Role of Arterial Chemoreceptors in Mediating the Effects of Endogenous Adenosine on Sympathetic Nerve Activity

Erica D. Engelstein, MD; Bruce B. Lerman, MD; Virend K. Somers, MD, DPhil; Robert F. Rea, MD

**Background** Exogenous adenosine has been shown to increase muscle sympathetic nerve activity (MSNA), blood pressure, heart rate, and ventilation in conscious humans, effects attributed to peripheral chemoreceptor activation. Adenosine, an endogenous nucleoside, has potent cardiac electrophysiological actions that are mediated primarily through its effects on potassium conductance, whereas its actions on ventricular myocardium are mediated through an antiadrenergic effect. Adenosine is also a vasodilator in most vascular beds and produces sustained hypotension in anesthetized subjects, mainly by decreasing peripheral vascular resistance. The relative lack of reflex sympathetic activation in response to adenosine-induced hypotension in anesthetized subjects has been attributed to the inhibitory role of adenosine as a neuromodulator, that is, inhibition of neurotransmission in sympathetic ganglia and inhibition of norepinephrine release from efferent sympathetic nerves.

In contrast to its effects in anesthetized patients, exogenous adenosine results in sympathetic neural activation rather than inhibition in conscious subjects. Adenosine increases systolic blood pressure, heart rate, and ventilation, effects shown to correlate with an increment in plasma norepinephrine and efferent muscle sympathetic nerve activity related only in part to baroreflex-mediated sympathetic activation. Because acute hypoxia results in a similar ventilatory, hemodynamic, and sympathetic responses and because adenosine has been shown to increase afferent nerve activity in both carotid and aortic body chemoreceptors, it has been suggested that the sympathoexcitatory and ventilatory effects of adenosine are mediated by chemoreceptor activation.

Although the effects of exogenous adenosine on sympathetic activity are well defined, the effect of endogenous adenosine on sympathetic nerve activity and its potential mediation through chemoreceptor activation has not been examined. To determine whether endogenous adenosine has sympathoexcitatory effects and, if so, whether they are mediated through chemoreceptor activation, we examined the effects of dipyridamole on sympathetic nerve activity and ventilation. In addition to its inhibitory effects on phosphodiesterase, dipyridamole inhibits the cellular reuptake and metabolism of adenosine, thereby increasing its extracellular concentration and activity at the adenosine receptor.

**Methods**

Fifteen volunteers (13 men, 2 women) with a mean age of 23.6±3.3 years (range, 20 to 34 years) were studied in a series of three protocols. Some subjects participated in two different
protocols on separate days. All subjects were healthy, none took medication, and all had abstained from caffeine-containing beverages for at least 24 hours before the study. The experiment was explained in detail to each subject by one of the investigators, and informed consent was obtained. The studies were approved by the Institutional Review Board for Studies in Human Subjects.

**Sympathetic Nerve Recordings**

Sympathetic activity was measured by direct microneurographic recordings of efferent muscle sympathetic nerve activity (MSNA) in the peroneal nerve. Measurements obtained using this technique reflect sympathetic discharge to the skeletal muscle vascular bed and correlate well with measurements of plasma norepinephrine and norepinephrine spillover.

To measure MSNA, the course of the peroneal nerve around the head of the fibula was mapped with transcutaneous electrical stimulation (10 to 60 V). A tungsten microelectrode with a shaft diameter of 200 μm and an uninsulated tip diameter of 1 to 5 μm was then inserted into the region of the nerve, and a similar electrode was inserted subcutaneously a few centimeters away to serve as an electrical reference. Weak electrical stimuli (1 to 5 V) were delivered to the recording electrode from a Grass stimulator (model S-48) connected to an isolation unit. The electrode was advanced toward the nerve until weak, involuntary, painless twitches were elicited in the lower leg, indicating that a muscle nerve fascicle had been impaled. The electrode was then switched to a recording mode, and its position was adjusted to obtain a satisfactory recording site.

