Cardiovascular and Respiratory Effects of Adenosine in Conscious Man
Evidence for Chemoreceptor Activation

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The cardiovascular and respiratory effects of intravenous adenosine were studied in conscious normal volunteers. Bolus injections of adenosine increased systolic and diastolic pressures initially (+15 and +13 mm Hg after 100 µg/kg) followed by a subsequent reduction in systolic and diastolic pressures (−12 and −16 mm Hg). Heart rate increased during trough blood pressure (R-R interval shortening of 298 msec after 100 µg/kg). Adenosine steady-state infusions increased heart rate (+30 beats/min during 140 µg/kg/min), systolic pressure (+16 mm Hg), and pulse pressure (+21 mm Hg) but decreased diastolic pressure slightly (−5 mm Hg), resulting in no significant change in mean arterial pressure. Adenosine stimulated respiration, resulting in decreased Paco, (41 to 31 mm Hg), increased Pao (101 to 113 mm Hg), and increased pH (7.42 to 7.50). The increased ventilation was not explained by bronchoconstriction, hypotension, or hypoxia. The observed pressor and tachycardic effects are mediated through reflex autonomic mechanisms since they are completely abolished in patients with severe autonomic failure. These autonomic mechanisms probably involve chemoreceptor activation since adenosine is pressor when infused in the aortic arch proximal to the origin of the carotid arteries but depressor when infused in the descending aorta. It is concluded that the hemodynamic and respiratory effects of adenosine observed in normal volunteers are in part due to chemoreceptor stimulation. These findings raise the possibility that adenosine is an endogenous modulator of respiration in man. (Circulation Research 1987;61:779–786)

The physiologic relevance of adenosine, an intermediate product in the metabolism of adenosine triphosphate (ATP), has been increasingly recognized. Commonly used drugs may act at least partially through adenosine receptor blockade, e.g., methylxanthines like theophylline and caffeine, at least partially through adenosine receptor blockade, e.g., methylxanthines like theophylline and caffeine, or adenosine uptake inhibition, e.g., dipyridamole. It has been postulated that endogenous adenosine is involved in the regulation of local blood flow, renin release, and neurotransmission among other physiologic processes. Adenosine, given as a rapid bolus injection, is an effective agent in the treatment of supraventricular tachyarrhythmias by slowing atrioventricular (AV) nodal conduction and may become the treatment of choice for this arrhythmia. The possible role of adenosine as an antiarrhythmic agent underscores the need to study further the cardiovascular effects of this agent in man. Accordingly, one of the purposes of this study was to define the dose-response relation for the cardiovascular effects of bolus injections of adenosine in man.

Previous in vitro studies and animal experiments suggest that adenosine may also be a useful hypotensive agent. Adenosine is a potent vasodilator both in vitro and in vivo, acting on specific vascular receptors. Adenosine also produces bradycardia due to AV nodal conduction delay and slowing of intrinsic sinoatrial (SA) node firing, inhibits norepinephrine release through presynaptic receptors, and inhibits renin release. With these characteristics, adenosine would theoretically produce hypotension with little or no reflex sympathetic activation, tachycardia, or tachyphylaxis secondary to renin activation. Indeed, in anesthetized patients, adenosine induces a significant and sustained reduction in blood pressure (−35 mm Hg) with only a mild increase in heart rate (+9 beats/min). However, in contrast to the observed effects of adenosine in anesthetized patients, the authors have previously reported that in conscious man, adenosine causes a dose-related increase in heart rate and in systolic blood pressure, while producing only a slight decrease in diastolic blood pressure. It was hypothesized that these effects were the result of activation by adenosine of a reflex autonomic mechanism that is probably blunted during anesthesia. The present study tested this hypothesis by determining the effects of adenosine in patients with severe autonomic failure. Since these patients are functionally devoid of
autonomic reflexes, the intrinsic effects of adenosine should be apparent in them.

Finally, it has been observed that the intravenous administration of adenosine is associated with an urge to breathe deeply, suggesting that adenosine stimulates respiration in man. A final purpose of this study was to evaluate the respiratory effects of adenosine.

