Comparison of pulmonary and systemic effects of adenosine triphosphate in chronic obstructive pulmonary disease - ATP: a pulmonary controlled vasoregulator?

S.J.M. Gaba, C. Préfaut

ABSTRACT: During stepwise incremental intravenous adenosine triphosphate (ATP) infusion, systemic and pulmonary vascular effects were compared in 10 patients with stable chronic obstructive pulmonary disease (COPD). Pulmonary vasodilatation was 1) predominant and maximal as early as the lowest dose infusion (0.1 μmol·kg⁻¹·min⁻¹) with pulmonary arterial mean pressure (Ppa) (-16%; p<0.01) and pulmonary vascular resistance (PVR) decreases (-28%; p<0.005) and simultaneous increasing ΔPVR/ΔSVR ratio; 2) associated with worsening hypoxaemia (-14%; p<0.001), but also with increasing alveolar-arterial oxygen pressure difference (P(A-a)O₂) and venous admixture (Qw/Qs) suggesting some inhibition of hypoxic pulmonary vasoconstriction. Systemic vasodilatation was: 1) clearly dose-dependent, but only reached significant level at 0.2 μmol·kg⁻¹·min⁻¹ with systemic arterial mean pressure (Psao) (-12.5%; p<0.05) and systemic vascular resistance (SVR) decreases (-30%; p<0.01); 2) associated with arterial carbon dioxide tension (Paco₂) decrease (-28%; p<0.005) and recurring uncontrollable hyperpnoea, suggesting a ventilatory stimulatory effect of ATP in man. In patients with stable COPD, ATP infusion has dual acute haemodynamic effects depending on the dose-level. The predominant pulmonary vasodilator effect occurs as early as the lowest dose-levels without any further increase of pulmonary vasodilatation. This contrasts with the dose-related systemic vasodilatation effect. Such a dual haemodynamic effect is an indirect indication of in vivo lung metabolism of ATP.

Adenosine triphosphate (ATP) is the high energy intra-cellular natural compound. Many extra-cellular effects have also been described, particularly on vessels [1, 2].

In man, ATP-induced systemic hypotension has been observed in anaesthetized patients during surgery [3, 4]. However, haemodynamic data have never been analysed in conscious man during ATP-induced systemic vasodilatation.

Recently, we have described ATP-induced pulmonary vasodilatation during low dose-level infusion (0.05 and 0.1 μmol·kg⁻¹·min⁻¹) in chronically hypoxaemic patients [5] with chronic obstructive pulmonary disease (COPD). In this study we did not observe systemic vasodilatation; however, the dose levels we used were four times lower than that used in anaesthetized patients [3]. These different results may indicate different ATP reactivity levels in pulmonary and systemic circulation, which in turn could be accounted for by lung metabolism of ATP. Indeed, a saturable metabolic pathway has previously been described for ATP on pulmonary endothelial cells in culture [6].

The aim of this study was to determine the dose-effect relationship of ATP on pulmonary and systemic circulation in order to ascertain whether regional differences exist. Such differences could illustrate indirectly an in vivo metabolism of circulating ATP by the pulmonary vascular bed.

Methods

Patients

Ten patients (10 men), 52–78 yrs of age, with stable moderate to severe COPD, were studied (table 1). Selection criteria [7] included clinical data, chest roentgenogram, electrocardiogram (ECG) and pulmonary function testing; the minimal amount of bronchial obstruction required was percentage forced expiratory
volume in one second/forced vital capacity (FEV₁/FVC %) lower than 60. Patients with reversible airway obstruction were excluded. None of the patients had any other lung disease or a history of thromboembolism or left heart disease.

Treatment with methylxanthines or corticoids was continued; on the other hand, patients using vasodilating drugs (calcium-blockers, beta-adrenergic drugs or nitrates), those requiring continuous oxygen therapy, and almitrine-treated patients were excluded from the study.

Preliminary informed consent was obtained from each patient.

