Effect of adenosine on heart rate variability in humans

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ABSTRACT

By stimulating afferent nerve endings in skeletal muscle, heart, kidney and the carotid body, adenosine infusion evokes a receptor-specific sympatho-excitatory reflex in humans that overrides its direct negative chronotropic effect. We tested the hypothesis that adenosine increases heart rate by suppressing parasympathetic and augmenting sympathetic components of heart rate variability. High-frequency ($P_H$; 0.15–0.50 Hz) and low-frequency ($P_L$; 0.05–0.15 Hz) components of heart rate variability total power ($P_T$) were determined by spectral analysis. The ratios $P_H/P_T$ and $P_L/P_H$ respectively were used to estimate parasympathetic and sympathetic input to the sino-atrial node. Heart rate was recorded before and during a 5 min intravenous infusion of adenosine (140 $\mu$g $\cdot$ min$^{-1} \cdot$ kg$^{-1}$) in seven healthy men. Adenosine did not affect blood pressure, but increased heart rate by 33 ± 6 beats/min, and reduced $P_T$, $P_H$, $P_L$ and $P_H/P_T$. In contrast, there was an increase in $P_L/P_H$. In a second experiment in nine men, brachial artery infusion of adenosine (15 $\mu$g $\cdot$ min$^{-1} \cdot$ 100 ml$^{-1}$ forearm tissue) increased heart rate by 3 beats/min, had no effect on $P_T$, $P_H$, $P_L$ or $P_H/P_T$, yet increased $P_L/P_H$. Intra-arterial adenosine exerts a modest effect on heart rate by modulating cardiac sympathetic indices, without affecting parasympathetic indices, of heart rate variability, whereas intravenous infusion of adenosine reduces heart rate variability and raises heart rate by decreasing parasympathetic and increasing cardiac sympathetic tone. These reflex effects may become clinically relevant during adenosine stress testing, or when endogenous adenosine is increased, such as during ischaemia, exercise or vasodepressor reactions, or in heart failure.

INTRODUCTION

The cardiovascular actions of adenosine are a topic of current interest [1]. Adenosine can act directly on the sinus node to reduce heart rate and slow conduction within the atrial–ventricular node [2]. These properties are the basis for one clinical application of adenosine, namely the interruption of supraventricular tachycardia by bolus injection. However, when infused intravenously into conscious humans, to achieve lower plasma concentrations, adenosine increases both heart rate and sympathetic nerve traffic to muscle [3,4]. There are two stimuli to this activation of the sympathetic nervous system: peripheral vasodilation, which reduces baroreceptor afferent nerve discharge, and a receptor-specific sympatho-excitatory reflex elicited by stimulating afferent nerve endings in the carotid body, skeletal muscle, heart and kidney [4–10].
Under resting conditions, there is a good correlation between sympathetic nerve traffic to skeletal muscle and biochemical estimates of sympathetic outflow to the human heart [11]. Whether this relationship persists when sympathetic nerve traffic to skeletal muscle is activated reflexively by adenosine is unknown. If so, the tachycardia observed during adenosine infusion could arise from a concordant increase in sympathetic neural drive to the heart, which would override the direct negative chronotropic effects of this purine. On the other hand, decreased parasympathetic tone [12] could also contribute to this increase in heart rate. Indeed, in a study involving six young healthy subjects given intravenous propranolol and atropine, Conradson et al. [13] concluded that the heart rate response to an infusion of 120 μg of adenosine min⁻¹ kg⁻¹ was due to a reduction in vagal tone. However, the chronotropic response to adenosine tended to be less after β-adrenoceptor blockade alone. Thus the relative contributions of sympathetic nervous system activation and parasympathetic nervous system withdrawal to the increase in heart rate observed when adenosine is infused in normal humans for clinical purposes is unclear.

