Intravenous adenosine and dyspnea in humans

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1Division of Pulmonary Medicine, Department of Medicine, University of Connecticut Health Center, Farmington, Connecticut; 2Department of Medicine, University of Kentucky Medical Center, and 3Department of Physiology, University of Kentucky, Lexington, Kentucky

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Burki, Nausherwan K., Wheeler J. Dale, and Lu-Yuan Lee. Intravenous adenosine and dyspnea in humans. J Appl Physiol 98: 180–185, 2005. First published September 17, 2004; doi:10.1152/japplphysiol.00913.2004.—Intravenous adenosine for the treatment of supraventricular tachycardia is reported to cause bronchospasm and dyspnea and to increase ventilation in humans, but these effects have not been systematically studied. We therefore compared the effects of 10 mg of intravenous adenosine with placebo in 21 normal subjects under normoxic conditions and evaluated the temporal sequence of the effects of adenosine on ventilation, dyspnea, and heart rate. The study was repeated in 11 of these subjects during hyperoxia. In all subjects, adenosine resulted in the development of dyspnea, assessed by handgrip dynamometry, without any significant change (P > 0.1) in lung resistance as measured by the interrupter technique. There were significant increases (P < 0.05) in ventilation and heart rate in response to adenosine. The dyspnic response occurred slightly before the ventilatory or heart rate responses in every subject, but the timing of the dyspnic, ventilatory, and heart rate responses was not significantly different when the group data were analyzed (18.9 ± 5.8, 20.3 ± 5.5, and 19.7 ± 4.5 s, respectively). During hyperoxia, adenosine resulted in similar effects, with no significant differences in the magnitude of the ventilatory response; however, compared with the normoxic state, the intensity of the dyspnic response was significantly (P < 0.05) reduced, whereas the heart rate response increased significantly (P < 0.05). These data indicate that intravenous adenosine-induced dyspnea is not associated with bronchospasm in normal subjects. The time latency of the response indicates that the dyspnea is probably not a consequence of peripheral chemoreceptor or brain stem respiratory center stimulation, suggesting that it is most likely secondary to stimulation of receptors in the lungs, most likely vagal C fibers.

We therefore studied normal human subjects to measure the temporal relationship of dyspnea and changes in ventilation after bolus intravenous adenosine administration to ascertain whether these effects are related to chemoreceptor activation or a consequence of direct pulmonary vagal receptor activation. We also examined the effects of hyperoxia on the response to adenosine to further differentiate the contribution of carotid chemoreceptors and pulmonary vagal receptors.

METHODS

Twenty-one healthy, nonsmoking subjects (mean age 26.6 ± 8.0 yr, range 18–48 yr, 8 women) were studied; written, informed consent was obtained from each subject.

The subject was seated, and a forearm vein was cannulated and connected to a normal saline drip. A curtain between the subject and the cannulated forearm prevented the subject from being able to see when an injection was given (see below). Minute ventilation (Ve) and ventilatory pattern were recorded with the subject breathing via a mouthpiece attached to a two-way valve (Hans-Rudolph, Kansas City, MO); expiratory flow was recorded on a multichannel recorder (Grass Medical Instruments, Astro-Med, West Warwick, RI) as the differential pressure signal from a heated pneumotachograph on the expiratory side of the valve, which was connected to a differential pressure transducer (Hans-Rudolph). The flow signal was electronically integrated to volume and recorded. The system was calibrated before each experiment, using a calibrated syringe (Spirometrix).

 Airways resistance (Rint) was measured by the interrupter technique (6, 24, 28) at baseline and 90 s after the adenosine injection. Inspiratory flow was interrupted with an electronically operated shutter at a flow rate of ∼0.5 l/s, and the change in mouth pressure, measured at the mouthpiece by a pressure transducer, was related to the flow rate to calculate Rint.

Each subject indicated the presence and intensity of dyspnic sensation by squeezing an isometric handgrip dynamometer (6, 32, 55); the resultant voltage deflection was recorded and measured as millimeters of deflection from baseline. The subject was instructed to respond immediately when any sensation was felt with a magnitude of handgrip force proportional to the intensity of the sensation. Subjects were asked to focus on respiratory symptoms such as chest tightness, shortness of breath, increased urge to breathe, burning sensation in the chest and throat; preliminary studies by N. K. Burki, M. Alan, and L.-Y. Lee had indicated that the commonest symptoms expressed were shortness of breath and chest tightness.

End-tidal CO2 was sampled at the mouthpiece and analyzed by a CO2 meter (Ohmeda, Englewood, CO), the output from which was continuously recorded.

