Role of Intravenous Adenosine-tri-phosphate (ATP) on Cerebral Blood Flow: assessed by bolus $^{15}$O-labeled water PET

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PET!
Introduction:

**Background:**

- Adenosine triphosphate (ATP) is the parent compound of adenosine.
- Powerful vasodilator
- Used for measurement of coronary flow reserve.
- Role of intravenous inj. on cerebral blood flow (CBF) has not yet been investigated
Mechanism of Adenosine:

- Adenosine - endogenous vasodilator
- Involved in the local blood flow regulation of brain
- Stimulate adenylate cyclase >>> increase in cyclic AMP
  (through adenosine A2-subtype receptor)
- Stimulation results in relaxation of vascular smooth muscle
- Extremely short plasma half life (<2 sec.)
- Quickly metabolized into ATP or uric acid.
Mechanism of ATP:

- ATP also has a short plasma half-life (<20 sec)

- Rapidly metabolized to adenosine diphosphate (ADP) >>> adenosine monophosphate (AMP) >>> adenosine >>> allantoin.

- Vasodilatory effect mainly depends on its degradation to adenosine

- Initially works by direct stimulation

- Although ATP itself has a greater initial action, adenosine as the metabolic product then maintains it.
Effects in CBF after i/v administration of adenosine:

- Cats and dogs --- no effect
- Rabbits and baboons --- cerebral vasodilation

- There are conflicting reports on human study.
- Sollevi et al. demonstrated increase in CBF.
- Ito et al. demonstrated significant decrease in CBF with intravenous dipyridamole (which increases the action of adenosine)

- But to our knowledge, there is no report regarding the role of i/v ATP on human CBF.
- This study investigated the effect of i/v ATP on human CBF using $^{15}$O-labeled water employing PET.

MATERIALS & METHODS:

- 8 healthy young male volunteers (20 to 25 years)

- PET: ADVANCE, General Medical Electric System, Milwaukee, WI, USA.

- A transmission scan was performed for attenuation correction.

- PET data were reconstructed using a Hanning filter with 6.0 mm FWHM in the transaxial direction.

- Arterial line in the right arm and venous line in the left arm.

- Arterial blood was drawn by a mini pump with a rate of 7ml/min for the first 90 sec followed by manual sampling of 1 ml blood every 15 sec at 90 sec, 105 sec and 120 sec.

- Radioactivity in the arterial blood was counted continuously using an automatic coincidental radioactive counter.

- Automatic counter was calibrated by the blood radioactivity obtained manually.

- Decay of the radioactivity from PET and blood data was corrected and dispersion in the arterial curves was corrected.

Protocol:

- **1st baseline:** A bolus of 750 MBq $\text{H}_2\text{^{15}O}$ was given i/v. Acquisition was done for 2 min along with the arterial blood study as described before.

- **3min post-ATP:** Then after 7 min ATP was started (0.16mg/kg/min) i/v. A 2nd bolus of 750 MBq $\text{H}_2\text{^{15}O}$ was given i/v after 3 min. Acquisition was done as before.

- **2nd baseline:** Then after 10 min a 3rd bolus of 750 MBq $\text{H}_2\text{^{15}O}$ was given i/v. Acquisition was done as before.

- **1min post-ATP:** Then after 9 min ATP was started (0.16mg/kg/min) i/v. A 4th bolus of 750 MBq $\text{H}_2\text{^{15}O}$ was given i/v after 1 min. Acquisition was done as before.

- **3rd baseline:** Then after 10 min a 5th bolus of 750 MBq $\text{H}_2\text{^{15}O}$ was given i/v. Acquisition was done as before.
CBF images were calculated from the dynamic PET data and arterial blood curves by autoradiographic method.

Multiple ROIs were placed in each cerebral hemisphere in the territories of bilateral middle cerebral arteries (6+6 = 12 per slice, 5 slices).

Regional CBF values were averaged.

Statistical parametric mapping (SPM) was also utilized.