Spectral analysis can provide quantitative information on the relative balance between the parasympathetic neural and sympathetic neural contributions to heart rate variability [14–16]. Dipyridamole inhibits the cellular uptake of adenosine, leading to its accumulation [2]. The effects of dipyridamole on frequency-domain indices of heart rate variability have been studied in both normal subjects and patients with ischaemia [17], but the effects of the purine itself on heart rate variability have not been reported. Our objective in the present study was to test the hypothesis that adenosine reduces the parasympathetic and augments the sympathetic components of heart rate variability in healthy subjects.

Two series of experiments were performed. In the first series, we determined the effect of a systemic infusion of adenosine, as given commonly during myocardial perfusion imaging [18], on heart rate variability. In the second series, we determined the effect on heart rate variability of brachial artery infusion of adenosine at a dose that is without systemic haemodynamic effect, but which has a demonstrated reflex sympato-excitatory action [9].

**METHODS**

**Series 1 : effect of intravenous adenosine infusion on heart rate variability**

**Subjects**

Seven healthy, non-smoking, male volunteers [age 37±10 years; weight 82±10 kg; height 178±5 cm (means ± S.D.)], known to consume at least two cups of coffee per day, were enrolled in this series [19]. All subjects provided written informed consent for this study, and the study was approved by the Ethics Committee of our Institute.

**Protocol**

Because caffeine is a competitive antagonist that inhibits virtually all actions of adenosine studied, adenosine was infused after 30 h of abstinence [19,20]. All studies were performed in the same quiet temperature-controlled room at the same time of day (afternoon), at least 2 h after subjects’ last food intake. An antecubital vein of the left arm was cannulated, and a blood sample was collected for measurement of total (protein-bound plus free) serum caffeine concentration by a homogeneous enzyme immunoassay technique using a commercially available kit ( Emit Caffeine Assay; Syva Canada, Kanata, Ontario, Canada). The limit of detection of this assay is 5 μg/ml. In our clinical laboratory, the batch-to-batch coefficient of variation is 4.2% at a concentration of 77.2 μmol/l.

Lead II of the ECG was recorded continuously during spontaneous respiration, inscribed on to paper by an ink recorder and digitized at 1000 Hz into a personal computer for data analysis. Blood pressure was measured at 1 min intervals, using a non-invasive oscillometric technique with an inflatable cuff applied on each occasion to the right arm (Dinamap; Kritikon, Tampa, FL, U.S.A.). At 20 min after the intravenous cannulation, a 5 min baseline was recorded. Adenosine was infused to a maximum concentration of 140 μg min⁻¹ kg⁻¹, which was sustained for 5 min (this being the dose most commonly administered during myocardial perfusion imaging [18]).

**Series 2 : effect of intra-arterial adenosine infusion on heart rate variability**

**Subjects**

Nine healthy, non-smoking, male volunteers (age 33±9 years; weight 79±6 kg; height 178±5 cm) were enrolled in this series, which was approved by our institutional Ethics Committee [9]. All subjects provided written informed consent prior to their participation.

**Protocol**

All studies were performed in the same quiet temperature-controlled laboratory, at the same time of day, after 24 h of caffeine abstinence, with subjects supine. Lead II of the ECG was recorded continuously, inscribed on to paper by an ink recorder and digitized at 1000 Hz into a personal computer for data analysis. After local anaesthesia, the brachial artery of the non-dominant arm (mean volume 1156±151 ml) was cannulated (5 cm;
Adenosine and heart rate variability

20 G catheter) for the continuous recording of intrarrenal blood pressure, and for intra-arterial infusions. Forearm blood flow was measured by venous occlusion strain gauge plethysmography. After a rest period of at least 30 min, saline (as vehicle) was infused into the brachial artery for 5 min, followed by adenosine, which was infused to a maximum concentration of 15 μg·min⁻¹·100 ml⁻¹ forearm tissue, which was sustained for 5 min. After a further rest period of at least 30 min, glucose (5%, w/v; as vehicle) was infused into the brachial artery for 5 min, followed by sodium nitroprusside, which was infused as a time and vasodilator control to a maximum concentration of 0.6 μg·min⁻¹·100 ml⁻¹ forearm tissue, which was sustained for 5 min. In five subjects (randomly allocated), adenosine was infused before nitroprusside. In the remainder, the order of infusions was reversed.