Methods

Heart rate (HR) and ECG were continuously monitored. A Swan-Ganz flow-directed thermodilution catheter (Edwards laboratories, Santa-Anna, CA) was inserted through the right internal jugular vein into the pulmonary artery under continuous pressure wave monitoring. Pressures were measured using a Statham P 23 DB pressure transducer (Statham instrument, Hato Rey, PR). The zero reference was situated at mid-chest, with the subject lying supine. Pressures were recorded using a thermal-writing recorder (Philip EM 110) during two spontaneous breathing cycles for each assessment. Mean pulmonary artery pressure (Ppa), mean pulmonary wedge pressure (Ppaw) and mean right atrium pressure (Pra) were recorded. Cardiac output (Qt) was assessed in triplicate by the thermodilution method using a cardiac index computer (SP 1435; Gould Instruments, Cleveland, OH). Iced (4°C) 9% saline serum was used for this. A teflon catheter was inserted percutaneously into the brachial artery. Mean systemic artery blood pressure (Psa) was recorded using a Statham P 23 DB pressure transducer and the same thermal writing recorder. Arterial and mixed venous blood gases were assessed immediately, using standard electrodes (pH-blood gas analyser 168, Corning Medical Instruments, Medfield, MA).

Calculated data

Cardiac index (CI) was computed as CI = Qt/body area (l·min⁻¹·m⁻²); stroke index (SI) was calculated as SI = CI/HR (ml·m⁻²·per pulse); pulmonary vascular resistance (PVR) was calculated as PVR = 80·Ppa - Ppaw/Qt (dyne·cm⁻²·s⁻¹) and systemic vascular resistance (SVR) was calculated as SVR = 80·Psa - Pra/Qt (dyne·cm⁻²·s⁻¹). Pulmonary and systemic vasodilating effects were compared using their variation ratio (ΔPVR/ΔSVR), calculated as the ratio of variation of PVR (%) from baseline level to the variation of SVR (%) during the same dose-level of ATP infusion. An increase of this ratio indicates a predominant effect on systemic circulation.

Gasometric data allowed us to calculate arterial (Cao₂) and mixed venous (Cvo₂) oxygen content as Cx₀₂ (ml·l⁻¹) = (1.39·Hb·Sx₀₂ + 0.003·Pxo₂)·10, where Hb in the haemoglobulin level and Sx₀₂ and Pxo₂ the arterial and mixed venous oxygen saturation and tension, respectively. The indexed oxygen consumption was calculated as Vco₂ (ml·min⁻¹·m⁻²) = Cao₂-CI·10. The alveolar-arterial oxygen pressure gradient (P(a-a)O₂) was calculated as P(a-a)O₂ (kPa) = Pao₂ - Paco₂/R-Paco₂, where Pao₂ was the inspiratory pressure of O₂, Paco₂ was the alveolar pressure of CO₂ (assumed to be equal to the arterial Pco₂ (Paco₂)), R was the respiratory exchange ratio, (assumed to be 0.8) and Pao₂ was the arterial pressure of O₂. The venous admixture (Qs/Qt) was calculated on ambient air as Qs/Qt (%) = Cc'o₂ - Cao₂/Cc'o₂ - Cvo₂ (%) where Cc'o₂ was the capillary oxygen content, estimated using the calculated alveolar oxygen pressure (Pao₂), corresponding saturation being determined using Kelman's subroutine [8].

Table 1. – Anthropometric and lung function data of the 10 patients

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Hb (g·l⁻¹)</th>
<th>FVC (%)</th>
<th>FEV₁ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean</td>
<td>61</td>
<td>167</td>
<td>70.6</td>
<td>155</td>
<td>68</td>
</tr>
<tr>
<td>std</td>
<td>10</td>
<td>4.1</td>
<td>13.2</td>
<td>10</td>
<td>15.1</td>
</tr>
</tbody>
</table>

FVC: forced vital capacity; FEV₁: forced expiratory volume in one second; Reference values are those of the Commission des Communautés Européennes [9].