The electrodes were connected to a preamplifier with a gain of 1000 and to an amplifier with a gain of 70. The nerve signals underwent bandpass filtering (700 to 2000 Hz), and the filtered signal was rectified and integrated with a resistance-capacitance network with a time constant of 0.1 second (Nerve Traffic Analysis System, model 662C-3, University of Iowa) to obtain a display of the mean voltage neurogram. The nerve signals were displayed on an oscilloscope (Tektronics, model 5111A), played through a loudspeaker to identify noise artifacts, and were recorded with a paper chart recorder (Gould Electronics, model ES 2000).

A recording was considered acceptable if it fulfilled three criteria. First, weak electrical stimulation through the recording electrode elicited involuntary muscle contractions but no paradoxes. Second, tapping or stretching the muscles or tendons supplied by the impaled fascicle elicited afferent mechanoreceptor discharges, whereas stroking the skin in the sensory field of the nerve evoked no afferent response. Third, spontaneous, intermittent, pulse-synchronous bursts of activity emerged from the background signal and increased in frequency and amplitude during held expiration and during phases 2 and 3 of the Valsalva maneuver. Evidence that this burst activity represents efferent sympathetic nerve activity is derived from earlier studies and includes (1) interruption of the activity by local nerve block proximal but not distal to the recording site, (2) elimination of the activity by ganglionic blockade, and (3) conduction velocity approximately 1 m/sec, consistent with the behavior of unmyelinated C-fibers.

**Other Measurements**

Arterial blood pressure was measured in 7 subjects through an indwelling catheter placed in a radial or brachial artery. In the remaining subjects, continuous finger plethysmographic measurements of blood pressure (Finapres, Ohmeda) were recorded and confirmed with an automatic oscillometric sphygmomanometer (Dinamap, Critikon) at 1-minute intervals. Heart rate was derived from a continuous recording of the ECG. Central venous pressure was recorded directly from a polyethylene catheter inserted in an antecubital vein and advanced into an intrathoracic position. Respiratory phase was recorded with a bellows strain-gauge encircling the upper abdomen (Pneumotrace, model 1130, UFI). End-tidal CO₂ (Hewlett-Packard 47210A capnometer), oxygen saturation (Nellcor N-100 C pulse oxymeter), ventilatory rate, and minute ventilation (Bourns LS-75 ventilation monitor) were also recorded. Subjects breathed through a mouthpiece, with a nose clip used to ensure exclusive mouth breathing. The mouthpiece was connected to a three-way valve, which could be switched between room air and a reservoir bag containing 100% O₂. The mean voltage neurogram, arterial and central venous blood pressure, ECG, and respiratory phase were continuously recorded with a paper chart recorder, and all parameters were acquired for further analysis with a computer using customized LabVIEW software (LabView 2 Software System, National Instruments).

**Experimental Protocols**

After placement of all catheters and microelectrodes for nerve recordings, the subjects rested for 10 to 15 minutes. All experiments were performed with the subjects in supine position. Three protocols were performed.

**Effects of Dipyridamole During Room Air Breathing and Hyperoxia**

To determine the cardiovascular and respiratory effects of dipyridamole and to assess the role of peripheral chemoreceptors in mediating these actions, we compared the effects of dipyridamole during room air breathing (protocol 1) with those during hyperoxia (suppression of peripheral chemoreceptor activity, protocol 2) (Fig 1). Five minutes of baseline data were first recorded, and values for MSNA, systolic, diastolic, and central venous pressures, heart rate, minute ventilation, respiratory rate, end-tidal CO₂, and oxygen saturation were averaged over this period. Subjects were then switched (blindly) to breathe either room air (n=7) or 100% O₂ (n=6) for the remaining part of the protocol. Data were again recorded and averaged for a 3-minute period before dipyridamole 0.56 mg/kg was infused over 4 minutes. After an equilibration period of 5 minutes, data were collected for 3 minutes. Comparisons were made between “control” and “dipyridamole” in the group breathing room air throughout the experiment and between “control,” “hyperoxia,” and “dipyridamole+hyperoxia” in the subjects switched to breathing 100% O₂.