Spectral analysis
The ECG was sampled at 1000 Hz to determine the interval between successive R waves (R–R interval). Data over the last 3.5 min of the baseline period and for each infusion were subjected to spectral analysis by fast Fourier transformation, as described in [20]. Extra or missing beats were edited and replaced with substitute R–R intervals calculated by linear interpolation from adjacent cycles. The unequal R–R intervals were aligned sequentially to obtain equally spaced samples with spectra that do not differ significantly from heart rate variability spectra for the interpolated time series [21]. The 3.5 min data set was subdivided into five overlapping segments. The mean and linear trend were subtracted from each segment. A cosine tapered window was applied to each segment to reduce spectral leakage. Power spectra were obtained and ensemble-averaged over the five segments using the Coolman–Tukey algorithm. Total spectral power (P₀) and integrated power within the low-frequency (0.05–0.15 Hz; Pᵢ) and high-frequency (0.15–0.50 Hz; Pₕ) regions were then computed. The ratios Pᵢ/P₀ and Pₕ/P₀ were used as conventional indices of parasympathetic nervous system and sympathetic nervous system modulation respectively of sino–atrial node discharge [14–16].

Statistics
Baseline values and responses to adenosine (140 μg·min⁻¹·kg⁻¹ intravenously for Series 1; 15 μg·min⁻¹·100 ml⁻¹ forearm tissue intra-arterial for Series 2) were compared. Mean values for blood pressure and heart rate, acquired over the 5 min baseline periods and during the last 3.5 min of adenosine infusions, were calculated. Student’s t-test was used for paired comparisons of heart rate and blood pressure, whereas the Wilcoxon signed rank test was used to assess changes in frequency-domain indices of heart rate variability from baseline values. P values of < 0.05 were considered statistically significant. Results are presented as means ± S.D.

RESULTS

Series 1: effect of intravenous adenosine infusion on heart rate variability
All subjects reported complete abstinence from any caffeine intake during the preceding 30 h, and plasma caffeine concentrations in all seven subjects were below the limits of detection. Adenosine (140 μg·min⁻¹·kg⁻¹, intravenous) increased heart rate by 33.3 ± 6.2 beats/min (P < 0.001). Systolic (+4.2 ± 8.2 mmHg) and diastolic (+0.5 ± 5.4 mmHg) blood pressure did not change significantly (Table 1; Figure 1). Adenosine suppressed Pᵢ (P < 0.02), Pₕ (P < 0.02) and P₀ (P < 0.02), as well as the parasympathetic nervous system indicator Pᵢ/P₀ (P < 0.02). In contrast, there was an increase in the sympathetic nervous system indicator Pₕ/P₀ (Table 1; Figure 2).

Series 2: effect of intra-arterial adenosine infusion on heart rate variability
Adenosine (15 μg·min⁻¹·100 ml⁻¹ forearm tissue, intra-arterial) increased forearm blood flow from 3.3 ± 0.36 to 6.2 ± 3.00 ml·min⁻¹·100 ml⁻¹ forearm tissue (P < 0.01). There was no significant effect on systolic blood pressure, but diastolic blood pressure was increased by 2.7 ± 2.4 mmHg (P < 0.01). Mean heart rate rose from 58 to 61 beats/min (P < 0.02) (Table 2). Adenosine had no effect on Pᵢ, Pₕ or P₀, or on the parasympathetic nervous system indicator Pᵢ/P₀. In contrast, there was a significant increase in the sympathetic nervous system indicator Pₕ/P₀ (P = 0.04) (Table 2; Figure 2).