Subjects and Methods

Normal Volunteers

Healthy male volunteers, age 28 ± 2 years, were asked to abstain from methylxanthine-containing beverages (coffee, tea, chocolates, or soft drinks) for at least 3 days prior to the study. Plasma levels of caffeine were measured to assure compliance. Throughout the study, blood pressure was monitored continuously through a radial artery catheter with a pressure transducer connected to a Hewlett-Packard 8805c pressure amplifier (Hewlett-Packard Co., Waltham, Mass.). Heart rate was monitored by surface ECG connected to an HP 8812A beat-to-beat rate computer. Thoracic excursion and respiratory rate were monitored with a corrugated tube placed around the chest and connected to a pressure transducer. Intravenous lines were placed in an antecubital vein for adenosine or saline administration. After instrumentation, subjects were allowed to rest in a quiet room for a period of 30 minutes before any study was begun.

Nine subjects received increasing doses of adenosine as rapid intravenous bolus injections into the left antecubital vein, starting at 20 μg/kg with increments of 20 μg/kg to a maximum dose of 200 μg/kg or until intolerable side effects developed (as defined by the subject) or until cardiac arrhythmias appeared. Similar injections of saline were given before, after, and randomly during adenosine administration in a single-blind fashion. The concentration of adenosine used was either 1 or 10 mg/ml so that total volume injected was less than 5 ml.

Eight subjects received in a single-blind fashion intravenous infusion of saline followed by increasing doses of adenosine (80 to 180 μg/kg/min) of 15 minutes duration each, using a Harvard syringe pump (model 2720, C.R. Bard MedSystems Inc., North Reading, Mass., recalibrated for 35-cc plastic syringes). Near the end of each infusion, blood samples from the arterial catheter were obtained for catecholamines and arterial blood gases determinations. Spirometry was also obtained during saline and at the maximal adenosine dose for forced vital capacity (FVC) and forced expiratory volume at 1-second (FEV1) measurements. (Spirometer 2400, Breon Laboratories Inc., New York). After the adenosine infusions, saline was infused again. Hemodynamic and respiratory functions were monitored during this recovery period.

Patients With Severe Autonomic Failure

To determine the cardiovascular effects of bolus injections of adenosine in the absence of autonomic reflexes, adenosine was administered to 4 patients with severe autonomic failure (age 66 ± 5 years, 3 females). Three patients had primary autonomic failure (idiopathic orthostatic hypotension), and 1 had multiple system atrophy (Shy-Drager syndrome). All patients had severe orthostatic hypotension (average fall in systolic blood pressure on standing of 104 ± 18 mm Hg and in diastolic blood pressure of 59 ± 6 mm Hg) without adequate compensatory heart rate response. The infusion protocol was similar to the one described in the preceding section. Because of the known hypersensitivity of these patients to a variety of pressor and depressor stimuli, initial doses of 2.5 μg/kg and 5 μg/kg/min were used, with gradual increments until a blood pressure change of 25 mm Hg was observed.

Patients Undergoing Diagnostic Angiography

To determine if the site of injection would alter its cardiovascular actions, adenosine was administered to 4 patients undergoing diagnostic coronary arteriography. After the routine cardiac catheterization, adenosine boluses were injected through a catheter placed sequentially at 2 different sites: in the aortic arch proximal to the origin of the carotid arteries and in the descending aorta distal to the origin of the renal arteries. An initial dose of 1 μg/kg was given, followed by sequential increments of 2.5 μg/kg until a change in blood pressure of 25 mm Hg was observed. All protocols were reviewed and approved by the Vanderbilt University Institutional Review Board.

Measurements

To determine the effects of bolus injections, baseline blood pressure prior to each bolus injection was measured from the arterial tracings by averaging the normal respiratory fluctuations of blood pressure. The maximal increase or decrease seen after bolus injections was compared with individual baseline values. Baseline heart rate was measured by averaging 10 R-R intervals before each injection. To determine if adenosine induced transient bradycardia, the single longest R-R interval after bolus injections was measured. Five R-R intervals were also averaged around the maximal decrease in blood pressure where significant tachycardia was observed. These measurements were compared with individual baselines and expressed as changes.

To determine the effects of adenosine infusions, an average of 12 blood pressure determinations during the last minute of saline infusion was taken as baseline and compared to similar averages obtained during adenosine infusions. Mean arterial blood pressure was calculated (½ systolic + ½ diastolic). Heart rate was measured from the rate computer tracings.

