Atrioventricular conduction during adenosine-induced hypotension in dogs anaesthetized with sevoflurane

R. ISHII, S. AKAZAWA, R. SHIMIZU, Y. NAKAIGAWA, S. IKENO AND R. YAMATO

Summary

We have studied the effects of adenosine-induced hypotension on A-H interval (atrioventricular (AV) nodal conduction time during sinus rhythm), St-H interval (intra-atrial plus AV nodal conduction time during atrial pacing), H-V interval (His–Purkinje conduction time) and H-S interval (total ventricular conduction time) by His-bundle electrocardiography in addition to surface electrocardiogram during both sinus rhythm and atrial pacing in nine dogs anaesthetized with 1 MAC of sevoflurane. Stepwise increases in infusion rates of adenosine to 0.1, 0.3, 0.5 and 1.0 mg kg\(^{-1}\) min\(^{-1}\) produced a dose-related decrease in mean arterial pressure from 91 (6) to 38 (2) mm Hg. Adenosine significantly increased the A-H interval at infusion rates of 0.5 mg kg\(^{-1}\) min\(^{-1}\) and above, and the St-H interval at 1.0 mg kg\(^{-1}\) min\(^{-1}\). The H-V and H-S intervals remained unchanged. Heart rate decreased significantly only at 1.0 mg kg\(^{-1}\) min\(^{-1}\) with a significant increase in the PR interval. Adenosine-induced hypotension did not have deleterious effects on AV conduction times and the surface electrocardiogram in dogs anaesthetized with 1 MAC of sevoflurane. This may indicate that the effects of adenosine on AV conduction were small and therefore are unlikely to be a contraindication to the use of adenosine for inducing hypotension in patients with initially normal conduction during sevoflurane anesthesia. (Br. J. Anaesth. 1996;77:393–398)

Key words


Although adenosine has been shown to cause depression of sinus node automaticity\(^7\) and atrioventricular (AV) nodal conduction in vitro\(^9\), it is known to be highly effective clinically in terminating re-entrant tachycardia involving the AV node\(^10\). However, there has been no study on the electrophysiological effects of adenosine on the cardiac conduction system in the presence of inhalation anaesthetics.

Sevoflurane provides rapid control of arterial pressure as a result of its low blood solubility\(^11\) and it has no adverse cardiac electrophysiological effects\(^13\). Therefore, a combination of sevoflurane and adenosine may be used to safely induce hypotension.

We have studied atrioventricular conduction and the surface electrocardiogram during adenosine-induced hypotension in dogs anaesthetized with sevoflurane.

Materials and methods

ANIMAL PREPARATION

The study was approved by the management committee of the Jichi Medical Laboratory of Experimental Medicine, based on the school’s 1993 Guide for Laboratory Animals.

Anaesthesia was induced in nine mongrel dogs, weighing 13–21 kg (mean 16.6 kg), by insufflating 3–5% (1.3–2.1 MAC) sevoflurane via a funnel-shaped plastic mask fitted to the dog’s face connected to a Jackson–Rees circuit. The trachea was intubated and ventilation was adjusted to maintain normocapnia with a Harvard pump respirator (R-60, Aika, Co., Ltd).

Anaesthesia for surgical preparation was maintained with 2–3% end-tidal concentrations of sevoflurane and 50% nitrous oxide in oxygen delivered into the inspiratory limb of a Harvard pump respirator. Sevoflurane was vaporized using a Sevotec vaporizer (Penlon Inst., Ltd). A micromanometer-tipped catheter (7F 45326, Toyoda Instr., Ltd) was inserted via the left femoral artery into the abdominal aorta to measure systolic (SAP), diastolic (DAP) and mean (MAP) arterial pressures.