Sodium nitroprusside (0.6 μg·min⁻¹·100 ml⁻¹ forearm tissue, intra-arterial) had no significant effect on

<table>
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<tr>
<th>Variable</th>
<th>Baseline</th>
<th>+ Adenosine</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>122 ± 6</td>
<td>126 ± 12</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>68 ± 8</td>
<td>68 ± 9</td>
<td>n.s.</td>
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<tr>
<td>Heart rate (min⁻¹)</td>
<td>67 ± 4</td>
<td>100 ± 6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>P₀ (ms²)</td>
<td>1496 ± 1829</td>
<td>280 ± 410</td>
<td>0.02</td>
</tr>
<tr>
<td>Pᵢ (ms²)</td>
<td>440 ± 421</td>
<td>32 ± 56</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>Pₕ (ms²)</td>
<td>437 ± 305</td>
<td>43 ± 41</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>Pᵢ/P₀</td>
<td>0.28 ± 0.11</td>
<td>0.08 ± 0.05</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>Pₕ/P₀</td>
<td>1.15 ± 0.36</td>
<td>3.00 ± 1.54</td>
<td>0.03</td>
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Figure 1  Effects of intravenous adenosine infusion on heart rate variability
Shown are representative tracings in a single subject of pulse (RR) intervals over 5 min (A) and corresponding coarse graining power spectra across the frequency range 0.0-0.5 Hz (B) under supine rest (baseline; left panels) and during intravenous infusion of adenosine at 140 µg·min⁻¹·kg⁻¹ (right panels).

Figure 2  Effects of intravenous and intra-arterial adenosine infusion on heart rate variability
Shown are group mean values for heart rate, PT, PH/PT as an index of heart rate modulation by the parasympathetic nervous system, and PL/PH as an index of heart rate modulation by the sympathetic nervous system, at baseline and during intravenous (i.v.) infusion of adenosine (140 µg·min⁻¹·kg⁻¹; left panels) (n = 7; mean ± S.D.), and at baseline and during intra-arterial (i.a.) infusion of adenosine (15 µg·min⁻¹·100 ml⁻¹ forearm tissue; right panels) (n = 9; mean ± S.D.).

Significance of differences: * P < 0.05; ** P < 0.02; *** P < 0.001.

systolic or diastolic blood pressure, or on heart rate. This increase in forearm blood flow (+10.9 ± 8.8 ml·min⁻¹·100 ml⁻¹ forearm tissue) was not significantly different from that caused by adenosine...
Table 2 Influence of intra-arterial adenosine infusion on blood pressure, heart rate and its variability

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>+ Adenosine</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>119±20</td>
<td>120±22</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>67±11</td>
<td>69±11</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>58±9</td>
<td>61±9</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>$P_i$ (m²)</td>
<td>4668±6424</td>
<td>3833±3051</td>
<td>n.s.</td>
</tr>
<tr>
<td>$P_a$ (m²)</td>
<td>1200±178</td>
<td>839±1050</td>
<td>n.s.</td>
</tr>
<tr>
<td>$P_e$ (m²)</td>
<td>978±990</td>
<td>1042±859</td>
<td>n.s.</td>
</tr>
<tr>
<td>$P_i/P_e$</td>
<td>0.22±0.10</td>
<td>0.18±0.12</td>
<td>n.s.</td>
</tr>
<tr>
<td>$P_i/P_i^*$</td>
<td>1.65±0.92</td>
<td>2.24±1.29</td>
<td>0.04</td>
</tr>
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(+16.8±19.5 ml·min⁻¹·100 ml⁻¹ forearm tissue; $P = 0.15$). Nitroprusside had no effect on $P_i$, $P_e$ or $P_a$, or on the ratios $P_i/P_e$ and $P_i/P_i^*$. The latter was 1.69±1.24 during dextrose infusion and 1.81±1.44 during sodium nitroprusside infusion.

