HAEMODYNAMIC AND CEREBRAL EFFECTS OF ATP-INDUCED HYPOTENSION

H. V. Aken, C. Puchstein, W. Fitch and D. I. Graham

SUMMARY

Controlled decreases in mean arterial pressure to 20%, 40% and 60% of baseline were produced by the administration of increasing concentrations of adenosine triphosphate (ATP) i.v. in five anaesthetized baboons. Indices of the systemic circulation (arterial pressure, right atrial pressure, pulmonary artery pressures, cardiac output) and of the cerebral circulation (cerebral blood flow, cerebral metabolic rate for oxygen, cerebrovascular reactivity) were obtained as arterial pressure was decreased, and following discontinuation of the infusion of ATP. A neuropathological investigation was undertaken at the end of the experimental procedure. The infusion of ATP produced dose-dependent decreases in systemic vascular resistance and mean arterial pressure (MAP). Cardiac output and stroke volume were maintained close to baseline values, or increased slightly. Cerebral blood flow (CBF) increased initially (48 ± 4 ml min⁻¹/100 g to 68 ± 9 ml min⁻¹/100 g) and then decreased progressively as MAP was decreased to 40% and 60% of baseline. Cerebrovascular reactivity was shown to be impaired during, and for up to 90 min following, the administration of ATP. However, there was no morphological evidence of ischaemic cell damage in any animal. Tachyphylaxis was not observed during, and there were no instances of rebound hypertension following, the infusion of ATP. The concentration of uric acid had increased significantly by the 40% decrement in MAP, and remained so 60 min after the restoration of the arterial pressure.

Controlled hypotension is used widely in neurosurgical anaesthesia to decrease operative blood loss, and to facilitate dissection during the surgical management of intracranial aneurysms (Ferguson, 1982). Ideally, the pharmacological agent(s) used to produce the required decreases in systemic arterial pressure should allow easy and rapid modulation of the arterial pressure, and should not affect adversely the physiological responsiveness of the cerebral circulation. Moreover, the drugs themselves should be non-toxic to the patient, and should not produce toxic metabolites. Although effective, the commonly used agents such as trimetaphan, sodium nitroprusside, nitroglycerine and halothane do not meet all of the above requirements (Adams and Hewitt, 1982), and the search continues for an agent closer to the ideal.

Recently, it has been shown that the administration of adenosine triphosphate (ATP), or adenosine, i.v. will produce controllable decreases in systemic arterial pressure (Fukunaga, Flacke and Bloor, 1982; Lagerkranser et al., 1982; Puchstein et al., 1982; Kassel et al., 1983a). The present study was undertaken to evaluate the systemic and cerebrovascular responses in the baboon to ATP-induced hypotension, and to consider whether ATP fulfills more closely the criteria for the ideal hypotensive agent for use in neurosurgical anaesthesia.

MATERIALS AND METHODS

Five young adult baboons (13–17 kg), tranquilized with phencyclidine 12 mg i.m., were anaesthetized with thipentone 7.5 mg kg⁻¹ i.v. and 70% nitrous oxide in oxygen. In addition, phencyclidine 2 mg i.m. and suxamethonium 100 mg i.m. were administered every 30 min to prevent awareness, and to produce neuromuscular blockade. The trachea was intubated and ventilation was controlled throughout each investigation (Starling respiratory pump; C. F. Palmer Ltd), the minute volume and the inspired oxygen concentration being adjusted, as required, to produce neuromuscular blockade. The trachea was intubated and ventilation was controlled throughout each investigation (Starling respiratory pump; C. F. Palmer Ltd), the minute volume and the inspired oxygen concentration being adjusted, as required, to produce neuromuscular blockade. The trachea was intubated and ventilation was controlled throughout each investigation (Starling respiratory pump; C. F. Palmer Ltd), the minute volume and the inspired oxygen concentration being adjusted, as required, to produce neuromuscular blockade. The trachea was intubated and ventilation was controlled throughout each investigation (Starling respiratory pump; C. F. Palmer Ltd), the minute volume and the inspired oxygen concentration being adjusted, as required, to produce neuromuscular blockade.
rectal thermometer and maintained within normal limits (36–38 °C) by means of heating lamps. Correction was made, where necessary, for any temperature difference between the animal and the electrode system.