Adenosine has been used as a hypotensive agent during major surgery\(^1\). Unlike other hypotensive agents such as sodium nitroprusside and trinitroglycerin, adenosine is a naturally occurring purine nucleoside and produces rapid and stable hypotension without evidence of biochemical or haematological toxicity\(^7\). Tachyphylaxis and rebound hypertension have not been reported after induced hypotension with adenosine\(^1\). In addition, adenosine has an extremely short half-life (10–30 s) because of rapid uptake into cells, resulting in rapid termination of action when administration is discontinued\(^8\).
A catheter was inserted into the abdominal aorta via the right femoral artery to sample arterial blood for measurement of pH, P<sub>ao</sub>2, P<sub>aco</sub>2, and serum electrolyte concentrations. Lactated Ringer's solution was infused at a rate of 5–10 ml kg<sup>-1</sup> h<sup>-1</sup> via the left femoral vein throughout the study. Body temperature was measured with an oesophageal thermistor and maintained at 36–37 °C using an external heating blanket.

A right thoracotomy was performed at the fifth intercostal space. A quadrupolar electrode catheter introduced via the right femoral vein was positioned under manual control across the tricuspid valve to obtain a stable His-bundle electrogram (HBE). The His-bundle catheter electrodes were connected to a switch box that allowed selection of any combination of two electrodes. The output of the switch box was connected to a preamplifier with bandwidth cutoff frequencies of 40–1000 Hz. The electrodes of the surface electrocardiogram (ECG: lead II and V5) were connected to another preamplifier with a filter of two electrodes. The output of the switch box was transferred to a multichannel recorder (Recti-Horiz-8K, NEC San-ei, Ltd, Tokyo, Japan).

HBE was recorded at a paper speed of 500 mm s<sup>-1</sup> to calculate AV conduction intervals with 1.0-ms resolution (Visigraph 5L37, NEC San-ei, Ltd, Tokyo, Japan). An electrode for atrial pacing was attached to the surface of the right atrial appendage. An R-wave coupled cardiac stimulator (3F61, NEC San-ei, Instr., Ltd, Tokyo, Japan) delivering rectangular monophasic pulses of 1 ms duration was used for all atrial pacing.

**ELECTROCARDIOGRAPHIC AND ELECTROPHYSIOLOGICAL MEASUREMENTS**

RR, PR and St-R intervals, QRS duration and QT interval were measured from ECG lead II. The PR interval during sinus rhythm was measured from the onset of the P wave to the onset of the Q wave of the QRS complex. The St-R interval during atrial pacing was measured from the beginning of the stimulus artefact (St) in the HBE to the onset of the Q wave of the QRS complex. The QT interval was corrected for heart rate by dividing the QT interval by the square root of the RR interval (<i>t</i>) to obtain the QTc interval<sup>14</sup>. AV conduction times measured were as follows: A-H interval (AV nodal conduction time during sinus rhythm); St-H interval (intra-atrial plus AV nodal conduction time during atrial pacing); H-V interval (His-Purkinje conduction time); and H-S interval (total ventricular conduction time).

AV conduction times measured were as follows: A-H interval (AV nodal conduction time during sinus rhythm); St-H interval (intra-atrial plus AV nodal conduction time during atrial pacing); H-V interval (His-Purkinje conduction time); and H-S interval (total ventricular conduction time). The A-H interval was measured from the beginning of atrial deflection to the beginning of the His-bundle spike in the HBE<sup>15</sup>. The St-H interval was measured from the beginning of the St to the beginning of the His-bundle spike in the HBE<sup>16</sup>. The H-V interval was measured from the beginning of the His-bundle spike to the beginning of the ventricular deflection in the HBE<sup>15</sup>. The H-S interval was measured from the beginning of the His-bundle spike to the end of the rapid ventricular deflection in the HBE<sup>16</sup> (fig. 1).