Blood for catecholamines was collected into iced tubes containing reduced glutathione and EGTA and assayed radioenzymatically as previously described. Caffeine levels were determined in 100 μl of plasma purified with a 1-ml Bond Elut C18 column (Analytichem International, Harbor City, Calif.), using β-hydroxyethyltheophylline as an internal standard and analyzed by high performance liquid chromatography (HPLC), with a 2% acetic acid and 6% acetonitrile.
mobile phase at a flow rate of 1.5 ml/min and ultraviolet absorbance monitored at 280 nm.

Results are presented as mean ± SEM and evaluated by analysis of variance (CLINFO System, Clinical Research Center, BNN Software Products Corp., Cambridge, Mass.). When the analysis of variance revealed a difference, the residual mean square was applied in a Dunnett’s test to characterize which values were different from baseline. Group differences were analyzed by unpaired t tests. All null hypotheses were two-tailed, and the criterion of significance was p<0.05.

Adenosine for human use was obtained from Sigma Chemical Company, St. Louis, Mo. It was dissolved in normal saline under sterile conditions and tested for sterility and pyrogenicity. Both the concentration and purity of the compound was assessed by HPLC and by HPLC-mass spectrometry.

Results

Bolus Injections of Adenosine in Normal Volunteers

A typical cardiovascular and respiratory response to an adenosine bolus is shown in Figure 1. Adenosine consistently produced a biphasic blood pressure response. At 27±0.4 seconds, adenosine increased systolic (p<0.001) and diastolic (p<0.001) blood pressures, maximal increases being 17 and 13 mm Hg, respectively (Figure 2, left panels). Following this initial pressor response, at 39±0.4 seconds adenosine produced a decrease in systolic (NS) and diastolic (p<0.001) blood pressures (Figure 2, right panels). Maximal changes were —9 and —12 mm Hg, respectively. All these changes were dose-dependent, the threshold dose being 40 μg/kg.

Five out of nine subjects developed transient rhythm disturbances after bolus injections of adenosine. In all cases, these occurred at the peak of blood pressure and, in 4 subjects, were related to AV conduction delay. One subject developed a slow ectopic atrial rhythm (Table 1). However, on average, no definite bradycardia was observed (Figure 2, left panels). In contrast, a dose-dependent increase in heart rate was observed during the trough of blood pressure (p<0.002, Figure 2), maximal R-R interval shortening being 298 msec.

Adenosine infusions (80 to 140 μg/kg/min) produced dose-dependent increases in heart rate (p<0.001) and systolic blood pressure (p<0.003) and a small decrease in diastolic blood pressure (NS).
Table 1. R-R Interval Change Observed After 100 μg/kg Bolus Injection in Normal Volunteers

<table>
<thead>
<tr>
<th>Subject</th>
<th>R-R</th>
<th>Heart rhythm</th>
<th>Duration of arrhythmia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>258</td>
<td>PR prolongation (0.35 sec)</td>
<td>5 beats</td>
</tr>
<tr>
<td>2</td>
<td>-132</td>
<td>PR prolongation (0.22 sec)</td>
<td>2 beats</td>
</tr>
<tr>
<td>3</td>
<td>52</td>
<td>PR prolongation (0.23 sec)</td>
<td>3 beats</td>
</tr>
<tr>
<td>4</td>
<td>94</td>
<td>Sinus rhythm</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>-80</td>
<td>Sinus rhythm</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>+752</td>
<td>II AV block 2:1</td>
<td>5 beats</td>
</tr>
<tr>
<td>7</td>
<td>-120</td>
<td>Sinus rhythm</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>+450</td>
<td>Ectopic atrial rhythm</td>
<td>1 beat</td>
</tr>
<tr>
<td>9</td>
<td>-130</td>
<td>Sinus rhythm</td>
<td></td>
</tr>
</tbody>
</table>