Systemic arterial pressure was measured electronically from the abdominal aorta through a catheter inserted via the left femoral artery. A balloon-tipped flow-directed pulmonary artery thermodilution catheter (5 French gauge, Edwards Laboratories) was introduced through the right femoral vein to the pulmonary artery. Other catheters were inserted to the right femoral vein for the infusion of fluids (3 ml kg⁻¹ h⁻¹), and to the superior sagittal sinus to permit monitoring of cerebral venous pressure and the sampling of cerebrospinal fluid. Systemic arterial, right atrial, pulmonary arterial and sagittal sinus venous pressures (SSVP) were recorded continuously (Gould Statham P23 I.D. transducers). All pressures were zero-referenced to the level of the external auditory meatus. Mean arterial (MAP), mean right atrial (RAP) and mean pulmonary artery (PA) pressures were calculated as the diastolic pressure plus one-third pulse pressure. In addition, heart rate was monitored continuously (Devices heart rate meter). Mean pulmonary capillary wedge pressure (PCWP) was registered intermittently and cardiac output (CO) measured when indicated, using the thermodilution technique (2 ml of cold 5% dextrose solution: Cardiac Output Computer 9510, Edwards Laboratories). Systemic vascular resistance (SVR) and cerebral perfusion pressure (CPP) were calculated:

\[ \text{SVR} = \frac{(\text{MAP} - \text{RAP}) \times 80}{\text{CO}} \]

\[ \text{CPP} = \text{MAP} - \text{SSVP} \]

Cerebral blood flow was determined from the rate of clearance of xenon-133 by external scintillation counting over the right parietal area following the intracarotid injection of the isotope. Mean cerebral blood flow was calculated from the height/area equation (Høestead-Rasmussen, Sveinsdottir and Lassen, 1966). Xenon-133 0.4–0.8 μCi, dissolved in approximately 0.5 ml of saline, was injected to the internal carotid artery via a catheter in the linguofacial trunk. All other branches of the external carotid artery were ligated distally. The oxygen contents of the samples of arterial and cerebral venous blood were measured using a fuel cell once the oxygen had been released from the haemoglobin by carbon monoxide (Lex-O-Con Oxygen Analyser, Albury Instruments Ltd), and the cerebral metabolic rate for oxygen calculated:

\[ \text{CMRO}_2 = \text{CBF} \times (\text{CaO}_2 - \text{CVO}_2) \]

Following measurements of baseline values, MAP was decreased by approximately 20%, 40% and 60% from baseline by the administration of increasing doses of ATP. Each pressure was maintained for approximately 45 min. Haemodynamic variables and CBF were measured, and arterial and cerebral venous blood sampled during each decrement in systemic arterial pressure, and after the discontinuation of the infusion of ATP. In addition, CBF was measured during acute increases in MAP (induced by the administration of angiotensin II amide i.v.) in each animal before the induction of ATP-induced hypotension, during the period of hypotension (after 30 min of a 60% decrease in MAP), and after the discontinuation of the ATP once CBF had returned to control values.

Uric acid concentration was measured before the commencement of the ATP-infusion, at the end of the 40% decrease in MAP, and 60 min after the last dose of ATP.

Mean values and standard deviations were calculated for each measurement. Statistical data were obtained using Student's t test, and P < 0.05 was considered significant.

At the end of the procedure the animals were placed in the supine position. Following heparinization, thoracotomy was performed and a cannula was introduced to the ascending aorta via the left ventricle. The cannula was tied in position. Physiological saline (about 400 ml) was infused (at the same pressure as the mean arterial pressure) after incising the right atrium and clamping the descending thoracic aorta. Perfusion was continued at the same pressure with 4 litre of FAM fixative (40% formaldehyde : glacial acetic acid: absolute methanol, 1:1:8). After perfusion the animals were decapitated and the head was stored in the same fixative for 12 h. The brain was carefully removed from the skull and fixed by immersion in FAM for a further 24 h.

