Adenosine Increases Sympathetic Nerve Traffic in Humans

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Background. Adenosine is an effective hypotensive agent in experimental animals and in anesthetized patients, producing little if any evidence of reflex sympathetic activation. In contrast, adenosine increases systolic blood pressure and heart rate in conscious subjects. To determine whether this response is related to sympathetic activation, we studied the cardiovascular and respiratory effects of adenosine in normal subjects while measuring muscle sympathetic nerve traffic through direct recordings from a peroneal nerve.

Methods and Results. Adenosine (80 µg/kg/min i.v.) increased heart rate (+32±3 beats/min), systolic blood pressure (+10±2 mm Hg), and minute ventilation (+7±1 l/min). This was accompanied by a dose-dependent increase in muscle sympathetic nerve activity (from 198±52 to 451±92 units/min). Adenosine also produced a small, but consistent, decrease in diastolic blood pressure (−6±3 mm Hg). Adenosine produced a greater increase in sympathetic nerve traffic (145±32% above baseline) than did nitroprusside (65±16%) at doses that resulted in equivalent decreases in diastolic blood pressure. Arterial baroreceptor unloading, therefore, could not totally explain the increase in sympathetic traffic produced by adenosine.

Conclusions. Given the constellation of findings of increased ventilation and sympathetic activity, we, therefore, propose that adenosine increases sympathetic tone by activating afferent nerves, including arterial chemoreceptors. Contrary to the known inhibitory actions of adenosine on central and peripheral efferent systems, this and other reports suggest that adenosine-induced activation of afferent nerves, leading to sympathetic activation, may be a more widespread phenomenon than previously recognized. (Circulation 1991;83:1668–1675)

The cardiovascular effects of adenosine have received increasing attention since the recognition of its antiarrhythmic properties in humans and the possibility that it could become the agent of choice for the termination of supraventricular tachycardias involving atrioventricular node reentrant pathways. In addition to its antiarrhythmic action, adenosine is an effective hypotensive agent in nearly all animal models. Intravenous adenosine administration produces sustained hypotension in patients devoid of autonomic reflexes and in anesthetized patients. In anesthetized patients, blood pressure is decreased by 30% primarily because of a decrease in systemic vascular resistance, without evidence of reflex sympathetic activation; heart rate remains practically unchanged, and the expected compensatory increase in plasma catecholamines and plasma renin activity is absent.

Several of the actions of adenosine can explain the lack of reflex sympathetic and renin activation. Microinjections of adenosine into discrete vasomotor centers of the brain stem produce a decrease in sympathetic tone and in blood pressure. In the periphery, adenosine inhibits the release of norepinephrine from efferent sympathetic nerves and inhibits ganglionic neurotransmission. In addition to its effects on the sympathetic system, adenosine also has negative chronotropic and dromotropic actions and inhibits renin release. The relative contribution of these actions to the hypotensive effects of adenosine given intravenously is not entirely known.

In contrast to its hypotensive actions in patients with impaired autonomic reflexes, adenosine increases systolic blood pressure, increases heart rate, and stimulates respiration in unanesthetized normal
Furthermore, the increase in systolic blood pressure and in heart rate correlates significantly with an increment in arterial norepinephrine concentrations. These findings seem to indicate that contrary to suggestions from previous studies, adenosine stimulates, rather than inhibits, sympathetic tone in unanesthetized humans.

Although the measurement of plasma norepinephrine levels is a useful indicator of sympathetic activity, it has the limitation of measuring only the spillover of the relevant concentrations of norepinephrine present in the synaptic cleft. Once in plasma, norepinephrine concentrations may change because of altered metabolism or other factors that are not a direct result of sympathetic tone. It is now possible, however, to directly record sympathetic nerve traffic in humans by placing an electrode in a peripheral nerve that provides efferent sympathetic innervation to muscles. Muscle sympathetic nerve activity recorded with this microneurographic technique has been shown to be coupled to blood pressure modulation by the baroreflex arc. In studies in which muscle sympathetic nerve activity has been compared with plasma norepinephrine concentration during stimulation of sympathetic drive, a significant correlation exists between those measurements, but peak levels of plasma norepinephrine lag behind the increase in muscle sympathetic nerve activity. In other studies, measurements of arterial norepinephrine spillover underestimated the degree of the sympathetic activation induced by hypotension when compared with measurements of muscle sympathetic nerve activity. The purpose of this study was, therefore, to use this sensitive technique to investigate the effects of adenosine on sympathetic nerve activity in humans.

