summarized in Table 2.

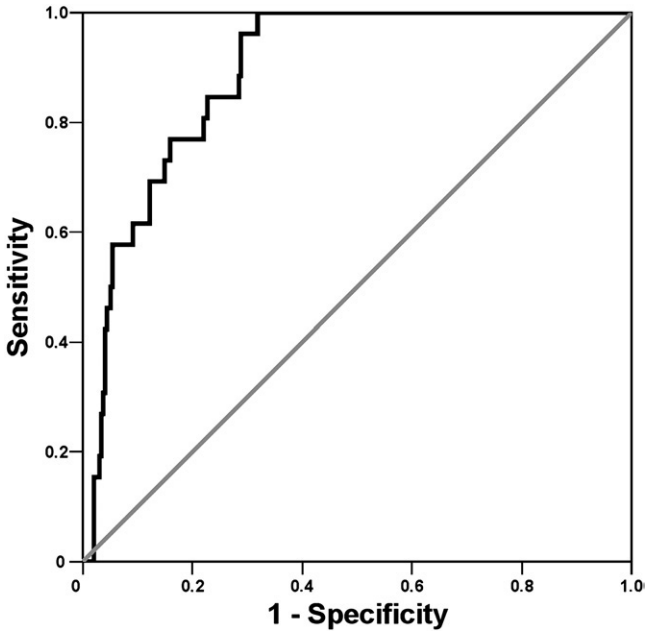

Fig. 2 Receiver operator characteristic curve indicating predictive accuracy of the prognostic index (age / heart rate) + past PSVT episodes.

It is important to note that clusters I and IV included all the nonresponsive patients to adenosine treatment. Based on this remark, the clusters were further divided into 2 groups: patients who responded well to adenosine treatment (clusters II and III) and patients who required further assistance (clusters I and IV). The individual characteristics of those clusters provided a useful insight and were used as a guide for the formation of a range of prognostic indices.

A straightforward index has been chosen that would aid the distinction of patients who failed to respond to adenosine treatment with adequate sensitivity and specificity. The formula: (age / heart rate at admission) + number of past PSVT episodes was chosen as the one that combined the highest sensitivity (96.2%) and specificity (71.2%) (cutoff value, 1.18; area under the curve [AUC], 0.89; $P < .001$) as well as ease of use. The relevant receiver operator characteristic curve is depicted in Fig. 2.

For example, a 34-year-old patient presenting with 205 beats/min and 1 past PSVT episode [(34/205) + 1] will give a result of 1.16. For a 68-year-old patient presenting with 171 beats/min and no past PSVT episodes, the result will be 0.4. In contrast, a 31-year-old patient with 183 beats/min and a history of 2 PSVT episodes yields a result of 2.17.

4. Discussion

Paroxysmal supraventricular tachycardia is a common clinical condition that may be explained by various pathophysiologic mechanisms. However, despite the heterogeneity of its pathogenesis, contemporary management of PSVT usually follows a general algorithm that initially includes vagal maneuvers and pharmaceutical management, with either adenosine or verapamil [8,9]. Diltiazem, β blockers, antiarrhythmics of class Ic and III, pharmacologic associations, new selective A_1 adenosine receptor agonists currently under clinical investigation, and transesophageal

atrial pacing may also be useful in the treatment or prevention of episodes of PSVT in adults [10]. Immediate electrical cardioversion is recommended in case of hemodynamically compromised patients [8].

Adenosine, administered either as the free base or as the 5′-triphosphate by rapid intravenous bolus, depresses AV nodal conduction, resulting in transient AV block. Adenosine is the active agent and adenosine triphosphate is rapidly converted to adenosine after exogenous administration. Adenosine has a negative chronotropic effect on the sinus node and a negative dromotropic effect on the AV node [11]. In atrial myocytes and sinoatrial and AV nodal cells, adenosine exerts direct as well as indirect, antiadrenergic, electrophysiologic effects. The direct effect consists of the activation of a K^+ outward current, as well as modulating the kinetics of the inward Ca^{2+} current; the indirect effect is manifested by the diminution of the catecholamine-induced enhancement of the inward Ca^{2+} current and the hyperpolarization-activated inward current. The cell membrane potential in atrial myocytes hyperpolarizes the action potential duration, and the effective refractory period shortens. In sinoatrial nodal cells, a reduced rate of phase IV depolarization is obtained, thereby slowing sinoatrial node automaticity. In the AV node, adenosine prolongs postrepolarization refractoriness and suppresses excitability, resulting in AV nodal conduction block of varying degrees [2].

Numerous reports have long ago established the clinical significance of adenosine use in prehospital or emergency settings. Gausche et al [12] and DiMarco et al [13] have already demonstrated the efficacy and feasibility of adenosine in a study population of 129 and 359 adult patients with PSVT, as identified by paramedic personnel and in emergency settings, respectively. The same results, although in smaller populations, were identified in other published studies [14-16]. More recently, Ballo et al [10] demonstrated that heart rate predicted restoration of sinus rhythm in adult subjects with symptomatic episodes of PSVT treated with adenosine and verapamil, with adenosine being highly effective in PSVT characterized by fast rates (>166 beats/min).