Protocol

Subjects rested at least 30 min after the insertion of catheters; no premedication was used and the protocol started when HR and Psa levels were stable. ATP was infused intravenously (iv) using STRIADYNE (Ayerst Laboratories, Montrouge, France) in incremental dose-levels of 0.05, 0.1, 0.15, 0.2 and 0.25 μmol·kg⁻¹·min⁻¹, each infusion lasting for 20 min. The solvent (chlorbutol), an alcoholised compound, was infused at an average total dose of 522.6 ml. Data were serially collected before and during the infusion, between the 15th and 20th min for each infusion.

Statistical analysis

Data variations during incremental ATP infusion were assessed by ANOVA. When significant, variations on data were compared for each dose-level to baseline, by using the t-test for paired data. The Bonferroni method [9] for correcting simultaneous comparison procedure was used (critical Z-value at p=0.005).

Results

All data are summarised in table 2. During the whole procedure, significant variations were found in HR and CI, Psa and SVR, Ppa and PVR, Pao₂, Paco₂, P(a-a)O₂ and Qs/Qt. Some were observed beginning with the first dose (0.05 μmol·kg⁻¹·min⁻¹) (fig. 1). The SVR variations only reached significant level with the
Table 2. - Effects of ATP infusion using stepwise incremental dose-levels

<table>
<thead>
<tr>
<th></th>
<th>0.05</th>
<th>0.1</th>
<th>0.15</th>
<th>0.2</th>
<th>0.25</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{P}_{\text{aO}_2}$ kPa</td>
<td>8.4±0.3</td>
<td>7.5±0.3</td>
<td>7.2±0.3</td>
<td>7.4±0.3</td>
<td>7.5±0.4</td>
<td>7.3±0.4</td>
</tr>
<tr>
<td>$\text{P}_{\text{aCO}_2}$ kPa</td>
<td>5.6±0.3</td>
<td>5.4±0.4</td>
<td>5.5±0.4</td>
<td>5.2±0.4</td>
<td>5.6±0.4</td>
<td>4.9±0.4</td>
</tr>
<tr>
<td>$\text{P}_{\text{aO}_2}$ kPa</td>
<td>4.7±0.2</td>
<td>4.6±0.2</td>
<td>4.5±0.2</td>
<td>4.7±0.2</td>
<td>4.8±0.3</td>
<td>4.7±0.3</td>
</tr>
<tr>
<td>$\text{HR}$ c·min·1</td>
<td>81.5±3.7</td>
<td>81.9±3.7</td>
<td>82.9±3.4</td>
<td>84.6±3.3</td>
<td>87.6±3.3</td>
<td>90.2±3.7</td>
</tr>
<tr>
<td>$\text{P}_{\text{aO}_2}$ mmHg</td>
<td>20.1±1.9</td>
<td>18.3±1.9</td>
<td>16.9±1.5</td>
<td>17.8±1.6</td>
<td>18±1.7</td>
<td>17.9±1.5</td>
</tr>
<tr>
<td>$\text{P}_{\text{aCO}_2}$ kPa</td>
<td>4.7±0.2</td>
<td>4.6±0.2</td>
<td>4.5±0.2</td>
<td>4.7±0.2</td>
<td>4.8±0.3</td>
<td>4.7±0.3</td>
</tr>
<tr>
<td>$\text{P}_{\text{aO}_2}$ mmHg</td>
<td>6.2±1.6</td>
<td>5.9±1.5</td>
<td>5.6±1.5</td>
<td>6.0±1.3</td>
<td>6.2±1.6</td>
<td>5.8±1.6</td>
</tr>
<tr>
<td>$\text{HR}$ c·min·1</td>
<td>4.2±1.2</td>
<td>4.2±1.8</td>
<td>3.7±1.5</td>
<td>4.3±1.9</td>
<td>3.9±1.6</td>
<td>4.4±2.1</td>
</tr>
<tr>
<td>$\text{P}_{\text{aO}_2}$ mmHg</td>
<td>3.9±0.86</td>
<td>3.59±1.04</td>
<td>3.77±1.07</td>
<td>3.88±1.04</td>
<td>4.19±1.04</td>
<td>4.21±1.16</td>
</tr>
<tr>
<td>$\text{CI}$ l·min·1·m$^{-3}$</td>
<td>41.9±2.7</td>
<td>44.0±3.3</td>
<td>45.3±3.5</td>
<td>45.4±3</td>
<td>47.8±3.2</td>
<td>46.8±3.6</td>
</tr>
<tr>
<td>$\text{PVR}$ D·cm·5·s·1</td>
<td>189±7.6</td>
<td>159±6.9</td>
<td>137±5.7</td>
<td>138±5.9</td>
<td>126±5.6</td>
<td>132±5.4</td>
</tr>
<tr>
<td>$\text{SVR}$ D·cm·5·s·1</td>
<td>3.39±0.86</td>
<td>3.59±1.04</td>
<td>3.77±1.07</td>
<td>3.88±1.04</td>
<td>4.19±1.04</td>
<td>4.21±1.16</td>
</tr>
<tr>
<td>$\text{P(A-a)O}_2$ kPa</td>
<td>5.0±0.4</td>
<td>4.9±0.4</td>
<td>4.8±0.3</td>
<td>4.7±0.3</td>
<td>4.7±0.3</td>
<td>4.7±0.3</td>
</tr>
<tr>
<td>$\text{Qs/Qt}$ %</td>
<td>87.4±3.6</td>
<td>83.4±3.5</td>
<td>81.2±3.5</td>
<td>81.2±3.5</td>
<td>81.2±3.5</td>
<td>81.2±3.5</td>
</tr>
</tbody>
</table>