Arterial O2 saturation (SaO2) was recorded continuously by using a pulse oximeter (Criticare Systems, Waukesha, WI). Electrocardiogram lead II was recorded continuously, and heart rate (HR) was measured from the R-R interval.

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Baseline measurements of Rint were made, and when the subject had a stable breathing pattern (as judged by <5% variation in the end-tidal CO₂), VE, ventilatory pattern, end-tidal CO₂, HR, and SaO₂ were recorded over 3 min, and a baseline handgrip dynamometry score was recorded.

The subject then received an injection of 10 mg of adenosine, with care being taken to avoid awareness of the injection by the subject. The time latency between the bolus injection and the initial change in VE (measured as the onset of the first breath exhibiting an increase in volume or frequency), handgrip (measured as the beginning of the first deflection from baseline of the dynamometer tracing), and HR (measured as the beginning of the first R-R interval change) were measured. Further measurements of VE (calculated from 2–3 breaths within a 10-s time block at each measurement time), handgrip dynamometry, end-tidal CO₂, SaO₂, and HR were made continuously over the next 3 min; preliminary studies by N. K. Burki, M. Alan, and L.-Y. Lee had shown that all measured parameters returned to baseline 90–120 s after adenosine injection. Rint was measured 60–90 s after the injection. In 10 subjects, an injection of 10 ml of normal saline was given before the injection of adenosine, and the response was recorded in the same manner. In 11 subjects, the study was performed under both normoxic and hyperoxic conditions; the sequence of the studies, normoxia and hyperoxia, was varied randomly such that in 5 subjects the normoxic study was performed before the hyperoxic study and the order was reversed in the other 6. Under hyperoxic conditions, the subject breathed 100% O₂ from a Douglas bag attached to the inspiratory side of the two-way valve for 10 min before the adenosine injection.

Differences among the initial response times for handgrip, change in VE, and change in HR within each condition, normoxia or hyperoxia, were compared by the Student-Newman-Keuls multiple-comparison technique (1). The significance of changes from baseline in handgrip response, VE and ventilatory parameters, and HR were analyzed by one-way repeated-measures ANOVA, with post hoc Tukey’s analysis (1). Comparison of the effects of adenosine during normoxia compared with hyperoxia were analyzed by two-way ANOVA.

RESULTS

In the 10 subjects who received placebo injection, there was no significant (P > 0.5) effect on the VE, handgrip, ventilatory pattern, Rint, HR, end-tidal CO₂, or SaO₂.

Rint did not change significantly after adenosine injection (baseline Rint: 2.22 ± 0.37 and 2.24 ± 0.43 cmH₂O·l⁻¹·s⁻¹ after adenosine; P > 0.1; n = 21). Adenosine injection resulted in significant increases in dyspnea, as represented by handgrip dynamometry, and in VE and HR (Table 1). The increase in VE was primarily due to an increase in tidal volume, with no significant change in respiratory frequency (Table 1).

The initial handgrip response after the adenosine injection occurred before the change in VE in every subject except one in whom it was simultaneous, although the group data indicated that response times between handgrip (18.90 ± 5.76 s, range 11.8–29.6 s; n = 21), VE (20.31 ± 5.54 s, range 11.8–32.2 s; n = 21), and HR (19.65 ± 4.52 s, range 14.1–29 s; n = 21) were not significantly different (P > 0.05). There was no significant difference (P > 0.05) in the response times between normoxia and hyperoxia (handgrip: 20.5 ± 7.1 and 21.4 ± 4.5 s; VE: 21.4 ± 6.5 and 23.5 ± 5.3 s; HR: 22.0 ± 5.2 and 22.7 ± 3.7 s, respectively; n = 11).

The change in handgrip and the percent change from baseline in VE and HR are shown in Fig. 1. There were significant