**EXPERIMENTAL PROCEDURE**

At the end of the surgical procedure, nitrous oxide was discontinued and the end-tidal concentration of sevoflurane was adjusted to 2.4% (1 MAC) and maintained for at least 20 min. After haemodynamic stabilization, control values of the variables noted above were obtained during both sinus rhythm and subsequent atrial pacing. The right atrium was constantly paced at 100 (8) beat min<sup>-1</sup> compared with control. A = Atrial deflection; H = His-bundle spike; V = ventricular deflection; A-H (atrioventricular nodal conduction time) = interval from the beginning of atrial deflection to the beginning of the His-bundle spike in the HBE; H-V (His–Purkinje conduction time) = interval from the beginning of the His-bundle spike to the beginning of the ventricular deflection in the HBE; H-S (total ventricular conduction time) = interval from the beginning of the His-bundle spike to the end of the rapid ventricular deflection in the HBE.

**DATA ANALYSIS**

Data are given as mean (SEM). Statistical analysis was performed using analysis of variance (ANOVA) with repeated measures, followed by Scheffe’s F test. <i>P</i>&lt;0.05 was considered statistically significant.
Results

HAEMODYNAMIC EFFECTS (TABLE 1)
Adenosine produced dose-related stable decreases in SAP, DAP and MAP. MAP decreased significantly from 91 (6) to 62 (6), 45 (4), 42 (3) and 38 (2) mm Hg with adenosine infusion rates of 0.1, 0.3, 0.5 and 1.0 mg kg\(^{-1}\) min\(^{-1}\), respectively. Heart rate remained unchanged at 0.1 mg kg\(^{-1}\) min\(^{-1}\) and tended to decrease at 0.3 and 0.5 mg kg\(^{-1}\) min\(^{-1}\), and decreased significantly at 1.0 mg kg\(^{-1}\) min\(^{-1}\). There were no significant differences in SAP, DAP and MAP between control values and those at 5 min after termination of adenosine infusion: rebound hypertension did not occur.

Table 1  Effects of adenosine on arterial pressures and heart rate during sinus rhythm (mean (SEM)). SAP = Systolic arterial pressure; DAP = Diastolic arterial pressure; MAP = Mean arterial pressure. HR = Heart rate. *P < 0.05 compared with control value; †P < 0.05 compared with preceding value

<table>
<thead>
<tr>
<th>Infusion rate of adenosine (mg kg(^{-1}) min(^{-1}))</th>
<th>0.0</th>
<th>0.3</th>
<th>0.5</th>
<th>1.0</th>
<th>5 min after infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>119 (7)</td>
<td>90 (8)*</td>
<td>68 (6)*†</td>
<td>63 (5)*</td>
<td>57 (3)*</td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td>76 (6)</td>
<td>47 (5)*</td>
<td>33 (3)*†</td>
<td>31 (2)*</td>
<td>29 (2)*</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>91 (6)</td>
<td>62 (6)*</td>
<td>45 (4)*†</td>
<td>42 (3)</td>
<td>38 (2)*</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>90 (7)</td>
<td>89 (6)</td>
<td>82 (5)</td>
<td>79 (5)</td>
<td>73 (5)*</td>
</tr>
<tr>
<td>HR (beat min(^{-1}))</td>
<td>90 (7)</td>
<td>89 (6)</td>
<td>82 (5)</td>
<td>79 (5)</td>
<td>73 (5)*</td>
</tr>
</tbody>
</table>

ELECTROPHYSIOLOGICAL AND ELECTROCARDIOGRAPHIC EFFECTS (TABLES 2, 3)
Adenosine significantly increased the A-H interval at infusion rates of 0.5 mg kg\(^{-1}\) min\(^{-1}\) and above, during sinus rhythm, and the St-H interval only at 1.0 mg kg\(^{-1}\) min\(^{-1}\) during atrial pacing. There were significant differences between the A-H and St-H intervals under control conditions and at each infusion rate. The H-V and H-S intervals were unchanged during both sinus rhythm and atrial pacing at all infusion rates.

The RR interval was unchanged at an infusion rate of 0.1 mg kg\(^{-1}\) min\(^{-1}\), tended to decrease at 0.3 and 0.5 mg kg\(^{-1}\) min\(^{-1}\) and decreased significantly at 1.0 mg kg\(^{-1}\) min\(^{-1}\).