**Effects of Aminophylline on the Actions of Dipyridamole**

To determine whether aminophylline, an adenosine receptor antagonist, prevents the sympathoexcitatory and respiratory effects of dipyridamole, we performed the following protocol (protocol 3, Fig 1). After baseline measurements, aminophylline 5.6 mg/kg was infused over 20 minutes, which was followed by a maintenance infusion of 0.04 mg/kg per minute. Ten minutes into the maintenance infusion, blood samples were drawn for determination of aminophylline levels, and a second period of data collection (over 3 minutes) was obtained to assess the effects of aminophylline alone on MSNA, heart rate, blood pressure, and respiratory function during room air breathing. Dipyridamole was then administered in the same manner as described above and after 5 minutes of equilibration, data were collected for another 3-minute period. Aminophylline levels were determined with a commercially available immunoassay (Abbott Laboratories).

**Data Analysis**

Sympathetic bursts in nerve recordings were identified by their characteristic morphology and relation to ECG R waves. Burst amplitude was analyzed with a digitizing tablet (Sigma Scan, Jandel Scientific), and burst amplitudes were summed over 1-minute periods to yield an estimate of MSNA in
Protocol 1

Breathing Room Air (Normoxia)

Control 5 min
Room air 2
3 min
Diprydamole 0.56 mg/kg/4 min
4 min
5 min
Diprydamole + Room air 3 min

Protocol 2

Breathing 100 % O2 (Hyperoxia)

Control 5 min
Hyperoxia 2
3 min
Diprydamole 0.56 mg/kg/4 min
4 min
5 min
Diprydamole + Hyperoxia 3 min

Protocol 3

Control 5 min
Aminophylline 20 min
3 min
Aminophylline + Diprydamole 4 min
5 min
Diprydamole 0.56 mg/kg/4 min
3 min

Fig 1. Chart of experimental protocols. Protocol 1: Effects of diprydamole during room air breathing. Baseline recordings were obtained during room air breathing and averaged over a 5-minute period (control). Subsequently, subjects breathed through a mouthpiece a gas mixture, which was room air. Two minutes after breathing the gas mixture, data were recorded for a 3-minute period (room air). Diprydamole was then infused over 4 minutes, and another 5 minutes was allowed as an equilibration period. After that, data were recorded for another 3-minute period (diprydamole + room air). Protocol 2: Effects of diprydamole during hyperoxia. The protocol was identical to protocol 1 except that subjects breathed 100% O2 through the mouthpiece. Protocol 3: Effects of diprydamole after pretreatment with aminophylline. After baseline recordings were obtained over 5 minutes, a loading dose of 5.6 mg/kg of aminophylline was infused over 20 minutes followed by a maintenance infusion. After the loading dose, data were recorded over 3 minutes to assess the effects of aminophylline alone. Diprydamole was then infused as described above, and data were recorded for another 3-minute period after an equilibration phase.

Results

Diprydamole During Room Air Breathing

Diprydamole increased MSNA by 108%, from 231±42 to 504±136 U/min ($P<.01$), and nearly doubled burst frequency, from 24±2.8 to 47±6 bursts per minute ($P<.001$) (Table and Fig 2). Heart rate increased by 49%, from 65±3.8 to 96±4.7 beats per minute ($P<.001$). Systolic blood pressure increased from 129±3.5 to 140±4.8 mm Hg ($P<.001$), but there was no significant change in diastolic blood pressure (65.6±3.4 to 66.5±4 mm Hg, $P=NS$). The mean arterial pressure thus increased from 87±2.6 to 91±3.4 mm Hg ($P<.01$). Diprydamole had a small effect on central venous pressure, which decreased from 5.5±0.4 to 4.5±0.3 mm Hg ($P<.01$). Diprydamole also increased mean minute ventilation by 20±7%, from 7.8±0.6 to 9.1±0.5 L/min ($P<.01$), which was reflected by a decrease in end-tidal CO2, from 43.6±1 to 39.3±0.9 mm Hg ($P<.001$). The increase in minute ventilation was due to an increase in tidal volume, as there was no significant change in the respiratory rate, 15±1.4 versus 14.7±2.2/min. Most subjects experienced mild to moderate chest discomfort, anxiety, dyspnea, flushing, and heart pounding during diprydamole infusion, all of which completely resolved within 5 minutes after completing the diprydamole infusion.