Values are mean±SEM; T0: baseline data; 0.05, 0.1, 0.15, 0.2 and 0.25: dose-level as μmol·kg$^{-1}$·min$^{-1}$; $\text{P}_{\text{aO}_2}$: arterial oxygen tension; $\text{P}_{\text{aCO}_2}$: arterial carbon dioxide tension; $\text{P}_{\text{aO}_2}$: mixed venous O$_2$ pressure; $\text{P}_{\text{aO}_2}$: mean pulmonary artery pressure; $\text{P}_{\text{paw}}$: mean pulmonary artery wedge pressure; $\text{P}_{\text{paw}}$: mean right atrium pressure; Cl: cardiac index; SI: stroke index; $\text{P}_{\text{VR}}$: pulmonary vascular resistance; $\text{SVR}$: systemic vascular resistance; $\Delta \text{PVR/ASVR}$: $\text{PVR}$ over $\text{SVR}$ relative variation ratio; $\text{P(A-a)O}_2$: alveolar-arterial oxygen pressure gradient; $\text{Qs/Qt}$: venous admixture; NS: not significant; ANOVA: analysis of variance.

Fig. 1. - Pulmonary data variations during stepwise incremental ATP infusion. Variations are expressed as percent of baseline level (mean±SEM). For definitions of significant values, see table 2. p: ANOVA significance level; when significant, Bonferroni corrected paired t-test over T0 level (**: p<0.005, *: p<0.001).

fourth dose-level (0.20 μmol·kg$^{-1}$·min$^{-1}$); three variables: HR, $\text{P}_{\text{sa}}$, and $\text{P}_{\text{aCO}_2}$ reached significant variations only with the fifth dose-level (0.25 μmol·kg$^{-1}$·min$^{-1}$) (fig. 2). During this study, other haemodynamic and gasometric variables showed no changes.

The $\Delta \text{PVR/ASVR}$ variation ratio reached its highest value: 211% (fig. 3), with the second dose-level (0.1 μmol·kg$^{-1}$·min$^{-1}$) indicating an initial predominant pulmonary vascular effect. This ratio then decreased regularly towards its lowest value: 90%, reached with the highest dose-level (0.25 μmol·kg$^{-1}$·min$^{-1}$), indicating a subsequent predominant systemic vascular effect.

Occasional side-effects occurred during high dose-level ATP infusion in 7 out of 10 patients: nausea, flush or hyperventilation; all remained moderate and transient and it was never necessary to stop the procedure. However, such side-effects reoccurred periodically at 1–2 min intervals until the end of the infusion.
PULMONARY VS SYSTEMIC EFFECTS OF ATP IN COPD

Discussion

In patients with stable COPD during incremental ATP infusion, our results show that: 1) low dose-levels induced predominant pulmonary vasodilation, with Psa and PVR decrease and an increase of ΔPVR/ΔSVR; 2) the highest dose-level induced predominant systemic vasodilation, with Psa and SVR decrease, a drop of ΔPVR/ΔSVR ratio to its lowest level, and intermittent side-effects.