Methods

We studied 10 normal, healthy men, 22–33 years old (mean, 27±1 years). Subjects were nonsmokers, were free of medications, and had abstained from methylxanthines for at least 24 hours before the study day. Volunteers were informed of the characteristics of the study, and they gave written consent. The protocol was approved by the Vanderbilt University Institutional Review Board.

Subjects were studied after having fasted and while in the supine position. Heart rate was monitored by surface electrocardiography coupled to a rate computer. Arterial blood pressure was measured through an indwelling catheter placed in a radial artery and connected to a transducer. The subjects breathed through a mouthpiece, and inspiration and expiration were isolated with one-way valves. Expiratory flow was measured with a heated pneumotachograph (Fleisch pneumotach, A. Fleisch, Switzerland) connected to a differential transducer (Validyne Engineering Corp., Northridge, Calif.). Expiratory volume was measured by integrating the expiratory flow signal over time (Integrator signal conditioner, Gould Inc., Cleveland, Ohio). In five subjects, a catheter was inserted into an antecubital vein and advanced to an intrathoracic position to measure central venous pressure. Cardiovascular signals were modulated on signal conditioners and displayed on a thermal array recorder (model TA2000, Gould Inc.).

Sympathetic nerve traffic was measured as previously described. The approximate location of the right peroneal nerve at the level of the fibular head was determined by transdermal electrical stimulation (10–60 V, 0.01 msec duration), which produced painless muscle contractions of the foot. A tungsten needle electrode, with a shaft diameter of 200 μm and an uninsulated tip diameter of 1–5 μm, was inserted into the nerve. A similar electrode with a larger uninsulated tip was inserted subcutaneously near the recording electrode to serve as a reference electrode. The recording electrode was positioned within the nerve to obtain multiunit recordings of sympathetic efferent activity. Placement of the electrode was guided by electrical stimulation (1–4 V, 0.01 msec duration), which produced muscle twitches of the foot but not paresthesia. Electrical stimulation was performed with a stimulator (S88, Grass Instruments, Quincy, Mass.) connected to an isolation unit (model SIU8TB, Grass Instruments). The electrode was then switched to a recording mode, and fine adjustments of its position were made to obtain a satisfactory recording site as described below. Recorded signals were fed to a preamplifier (1,000-fold amplification) and were filtered using a band width between 700 and 2,000 Hz. The filtered signal was rectified, amplified 100-fold, and integrated in a resistance-capacitance network using a time constant of 0.1 second (Nerve traffic analysis system 662C-3, University of Iowa Bioengineering, Iowa City). The final signal was monitored using a storage oscilloscope (model S111A, Tektronics, Beaverton, Ore.) and recorded after fourfold amplification (TA-2000 Recorder, Gould Inc.).

Criteria for an adequate muscle sympathetic nerve activity recording were 1) electrical stimulation produced muscle twitches but not paresthesia, 2) stretch of the tendons in the foot evoked proprioceptive afferent signals, whereas cutaneous stimulation by slight stroking of the skin did not, 3) held expiration increased neural activity at a site where arousal stimuli did not, and 4) nerve activity increased during the hypotensive phase of the Valsalva maneuver and was suppressed after the release of the Valsalva maneuver during blood pressure overshoot. Muscle sympathetic nerve activity was also monitored throughout the study using a loudspeaker. This helped in identifying potential artifacts such as electrostatic discharges that were also identified in the integrated neurogram by their rapid onset and offset.