Changes during the 140 μg/kg/min dose were +30 beats/min, +16 mm Hg, and -5 mm Hg, respectively (Figure 3). As a result of the divergent effects on systolic and diastolic blood pressures, mean arterial blood pressure remained unchanged, whereas pulse pressure widened (p<0.001, 21 mm Hg for the 140 μg/kg/min dose). Adenosine infusions also increased thoracic excursion (p<0.001, Figure 4) without significantly affecting respiratory rate (14±1 resp/min during 140 μg/kg/min adenosine infusion compared with 15±1 resp/min at baseline). This increase in ventilation resulted in respiratory alkalosis, with a decrease in Paco₂ (p<0.001) and increases in Pao₂ (NS) and pH (p<0.001). Maximal changes were -11 mm Hg, 12 mm Hg, and 0.08, respectively (Figure 4). No change was seen on the P(A-a)o₂ difference during adenosine infusions (4.0 mm Hg during the 140 μg/kg/min dose versus 6.0 mm Hg at baseline). Adenosine infusions produced no change in FEV₁ (4.14±0.24 l), FVC (5.12±0.35 l), or the FEV₁:FVC ratio (0.82±0.02) compared with saline infusion (4.28±0.25, 5.25±0.35, and 0.82±0.02, respectively). Threshold dose for respiratory stimulation was 80 μg/kg/min, while threshold dose for cardiovascular effects was 100 μg/kg/min. These effects were dose dependent and were reversed shortly after discontinuation of the infusion (right side of Figures 3 and 4).

Adenosine infusions were associated with a dose-dependent increase in plasma catecholamines. Plasma norepinephrine rose from 222 ± 26 pg/ml during saline infusion to 323 ± 34 pg/ml during 140 μg/kg/min adenosine infusion (41% increase, p<0.05). Similarly, plasma epinephrine rose from 77 ± 11 pg/ml to 148 ± 29 pg/ml (80% increase, p = 0.08).

Cardiovascular Effects of Adenosine in Patients With Autonomic Failure

Bolus injections of adenosine were given to 4 patients with severe autonomic failure with both parasympathetic and sympathetic involvement, as assessed by loss of sinus arrhythmia, lack of normal blood pressure response, and reduced heart rate variability. Adenosine decreased heart rate by 15 beats/min, increased systolic blood pressure by 10 mm Hg, and decreased diastolic blood pressure by 5 mm Hg. These effects were dose dependent and reversed shortly after discontinuation of the infusion (right side of Figures 3 and 4).
pressure overshoot during phase IV of Valsalva maneuver, absence of heart rate response to Valsalva, and lack of pressor response to sustained handgrip or cold exposure. Furthermore, supine plasma norepinephrine was low (130 ± 21 pg/ml), considering their ages, and failed to increase on assuming the upright posture (149 ± 24 pg/ml), especially considering their fall in blood pressure on standing. Although individual responses to adenosine were variable, these patients were more sensitive to its actions than normal subjects. Individual doses that met the predetermined hemodynamic endpoints (see “Subjects and Methods”) were 7.5, 10, 20, and 80 μg/kg. Representative results are shown in Figure 5. The effects of maximal doses of adenosine observed in patients with autonomic failure are compared in Figure 6A with the effects seen in normal volunteers. The initial pressor effect of adenosine seen in normal volunteers was greatly attenuated in patients with autonomic failure. Furthermore, even though the subsequent decrease in blood pressure was accentuated in autonomic failure patients, the tachycardia observed in normal volunteers during the trough blood pressure was totally abolished in autonomic failure patients. Instead, significant bradycardia occurred (R-R interval prolongation of 176 ± 68 msec). The ventilatory response to adenosine, as assessed by the increase in thoracic excursion, was also blunted in these patients compared with normals (Figure 5).

Two patients also received continuous infusions of adenosine (60 and 120 μg/kg/min). Again, in contrast to the effects seen in normal volunteers, dramatic decreases in both systolic and diastolic blood pressure were observed, with no change in heart rate, in contrast to the increase in heart rate and systolic blood pressure observed in normal volunteers (Figure 6B).