Many compounds have previously been described as pulmonary vasodilators but have shown, in fact, only unspecific vasodilating effects, acting simultaneously on pulmonary and systemic vessels with predominant systemic effects [10]. Some of these drugs, like hydralazine, may induce dramatic deleterious effects such as sustained systemic hypotension or a worsening of hypoxaemia making them difficult to use in the management of pulmonary hypertension in COPD [11]. The theoretically ideal pulmonary vasodilating compound would induce predominant pulmonary vasodilation [12]. Thus far, this pulmonary predominant activity has been described only during short term infusion of urapidil, a post-synaptic alpha-blocker [13], or prostaglandin E1 [14], but has not been recorded during low rate infusion of prostacyclin [15], isoproterenol [16] and acetylcholine [17] in man.

In the present study, we describe a natural short-lived compound leading to a predominant pulmonary vasodilating effect during low dose-level infusion.
(maximal during ATP infusion using 0.1 μmol·kg⁻¹·min⁻¹). The effect of ATP on pulmonary vessels was not dose-dependent and remained unchanged at higher dose-levels. However, at these higher levels, there was a shift in the predominance of vasodilation from the pulmonary system to the systemic circulation. All these data suggest a selective pulmonary vasodilating effect only during low dose ATP infusion. This predominant pulmonary effect disappears at a certain dose level and may be explained by some saturable metabolic pathway in pulmonary vessels, which acts like a metabolic filter on circulating infused ATP. Such a saturable pathway could be the endothelium specific uptake of ATP [6], endothelium endocytosis using caveolae [18], or the ATP dephosphorylation induced by endothelium ectonucleotidases [19]. Although in vivo pulmonary vascular uptake of ATP was described as early as 1950 in dogs [20], in vivo studies remain incapable of assessing the respective roles of the above-mentioned mechanisms in the function of the pulmonary endothelium as a metabolic filter of ATP.

In our study systemic hypotension was associated with a corresponding increase of CI and HR without any change of SI. This fact, previously observed in conscious dogs with intact baroreflex [21], is suggestive of a reactive adrenergic state which probably interferes with the vasodilating effect of ATP [22]. On the contrary, in ATP-induced hypotension during anaesthesia in animals and in man no change or a slight decrease of heart rate has usually been recorded [23]. This result could be accounted for by decreased baroreflex control during anaesthesia. It has, however, been shown that baroreflex control is still effective during this state [24]. It must be taken into consideration that during anaesthesia ATP dose-levels were nearly fourfold higher than in our study and could have raised bradycardia by direct cardiac effect [25]. Further studies are necessary to better understand these mechanisms; however, very high dose-levels of ATP remain impossible to use in conscious subjects as side effects occur.

Although there are only a few reports about the hypertensive effect of ATP in man [23], systemic vasodilating and hypotensive effects of adenosine have been evaluated during human surgery [26]. Adenosine vascular effects, however, cannot be extrapolated to ATP because these compounds act on different receptors (P, vs P2) and they use distinct mechanisms [25] for a relaxing effect, with ATP being the only one that induces an endothelium-dependent relaxation.

During ATP-induced pulmonary vasodilation, and in the same manner, Pao2 decreased and was associated with significant worsening of P(A-a)O2 and Qs/Qt. During the two lowest infusion levels these results, associated with the lack of variations in other data such as CI, Ppaw, Psa and Paco2, were highly suggestive of a worsening of the ventilation-perfusion relationship, as previously described during other pulmonary vasodilating drug trials [27]. During ATP infusion, as inhibition of hypoxic pulmonary vasoconstriction has previously been recorded in dogs [28] and could at least partly explain a worsening of the Va/Q relationship by increasing the low Va/Q lung units and therefore inducing a decrease of Pao2 in the patients. Results suggest that drug-induced pulmonary vasodilation on chronically hypoxaemic patients with stable COPD could be safe if the pulmonary vasodilation (i.e. pulmonary driving pressure drop) is associated with cardiac output increase. This phenomenon would limit the hypoxaemia worsening and could also increase the oxygen-delivery to peripheral tissues.