After instrumentation, subjects were allowed to rest in a quiet room for 20–30 minutes. They were then given increasing boluses of adenosine (20, 40, 60, and 80 μg/kg i.v.) until respiratory stimulation was observed. This was done to familiarize the volunteers with the actions of adenosine so that its effects during the study would not be unexpected. After a second rest period, the subjects received
saline followed by increasing infusions of adenosine (20, 40, 60, and 80 μg/kg/min) for 5–10 minutes each, in an antecubital vein, using a syringe infusion pump (model 22, Harvard Apparatus, South Natick, Mass.). Higher doses can be given to conscious subjects but were avoided because the magnitude of the respiratory stimulation produced can be uncomfortable. In the present study, adenosine infusion was stopped when the subjects complained of uncomfortable side effects. This happened to one subject at a dose of 60 μg/kg/min, and therefore, his data are not included. Even with steady-state infusions, the effects of adenosine were not sustained but rather cyclic in nature. Respiratory stimulation was maximal at 1.5–2-minute intervals and returned toward baseline in between. The changes in heart rate, blood pressure, and muscle sympathetic nerve activity followed the same pattern. The reasons for this cyclic pattern are unclear and under investigation. Measurements were obtained during periods of maximal effects of adenosine by averaging the cardiovascular, respiratory, and microneurographic parameters during a 1-minute period. Similar measurements were obtained at periods of maximal spontaneous nerve activity during saline administration and were used as baseline measurements.

Measurements of muscle sympathetic nerve activity were made from the original tracings of the mean voltage neurograms using a digitizer tablet coupled to Sigma Scan software (Jandel Scientific, Corte Madera, Calif.) in a microcomputer. The amplitude of each “burst” was measured in millimeters, and total activity was defined as the sum of “burst” amplitude during a 1-minute period and expressed in arbitrary units.

In a subset of five patients, the effects of intravenous adenosine were compared with those produced by intravenous administration of nitroprusside. Nitroprusside was given as a bolus at increasing doses (0.01–0.1 μg/kg i.v.) until a decrease in diastolic blood pressure comparable to that produced by adenosine was reached. All infusions (saline, adenosine, or nitroprusside) were given randomly, and the subject was unaware of which infusion he received. At least 20 minutes was allowed between infusions. In a subset of four patients, the effects of intravenous administration of adenosine were compared with those produced by acute hypoxia. Hypoxia was induced by having the subjects breathe a mixture containing 10% O₂ and 90% N₂ for 5 minutes. This mixture was prepared from cylinders containing nitrogen and compressed air connected to a calibrated gas blender (Bird Corp., Palm Springs, Calif.) and delivered to the volunteer during inspiration by a demand valve connected to a one-way valve.

**Drugs**

Adenosine was purchased from Sigma Chemical Company (F&D Division, St. Louis) and dissolved in normal saline at a concentration of 10 mg/ml. The solution was tested for sterility and pyrogenicity.

**Statistical Analysis**

Data were analyzed in a microcomputer using the Number Cruncher Statistical System (NCSS, Kaysville, Utah). Analysis of variance (ANOVA) with repeated measures for each subject was used to determine dose-related differences, using the dose of adenosine as a fixed variable (five levels). Paired t tests were used to determine differences between...
groups (adenosine versus nitroprusside, adenosine versus hypoxia). All hypotheses were two-tailed, and the criterion for significance was $p<0.05$. Results are expressed as mean±SEM.

**Results**

Actual tracings from a representative study are shown in Figure 1. Dose-response curves for the variables measured are shown in Figures 2 and 3. At the highest dose given (80 $\mu$g/kg/min), adenosine produced a small, but consistent, increase in systolic blood pressure from 128±4 to 138±4 mm Hg ($p<0.001$ by ANOVA) and a small, but consistent, decrease in diastolic blood pressure from 69±4 to 63±5 mm Hg ($p<0.001$). Mean arterial blood pressure was 89±3 mm Hg during saline infusion and remained unchanged (88±4 mm Hg) during the infusion of adenosine at 80 $\mu$g/kg/min. Likewise, adenosine had no effect on central venous pressure (4±1 mm Hg during saline and 4±1 mm Hg during adenosine). Adenosine also produced a significant increase in heart rate from 65±4 to 97±6 beats/min ($p<0.001$) and in ventilation from 7.8±0.7 to 14.7±1.2 l/min ($p<0.001$). A dose-dependent increase in muscle sympathetic nerve activity was observed (Figure 3). Nerve activity increased from 198±52 to 452±92 units/min during the infusion of adenosine at 80 $\mu$g/kg/min.