The hindbrain was detached by a cut through the midbrain and the cerebral hemispheres were cut into coronal slices 8 mm thick. The brain stem was cut at right angles to its long axis into slices 6 mm thick and the cerebellum into two slices perpendicular to the folia of the dorsal surface of each hemisphere. Large representative bilateral blocks of brain were embedded in paraffin wax. Sections (7 mm thick) stained by haematoxylin and eosin, and by a
TABLE I. Changes in systemic haemodynamic indices (mean values ± SD) during and after hypotension induced with increasing doses of ATP in baboons (n = 5). *P < 0.05; **P < 0.01; ***P < 0.001. MAP = mean systemic arterial pressure; PA = pulmonary arterial pressure; RAP = right atrial pressure; PCWP = pulmonary capillary wedge pressure; HR = heart rate; CO = cardiac output; SV = stroke volume; SVR = calculated systemic vascular resistance.

<table>
<thead>
<tr>
<th>ATP dose (mg kg⁻¹ min⁻¹)</th>
<th>0</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>107</td>
<td>84*</td>
<td>66**</td>
<td>45**</td>
<td>94</td>
</tr>
<tr>
<td>±19</td>
<td>±7</td>
<td>±5</td>
<td>±4</td>
<td>±10</td>
<td></td>
</tr>
<tr>
<td>PA (mm Hg)</td>
<td>16.6</td>
<td>15</td>
<td>14</td>
<td>14.8</td>
<td>21.2</td>
</tr>
<tr>
<td>±8.3</td>
<td>±4.6</td>
<td>±3.8</td>
<td>±3.9</td>
<td>±5.9</td>
<td></td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>5.2</td>
<td>5.5</td>
<td>5.7</td>
<td>4.4</td>
<td>4.7</td>
</tr>
<tr>
<td>±2.5</td>
<td>±3.0</td>
<td>±3.2</td>
<td>±1.8</td>
<td>±1.0</td>
<td></td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>6.3</td>
<td>5.8</td>
<td>6.4</td>
<td>7.2</td>
<td>7.8</td>
</tr>
<tr>
<td>±1.4</td>
<td>±0.5</td>
<td>±1.5</td>
<td>±2.4</td>
<td>±2.2</td>
<td></td>
</tr>
<tr>
<td>HR (beat min⁻¹)</td>
<td>104</td>
<td>118</td>
<td>104</td>
<td>108</td>
<td>126*</td>
</tr>
<tr>
<td>±7</td>
<td>±12</td>
<td>±8</td>
<td>±9</td>
<td>±9</td>
<td></td>
</tr>
<tr>
<td>CO (litre min⁻¹)</td>
<td>1.79</td>
<td>2.31**</td>
<td>2.28*</td>
<td>2.45*</td>
<td>2.47</td>
</tr>
<tr>
<td>±0.3</td>
<td>±0.43</td>
<td>±0.38</td>
<td>±0.25</td>
<td>±0.80</td>
<td></td>
</tr>
<tr>
<td>SV (ml beat⁻¹)</td>
<td>17.8</td>
<td>19.6</td>
<td>22*</td>
<td>23.6*</td>
<td>17.6</td>
</tr>
<tr>
<td>±4.0</td>
<td>±3.2</td>
<td>±3.1</td>
<td>±2.9</td>
<td>±4.2</td>
<td></td>
</tr>
<tr>
<td>SVR (dyn s cm⁻⁵)</td>
<td>4562</td>
<td>2838***</td>
<td>2177***</td>
<td>1309***</td>
<td>3101*</td>
</tr>
<tr>
<td>±1000</td>
<td>±675</td>
<td>±498</td>
<td>±146</td>
<td>±1080</td>
<td></td>
</tr>
</tbody>
</table>