DISCUSSION

In conscious humans, adenosine evokes a receptor-specific sympatho-excitatory reflex by stimulating afferent nerve endings in the carotid body, skeletal muscle, heart and kidney [3–8]. Several independent, yet complementary, methods have been used to characterize the reflex adrenergic response to adenosine infusion: peroneal muscle sympathetic nerve traffic [3,4], plasma noradrenaline concentration [22] and total body noradrenaline spillover [23]. However, the effect of exogenous adenosine on cardiac sympathetic neural drive, as assessed by heart rate variability, has not been described. From experiments in six healthy volunteers in which intravenous propranolol plus atropine abolished the increase in heart rate elicited by adenosine, but propranolol alone did not, Conradson et al. [13] concluded that vagal inhibition is the primary mechanism by which adenosine infusion increases heart rate. However, these authors did not report on the interaction of adenosine with atropine alone. Moreover, the combination of propranolol and atropine increased baseline heart rate significantly, complicating the interpretation of the results.

Systemic infusion of adenosine could affect heart rate variability through a number of pathways: by a direct negative chronotropic action on the sino-atrial node; or indirectly, either by a central neural action or reflexively by unloading arterial baroreceptors or by stimulating adenosine-sensitive afferent nerve endings in the carotid body, myocardium, kidney and skeletal muscle. Previously we reported that intra-arterial infusion of adenosine increased total body noradrenaline spillover, presumably by stimulating selectively the latter set of afferents [9]. In the present series, we determined whether selective stimulation of skeletal muscle afferent nerve endings by local infusion of adenosine has similar reflex effects on the sympathetic neural modulation of heart rate variability. If so, this mechanism could assume importance during local ischaemia or exercise.

In the first series of experiments, systemic infusion of adenosine caused a 50% rise in heart rate and increased the $P_i/P_a$ ratio, a frequency-domain representation of heart rate modulation by the sympathetic nervous system. Because diastolic blood pressure did not fall significantly, arterial baroreflex unloading [23] is probably less important than the stimulation of adenosine-receptor sympathetic neural afferents in mediating these sympathoneural responses. In the second series, intra-arterial infusion of adenosine also increased the sympathetic nervous system indicator $P_i/P_i^*$; this increase occurred in the setting of a much more modest (3 beats/min) increase in heart rate. This was not a time effect, or a non-specific response to forearm vasodilation, since nitroprusside infusion did not alter either variable. High local concentrations of adenosine, as may be achieved clinically by bolus administration, have a direct negative chronotropic effect and a direct inhibitory action on cardiac noradrenergic neurotransmission [24,25], yet heart rate increased during the intravenous and the intra-arterial infusions. Thus observations with both protocols are consistent with the concept that the cardiac adrenergic nervous system participates in the efferent reflex sympatho-excitatory response to infused adenosine.

Systemic infusion of adenosine reduced spectral power across all frequency bands. This effect, not observed during local infusion, can be attributed to the additional stimulation of adenosine-sensitive neural afferents in other skeletal muscle vascular beds, and in the heart, kidneys and carotid bodies. Several mechanisms could account for this broad-band decrease in spectral power. First, by acting directly on the sinus node [2], adenosine could exert a damping effect that would render the heart rate less responsive to neural modulation. Secondly, adenosine reduced two generally accepted indices of the parasympathetic modulation of heart rate: $P_i$ and the ratio $P_i/P_i^*$. These actions were not observed during intra-arterial infusion, indicating that the reflex stimulated by adenosine-receptor-specific neural afferents in the forearm does not include the parasympathetic nervous system in its efferent limb. Observations during systemic infusion indicate that sympathetic activation and vagal withdrawal are important effectors of the marked chronotropic response to adenosine. Such parasympathetic withdrawal could occur through several mechanisms, or their interactions: as an appropriate arterial baroreflex-mediated efferent response to peripheral vasodilation, via central inhibition of acetyl-
Chemoreceptor reflex stimulation is an important component of the sympato-excitatory response to the systemic infusion of adenosine in humans [5,27]. Adenosine infusion at $140 \mu g \cdot min^{-1} \cdot kg^{-1}$ increases tidal volume and causes respiratory alkalosis, but does not change breathing frequency [5]. Increasing the depth of respiration will increase vagal drive reflexively (which should augment power within the high-frequency spectral band) and decrease sympathetic outflow [28], i.e. effects opposite to those observed. Because tidal volume (and hence these additional respiratory influences) was not controlled in the present experiments, our results might have underestimated both the potential inhibitory effect of exogenous adenosine on parasympathetic tone and its excitatory influence on cardiac sympathetic neural drive.