The effects of diprydamole on sympathetic activity and ventilation had different time courses (Fig 3). Sympathetic nerve activity increased immediately during the infusion of diprydamole and remained at approximately 80% of the maximal effect for at least 25 minutes. The changes in heart rate paralleled the changes in MSNA during the 25 minutes after diprydamole infusion. Systolic blood pressure increased gradually over 10 minutes after the infusion was begun and returned to baseline over the following 20 minutes. Diastolic blood pressure showed an initial transient decrease of 10% during infusion of diprydamole, which
Effects of Dipyridamole During Room Air Breathing and Hyperoxia

<table>
<thead>
<tr>
<th>Burst</th>
<th>MSNA, U/min</th>
<th>Heart Rate, bpm</th>
<th>SBP, mm Hg</th>
<th>DBP, mm Hg</th>
<th>CVP, mm Hg</th>
<th>Minute Ventilation, L/min</th>
<th>Respirations, n/min</th>
<th>End-Tidal CO₂, mm Hg</th>
<th>O₂ Saturation, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Room air</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>231±24</td>
<td>24±2.8</td>
<td>65±3.8</td>
<td>129±3.5</td>
<td>66±3.4</td>
<td>5.5±0.4</td>
<td>7.8±0.6</td>
<td>15.0±1.4</td>
<td>43.6±1.1</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>547±136*</td>
<td>47±6.0*</td>
<td>96±4.7*</td>
<td>140±4.8*</td>
<td>67±4.0</td>
<td>4.5±0.3*</td>
<td>9.1±0.5*</td>
<td>14.7±2.2</td>
<td>39.3±0.9*</td>
</tr>
<tr>
<td>Hyperoxia (100% O₂)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>173±38</td>
<td>17±2.2</td>
<td>65±4.5</td>
<td>126±7.4</td>
<td>66±3.9</td>
<td>4.5±0.5</td>
<td>6.8±0.9</td>
<td>13.2±1.6</td>
<td>42.8±1.2</td>
</tr>
<tr>
<td>Hyperoxia</td>
<td>157±37</td>
<td>16±2.5</td>
<td>61±3.7</td>
<td>127±4.9</td>
<td>66±2.8</td>
<td>4.2±0.5</td>
<td>7.6±0.7</td>
<td>14.6±1.5</td>
<td>39.0±1.1*</td>
</tr>
<tr>
<td>Hyperoxia + dipyridamole</td>
<td>333±89†</td>
<td>30±4.8†</td>
<td>82±5.2†</td>
<td>136±6.3†</td>
<td>67±3.7</td>
<td>3.9±0.6</td>
<td>7.9±1.0</td>
<td>13.9±1.1</td>
<td>36.8±1.8†</td>
</tr>
</tbody>
</table>

MSNA indicates muscle sympathetic nerve activity; bpm, beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; and CVP, central venous pressure.

Values are mean±SEM of 7 subjects for room air values and 6 subjects for hyperoxia.

*P<.05 dipyridamole vs control; †P<.05 dipyridamole during hyperoxia vs hyperoxia alone.

returned to baseline or slightly above baseline levels within 5 minutes after completion of the dipyridamole infusion. Central venous pressure (not shown) decreased by 20% during the infusion of dipyridamole and remained at that level throughout the protocol. The time course of the ventilatory response to dipyridamole was different from that of the cardiovascular changes. There was an initial increase in ventilation by approximately 50% at the end of the infusion of dipyridamole, which lasted for less than 3 minutes and was followed by a rapid return toward baseline (Fig 3). The increase in minute ventilation at 5, 10, and 20 minutes after dipyridamole infusion was 20%, 10%, and 5%, respectively. The time course of changes in end-tidal CO₂ reflected the changes in hyperventilation.