We compared the effects of sodium nitroprusside with those produced by adenosine in five subjects to determine the contribution of the reduction in diastolic blood pressure to the overall increase in sympathetic nerve traffic. The doses of sodium nitroprusside (0.57±0.12 $\mu$g/kg) and adenosine (72±5 $\mu$g/kg/min) were matched in each subject to produce a similar decrease in diastolic blood pressure ($-8±1$ and $-6±2$ mm Hg, respectively). Sodium nitroprusside also decreased systolic and mean arterial blood pressure ($-15±3$ and $-10±2$ mm Hg). By comparison, adenosine increased systolic blood pressure by 6±1 mm Hg and had no effect on mean arterial blood pressure. However, the increase in muscle sympathetic nerve activity was greater with adenosine (145±32% above baseline) than with nitroprusside (65±16% above baseline, $p<0.005$) (Figure 4).

Acute hypoxia is known to activate arterial chemoreceptors, resulting in respiratory stimulation and increased sympathetic nerve activity.19 Because we hypothesized that adenosine also activates arterial chemoreceptors, we compared the increase in sympathetic nerve activity produced by adenosine to that produced by hypoxia. Adenosine was given at a dose (60 $\mu$g/kg/min) found to produce the same increase in ventilation (+3.8±1 l/min) as that pro-

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**Figure 2.** Plots of dose-response relations for effects of adenosine on systolic blood pressure (SBP, mm Hg), diastolic blood pressure (DBP, mm Hg), central venous pressure (CVP, mm Hg), minute ventilation (VENT, l/min), and heart rate (HR, beats/min). $p$ values are from analysis of variance; n=eight normal subjects, except for central venous pressure, which was n=five. Data are expressed as mean±SEM.

**Figure 3.** Plot of dose-response relation for effects of an intravenous infusion of adenosine on muscle sympathetic nerve activity (MSNA, arbitrary units/min). $p$ values are from analysis of variance; n=eight normal subjects. Data are expressed as mean±SEM.
duced by hypoxia (+3.8±1 l/min). At this dose, adenosine produced increases in heart rate (21±6 beats/min) and muscle sympathetic nerve activity (75±25% increase above baseline) similar to those produced by hypoxia (29±3 beats/min and 50±22% increase above baseline) (p>0.05 by paired t test, Figure 5). Mean arterial blood pressure was not affected by either maneuver.

Discussion

Contrary to what previous studies in experimental animals and anesthetized patients suggest, adenosine administration in normal, conscious subjects results in increased systolic blood pressure and heart rate. The present study confirms that these effects are associated with an increase, rather than the expected decrease, in sympathetic nerve activity. Because these findings seem to contradict the known inhibitory actions of adenosine, we first need to consider the possibility that the sympathetic activation observed is just a compensatory effect secondary to the cardiovascular or respiratory actions of adenosine, for example, through activation of baroreceptors or lung mechanoreceptors.

Although adenosine increased systolic blood pressure and pulse pressure, it did not change mean arterial blood pressure significantly. However, it did produce a small, but consistent, decrease in diastolic blood pressure. Therefore, the increase in sympathetic nerve traffic can be attributed to arterial baroreceptor unloading secondary to the decrease in diastolic blood pressure. It is especially important to consider this alternative because diastolic blood pressure appears to be the primary determinant of muscle sympathetic nerve activity.20 However, adenosine produced a greater increase in sympathetic nerve activity than did nitroprusside at doses that produced equivalent decreases in diastolic blood pressure (Figure 4). This was true even though nitroprusside also decreased systolic and mean arterial blood pressures, producing perhaps greater unloading of arterial baroreceptors than did adenosine; nitroprusside would, therefore, be expected to increase efferent muscle sympathetic nerve activity to a greater degree

![Figure 4](.Bar graph of comparing effects of adenosine (72±5 μg/kg/min i.v.) and nitroprusside (0.57±0.12 μg/kg i.v.) on diastolic and mean arterial blood pressures (DBP, MABP, respectively; left vertical axis, expressed as changes from baseline) and muscle sympathetic nerve activity (MSNA; right vertical axis, expressed as percent change from baseline). P values are from paired t tests. N=five normal subjects. Data are expressed as mean±SEM.)