Systemic haemodynamic indices

Changes in the systemic circulation during and after ATP-induced hypotension are summarized in Table I. A dose-dependent decrease in MAP was demonstrable during the infusion of ATP: mean arterial pressure decreased significantly from its baseline value of 107 ± 19 mm Hg to 45 ± 4 mm Hg with increases in the concentration of ATP of up to 6.4 ± 1.8 mg kg⁻¹ min⁻¹ (fig. 1). Once the desired hypotension had been achieved, it was not necessary to increase the dose of ATP to maintain this value for the following 45 min. After discontinuation of the infusion of ATP, MAP increased promptly. However, baseline values of MAP were not attained fully, MAP remaining approximately 12% below baseline (P > 0.05). There was no evidence of rebound hypertension.

The decrease in MAP was entirely the result of a dose-dependent and significant decrease in SVR, since CO increased in a dose-independent manner.

The increase in CO was more pronounced with the smallest dose of ATP, as a result of the simultaneous increases (n.s.) in stroke volume and heart rate. The increase in stroke volume was significant (P < 0.05) only with the two larger doses of ATP. Because of
the variability in the response of the pulmonary artery pressure, the decrease which was observed was not significant. There were no significant changes in right atrial pressure or pulmonary capillary wedge pressure.

**Cerebrovascular indices**

**Decreases in mean arterial pressure.** The changes in cerebrovascular indices during and after ATP-induced hypotension are summarized in Table II. As MAP was decreased moderately by the administration of increasing doses of ATP, mean CBF increased initially from $48 \pm 4$ ml min$^{-1}$/100 g to $68 \pm 9$ ml min$^{-1}$/100 g (44±22%) ($P < 0.05$). Although mean CBF was still greater than control values once MAP had been decreased by 40%, the difference was not significant. As MAP was decreased to less than 65 mm Hg, CBF decreased further such that a linear relationship was evident between CBF and MAP over the range 85-45 mm Hg (fig. 2). Fifteen minutes after the infusion of ATP was stopped, CBF was greater than the control value. However, because of the variability between the individual animals this increase was not significant ($P > 0.05$) (fig. 2).

The changes in SSVP mirrored those in CBF and, as a result, the decreases in cerebral perfusion pressure were similar at the 20% and 40% decrements in arterial pressure. The lowest mean cerebral perfusion pressure was 29 mm Hg (±6) (table II).

The cerebral metabolic rate for oxygen remained constant throughout each investigation.

---

**TABLE II.** Changes in cerebrovascular indices (mean values ± SD) during and after hypotension induced with increasing doses of ATP in baboons (n = 5). *P < 0.05; ***P < 0.001. CBF = cerebral blood flow; CMRO$_2$ = cerebral metabolic rate for oxygen; SSVP = superior sagittal sinus venous pressure; CPP = cerebral perfusion pressure.

<table>
<thead>
<tr>
<th>Reduction in MAP (% of control)</th>
<th>0</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP dose (mg kg$^{-1}$ min$^{-1}$):</td>
<td>0</td>
<td>2.12±0.71</td>
<td>3.67±1.06</td>
<td>6.38±1.84</td>
<td>0</td>
</tr>
<tr>
<td>CBF (ml min$^{-1}$/100 g)</td>
<td>48±4</td>
<td>68±9</td>
<td>57±7</td>
<td>39*±5</td>
<td>62±15</td>
</tr>
<tr>
<td>CMRO$_2$ (ml O$_2$ min$^{-1}$/100 g)</td>
<td>2.98±0.89</td>
<td>3.17±0.61</td>
<td>3.05±0.89</td>
<td>2.94±0.54</td>
<td>2.74±0.87</td>
</tr>
<tr>
<td>SSVP (mm Hg)</td>
<td>19.50±6.20</td>
<td>27.80*±9.24</td>
<td>22.30±7.05</td>
<td>15.90±6.10</td>
<td>20.00±3.81</td>
</tr>
<tr>
<td>CCP (mm Hg)</td>
<td>88±6</td>
<td>56***±7</td>
<td>51***±5</td>
<td>29***±6</td>
<td>74*±8</td>
</tr>
</tbody>
</table>

