Interaction Between Autonomic Tone and the Negative Chronotropic Effect of Adenosine in Humans

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KOU, W.H., ET AL.: Interaction Between Autonomic Tone and the Negative Chronotropic Effect of Adenosine in Humans. *Prior studies have demonstrated that sympathetic tone may influence the effects of adenosine on His-Purkinje automaticity, and that enhanced vagal tone may influence its effects on the sinus node. However, the interaction between autonomic tone and the effects of adenosine on the sinus node in humans remains unknown. Therefore, this study was designed to investigate the interaction between different states of autonomic tone and the bradycardiac response of the sinus node to adenosine. In 11 patients without structural heart disease who underwent a clinically indicated electrophysiology procedure, the sinus cycle length was measured before and after a 12-mg bolus of adenosine in the baseline state, during an infusion of 2 mcg/min of isoproterenol, after the administration of 0.2 mg/kg of propranolol, and again after the administration of 0.04 mg/kg of atropine. Adenosine significantly lengthened the sinus cycle length in the baseline state (760 ± 165 vs 909 ± 188 ms, $P < 0.05$), during isoproterenol infusion (516 ± 67 vs 766 ± 146 ms, $P < 0.05$), after propranolol (850 ± 153 vs 914 ± 143 ms, $P < 0.05$) and after the combination of propranolol and atropine (662 ± 76 vs 801 ± 121 ms, $P < 0.05$). The degree of lengthening in sinus cycle length was significantly greater ($P < 0.05$) during isoproterenol infusion (253 ± 157 ms, or 51% ± 40%) than in the baseline state (149 ± 85 ms, or 20% ± 12%), after propranolol (68 ± 53 ms, or 8% ± 8%), and after propranolol and atropine (140 ± 110 ms, or 21% ± 18%). The negative chronotropic effect of adenosine is influenced by autonomic tone. The effect of adenosine on the sinus node is accentuated by beta-adrenergic stimulation and unaffected by beta-adrenergic blockade or combined beta-adrenergic and cholinergic blockade. (PACE 1999; 22:1792–1796)*

Introduction

Adenosine is a potent agent for termination of paroxysmal supraventricular tachycardia.[1–3] Its pharmacological effects in cardiac tissue are mediated primarily by activation of adenosine A_1 receptors. The A_1 receptor uses the same effector protein, guanine nucleotide binding protein (Gi) , as the cholinergic receptors. Activation of Gi results in a direct stimulatory effect on the outward potassium channel, $I_{K\text{-}Ach\ Ado}$, and also counteracts the effects of sympathetic stimulation by inhibition of adenyl cyclase.[4–6] Experimental studies have demonstrated that vagal input may modulate the negative chronotropic effects of adenosine.[7,8] However, no clinical studies have examined the influence of autonomic tone on adenosine's effects. Therefore, the purpose of this study was to examine the negative chronotropic effects of adenosine in the baseline state and during beta-stimulation, beta-adrenergic inhibition, and combined beta-adrenergic and cholinergic blockade.

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Methods

Characteristics of Subjects

The subjects of this study were 11 patients who underwent a clinically indicated electrophysiology procedure for evaluation and/or treatment of paroxysmal supraventricular tachycardia (5 patients), the Wolff-Parkinson-White syndrome

Table I.

Effect of Adenosine on Sinus

	Baseline				Isoproterenol			
Case	before A	after A	ΔCL	Δ%	before A	after A	ΔCL	Δ%
1	1008	1272	264	26	636	852	216	34
2	618	808	190	31	436	632	196	45
3	1064	1136	72	7	576	896	320	56
4	870	995	125	14	525	905	380	72
5	665	710	45	7	505	590	85	17
6	700	990	290	41	390	990	600	154
7	800	1020	220	28	480	720	240	50
8	620	732	112	18	556	813	257	46
9	750	792	42	6	550	556	16	1
10	536	700	164	31	496	636	140	28
11	730	840	110	15	530	840	310	58
Mean ± SD	760 ± 165	909 ± 188	149 ± 85	20 ± 12	516 ± 67	766 ± 146	253 ± 157	51 ± 40

All intervals are expressed in milliseconds A = adenosine.

(1 patient), unexplained syncope (1 patient), or nonsustained ventricular tachycardia (4 patients). The inclusion criteria for this study were informed consent, the presence of sinus rhythm, and the absence of structural heart disease based on physical examination, electrocardiogram, and echocardiogram. Exclusion criteria consisted of asthma, spontaneous atrial or ventricular ectopy, and ingestion of a caffeine-containing beverage within 12 hours of the study. There were eight men and three women and their mean age was 50 ± 15 years.