**Differential Effects of Adenosine According to Site of Infusion**

When adenosine (5 μg/kg) was infused into the aortic arch proximal to the origin of the carotid arteries, it produced an initial increase in heart rate (R-R interval shortening of 114 ± 48 msec at 8 ± 0.4 seconds) and in blood pressure (+19 ± 5 and +12 ± 3 mm Hg for systolic and diastolic pressures, respectively). At 18 ± 0.8 seconds, there was a decrease in blood pressure (−10 ± 3/−5 ± 1 mm Hg for systolic/diastolic pressure, Figure 7). In contrast, when adenosine (5 μg/kg) was infused in the descending aorta, neither the initial tachycardia nor the increase in blood pressure was observed (p<0.05 and p<0.01, respectively, **Figure 6A**).
compared with the ascending aorta injections). Furthermore, the subsequent decrease in blood pressure observed at 18 ± 0.8 seconds after injection in the descending aorta (-26 ± 2/-9 ± 1 mm Hg systolic/diastolic pressures) was significantly greater than that observed when adenosine was injected in the aortic arch (-10 ± 3/-5 ± 1 mm Hg, Figure 8).

**Side Effects**

High-dose adenosine administration in normal volunteers was accompanied by the appearance of side effects (an urge to breathe deeply, nervousness, head and neck flushing, and sometimes headache). These side effects were dose-dependent. Responses to bolus injections greater than 100 μg/kg and infusions greater than 140 μg/kg/min in normal volunteers were not analyzed because of the dropout rate at higher doses.

**Discussion**

The results reported here are similar to our previous observations that in conscious man, adenosine infusions increase heart rate and systolic blood pressure. Moreover, it has been found that bolus injections of adenosine produce an initial increase in both systolic and diastolic blood pressures, an observation not previously reported. It is unlikely that this increase is the result of a direct vascular action of adenosine since vasodilatory effects of adenosine in most vascular beds have been well described. Furthermore, adenosine is clearly hypotensive when given to anesthetized patients. Therefore, it was postulated that increases in heart rate and blood pressure could be due to adenosine-mediated activation of an autonomic reflex mechanism. The data obtained in patients with severe autonomic failure support this hypothesis. Increases in heart rate and blood pressure seen after adenosine infusion or bolus injections in normal volunteers were totally abolished in patients with autonomic failure. Since these patients are selectively devoid of autonomic reflexes, the observed cardiovascular effects more likely represent the direct actions of adenosine. Thus, the effects seen in normal volunteers are not due to the direct actions of adenosine but to an adenosine-induced activation of a reflex autonomic mechanism.

It is possible that a central sympathetic activation might be elicited as a reaction to unpleasant side effects of adenosine. This could explain some of the observed changes in plasma catecholamines and cardiovascular responses. However, it is unlikely that reaction to distress could explain, in the highly reproducible fashion observed, the discordant effects on systolic and diastolic blood pressures during adenosine infusion or the complex and concerted respiratory and cardiovascular responses occurring after bolus injections of adenosine.
Results in the present study also show that adenosine administration stimulates respiration in man. Although methodologic limitations of our measurement make the observed increase in thoracic excursion supportive but not conclusive of increased ventilation, our conclusion of respiratory stimulation is based on the changes observed in arterial blood gases. Increased ventilation was evidenced by a significant reduction of PaCO₂ and the development of respiratory alkalosis. Before it can be concluded that adenosine stimulates respiration, the possibility that the increase in ventilation is an epiphenomena associated with other effects of this substance must be ruled out. Inhaled adenosine may produce bronchoconstriction in asthmatics. Although bronchoconstriction is not found in normal subjects, it could theoretically produce the hyperventilation observed in our study as a compensatory mechanism. However, this possibility can be excluded since there was no change in spirometric data during adenosine infusions. Likewise, adenosine-induced hyperventilation was not secondary to hypotension since adenosine infusions had no effect on mean arterial blood pressure; on the contrary, systolic blood pressure increased. Neither can it be explained by hypoxia or diffusion abnormalities, e.g., secondary to ventilation/perfusion inequalities or pulmonary congestion, since Pao₂ increased and P(A-a)O₂ remained unchanged. Finally, a direct central activation is unlikely since intravenously administered adenosine does not enter the central nervous system in animals and, furthermore, adenosine applied directly into the central nervous system depresses respiration and reduces blood pressure. Therefore, it is concluded that adenosine administration produces direct respiratory stimulation.