---

**Acute increases in mean arterial pressure** (fig. 3). CBF did not differ significantly from baseline values, when MAP was increased acutely (by approximately 20 mm Hg) before the start of the infusion of ATP. Thus, the cerebral vessels were reacting physiologically to the acute alterations in systemic pressure.

In contrast, during and following the infusion of ATP, similar acute increases in MAP were accompanied by marked increases in CBF and indicated that the responsiveness of the cerebral blood vessels was impaired during the administration of ATP and for at least 90 min after its withdrawal.
ATP-INDUCED HYPOTENSION

FIG. 3. Effects of acute increases in systemic arterial pressure on cerebral blood flow. Acute increase in pressure was induced before the administration of ATP (+20 mm Hg ± 1.4), during the infusion of ATP once MAP had been decreased to approximately 40% of control (+19 mm Hg ± 1.3), and again after discontinuing the infusion of ATP once CBF was returned to control value (+20 mm Hg ± 0.4).

**Uric acid concentration**

Changes in uric acid concentration were observed in all animals (table III). At the end of the period of 40% decrease in MAP, there was a significant increase in the concentration of uric acid (P < 0.05). A further increase was noted 1 h after the end of the period of hypotension. The total dose of ATP administered to each animal was between 388 and 512 mg kg⁻¹.

**Neuropathology**

*Macroscopic observations.* The brains of all five animals appeared normal externally and in slices. Grossly, the brains appeared uniformly blanked, indicating that perfusion had been satisfactory. There was no evidence of brain swelling and internal herniae were not seen.

*Microscopic observations.* The brains of all five animals showed microscopic evidence of good tissue fixation. The cytological artefacts, the "dark cell" and "hydropic cell", were not seen. No histological abnormalities were seen in any of the five brains examined and, in particular, there was no morphological evidence of irreversible ischaemic damage.

**DISCUSSION**

Adenosine triphosphate and adenosine are potent vasodilators (Drury and Szent-Györgyi, 1929; Emmelin and Feldberg, 1948; Rowe and Henderson, 1962). ATP is decomposed rapidly to adenosine by a 5'-nucleotidase, present in serum, red blood cells and myocardial cells (Burnstock, 1980). This decomposition is extremely rapid, so that when ATP is given i.v. it is degraded entirely to adenosine and its metabolites during its passage through the lungs. Furthermore, the hypotensive effects of ATP are related to the arterial adenosine concentration (Sollevi et al., 1984). The active adenosine is inactivated to inosine in a reaction catalysed by adenosine deaminase or is taken up by the cells (Burnstock, 1972). Inosine is converted to hypoxanthine, which is oxidized to uric acid—the final product in man and primates. Since adenosine induces relaxation of vascular smooth muscle (Herlihy et al., 1976), it is concluded that adenosine mediates the vasodilator effects of i.v. administered ATP (Sollevi et al., 1984).

In these investigations a rapid and dose-related decrease in systemic arterial pressure was induced easily and maintained without tachyphylaxis. After discontinuation of the administration of adenosine, the arterial pressure returned promptly towards control values without any evidence of rebound hypertension. Since nitrous oxide and phencyclidine were given during the entire experiment, we cannot exclude totally some influence of these agents on systemic and cerebrovascular haemodynamics. However, since the baseline measurements and all measurements during and after ATP were obtained under similar anaesthetic conditions, it seems likely that the observed changes can be ascribed to the ATP.