Study Protocol

The study protocol was approved by the Human Research Committee and was performed upon completion of the clinically indicated portion of the electrophysiology procedure. Midazolam was used for conscious sedation. A 6 or 7 Fr electrode catheter was positioned in the high lateral right atrium. Five electrocardiographic leads and the right atrial electrogram were displayed on an oscilloscope and stored on an optical disc (Bard Labsystem 24, Boston, MA, USA), or recorded on paper at a speed of 25 mm/s (Mingograf-7 recorder, Siemens-Elema, Solna, Sweden). Adenosine was administered on four occasions: (1) in the baseline state; (2) after 12 minutes of infusion of isoproterenol at a rate of 2 mcg/min; (3) after discontinuation of the isoproterenol infusion and the infusion of 0.2 mg/kg of propranolol at a rate of 1–2 mg/min; and (4) after the administration of 0.04 mg/kg of atropine. These dosages of propranolol and atropine were used because a previous study demonstrated they were sufficient to result in complete beta-adrenergic and cholinergic blockade.[9]

Each administration of adenosine consisted of a 12-mg dose that was rapidly infused into the side port of an intravascular sheath within a femoral vein. The negative chronotropic effect of adenosine was assessed by comparing the mean sinus cycle length before adenosine administration with the longest sinus cycle length during the 3 minutes after injection of adenosine.

Statistical Analysis

Continuous variables are expressed as mean ± 1 SD. The Neuman-Keuls multiple comparison test was used to compare the effects of adenosine in the various autonomic states. P values less than 0.05 were considered significant.

Results

Table I lists the effects of adenosine on sinus cycle length in the baseline state, during isopro-

Cycle Length

Propranolol				Propranol + Atropine			
before A	after A	ΔCL	Δ%	before A	after A	ΔCL	Δ%
1148	1132	−16	−1	804	960	156	19
684	872	188	27	552	652	100	18
1127	1216	89	8	728	1000	272	37
895	970	75	8	610	980	370	61
705	755	50	7	630	750	120	19
790	880	90	11	560	790	230	41
820	910	90	11	680	710	30	4
780	784	4	0.5	648	708	60	9
830	900	70	8	720	780	60	8
770	844	74	10	715	756	41	6
800	800	0	0	640	730	90	14
850 ± 153	914 ± 143	68 ± 53	8 ± 8	662 ± 76	801 ± 121	140 ± 110	21 ± 18

terenol infusion, after beta-adrenergic blockade, and after combined beta-adrenergic and cholinergic blockade. Adenosine resulted in significant lengthening of the sinus cycle length under each of the four conditions. The magnitude of lengthening in sinus cycle length, in its absolute value or as a percentage of the cycle length before the administration of adenosine, was significantly greater during isoproterenol infusion (253 ± 157 ms, or 51% ± 40%) than in the baseline state (149 ± 85 ms, or 20% ± 12%, $P < 0.05$), after beta-adrenergic blockade (68 ± 53 ms, or 8% ± 8%, $P < 0.05$), or after combined beta-adrenergic and cholinergic blockade (140 ± 110 ms, or 21% ± 18%, $P < 0.05$) (Figs. 1 and 2).

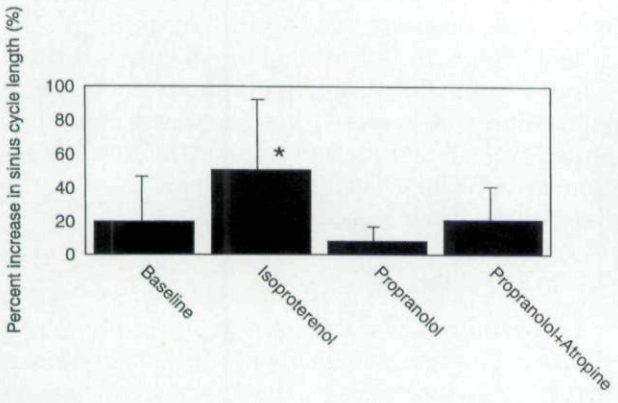

Figure 1. *Effect of adenosine on the change of percentage of sinus cycle length in different autonomic states. The effect of adenosine on sinus cycle length was significantly greater during isoproterenol infusion than in the baseline state, after propranolol, or after propranolol and atropine. Vertical bars represent 1 SD.* * $P < 0.05$.

Discussion

Main Findings

The results of this study demonstrate that adenosine exerts a significant negative chronotropic effect regardless of the autonomic tone. However, the magnitude of adenosine's negative chronotropic effect is more than four times greater in the setting of beta-adrenergic stimulation than in the setting of beta-adrenergic blockade. In the presence of beta-adrenergic blockade, there is only an insignificant change of the magnitude of adrenergic effect before and after administration of atropine (8% ± 8% vs 21% ± 18% or 68 ± 53 ms vs 140 ± 110 ms, $P > 0.05$). These findings suggest that the indirect effects of adenosine on the sinus node, mediated by the inhibition of adenyl cyclase, may be greater in magnitude than its direct effects, mediated by the Gi protein and activation of $I_{k\text{-}Ach,ado}$.