<table>
<thead>
<tr>
<th>Time</th>
<th>VE, l/min (BTPS)</th>
<th>VT, liters (BTPS)</th>
<th>f, breaths/min</th>
<th>VT/TI, l/s</th>
<th>HR, beats/min</th>
<th>HG Dyn, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8.53±2.21</td>
<td>0.65±0.16</td>
<td>13.9±5.9</td>
<td>0.53±0.13</td>
<td>80.8±12.0</td>
<td>0</td>
</tr>
<tr>
<td>20 s</td>
<td>14.1±4.9*</td>
<td>0.92±0.37*</td>
<td>16.3±6.0</td>
<td>0.75±0.22*</td>
<td>78.6±15.1</td>
<td>10.1±11.6*</td>
</tr>
<tr>
<td>40 s</td>
<td>17.0±5.0*</td>
<td>1.13±0.32*</td>
<td>16.1±6.4</td>
<td>0.90±0.20*</td>
<td>95.6±18.6</td>
<td>13.8±10.0*</td>
</tr>
<tr>
<td>60 s</td>
<td>14.5±4.4*</td>
<td>0.88±0.26*</td>
<td>17.4±7.0</td>
<td>0.79±0.18*</td>
<td>91.4±17.2</td>
<td>8.7±8.4*</td>
</tr>
<tr>
<td>80 s</td>
<td>10.8±3.8</td>
<td>0.78±0.28</td>
<td>15.2±7.5</td>
<td>0.65±0.18</td>
<td>79.0±17.8</td>
<td>4.0±5.2</td>
</tr>
<tr>
<td>100 s</td>
<td>9.5±3.4</td>
<td>0.67±0.27</td>
<td>15.8±8.5</td>
<td>0.54±0.14</td>
<td>75.5±18.1</td>
<td>3.2±6.3</td>
</tr>
<tr>
<td>120 s</td>
<td>9.1±3.5</td>
<td>0.61±0.23</td>
<td>15.9±6.2</td>
<td>0.48±0.15</td>
<td>83.7±13.3</td>
<td>2.2±4.4</td>
</tr>
</tbody>
</table>

Values are means ± SD for 21 subjects. VE, minute ventilation; VT, tidal volume; f, respiratory frequency; TI, inspiratory time; HR, heart rate; HG dyn, handgrip dynamometry. *Significantly different from baseline, P < 0.05.
ADENOSINE AND RESPIRATORY SENSATION

Table 2. Ventilatory and handgrip dynamometry values during hyperoxia after adenosine injection

<table>
<thead>
<tr>
<th>Time</th>
<th>VE, l/min (BTPS)</th>
<th>VT, liters (BTPS)</th>
<th>f, breaths/min</th>
<th>HR, beats/min</th>
<th>HG Dyn, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>10.0±2.0</td>
<td>0.76±0.21</td>
<td>14.2±4.6</td>
<td>76.9±11.4</td>
<td>0</td>
</tr>
<tr>
<td>20 s</td>
<td>13.5±3.4</td>
<td>0.86±0.14</td>
<td>16.2±5.7</td>
<td>80.5±13.6</td>
<td>4.3±6.4</td>
</tr>
<tr>
<td>40 s</td>
<td>14.7±3.5*</td>
<td>1.12±0.24*</td>
<td>13.9±5.3</td>
<td>103.3±14.0*</td>
<td>3.0±9.8*</td>
</tr>
<tr>
<td>60 s</td>
<td>13.8±3.5</td>
<td>0.95±0.24</td>
<td>15.3±4.9</td>
<td>95.4±17.9</td>
<td>7.8±6.4*</td>
</tr>
<tr>
<td>80 s</td>
<td>11.2±1.9</td>
<td>0.91±0.23</td>
<td>13.3±4.9</td>
<td>80.3±18.0</td>
<td>3.5±5.1</td>
</tr>
<tr>
<td>100 s</td>
<td>11.8±2.2</td>
<td>0.85±0.21</td>
<td>15.0±6.3</td>
<td>75.7±18.0</td>
<td>2.0±4.5</td>
</tr>
<tr>
<td>120 s</td>
<td>11.5±1.9</td>
<td>0.87±0.14</td>
<td>13.5±3.2</td>
<td>75.9±14.4</td>
<td>1.7±4.5</td>
</tr>
</tbody>
</table>

Values are means ± SD for 11 subjects. *Significantly different from baseline, P < 0.05.

In the present study, we noted an initial bradycardia in every subject, as measured by the R-R interval; this was present in each subject for only two to three beats followed by a significant tachycardia. Previous studies in normal subjects have reported no bradycardia (25, 40); however, in these studies, adenosine was not given as a bolus dose but as a continuous infusion, and it is not clear whether HR was averaged from a larger number of beats. In contrast, Biaggioni et al. (3) did note bradycardia in five of nine subjects. On the basis of the time latency of the effect, our data would suggest that the initial bradycardia may be secondary to vagal afferent stimulation (see below), which is then overridden by increasing cardiac sympathetic tone. The novel finding in this study of an increased heart rate response to adenosine during hyperoxia could be explained by an increased sympathetic effect of adenosine or decreased parasympathetic tone; however, this remains to be elucidated.