Dipyridamole During Hyperoxia

Breathing 100% oxygen, which increased O₂ saturation from 98±0.4% to 100±0.02% (P<.001), had no significant effect on sympathetic nerve activity, blood pressure, heart rate, or central venous pressure. Hyperoxia slightly decreased end-tidal CO₂ due to a small increase in minute ventilation (Table). The addition of dipyridamole during hyperoxia resulted in an increase in MSNA (157±37 to 333±89 U/min, P<.01), bursts per minute (16±3 to 30±5, P<.001), heart rate (61±4 to 82±5 beats per minute, P<.001), and systolic blood pressure (127±5 to 136±6 mm Hg, P<.05). However, dipyridamole did not significantly increase minute ventilation (7.6±0.7 to 7.9±1 L/min) when administered during hyperoxia (Table and Fig 4). There were no significant differences between changes in MSNA, blood pressure, and heart rate in response to dipyridamole during hyperoxia compared with those observed in response to dipyridamole during room air breathing.

Dipyridamole After Pretreatment

With Aminophylline

Aminophylline antagonized the effects of dipyridamole (n=7) during room air breathing (Fig 5). After pretreatment with aminophylline (mean plasma level, 14±1 µg/mL), dipyridamole increased MSNA by only 27±4%, the number of sympathetic bursts per minute by 17±5%, and heart rate by 11±1%. These changes were significantly less than the effects of dipyridamole without pretreatment with aminophylline (108±28%, 64 bpm, 127/60).
98±14%, and 49±4% for MSNA, bursts per minute, and heart rate, respectively). Furthermore, in the presence of aminophylline, dipyridamole had no effect on systolic, diastolic, and central venous pressures or on ventilation. No subject experienced any symptoms during dipyridamole infusion after pretreatment with aminophylline. Aminophylline infusion alone slightly increased MSNA from 248±66 to 316±77 U/min (*P<.05), systolic blood pressure from 117±7 to 128±6 mm Hg (*P<.001), diastolic blood pressure from 59±4 to 65±3 mm Hg (*P<.001) and decreased central venous pressure from 4.2±0.4 to 3.1±0.5 mm Hg (*P<.001). Aminophylline alone had no significant effect on heart rate or ventilation.

**Discussion**

The novel findings of this study are first, that endogenous adenosine increases sympathetic nerve activity and ventilation in conscious subjects and second, that chemoreflex suppression by hypoxia differentially inhibits ventilatory but not sympathetic or hemodynamic responses to endogenous adenosine. Thus, the sympathoexcitatory effects of endogenous adenosine may be mediated by additional afferent mechanisms independent of peripheral chemoreceptors.

The stimulatory effect of adenosine on ventilation, as reflected by a decrease in end-tidal CO₂, was related to an increase in tidal volume rather than an increase in respiratory rate or hypoxia. We observed a 20% increase in ventilation, similar to that reported by Maxwell et al (in response to 80 μg/kg per minute of adenosine) but less than the 100% increase observed by Biaggioni et al for the same dose of adenosine. The difference in magnitude of ventilatory stimulation in response to adenosine between our study and that of Biaggioni et al is probably related to the time of measurement. The maximal excitatory effect of adenosine on ventilation in our study was transient, lasting <3 minutes in each subject, as opposed to the more sustained cardiovascular and sympathoexcitatory effects. We averaged all measurements during a 3-minute steady-state period after administration of dipyridamole, whereas in the study by Biaggioni et al, the increase in minute ventilation was analyzed over a 1-minute period during which a maximal effect was noted, usually during or right after administration of adenosine. However, after infusion of 0.4 mg/kg of dipyridamole, plasma adenosine levels have been shown to increase steadily during dipyridamole infusion to approximately 90% of the peak value at the end of infusion and to remain above 90% of the peak value for at least 1 hour after the end of dipyridamole infusion.