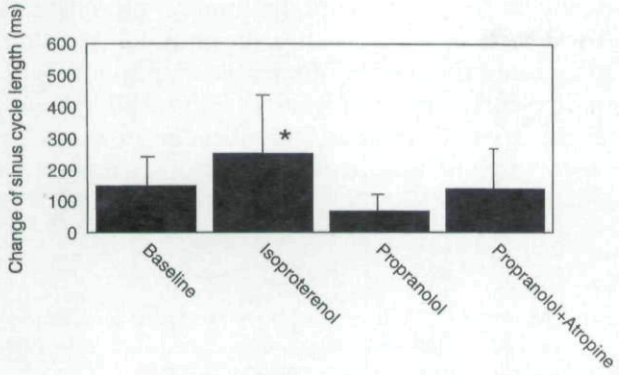

Figure 2. *Effect of adenosine on the change of sinus cycle length in milliseconds in different autonomic states. The magnitude of increase in sinus cycle lengths is only significantly greater during isoproterenol infusion. Vertical bars represent 1 SD. *P < 0.05.*

Results of Prior Studies

No prior studies have investigated the interaction between autonomic tone and the effects of adenosine on the sinus node in humans. However, the results of this study are consistent with the results of prior studies that have investigated the effects of adenosine on the atrial monophasic action potential and the interaction between autonomic tone and the effects of adenosine on His-Purkinje automaticity.[10,11] A more pronounced negative chronotropic effect on the His-Purkinje escape rhythm was observed when adenosine was administered in the presence of isoproterenol infusion. The increase in His-Purkinje cycle length was 41% before and 61% after intravenous infusion of isoproterenol. Similarly in the present study, adenosine increased the sinus cycle length by 20% before and 51% after administration of isoproterenol. However, in the present study adenosine maintained a significant negative chronotropic effect on sinus cycle length after pretreatment with propranolol, while its effect on His-Purkinje rhythmicity in the prior study[11] was only minimal after pretreatment with propranolol. This difference suggests that adenosine's action on the sinus node is mediated by its direct (activation of $I_{k\text{-}Ach\ Ado}$ channels) and indirect (antiadrenergic) effect.

In the present study, propranolol did not significantly alter the response of the sinus node to adenosine. This finding is consistent with the finding of a study on the effect of adenosine on human atrial repolarization.[10] The maximum shortening of atrial monophasic action potential duration by adenosine remained unaltered when subjects were pretreated with propranolol.

Effect of Cholinergic Blockade

Although animal studies showed that variations in vagal tone may have different effects on the bradycardic response to adenosine,[7,8] this finding was not reproducible in regards to His-Purkinje automaticity in conscious humans during the Valsava maneuver or carotid sinus massage.[10] The present study demonstrates that parasympathetic blockade has no significant influence on the magnitude of adenosine's negative chronotropic effect on the sinus node in the presence of β-blockade. Therefore, the vagal modulation of the electrophysiological effects of adenosine on human cardiac tissue is probably minimal.

Limitations

A limitation of this study is that the interaction between autonomic tone and the negative chronotropic effect of adenosine was assessed by the change in cycle length of the P wave. Since the sinus node electrogram was not recorded, it is not clear whether the change in P wave cycle length was purely the result of a direct negative chronotropic effect on the sinus node, or a combined result of its negative chronotropic effect on the sinus node and negative dromotropic effects on perinodal tissue.[12,13] Another limitation is the variability in basal autonomic tone between individual patients. This was reflected by a wide range of sinus cycle lengths, 536–1,064 ms, in the baseline state. Lack of control of the baseline autonomic tone may, in part, influence the estimation of the magnitude of the effect of adenosine on the sinus cycle length, expressed in absolute number or a percentage.

Clinical Implications

Episodes of paroxysmal supraventricular tachycardia often are associated with sympathetic activation in response to hypotension, anxiety, or uncomfortable symptoms. The therapeutic effects

of many antiarrhythmic agents, including verapamil, are antagonized by beta-adrenergic activation.[14] However, the results of this study indicate that the effects of adenosine, at least on the sinus node, are potentiated by beta-adrenergic activation, suggesting that it is particularly well suited for the treatment of paroxysmal supraventricular tachycardia. Another implication of the results of this study is that, because propranolol does not potentiate the effects of adenosine, patients with paroxysmal supraventricular tachycardia who are being treated with a beta-adrenergic blocking agent do not require a reduction in dosage of adenosine.

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