The effects of adenosine infusion on heart rate variability in normal subjects have not been reported, but Petrucci et al. [17] assessed heart rate variability changes, using a time variant spectral algorithm, during the infusion of dipyridamole, which inhibits the cellular uptake of adenosine, leading to its accumulation [2]. In control subjects without objective evidence for coronary artery disease, dipyridamole infusion increased heart rate, and decreased $P_L$, $P_H$ and $P_L$ [17]. The last parameter decreased to 31% of its baseline value. The sympathetnic nervous system indicator $P_L/P_H$ tended to increase, but this was not significant. These results indicate that our observations during adenosine infusion are qualitatively similar to the actions of endogenous adenosine on heart rate variability in healthy subjects. In contrast, during ischaemia, when adenosine accumulates, there was a 15-fold increase in $P_L$ in their experimental group of patients with functionally important coronary artery disease [17], consistent with an enhanced, adenosine-induced, sympathetic-excitatory response under these conditions [10].

The sympathetic nervous system responds to some internal or external challenges in a highly selective and organ-specific manner, whereas, under other circumstances, such stimuli elicit a generalized sympato-excitatory response [29–31]. When considered in the context of previous reports that adenosine, infused at the dose used in the present study, increases muscle sympathetic nerve activity and heart rate [3,4], these observations with respect to heart rate variability indicate that the systemic infusion of adenosine evokes a generalized reflex sympathetic-excitatory response involving the heart, in addition to other vascular beds.

The capacity to vary the heart rate appropriately allows the cardiovascular system a broad repertoire of responses to maintain stability when faced by acute pathology or external challenges. A reduction in the variability or complexity of heart rate is a risk factor for early mortality following myocardial infarction [32]. The increases in heart rate, reductions in heart rate variability and augmented adrenergic drive to the heart observed during adenosine infusion may be clinically relevant in the setting of adenosine-radiotracer stress testing, and may contribute to its pro-arrhythmic effects, as observed in clinical practice [33]. These actions may also have relevance for cardioprotective interventions involving adenosine or molecules designed to replicate or potentiate its local actions [34]. In conditions such as congestive heart failure or coronary artery disease, tissue ischaemia or relative hypoperfusion of skeletal or cardiac muscle could stimulate the local production of endogenous adenosine and cause reflex increases in sympathetic outflow to the heart and other vascular beds [9]. In a recent report, 10–20-fold increases in plasma adenosine concentrations were described in patients with NYHA (New York Heart Association) Class III and Class IV heart failure, as compared with healthy control subjects [35]. Decreases in both the variability and the complexity of the heart rate in heart failure [36] have been attributed to impaired neural circulatory control, and to decreased sino-atrial responsiveness to autonomic input in this condition. Increased interstitial and plasma adenosine concentrations might underlie both alterations.

In summary, exogenous adenosine reduces heart rate variability by decreasing parasympathetic and increasing cardiac sympathetic nervous system tone. These actions overwhelm adenosine’s direct negative chronotropic effects, resulting in a marked increase in heart rate. Brachial artery infusion of adenosine has a more modest, positive, effect on heart rate, and increases its modulation by the cardiac sympathetic nervous system without affecting parasympathetic tone. These findings indicate concordance between this purine’s reflex actions on the heart and on sympathetic discharge to other vascular beds. These reflex effects override its direct negative chronotropic and sympatho-inhibitory actions, and may be clinically relevant in the setting of exercise, vasodepressor syncope [37], congestive heart failure or myocardial ischaemia, or during adenosine-radiotracer stress testing.

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