Table 2  Effects of adenosine on atrioventricular conduction times during sinus rhythm and atrial pacing (mean (SEM)). A-H interval = Atrioventricular (AV) nodal conduction time, H-V interval = His-Purkinje conduction time, H-S interval = total ventricular conduction time, St-H interval = intra-atrial plus AV nodal conduction time during atrial pacing. *P < 0.05 compared with control value; ††P < 0.01 compared with corresponding value obtained during sinus rhythm

<table>
<thead>
<tr>
<th>Infusion rate of adenosine (mg kg(^{-1}) min(^{-1}))</th>
<th>0.0</th>
<th>0.3</th>
<th>0.5</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus rhythm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A-H interval (ms)</td>
<td>82.9 (6.7)</td>
<td>84.0 (7.5)</td>
<td>89.1 (8.0)</td>
<td>94.2 (7.6)*</td>
</tr>
<tr>
<td>H-V interval (ms)</td>
<td>33.1 (3.1)</td>
<td>33.6 (2.9)</td>
<td>32.2 (2.7)</td>
<td>33.8 (3.1)</td>
</tr>
<tr>
<td>H-S interval (ms)</td>
<td>109.4 (5.2)</td>
<td>109.3 (5.3)</td>
<td>108.8 (5.7)</td>
<td>108.7 (5.9)</td>
</tr>
<tr>
<td>Atrial pacing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>St-H interval (ms)</td>
<td>129.6 (12.1)††</td>
<td>124.0 (10.7)††</td>
<td>132.0 (10.8)††</td>
<td>138.7 (10.6)††</td>
</tr>
<tr>
<td>H-V interval (ms)</td>
<td>33.6 (3.2)</td>
<td>33.6 (3.2)</td>
<td>32.9 (3.2)</td>
<td>32.9 (3.5)</td>
</tr>
<tr>
<td>H-S interval (ms)</td>
<td>108.6 (5.2)</td>
<td>109.1 (5.3)</td>
<td>108.4 (6.0)</td>
<td>108.7 (6.1)</td>
</tr>
</tbody>
</table>

Table 3  Effects of adenosine on the surface electrocardiogram during sinus rhythm and atrial pacing (mean (SEM)). QTc interval = QT interval/RR (s) and St-R interval = interval from stimulus artefact to the onset of the QRS complex. *P < 0.05 compared with control value; †P < 0.05 compared with corresponding value obtained during sinus rhythm