To demonstrate that the ventilatory and cardiovascular actions of dipyridamole were mediated by its effects on endogenous adenosine (nucleoside transport inhibition), the effects of dipyridamole were evaluated after pretreatment with aminophylline, a nonselective competitive A₁- and A₂-adenosine receptor antagonist. Aminophylline either abolished the effects of dipyridamole (blood pressure, central venous pressure, minute ventilation, and end-tidal CO₂) or significantly attenuated its effects (sympathetic nerve activity and heart rate), thereby confirming that these effects of dipyridamole are mediated at the adenosine receptor level. Although methylxanthines may also inhibit phosphodiesterase and induce calcium release from the endoplasmic reticulum, the concentrations required to achieve these effects are generally 10 times higher than those achieved in this study. However, partial inhibition of phosphodiesterase by aminophylline may explain in part the baseline changes induced by aminophylline alone, for example, a small but significant increase in sympathetic nerve activity and blood pressure. Nevertheless, aminophylline antagonized (rather than potentiated) the cardiovascular and ventilatory effects of dipyridamole, indicating that its predominant effects...
were related to its antagonism of adenosine rather than to its effects on phosphodiesterase inhibition.

The sympathoexcitatory effects of dipyridamole could in theory also be attributed to the inhibitory effect of dipyridamole on cAMP phosphodiesterase rather than to potentiation of the effects of endogenous adenosine.\(^3^7\) That phosphodiesterase inhibition did not play a major role in our study is evident from the fact that the effects of dipyridamole could be almost completely abolished by aminophylline, which is also a phosphodiesterase inhibitor.\(^3^5\) It is also possible that activation of sympathetic nerve activity in response to dipyridamole was a nonspecific effect due to chest discomfort experienced by some of the subjects after administration of dipyridamole. This, however, is unlikely because an increase in sympathetic nerve activity was also present in subjects who did not experience chest discomfort during dipyridamole infusion, elevated sympathetic activity persisted much longer (>20 minutes) than the duration of symptoms (<5 minutes), and chest discomfort mimicking anginal pain has been shown to be a specific effect of adenosine thought to be mediated by stimulation of cardiac afferents.\(^3^8\) Although we did not measure plasma levels of adenosine after dipyridamole administration, the dose of dipyridamole used in this study is the same as that used in thallium imaging studies and previously has been shown to approximately double coronary sinus\(^5^9\) and plasma adenosine levels.\(^2^4\)

![Fig 4. Bar graphs show effects of hyperoxia on the sympatho-excitatory and ventilatory actions of dipyridamole. The effects of dipyridamole on muscle sympathetic nerve activity (MSNA) (left) and minute ventilation (VENT) (right) are shown during room air breathing (top, n=7) and hyperoxia (bottom, n=6). During room air breathing, dipyridamole significantly increased both sympathetic nerve activity and minute ventilation. However, peripheral chemoreceptor suppression (with hyperoxia) had a differential effect on the sympathoexcitatory and ventilatory responses to dipyridamole. The ventilatory response to dipyridamole was suppressed, but the increase in sympathetic nerve activity remained unaffected.](image)

**Fig 5.** Bar graphs show antagonism of effects of dipyridamole by aminophylline. Changes in sympathetic nerve activity (units per minute and number of bursts per minute [B/min]), heart rate (HR; bpm, beats per minute), SBP, DBP, CVP, minute ventilation (VENT), respirations (RESP) per minute, and end-tidal CO\(_2\) are shown for dipyridamole alone (open bars) and dipyridamole during infusion of aminophylline (black bars). Values are shown as absolute change from baseline measurements±SEM. Aminophylline significantly attenuated or abolished the dipyridamole-induced changes in MSNA, B/min, HR, SBP, CVP, VENT, and end-tidal CO\(_2\). Abbreviations as in previous figures. n=7 normal subjects.