The significant decrease of Paco2 during systemic vasodilation induced by the ATP infusion was an interesting observation. During pulmonary vasodilation trials in COPD patients with nifedipine or nitrendipine, Paco2 did not vary [27, 29]; on the contrary acute drug-induced pulmonary vasodilation with hydralazine [30] and isoproterenol [16] induced similar decreases of Paco2 in these patients. Hydralazine infusion induced a ventilatory drive increase that could explain, at least partly, the decrease of Paco2 [31]. During our study, many patients complained of dyspnoea with periodic difficulty of breathing and a peculiar recurring sensation of uncontrollable hyperventilation. Similar clinical side-effects were previously noticed during ATP infusion in conscious man [32] but these data have never been analysed. More specific studies are necessary to confirm the hypothetical ventilatory stimulant effect of ATP.

In this study of chronically hypoxaemic patients, ATP infusion induced dual haemodynamic effects: 1) pulmonary vasodilation was not dose-dependent but predominant during low dose-levels, with slightly worsening hypoxaemia, possibly due to partial inhibition of hypoxic pulmonary vasoconstriction; 2) on the contrary, systemic vasodilation was dose-dependent and became predominant only at the highest dose levels. Such a dual haemodynamic effect is an indirect argument in favour of a saturable metabolic pathway of pulmonary circulation for ATP. For these highest dose levels clinical side-effects were noticed which suggest a ventilatory stimulant effect of ATP.

Haemodynamic and ventilatory effects of ATP and other purinergic compounds in health and disease call for further studies. Physiological or therapeutic implications remain, so far, premature.

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References


**Effets pulmonaires et systémiques comparés du triphosphate d'adénosine dans les bronchopneumopathies chroniques obstructives. L'ATP: un vasorégulateur à contrôle pulmonaire?**

S. Gaba, C. Préfaut.

RÉSUMÉ: Nous avons comparé les effets vasculaires pulmonaires et systémiques de l'ATP administré en perfusion par voie intra-veineuse, à dose croissante, chez 10 patients atteints de BPCO stable. La vasodilatation pulmonaire obtenue était 1) préférentielle et maximale dès les plus faibles doses (0,1 μg·kg⁻¹·min⁻¹) connue en témoignent la diminution de la *Pap* (-16%; p<0,01), des RVP (-28%; p<0,005) et l'augmentation simultanée du rapport des variations des résistances pulmonaires et systémiques ΔRVP/ΔRVS, 2) associée à une aggravation de l'hypoxémie (-14%; p<0,001) mais aussi à une augmentation de P(A-a)O₂ et de ΔQs/Qt, suggérant une inhibition de la vasocstriction pulmonaire hypoxique. La vasodilatation systémique était par contre: 1) dépendante de la dose, ne devenant significative qu'à partir de la dose de 0,2 μg·kg⁻¹·min⁻¹ pour la *Pap* (-12,5%; p<0,05) et les RVS (-30%; p<0,01), 2) associée à des effets secondaires survenant de façon cyclique; 3) associée à une diminution de PCO₂ (-12,5%; p<0,005) et à un besoin insécable d’hyperventilation, suggérant un effet stimulant ventilatoire de l'ATP chez l'homme. Chez des patients atteints de BPCO stable, la perfusion d'ATP possède une dualité d'action selon la dose administrée: un effet vasodilatateur pulmonaire préférentiel est induit par les faibles doses sans être dose-dépendant contrairement à l’effet vasodilatateur systémique. Cette dissociation entre effet vasodilatateur pulmonaire et systémique en fonction de la dose administrée, pourrait traduire en vivo le rôle métabolique de l’endothélium pulmonaire chez l’homme vis à vis de l’ATP. *Eur Respir J.*, 1980, 3, 450-455.