**The systemic circulation**

The infusion of ATP resulted in a modest (not significant) increase in heart rate which was greatest with the lower doses. This was in contrast to the reports by Dedrick and colleagues (1982), Fukunaga, Flacke and Bloor (1982) and Kassell and co-workers (1983b). Adenosine, itself, produces a decrease in heart rate, which may be the result of a

**TABLE III. Changes in uric acid concentration (mean ± SD) during and after ATP-induced hypotension (n = 5).**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>During ATP</th>
<th>60 min after hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total dose of ATP</td>
<td>—</td>
<td>146–192</td>
<td>388–512</td>
</tr>
<tr>
<td>Uric acid (mg dl⁻¹)</td>
<td>1.04</td>
<td>2.38*</td>
<td>4.98**</td>
</tr>
<tr>
<td></td>
<td>0.52</td>
<td>1.02</td>
<td>1.42</td>
</tr>
</tbody>
</table>
direct inhibitory effect on the sinus node (James, 1965), and on the conduction system of the heart (Belardinelli, Mattas and Berne, 1981). In addition, there may be inhibition of cardiac sympathetic neurotransmission (Hedqvist and Fredholm, 1979). Our results may be explained by a compensatory increase in heart rate produced by the decrease in MAP, since compensatory reflexes are not abolished by the lower doses of ATP.

Hypotension was accompanied by increases in cardiac output and stroke volume and, since adenosine has no positive myocardial inotropic effect (Gross, Woltier and Hardman, 1976), the increase in SV must be indicative of a decrease in afterload in the presence of a constant preload. The increases in cardiac output noted in association with the 40% and 60% decreases in systemic arterial pressure appear to result primarily from the significant increases in stroke volume. The more marked increase in cardiac output at the 20% decrement in pressure was related presumably to the changes (although not significant) in both stroke volume and heart rate.

The cerebral circulation

The relationship between cerebral blood flow and the pressure perfusing the brain is of significance during controlled hypotension, and particularly so when increased intracranial pressure or decreased intracranial compliance are present.

During moderate decreases in MAP (20%), mean CBF was observed to increase initially. However, as MAP was decreased further, the pressure–flow relationship became linear. The pattern of change in SSVP was similar to that in CBF, the increase in SSVP representing an initial period of cerebral vasodilation and an increase in cerebral blood volume. Since CMRO₂ did not change, it seems unlikely that these changes in CBF were the result of an increase in metabolism. Thus, it appears likely that ATP decreased cerebrovascular resistance directly and this led to the increase in CBF. These results are in agreement with those of Forrester, Harper and MacKenzie (1975) that purine nucleotides are potent cerebral vasodilators, and with a previous observation that intracranial pressure increased during ATP-induced hypotension in dogs (Van Aken et al., 1984). Although Kassel and colleagues (1983b) noted that adenosine did not dilate cerebral vessels or alter cerebral autoregulation, this can be explained by the fact that these workers probably missed the transient increase in CBF (at moderate decreases in arterial pressure) because their first measurement of CBF was undertaken 30 min after a 61% decrease in MAP. Furthermore, specific tests of autoregulation were not performed.

The subsequent decreases in CBF in association with the more marked decreases in systemic arterial pressure can be ascribed to an impairment of the physiological reactivity (autoregulation) of the cerebral blood vessels which resulted in a pressure–passive relationship between CBF and arterial pressure. That this was indeed the case was confirmed by the significant changes in CBF induced, by the acute increases in mean arterial pressure, during the infusion of ATP. Whether this alteration in reactivity was a result of the direct effect of ATP per se on cerebrovascular smooth muscle, of local tissue acidosis, or of a combination of both mechanisms cannot be determined precisely from this investigation. However, the first of these possible explanations seems the most likely, since the relevant assessment of responsiveness was undertaken at a point in the experimental programme at which both mean arterial pressure (45 mm Hg ± 4) and cerebral blood flow (39 ml min⁻¹/100 g ± 5) were more than adequate, in the presence of a physiological arterial oxygen content, to maintain a normal oxygen supply. Moreover, no morphological abnormalities were seen in any of the animals. This absence of hypoxic damage indicates that, even though autoregulation was impaired, CBF was adequate to prevent the development of ischaemic cell damage—even once mean arterial pressure had been decreased to 60% of its baseline value, and mean cerebral perfusion pressure was around 30 mm Hg. In this context it should be pointed out that, in this study, cerebral perfusion pressure has been calculated as the difference between the mean arterial pressure and the sagittal sinus venous pressure. There is, of course, a pressure decrease between the veins on the surface of the brain and the superior sagittal sinus at the point of entry of the former to the latter. Since the resistance to tissue perfusion is overcome by the pressure gradient between the arterial pressure and the pressure in the veins on the surface of the brain, it may be that the actual cerebral perfusion pressures were a little lower than those calculated in this investigation.