Our results are therefore consistent with the hypothesis that the sympathoexcitatory effects of dipyridamole are due to augmentation of endogenous adenosine activity within a physiological range.

The mechanism(s) by which adenosine stimulates sympathetic activity and ventilation are not completely understood. One possibility is that the decrease in central venous pressure or systemic vascular resistance in response to dipyridamole is solely responsible for the increase in sympathetic nerve activity (by a baroreceptor reflex). Although mean systolic pressure increased, it is possible that even the small decrease in central venous pressure observed in our study contributed to sympathetic activation by unloading of low-pressure cardiopulmonary baroreceptors. In a previous study conducted in a similar group of volunteers, we showed that sympathetic nerve activity increases 27% in response to a decrease in central venous pressure of 1 mm Hg.\(^4^0\) Therefore, the increase in sympathetic nerve activity in this study (108%) cannot be solely accounted for by a fall in central venous pressure. In addition, the increased sympathetic nerve activity occurs despite a higher mean arterial pressure, increased minute ventilation, and hypoxemia, all of which would be expected to inhibit MSNA.\(^4^1,^4^2\) Thus, endogenous adenosine is a potent mechanism for increasing MSNA. Direct central actions of adenosine are also unlikely to have contributed to the observed effects of dipyridamole, because dipyridamole is not known to cross the blood-brain barrier (personal communication, DuPont Pharmaceutical Co). Any endogenous adenosine that crosses the blood-brain barrier would elicit a depressive, not a stimulatory effect.\(^1^2,^1^3\)

It has been suggested that the effects of adenosine on sympathetic activation and ventilation are related to
activation of chemoreceptors in the carotid sinus. This is based on two lines of evidence: First, Monteiro and Ribeiro\textsuperscript{21} have shown in anesthetized rats that intracarotid injection of adenosine and especially specific A\textsubscript{2}-adenosine receptor analogues stimulate ventilation and that these excitatory effects are abolished after sectioning the carotid sinus nerve. Second, it has been observed that infusion of exogenous adenosine, which has a half-life of <1.5 seconds,\textsuperscript{43} increases ventilation and systolic blood pressure when infused proximal to the origin of carotid arteries (and carotid chemoreceptors) but has minimal effect when infused in the descending aorta.\textsuperscript{19,44}

Based on the above data, we originally hypothesized that the sympathoexcitatory actions of endogenous adenosine in humans would also be mediated by peripheral chemoreceptors. Therefore, it was expected that suppression of peripheral chemoreceptors during inhalation of 100\% oxygen (hyperoxia) would attenuate or abolish the observed sympathoexcitatory and ventilatory effects of dipyridamole. Chemoreceptor discharge has been shown to be almost completely absent above a Pa\textsubscript{O\textsubscript{2}} of 190±40 mm Hg (range, 140 to 400 mm Hg).\textsuperscript{45} Under the conditions present in this study, an increase in Fio\textsubscript{2} from 21\% to 100\% is expected to increase Pa\textsubscript{O\textsubscript{2}} to at least 400 mm Hg.\textsuperscript{46} The fact that ventilation did not change in response to hyperoxia in our study is a physiological response to 100\% oxygen breathing rather than evidence against inhibition of chemoreceptor activity by hyperoxia. A decrease in ventilation reflecting the pure effect of hyperoxia on peripheral chemoreceptors can only be observed during the first few breaths after initiation of oxygen breathing ("single-breath O\textsubscript{2} test").\textsuperscript{31} After that, minute ventilation reflects the net effect of respiratory inhibition resulting from the effect of hyperoxia on peripheral chemoreceptors and the excitatory effect of hyperoxia on central chemoreceptors.\textsuperscript{47} In the present study, the effects of dipyridamole on minute ventilation were averaged during successive 60-second intervals. Therefore, the initial transient decrease in ventilation due to hyperoxia would not have been reflected by our method of measurement.