To explain both the increase in blood pressure and respiratory stimulation seen during adenosine administration, it was postulated that chemoreceptor activation was involved since adenosine has been shown to produce carotid body chemoreceptor activation in animals. The effects of adenosine are mediated through specific cell surface receptors. The magnitude of its action, therefore, depends on the extracellular concentration achieved. Because of the rapid uptake and degradation of adenosine by blood cells in man, its half-life in the circulation is extremely short; it has been postulated as being less than 10 seconds or even less than 1 second. Therefore, the site of injection and mode of administration will critically influence the concentration of adenosine that reaches the relevant functional sites responsible for its actions. This very short half-life of adenosine permitted the hypothesis of adenosine-induced chemoreceptor action to be tested by infusing adenosine proximal and distal to the origin of the carotid arteries. Indeed, the cardiovascular effects of adenosine were totally different at these two sites. When infused into the ascending aorta, adenosine increased blood pressure and heart rate. However, when adenosine was infused into the descending aorta, these initial responses were completely abolished. Rather, a profound reduction in blood pressure was observed (Figure 8).

It has also been shown that intrarenal infusions of adenosine produce an acute increase in blood pressure in dogs through activation of afferent renal sympathetic fibers. Activation of this mechanism could not explain the respiratory stimulation observed in our study but could contribute to the pressor effect of adenosine. However, intrarenal infusion of adenosine does not increase blood pressure acutely in conscious rats nor chronically in dogs. In our patients undergoing diagnostic catheterization, bolus injections above the origin of the renal arteries did not produce consistent increments in blood pressure (data not shown). Thus, this mechanism does not explain the results observed in our study. However, its occurrence in man cannot be completely excluded.

Taken together, our results support the hypothesis that the direct vascular effects of adenosine (which can be readily observed in patients with autonomic failure) are masked in normal volunteers by activation of autonomic reflex mechanisms, most likely chemoreceptor activation. Preliminary results from other investigators also suggest that adenosine activates carotid body chemoreceptors in man. Adenosine increased minute ventilation when administered as a constant infusion in the ascending aorta but not when infused distal to the origin of the carotid arteries. Furthermore, when infused constantly at subhemodynamic doses, adenosine enhances the ventilatory response to hypoxia, implying an action at the chemoreceptor level. Adenosine-induced carotid body chemoreceptor activation has been demonstrated in animals, and although this is the most likely site of action of adenosine in man, a contribution of aortic chemoreceptors cannot be excluded. Observed differences in cardiovascular response to adenosine between conscious volunteers and anesthetized patients may be related to a blunting of chemoreflexes during anesthesia.

Pure chemoreceptor activation results in increased blood pressure, bradycardia, and respiratory stimulation. However, unless ventilation is maintained constant, pulmonary stretch receptors are activated secondary to the hyperventilation, and they tend to blunt the increase in blood pressure and to produce tachycardia. Thus, in conscious man, the final hemodynamic effects of adenosine are the result of a complex interplay of different phenomena: direct cardiovascular effects of adenosine (bradycardia and vasodilatation), adenosine-induced activation of chemoreflexes (bradycardia and increased blood pressure), and secondary activation of pulmonary stretch receptors (tachycardia).

It has been shown in different organs that adenosine levels are greatly increased during hypoxia, and in this situation, adenosine may be an important modulator of physiologic process. It is obvious that conclusions on the role of endogenous adenosine cannot be drawn from the present study. However, our finding that adenosine is a direct respiratory stimulant raises the possibility that adenosine is an endogenous modulator of respiration in man.
In summary, in conscious normal human subjects, adenosine infusions increase heart rate, systolic blood pressure, and pulse pressure, while producing only a mild decrease in diastolic blood pressure and no change in mean arterial blood pressure. Adenosine bolus injections produce a biphasic response, with an initial increase in both systolic and diastolic blood pressure followed by a fall in blood pressure. Heart rate also increases during bolus injections. Adenosine stimulates respiration in man, producing a respiratory alkalosis that is not the result of bronchoconstriction, hypoxia, or hypotension. These changes are dose related and reflect adenosine-induced activation of reflex mechanisms, probably chemoreceptor activation, since initial increases in heart rate and blood pressure seen after intravenous bolus injections in normal volunteers were abolished in patients with autonomic failure and were not seen when adenosine was injected in the descending aorta in patients undergoing diagnostic catheterization. Although these results suggest that adenosine is not an effective hypertensive agent in conscious man, the physiologic role of adenosine in respiratory homeostasis and its therapeutic potential as a respiratory stimulant deserve further study.

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