The finding that autoregulation was affected in animals without evidence of intracranial pathology is of interest. Since physiological mechanisms were impaired during, and after, the administration of ATP, they can no longer modulate normally for
acute alterations in systemic arterial pressure. Under these circumstances, the intracranial contents not only become a target for the particular pharmacological activities of this drug, but will also closely reflect any changes taking place in the systemic circulation. Under these circumstances, the cerebral circulation is reacting in a manner similar to that observed when hypotension was induced with sodium nitroprusside or nitroglycerine (Pickard et al., 1981; Fitch et al., 1982).

ATP is a rapidly acting controllable hypotensive agent which does not induce tachyphylaxis during administration or rebound hypertension after discontinuation. However, in the doses used in this study, the final metabolic product, uric acid, accumulated significantly. Furthermore, ATP can increase CBF and SSVP, and impair cerebrovascular reactivity.

In summary, ATP does not fulfill all the basic requirements for the ideal hypotensive agent, and care should be taken if it is used in clinical practice, especially in patients with intracranial pathology.

ACKNOWLEDGEMENTS
The authors are grateful to the nursing and technical staff of the Wellcome Surgical Institute, University of Glasgow for their skilled assistance.

REFERENCES
EFFETS HEMODYNAMIQUES ET CEREBRAUX DE LA HYPOTENSION INDUITE PAR ATP

RESUME
Des diminutions contrôlées de la pression artérielle moyenne à 20%, 40% et 60% de la base ont été obtenues par l'administration de concentrations croissantes de triphosphate d'adénosine (ATP) i.v. chez cinq babouins anesthésiés. On a obtenu les indices de la circulation systémique (pression artérielle, pression atriale droite, pressions des artères pulmonaires, débit cardiaque) et de la circulation cérébrale (courant sanguin cérébral, taux métabolique cérébral pour l'oxygène, réactivité cérébrovasculaire) alors que la pression artérielle diminuait et après la cessation de l'infusion d'APT. On a entrepris une recherche neuropathologique à la fin de la procédure expérimentale. L'infusion d'ATP a produit des diminutions en rapport avec les doses en ce qui concerne la résistance vasculaire systémique et la pression artérielle moyenne (MAP). Le débit cardiaque et le volume systolique se sont maintenus au voisinage des valeurs de base ou ont augmenté légèrement. Le courant sanguin cérébral (CBF) a augmenté au début (48 ± 4 ml·min⁻¹/100 g jusqu'à 68 ± 9 ml·min⁻¹/100 g) puis il a diminué graduellement à mesure que la MAP descendait jusqu'à 40% et 60% de la ligne de base. Il a été observé que la réactivité cérébrovasculaire était entravée pendant l'administration de l'ATP et pendant 90 min à la suite de celle-ci. Cependant, il n'y a pas eu de preuve morphologique de lésion ischémique des cellules dans l'un quelconque des animaux. Il n'y a pas eu de tachyphylaxie pendant l'infusion d'APT et il n'y a pas eu de cas non plus d'hypertension de contre-coup à la suite de celle-ci. La concentration d'acide urique a augmenté de manière significative en raison de la diminution à 40% de la MAP et elle s'est maintenue à ce niveau pendant 60 min après restauration de la pression artérielle.