Suppression of peripheral chemoreceptors in this study with hyperoxia attenuated the ventilatory stimulation by dipyridamole, but the sympathoexcitatory and cardiovascular changes were mediated by activation of additional afferent inputs. This is also supported by the different time course for the effect of adenosine on ventilation and cardiovascular changes (Fig 4), since the latter were sustained over at least 20 minutes, whereas the increase in ventilation lasted <5 minutes. Our findings that adenosine's effect on ventilation can be modified by suppression of peripheral chemoreceptors are consistent with the experimental data reported by Monteiro and Ribeiro.\textsuperscript{21} Although the sympathoexcitatory effects of exogenous adenosine infusion into the proximal aortic arch are suggestive of an action by carotid body chemoreceptors, this does not exclude the possibility that increased levels of endogenous adenosine also activate other afferent inputs to the sympathetic nervous system. Several afferent inputs to the autonomic nervous system, in addition to the carotid chemoreceptors, have been shown to be activated by adenosine and may potentially contribute to its sympathoexcitatory effects. A reflex increase in blood pressure after intracoronary administration of adenosine (in concentrations that have no direct systemic effect) suggest that cardiac afferents are sensitive to adenosine and result in reflex sympathetic activation.\textsuperscript{48} Furthermore, adenosine and dipyridamole have been shown to increase renal sympathoexcitatory nerve activity by activation of cardiac sympathetic afferents mediated by the adenosine A\textsubscript{2}-receptor.\textsuperscript{49} In addition, infusion of adenosine into the renal artery as well as renal pelvic administration of adenosine in dogs with intact renal nerves are associated with increased activity of the sympathetic nervous system and an increase in blood pressure, providing evidence for adenosine-sensitive nerve endings located within or near the renal pelvis.\textsuperscript{50}

We cannot exclude the possibility that suppression of chemoreceptors by hyperoxia does not alter the ability of chemoreceptors to respond to stimulation by endogenous adenosine. The fact that hyperoxia altered the ventilatory response to dipyridamole indicates, however, that there is an interaction between the adenosine receptors and hyperoxia at the chemoreceptor level. Furthermore, hyperoxia has previously been shown to suppress the ability of chemoreceptors to respond to stimulation by catecholamines.\textsuperscript{51} A more likely explanation is the possibility of redundancy in the effects of adenosine on sympathetic activity and hemodynamics, namely that adenosine elicits sympathetic activation by stimulation of several different afferents, the net effect of which is less than additive. Attenuation of one of these afferent inputs (in this case, suppression of chemoreceptor afferents by hyperoxia) does not eliminate the sympathetic response because of persistence of activation of other afferents.

**Summary**

We have shown that endogenous adenosine elicits increases in minute ventilation, sympathetic nerve activity, heart rate, and blood pressure in normal humans. Suppression of peripheral chemoreceptors by hyperoxia attenuates the ventilatory but not the sympathetic or hemodynamic responses to endogenous adenosine. We speculate that activation of afferent other than the peripheral chemoreceptors contribute to the sympathetic and hemodynamic responses to adenosine. These afferents may interact with the chemoreceptors in a redundant fashion.

**Acknowledgments**

This study was supported in part by National Institutes of Health grants 44747 and 14388 and by the National German Research Society (Deutsche Forschungsgemeinschaft). Dr Lerman is an Established Investigator of the American Heart Association. We would like to thank Dr Allyn L. Mark for his review of the manuscript and thoughtful comments and Mary P. Clary for her excellent technical assistance in performing the study.

**References**

Role of arterial chemoreceptors in mediating the effects of endogenous adenosine on sympathetic nerve activity.
E D Engelstein, B B Lerman, V K Somers and R F Rea

_Circulation_. 1994;90:2919-2926
doi: 10.1161/01.CIR.90.6.2919

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/90/6/2919

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/