This current study examines not only the efficacy and safety of adenosine in patient with PSVT presenting in an emergency setting, but goes one step further by identifying patients who will or will not respond to adenosine treatment. Taking into account the patients' characteristics (age, sex, symptoms, past PSVT occurrences, heart rate, blood pressure, dose, and response to adenosine), the authors created a prognostic index of adequate sensitivity and specificity that would allow the emergency physician to keep in mind alternative methods of cardioversion. The formula, (age / heart rate at admission) + number of past PSVT episodes, presents a useful and reliable method to guide treatment planning.

More specifically, a patient presenting with a PSVT episode in an ED who—with the use of the aforementioned formula—yields a result lower than the cutoff value of 1.18, is more likely to respond to adenosine, after failure of vagal maneuvers. A patient whose result is higher than 1.18 has less probability to terminate his arrhythmia with adenosine administration. The especially high sensitivity (96.2%), the relatively high specificity (71.2%), and its simplicity in the emergency setting make the formula easy and attractive to use.

The current International Liaison Committee on Resuscitation guidelines suggest that stable narrow complex tachycardias (excluding atrial fibrillation or atrial flutter) should be treated first with vagal maneuvers; these will terminate about 20% of PSVTs. If vagal maneuvers are not used or if they fail, adenosine is recommended. A calcium-channel blocker (verapamil or diltiazem) infusion or amiodarone may be used as a second-line treatment for 10% to 15% of patients. In unstable patients with PSVT, electrical cardioversion is the treatment of choice [17]. This equation could rapidly indicate if adenosine is likely to solve the problem in an ED in a patient presenting with PSVT; if unlikely, electrical therapy could be directly applied on presentation.

References

[1] Lowenstein SR, Halperin BD, Reiter MJ. Paroxysmal supraventricular tachycardias. J Emerg Med 1996;14:39-51.

[2] Pelleg A, Pennock RS, Kutalek SP. Proarrhythmic effects of adenosine: one decade of clinical data. Am J Ther 2002;9: 141-7.

[3] Nolan JP, Deakin CD, Soar J, et al. European Resuscitation Council Guidelines for Resuscitation 2005. Section 4. Adult advanced life support. Resuscitation 2005;67S1:S39-86.

[4] Faulds D, Chrisp P, Buckley MM. Adenosine. An evaluation of its use in cardiac diagnostic procedures, and in the treatment of paroxysmal supraventricular tachycardia. Drugs 1991;41:596-624.

[5] Blashfield RK. Propositions regarding the use of cluster analysis in clinical research. J Consult Clin Psychol 1980;48:456-9.

[6] Hair JF, Anderson RE, Tatham RL, et al, editors. Multivariate analysis with readings. New York: MacMillan; 1992. p. 167-89.

[7] Zhang T, Ramakrishnon R, Livny M. BIRCH: an efficient data clustering method for very large databases. Proceedings of the ACM SIGMOD conference on management of data. Montreal, Canada: ACM Press; 1996. p. 103-14.

[8] Blomstrom-Lundqvist C, Scheinman MM, Aliot EM, et al. ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Supraventricular Arrhythmias). Circulation 2003;108:1871-909.

[9] Ferguson JD, DiMarco JP. Contemporary management of paroxysmal supraventricular tachycardia. Circulation 2003;107:1096-9.

[10] Ballo P, Bernabo D, Faraguti SA. Heart rate is a predictor of success in the treatment of adults with symptomatic paroxysmal supraventricular tachycardia. Eur Heart J 2004;25:1310-7.

[11] Hsieh IC, Yeh SJ, Wen MS, et al. Effects of adenosine on paroxysmal atrial tachycardia. Am J Cardiol 1994;74:279-81.

[12] Gausche M, Persse DE, Sugarman T, et al. Adenosine for the prehospital treatment of paroxysmal supraventricular tachycardia. Ann Emerg Med 1994;24:183-9.

[13] DiMarco JP, Miles W, Akhtar M, et al. Adenosine for paroxysmal supraventricular tachycardia: dose ranging and comparison with verapamil. Assessment in placebo-controlled, multicenter trials. The Adenosine for PSVT Study Group. Ann Intern Med 1990;113: 104-10.

[14] Cairns CB, Niemann JT. Intravenous adenosine in the Emergency Department management of paroxysmal supraventricular tachycardia. Ann Emerg Med 1991;20:717-21.

[15] McCabe JL, Adhar GC, Menegazzi JJ, et al. Intravenous adenosine in the prehospital treatment of paroxysmal supraventricular tachycardia. Ann Emerg Med 1992;23:358-61.

[16] Melio FR, Mallon WK, Newton E. Successful conversion of unstable supraventricular tachycardia to sinus rhythm with adenosine. Ann Emerg Med 1993;22:709-13.

[17] International Liaison Committee on Resuscitation. Part 4. Advanced life support. Resuscitation 2005;67:213-47.