HÄMODYNAMISCHE UND ZEREbraLE AUSWirkungen EINER DURCH ATP BEWirkten HYPOTENSION

ZUSAMMENFASSUNG
Kontrollierte Senkungen des mittleren arteriellen Druckes auf 20, 40 und 60% des Grundwertes wurden durch die Verabreichung immer stärkerer Konzentrationen von Adenosin Triphosphat (ATP) intravenös bei fünf narkotisierten Pavianen bewirkt. Werte des Systemkreislaufs (arterieller Druck, rechter Atriumsdruck, Lungenarteriendrucke, Herzmultipulenvolumen) und der zerebralen Zirkulation (zerebraler Blutkreislauf, zerebrale Stoffwechselrate für Sauerstoff, zerebrovaskuläre Reactivität) wurden erzielt, während der arterielle Druck gesenkt wurde, und nach der Einstellung von ATP – Infusion. Eine neuropathologische Untersuchung wurde nach dem experimentellen Verfahren durchgeführt. Die ATP – Infusion bewirkte dosisabhängige Senkungen des systemvaskulären Widerstandes und des mittleren arteriellen Druckes (MAP). Herzmultipulenvolumen und Puls wurden nahe den Grundwerten bewahrt, oder leicht erhöht. Der zerebrale Blutfuß (CBF) stieg zuerst an (48 ± 4 ml·min⁻¹/100 g auf 68 ± 9 ml·min⁻¹/100 g), fiel aber dann progressiv, als MAP auf 40 und 60% des Grundwertes gesenkt wurde. Die zerebrovaskuläre Reaktivität zeigte sich während und bis zu 90 min nach der ATP – Infusion beeinträchtigt. Es gab jedoch keine morphologischen Beweise für ischämische Zellenschädigung bei irgendeinem der Tiere. Tachyphylaxie wurde während der ATP – Infusion ebensowenig beobachtet wie Hypertension danach. Die Harnsäurekonzentration stieg beim 40%igen Sinken von MAP stark an und blieb auf diesem Stand für 60 min nach der wiederherstellung des arteriellen Druckes.

EFECTOS HEMODINAMICOS Y CEREBRALES DE LA HIPOTENSION INDUCIDA POR ATP

SUMARIO
En cinco babuinos anestesiados mediante la administración de concentraciones crecientes de trifosfato de adenosina (ATP) i.v., se obtuvieron descensos controlados de la presión arterial promedio en un 20%, 40% y 60% de la línea de base. Se obtuvieron asimismo los índices de la circulación sistémica (presión arterial, presión arterial derecha, presiones de las arterias pulmonares, volumen-minuto) y de la circulación cerebral (flujo sanguíneo cerebral, ritmo metabólico cerebral del oxígeno, reactividad cerebrovascular) a medida que se reducía la presión arterial y después de discontinuar la infusión de ATP. Se emprendió una investigación neuropatológica al fin del procedimiento experimental. La infusión de ATP produjo descensos de la resistencia vascular sistémica y de la presión arterial promedia (MAP) en relación con las dosis. El volumen-minuto y la descarga sistólica se mantuvieron en valores próximos a los valores de la línea de base o aumentaron ligeramente. El flujo sanguíneo cerebral (CBF) aumentó al principio (48 ± 4 ml·min⁻¹/100 g hasta 68 ± 9 ml·min⁻¹/100 g) y luego bajó progresivamente a medida que la MAP descendía hasta un 40% y un 60% de la línea de base. Se observó que la reactividad cerebrovascular se trastornaba durante y hasta 90 min después de la administración del ATP. Sin embargo, no hubo ninguna prueba morfológica de daño isquémico de las células en cualquiera de los animales. Se observó taquiplaxia durante la infusión de ATP, ni tampoco hubo casos de hipertensión de rebote después de la misma. La concentración de ácido úrico aumentó de manera significativa a raíz de la disminución del 40% de la MAP y se mantuvo así por 60 min después de la restauración de la presión arterial.