<table>
<thead>
<tr>
<th>Infusion rate of adenosine (mg kg(^{-1}) min(^{-1}))</th>
<th>0.0</th>
<th>0.3</th>
<th>0.5</th>
<th>1.0</th>
</tr>
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<tbody>
<tr>
<td>Sinus rhythm</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>RR interval (ms)</td>
<td>723.7 (47.7)</td>
<td>696.4 (42.4)</td>
<td>750.1 (37.6)</td>
<td>783.2 (43.8)</td>
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<tr>
<td>PR interval (ms)</td>
<td>127.4 (8.4)</td>
<td>127.2 (9.0)</td>
<td>129.9 (9.3)</td>
<td>133.9 (9.3)</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>62.8 (2.2)</td>
<td>61.8 (2.2)</td>
<td>62.0 (1.9)</td>
<td>63.2 (2.1)</td>
</tr>
<tr>
<td>QT interval (ms)</td>
<td>367.1 (23.1)</td>
<td>362.5 (22.0)</td>
<td>367.7 (19.4)</td>
<td>380.5 (20.5)</td>
</tr>
<tr>
<td>QTc interval (ms)</td>
<td>430.9 (16.7)</td>
<td>433.2 (15.4)</td>
<td>424.0 (14.4)</td>
<td>429.8 (14.3)</td>
</tr>
<tr>
<td>Atrial pacing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR interval (ms)</td>
<td>629.6 (47.4)</td>
<td>629.6 (47.4)</td>
<td>629.6 (47.4)†</td>
<td>629.6 (47.4)†</td>
</tr>
<tr>
<td>St-R interval (ms)</td>
<td>159.6 (14.3)†</td>
<td>153.4 (12.3)†</td>
<td>161.1 (11.7)†</td>
<td>167.7 (12.3)†</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>62.8 (2.1)</td>
<td>62.7 (2.5)</td>
<td>62.7 (2.1)</td>
<td>62.6 (1.9)</td>
</tr>
<tr>
<td>QT interval (ms)</td>
<td>351.8 (21.4)</td>
<td>350.6 (23.2)</td>
<td>353.4 (21.9)</td>
<td>357.4 (22.9)</td>
</tr>
<tr>
<td>QTc interval (ms)</td>
<td>443.3 (13.5)</td>
<td>441.1 (15.2)</td>
<td>445.0 (13.2)</td>
<td>449.8 (14.0)</td>
</tr>
</tbody>
</table>
kg·min⁻¹. Pacing rate was 100 (8) beat min⁻¹, which was slightly greater than the control rate at sinus rhythm (90 (7) beat min⁻¹). Adenosine significantly increased the PR interval during sinus rhythm and the St-R interval during atrial pacing, but only at an infusion rate of 1.0 mg kg⁻¹ min⁻¹. However, a PR interval longer than 200 ms and AV conduction block did not appear at any infusion rate. The QT interval tended to increase during sinus rhythm, while it was unchanged during atrial pacing. QRS duration and the QTc interval were unchanged during both sinus rhythm and subsequent atrial pacing.

**Discussion**

We have found that infusion of adenosine produced rapid and dose-related decreases in systolic, diastolic and mean arterial pressures and significantly increased the A-H interval at infusion rates of 0.5 mg kg⁻¹ min⁻¹ and above during sinus rhythm, and the St-H interval at 1.0 mg kg⁻¹ min⁻¹ during atrial pacing under anaesthesia with 1 MAC of sevoflurane.

Decreased arterial pressures became stable within 1–1.5 min after the beginning of the infusion of adenosine at each rate. Adenosine-induced hypotension can be attributed to systemic arterial vasodilatation, as shown previously in dogs, pigs and humans. Rebound hypertension did not occur. This finding is in agreement with a previous report.

The haemodynamic and electrophysiological effects of adenosine are influenced by a complex interplay of A₁ and A₂ receptors located on the surface of cell membranes and coupled to G proteins. A₂ receptors in endothelial and vascular smooth muscle cells mediate vasodilation in almost all vascular beds, including the coronary artery, whereas A₁ receptors in cardiomyocytes mediate two types of actions: one is cyclic AMP (cAMP)-independent (direct actions), shortens the action potential in atrial cells, elicits sinus slowing and hyperpolarization of SA nodal cells and causes depression of the action potential in AV nodal cells; the other is cAMP-dependent (indirect actions) and antagonizes positive chronotropic, dromotropic and inotropic effects through antagonism of the increase in activity of adenylate cyclase and accumulation of cAMP caused by β agonists and forskolin.

In general, adenosine-induced hypotension produces reflex tachycardia via activation of baroreflexes, as is the case with other hypotensive agents, in conscious dogs, conscious humans and patients anaesthetized with phenoperidine–droperidol. In this study, adenosine-induced hypotension during 1 MAC of sevoflurane anaesthesia was not accompanied by an increase in heart rate. In fact, heart rate tended to decrease with an increase in the infusion rate of adenosine and decreased significantly at an infusion rate of 1.0 mg kg⁻¹ min⁻¹. This finding is in agreement with previous results in pigs anaesthetized with methohexital, in dogs anaesthetized with phenoperidine–droperidol, in rabbits anaesthetized with halothane and in dogs anaesthetized with halothane–nitrous oxide. These results may be attributed to a direct inhibitory effect of adenosine on the sinus node cells and an indirect inhibitory effect of adenosine on cardiac sympathetic neurotransmission. Our results also suggest that the direct and indirect effects of adenosine on the sinus node during sevoflurane anaesthesia may predominate over activation of baroreflexes induced by hypotension with adenosine.