![Figure 5](Bar graph comparing effects of adenosine (60 μg/kg/min i.v.) and acute hypoxia (10% O2–90% N2 for 5 minutes) on minute ventilation and muscle sympathetic nerve activity (VENT, MSNA, respectively; left vertical axis, expressed as percent change from baseline) and heart rate (HR; right axis, in beats/min, expressed as changes from baseline). No differences between effects of hypoxia and adenosine were found by paired t test. N=four normal subjects. Data are expressed as mean±SEM.)
than would adenosine. We interpret these results as evidence that baroreceptor unloading by adenosine can contribute to, but not be solely responsible for, the increase in sympathetic activity.

Unloading of low-pressure cardiopulmonary baroreceptors can also increase muscle sympathetic nerve activity. Even minor decreases in central venous pressure may produce measurable increases in muscle sympathetic nerve activity. Because central venous pressure was unaffected by adenosine, however, it seems unlikely that unloading of low-pressure receptors contributes significantly to the increase in muscle sympathetic nerve activity observed.

Adenosine produces substantial respiratory stimulation. The resultant increase in thoracic excursion will activate lung mechanoreceptors that can modulate sympathetic tone. Activation of lung mechanoreceptors, however, will restrain, rather than increase, muscle sympathetic nerve activity. Therefore, this mechanism would actually oppose the increase in muscle sympathetic nerve activity produced by adenosine and lead to an underestimation of its magnitude.

It seems possible, therefore, that adenosine produces sympathetic activation by a direct, rather than secondary, effect. This effect can theoretically be produced at any of the different levels of the sympathetic arc, that is, the afferent limb, the brain, or the efferent limb. A stimulatory effect of adenosine on efferent sympathetic nerves seems unlikely, given the well-established inhibitory actions of adenosine on neurotransmitter release, particularly norepinephrine. Adenosine may also inhibit neurotransmission in sympathetic ganglia. A central effect is also unlikely because studies in dogs have reported that intravenous adenosine does not cross the blood–brain barrier. Certain circumventricular nuclei, such as the area postrema, are devoid of an effective blood–brain barrier and, thus, may be accessible to blood-borne adenosine. However, microinjection of adenosine in this and other vasomotor brain stem centers results in decreased renal sympathetic nerve activity and decreased blood pressure. Therefore, even if these central effects are seen in humans these effects would be opposite to those observed with intravenously administered adenosine.

Given the constellation of findings observed in the present study (increased ventilation, blood pressure, and sympathetic activity), these effects are probably explained by adenosine-induced chemoreceptor activation. In agreement with this hypothesis, prior studies showed that intracarotid injections of adenosine in rats and cats increase carotid sinus nerve activity, implying carotid body chemoreceptor activation. In humans, adenosine increases blood pressure and stimulates respiration if infused into the aortic arch, proximal to the origin of the carotid arteries, but it decreases blood pressure and does not affect ventilation when infused into the descending aorta. The fact that the effects of adenosine on cardiovascular parameters and sympathetic activity were of similar magnitude to those produced by hypoxia is also in agreement with this hypothesis.

The proposal that adenosine activates the sympathetic nervous system is contrary to the widely held view of adenosine as an inhibitory neuromodulator. Most of the actions of adenosine are indeed consistent with an inhibitory role. Adenosine produces hyperpolarization of neurons, resulting in decreased nerve firing and inhibits neurotransmitter release through putative presynaptic inhibitory receptors, both in the brain and in the periphery. Adenosine inhibits the release of practically all neurotransmitters studied, including norepinephrine, acetylcholine, dopamine, glutamic acid, aspartame, γ-aminobutyric acid, and serotonin. Adenosine also has a central depressor action, independent of its cardiovascular effects, and because it prevents seizure activity, it has been proposed as an endogenous anticonvulsant.