Among the reported side effects (40) of intravenous adenosine are bronchospasm and dyspnea; however, these are anecdotal reports (3, 40) in asthmatic subjects receiving intravenous adenosine for the treatment of arrhythmia; actual bronchoconstriction has not been documented in these reports by any measurements of airway function. In a study (2) of 122 consecutive patients, including 36 with chronic bronchitis, under-

Fig. 2. Comparison of changes in handgrip dynamometry and percent change in VE and HR after adenosine injection in normal subjects (n = 11) during normoxia (solid lines) and hyperoxia (dashed lines). Bottom: ▼, ▼%ΔVE; ◦, ◦%ΔHR. *Significantly different from normoxia, P < 0.05. The handgrip response was significantly less and the HR response significantly increased during hyperoxia, whereas the ventilatory response did not change significantly between normoxia and hyperoxia.
going adenosine stress testing for myocardial perfusion imaging, dyspnea was noted in over 50% of subjects, but no changes in spirometric indexes were noted; the response latency and the relationship of the dyspnea to ventilation were not further characterized. Changes in spirometric indexes after intravenous adenosine were also absent in other studies (3, 17, 20). However, it could be argued that acute changes in airways resistance may not be detected by spirometry, because the necessity of a deep inspiration before the measurement may itself attenuate any existing bronchoconstriction (8). We measured airways resistance by the interrupter technique in the present study; this measurement is rapid and does not require a deep breath or any special ventilatory maneuver by the subject (6, 24, 28), thus obviating any effects such maneuvers may have in masking an increase in airways resistance (8). Our results confirm that significant changes in airways resistance do not occur after intravenous adenosine. Extensive previous data indicate that the perception of changes in airways resistance and the development of dyspnea in normal and asthmatic subjects occurs with significant and relatively large changes in airways resistance (7, 19, 33, 34, 38, 43, 48). Thus any changes in airway smooth muscle tone and airways resistance not reflected in Rint are unlikely to be of significance relative to the observed dyspnea. Our data confirm that the sensation of dyspnea or chest tightness reported in normal subjects is not related to bronchospasm.

On the other hand, inhaled adenosine and adenosine 5’-monophosphate are known to cause bronchoconstriction in asthmatic human subjects (12, 14), probably via mast cell mediator release. However, this effect has only been demonstrated with inhaled adenosine, and has not been demonstrated with parenteral adenosine (2, 3, 17, 20), and suggests that the bronchoplastic effects of adenosine are related to the route of administration.

The ventilatory effects of adenosine could be due to peripheral chemoreceptor or pulmonary receptor activation. Adenosine activates carotid chemoreceptors in cats (31), and this effect is dose dependent and not related to changes in systemic blood pressure or blood flow (44). In carotid body-denervated cats, adenosine acts as a central respiratory depressant (15). In humans, the ventilatory effects of adenosine have also been ascribed to carotid body chemoreceptor stimulation, but the results have been inconclusive (16, 17, 21, 50). Griffiths et al. (21) studied the ventilatory response to hypoxia and adenosine in five human subjects with carotid endarterectomies with variable results; Engelstein et al. (16) noted increased sympathetic activity and ventilation with dipyridamole, which increases endogenous adenosine concentration and activity but did not specifically exclude causes other than chemoreceptor stimulation for the increase in ventilation. Fuller et al. (17) provided persuasive evidence of carotid chemoreceptor activation by adenosine on the basis of the site of infusion in the aorta; nevertheless, the evidence was not conclusive. Similarly, whereas some studies have shown that intravenous adenosine enhances the hypoxic ventilatory response (30, 53), other studies (37) have not supported this conclusion.

Dyspnea, or shortness of breath (4, 5, 29), is a common accompaniment of most lung diseases. However, knowledge of this sensation remains imperfect, and a number of theories have been put forth as to the genesis of this sensation (4, 5). It is now generally accepted that the sensation(s) of dyspnea involves central, chemoreceptor, and peripheral (chest wall mechanoreceptor and lung receptor) mechanisms (5, 29, 49). The adenosine-induced dyspnea documented in the present study could be due to a direct central effect, chemoreceptor stimulation, or stimulation of pulmonary receptors. Previous animal and human studies of chemoreceptor response time after peripheral intravenous injection (11, 13, 18, 51) make it very unlikely that the dyspnogenic or ventilatory responses noted in the present study can be secondary to a direct central dyspnogenic effect.