Inhalation anaesthetics have been shown to depress baroreflex function; the extent of depression varies between anaesthetics, with both halothane and enflurane being more depressant than isoflurane. Recently, sevoflurane has been shown to depress baroreflex function in chronically instrumented dogs. In addition, we found in our earlier study that sevoflurane suppressed tachycardia associated with nicardipine-induced hypotension in dogs. Therefore, the direct and indirect inhibitory effects of adenosine could be enhanced by sevoflurane anaesthesia.

Prolongation of the A-H interval with adenosine 0.5 and 1.0 mg kg⁻¹ min⁻¹ can be attributed to direct depression of the action potential in AV nodal cells. This negative dromotropic effect of adenosine may be responsible for the significant prolongation of the PR interval at 1.0 mg kg⁻¹ min⁻¹ compared with the control value. Because the sensitivity of the AV node to adenosine in the dog is known to be less than that in human, the responses to approximately 5–10 times the clinical dose were examined in this study. Heart block did not develop at any infusion rate of adenosine in this study, even in the presence of profound hypotension.

In this study, the right atrium was paced at a slightly higher rate than the original sinus rhythm to exclude the influence of heart rate on AV conduction times. Although the St-H interval increased significantly at 1.0 mg kg⁻¹ min⁻¹, no significant differences were observed in the degree of increases between the A-H and St-H intervals at any infusion rate of adenosine. Although it is not clear why the St-H interval was 40–50 ms longer than the A-H interval during sinus rhythm, the differences between the A-H and St-H intervals probably reflected latency between the stimulus and atrial activation. Because incremental increases in atrial-paced rate were not performed, the effects of adenosine on the rate-dependence of AV nodal conduction times during sevoflurane anaesthesia is unclear.

Adenosine did not affect the H-V interval, indicating that the site of the dromotropic action of adenosine is proximal to the His bundle, that is the AV node. Our results are consistent with this finding, because both the H-V and H-S intervals were unchanged during both sinus rhythm and subsequent atrial pacing. The lack of effect of adenosine on QRS duration and the QTc interval during both sinus rhythm and subsequent atrial pacing might reflect the absence of effects of adenosine on the His–Purkinje ventricular conduction system and on the average action potential duration of ventricular muscle, respectively.

Electrophysiological studies with inhalation anaesthetics demonstrated that halothane and enflurane were more depressant of A-V nodal conduction time than isoflurane. However, the electrophysiological effects of sevoflurane have not been studied fully. We compared the effects of 1 and 2 MAC of sevoflurane, isoflurane and halothane on specialized AV conduction times in dogs anaesthetized with pentobarbital where we found that both sevoflurane and iso-
flurane did not affect the A-H, H-V and H-S intervals, whereas halothane significantly prolonged only the A-H interval at 2 MAC during sinus rhythm, although pentobarbitone might modify the effects of subsequently administered inhalation anaesthetics. A battery of electrophysiological tests, including measurements of sinus node recovery time, AV nodal refractory periods and Wenkebach cycle length should be performed to provide sufficient information for measurement of the possible clinical electrophysiological risk of adenosine. Non-invasive methods using more adenosine-sensitive animals and higher concentrations of sevoflurane may also be highly desirable. Although there are several limitations, as mentioned above, our results suggest that adenosine should not exert adverse effects on AV conduction times in combination with sevoflurane anaesthesia.

In summary, adenosine-induced hypotension did not elicit reflex tachycardia and adenosine did not produce detrimental heart block during anaesthesia with 1 MAC of sevoflurane. Adenosine may therefore be used as a hypotensive agent during sevoflurane. However, the potential for coronary steal and renal vasoconstriction during adenosine administration may limit its clinical usefulness.

Acknowledgments

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