Although the finding that adenosine increases sympathetic tone seems to be at odds with its putative inhibitory role, other lines of evidence that have received less attention suggest that adenosine does activate afferent nerves, leading to sympathetic activation. In addition to the evidence for afferent arterial chemoreceptor activation described above, Cox et al. showed that intracoronary administration of adenosine produces a pressor response in humans. This effect could not be explained by spillover into the systemic circulation because administration of a similar dose of adenosine into the coronary sinus had no effect on blood pressure. This pressor effect was not observed in patients with transplanted, and therefore denervated, hearts. This suggests that adenosine activates myocardial afferent nerves in humans. To our knowledge, this phenomenon has not been reported in dogs, even though this animal model has been used extensively to study the effects of adenosine on the coronary circulation. It is, therefore, conceivable that species differences exist and that this effect is seen to a greater extent in humans. Last, intrarenal administration of adenosine has also been reported to activate renal afferents in dogs, thereby increasing blood pressure. Whether this effect is operative in humans is unknown. In addition to sympathetic afferent activation, adenosine has been postulated to activate sensory afferents in the heart and human forearm.

We, therefore, suggest that adenosine activates afferent fibers resulting in sympathetic activation and that this phenomenon is more widespread than previously recognized. In the present study, adenosine-induced activation of other afferents, in addition to arterial chemoreceptors, can theoretically contribute to sympathetic activation. They cannot, however, explain the increase in ventilation observed.

It could be argued that the doses of adenosine used in this study (20–80 µg/kg/min) are smaller than those used to lower blood pressure in anesthetized subjects (approximately 200 µg/kg/min) and that higher doses may produce a different hemody-
Adenosine also induced sympathetic activation in normal volunteers12 young healthy volunteers, but lowering of blood pressure was prevented by an increase in stroke volume and heart rate. Therefore, the increase in sympathetic activity produced by intravenous administration of adenosine in conscious subjects probably predominates over its putative effect in the brain stem and efferent sympathetic nerves as well as its bradycardic and vasodilatory effects. We can speculate that the reason for this is that arterial chemoreceptors are more sensitive to the actions of adenosine than the vasculature. Perhaps a more likely explanation, given the extremely short half-life of adenosine, is that when given intravenously, a greater concentration of adenosine reaches arterial chemoreceptors before reaching other sites of action.

Sympathetic activation probably explains why bolus injections of adenosine in normal subjects who are in sinus rhythm do not consistently produce bradycardia12 and why continuous infusions consistently produce tachycardia even though adenosine consistently terminates episodes of supraventricular tachycardia involving the atrioventricular node.2 The bradycardic effects of adenosine are also probably obscured by the increase in heart rate produced by activation of lung mechanoreceptors secondary to the increased ventilation.22

On the other hand, the hypotensive effects of adenosine are evident in anesthetized subjects, possibly because of blunting of chemoreflexes by anesthesia,22 leaving unopposed the vasodilatory actions of adenosine. Likewise, the bradycardic and vasodilatory actions of adenosine are evident in patients devoid of autonomic reflexes.12 In these patients, extremely low doses of adenosine (10 µg/kg) reduce heart rate and blood pressure, whereas these low doses are ineffective in normal subjects. A similar degree of hypersensitivity to adenosine has been found in patients with transplanted, and therefore denervated, hearts.47 This has been interpreted as an “intrinsic” hypersensitivity to adenosine, analogous to the hypersensitivity to sympathomimetics secondary to chronic absence of adrenergic stimulation.48 It is also possible, however, that this “hypersensitivity” is just a reflection of the absence of adenosine-induced sympathetic activation that would normally exert an opposing effect.

In summary, our results indicate that adenosine stimulates sympathetic nerve traffic in humans. This effect cannot be attributed solely to baroreceptor unloading. Adenosine also stimulates respiration in humans. Although activation of additional afferents cannot be excluded, these results may be explained by activation of arterial chemoreceptors in humans. Even though adenosine can theoretically inhibit norepinephrine release from efferent sympathetic terminals and inhibit sympathetic tone in the brain stem, we suggest that when given intravenously to humans, adenosine primarily activates afferent nerves, resulting in sympathetic activation. Evidence to date indicates that this may be a widespread, rather than an isolated, phenomenon. In humans with intact autonomic reflexes, sympathetic activation probably counteracts the bradycardic and vasodilatory effects of adenosine.

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