Two considerations argue against carotid chemoreceptor activation as an explanation of the ventilatory and dyspnogenic effects: the time latency of the effects and the effects of hyperoxia. Studies (18, 51) indicate that the circulation time in humans between a peripheral intravenous injection and the pulmonary circulation ranges between 15 and 20 s. In contrast, between the central veins and the radial artery, the minimum circulation time ranges between 19 and 24 s (41). This makes it unlikely that the bolus injection of adenosine into a peripheral vein resulting in dyspnea and ventilatory effects in 19–20 s could be attributed to carotid chemoreceptor activation. In addition, during hyperoxia, there was no change in the increase in ventilation after adenosine, whereas dyspnea was significantly attenuated; this argues further against a role for the carotid chemoreceptors. Indeed, the time latency argues toward a pulmonary receptor effect. Maxwell et al. (30) first suggested that the ventilatory effects of adenosine may be mediated by intrapulmonary receptors.

Sensory receptors in the lungs consist of stretch and irritant receptors in the large airways, innervated both by myelinated fibers of the vagus nerve and by unmyelinated vagal C fibers (11). The irritant receptors appear to modify the intensity of dyspnea associated with induced bronchoconstriction (48), and airway stretch receptors appear to modify breathlessness by altering ventilatory pattern (22, 52). However, neither of these receptors has been shown to be specifically dyspnogenic.

Vagal afferent C fibers lie in close proximity to the pulmonary capillaries and alveoli, and they are also present in the mucosa and deeper tissue of the conducting airways (11). Coleridge and coworkers (11) from studies in larger mammals (i.e., dogs and cats) have subdivided them further into pulmonary and bronchiolar groups, on the basis of pulmonary and bronchial arterial blood supply, and have suggested that the groups have different sensitivities to chemical and mechanical stimuli. However, this concept of different physiological and pharmacological properties between “airway” and “pulmonary” C fibers has been challenged by other investigators (45) on the grounds that substantial vascular anastomosis exists between the bronchial and pulmonary circulations (9). Pulmonary C fibers are now considered synonymous (18, 36) with the “J” receptors described by Paintal (35) in the lung parenchyma.

In humans, pulmonary C fibers have been implicated in the sensation of dyspnea (36), although direct evidence of this has been hard to obtain (46). Human studies attempting to characterize C fibers have utilized intravenous lobeline or intravenous or aerosolized capsaicin; these produce coughing and burning or irritating sensations in the throat and midsternum (18, 25, 36, 39, 51). These sensations are often so powerful that they limit the dose of the drug that can be administered. However, the development of a cough raises the possibility that other
receptors, such as the irritant receptors, may also be stimulated by these drugs (18).

Evidence implicating a role for airway and/or alveolar C fibers in dyspnea comes from studies of nebulized morphine in dyspneic patients (54), which reduced exercise-induced dyspnea, and the finding of an increase in exercise-induced dyspnea in normal subjects after inhalation of prostaglandin E2, which is known to increase vagal afferent C-fiber sensitivity (47). Thus, whereas previous evidence is suggestive, the results of studies of dyspnea and the role of pulmonary vagal C fibers have been inconclusive.

A study in rats in our laboratory (23) provided the first evidence that adenosine stimulates pulmonary C fibers through activation of A1 receptors. In the present study, our experiments were designed to specifically measure the time latency of response, and the results indicate that dyspnea develops before the ventilatory response, making it unlikely that the dyspnea was secondary to the increase in ventilation. Similarly, because the dyspnea occurred before any change in HR, it is unlikely that it was a response to the tachycardia. Although we have no direct evidence, our animal data (23, 27) would suggest that the dyspnea is caused by direct stimulation of pulmonary C-fiber endings by adenosine. In rats, the respiratory reflex response to adenosine is completely blocked by selective blockade of conduction of the pulmonary C fibers (27). The probability that the dyspnea is caused by stimulation of C fibers is further supported by the fact that C-fiber stimulation with adenosine in nonhuman primates stimulates ventilation and results in an initial bradycardia as seen in the present study (13).

It has been suggested (10) that hyperoxia may directly influence the cerebral cortex to modify the perception of sensory information, and this may explain the attenuation of the dyspnogenic effects of adenosine during hyperoxia. This attenuation of the dyspnogenic effect of intravenous adenosine by hyperoxia, in the absence of any significant change in the ventilatory response, would suggest that there is a complex interrelationship between the peripheral effects of adenosine and the central perception of dyspnea.

In conclusion, this study has shown that intravenous adenosine results in dyspnea in normal subjects and that it also causes an increase in ventilation; however, the dyspnogenic effect is clearly not a consequence of the increase in ventilation. The timing of the dyspnogenic response makes it unlikely that it is secondary to carotid chemoreceptor activation, and it is possible that it is a consequence of direct stimulation of pulmonary vagal C fibers.

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REFERENCES


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