Several parameters e.g. PaCO$_2$, Vascular response to PaCO$_2$, CVR as well as MABP/HR were analysed.
RESULTS:

- Cortical CBF values were slightly reduced after intravenous ATP compared to the baseline.
- At 3min post-injection, it was 54.9 ± 5.3 as compared to baseline of 56.2 ± 5.0 ml/100g/min.
- At 1min post-injection, CBF was 55.4 ± 5.0 as compared to baseline of 55.9 ± 5.6 ml/100g/min.
- Repeated measures ANOVA did not show any significant differences between the different conditions.
Baseline & 3min Post-ATP study
## Changes in CBF (Pre & Post ATP)

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Baseline1</th>
<th>3min post-ATP</th>
<th>Baseline2</th>
<th>1min post-ATP</th>
<th>Baseline3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53.09</td>
<td>55.40</td>
<td>57.70</td>
<td>61.93</td>
<td>61.27</td>
</tr>
<tr>
<td>2</td>
<td>60.46</td>
<td>60.78</td>
<td>64.82</td>
<td>51.63</td>
<td>61.90</td>
</tr>
<tr>
<td>3</td>
<td>55.27</td>
<td>53.69</td>
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<td>6</td>
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<td>61.70</td>
<td>61.35</td>
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</tr>
<tr>
<td>7</td>
<td>51.67</td>
<td>47.40</td>
<td>51.39</td>
<td>53.82</td>
<td>52.81</td>
</tr>
<tr>
<td>8</td>
<td>50.22</td>
<td>48.41</td>
<td>46.94</td>
<td>49.83</td>
<td>49.13</td>
</tr>
<tr>
<td>Mean</td>
<td>56.2</td>
<td>54.9</td>
<td>55.9</td>
<td>55.4</td>
<td>57.6</td>
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<tr>
<td>SD(±)</td>
<td>5.2</td>
<td>5.3</td>
<td>5.6</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>
CBF (Pre and Post ATP)

Different Conditions

Baseline1  3min post ATP  Baseline2  1min post ATP  Baseline3

ml/100g/min

Baseline1: 56.2
3min post ATP: 54.9
Baseline2: 55.9
1min post ATP: 55.4
Baseline3: 57.6
No regional differences in the cortices could be found in Statistical parametric mapping (SPM).
PaCO$_2$ :

- There was also slight decrease of PaCO$_2$ after ATP (41.6 vs. 39.6 mmHg), which was non-significant.
- Vascular response to PaCO$_2$ was calculated by the following formula

\[
100 \times \frac{\text{CBF}_a - \text{CBF}_r}{\text{CBF}_r} \times \frac{1}{\frac{\text{PaCO}_2a - \text{PaCO}_2r}{\text{PaCO}_2a}}
\]

(where the subscripts ‘r’ and ‘a’ represent rest and post ATP conditions.)
## Changes in Vascular response to PaCO$_2$ change (Pre & Post ATP)

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Baseline1</th>
<th>3min post-ATP</th>
<th>Vascular response to PaCO$_2$ change</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>42.9</td>
<td>38.8</td>
<td>-0.10%</td>
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<td>35.1</td>
<td>40.5</td>
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<td>3</td>
<td>45.2</td>
<td>37.5</td>
<td>0.40%</td>
</tr>
<tr>
<td>4</td>
<td>46.4</td>
<td>41.6</td>
<td>2.10%</td>
</tr>
<tr>
<td>5</td>
<td>41.4</td>
<td>38.6</td>
<td>-1.40%</td>
</tr>
<tr>
<td>6</td>
<td>41.3</td>
<td>43.7</td>
<td>-0.40%</td>
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<tr>
<td>7</td>
<td>39.6</td>
<td>38.5</td>
<td>-7.30%</td>
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<tr>
<td>8</td>
<td>41.2</td>
<td>37.5</td>
<td>0.80%</td>
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<tr>
<td>Mean</td>
<td>41.6</td>
<td>39.6</td>
<td>0.70%</td>
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</table>
MABP/HR:

- BP and heart rates were recorded.
- MABP: 7% and 6% reduction after 3 min and 1 min post ATP corresponding to baseline.
- HR: 33% and 31% increase after 3 min and 1 min post ATP corresponding to baseline.
## Changes in MABP/HR (Pre & Post ATP)

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Baseline1</th>
<th>3min post-ATP</th>
<th>Baseline2</th>
<th>1min post-ATP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BP</td>
<td>MABP</td>
<td>HR</td>
<td>BP</td>
</tr>
<tr>
<td>1</td>
<td>133/74</td>
<td>94</td>
<td>61</td>
<td>127/63</td>
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<tr>
<td>2</td>
<td>117/66</td>
<td>83</td>
<td>65</td>
<td>107/46</td>
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<tr>
<td>3</td>
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<tr>
<td>4</td>
<td>127/62</td>
<td>84</td>
<td>56</td>
<td>137/57</td>
</tr>
<tr>
<td>5</td>
<td>132/67</td>
<td>89</td>
<td>73</td>
<td>134/57</td>
</tr>
<tr>
<td>6</td>
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<td>7</td>
<td>136/61</td>
<td>83</td>
<td>61</td>
<td>139/56</td>
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<tr>
<td>8</td>
<td>123/72</td>
<td>89</td>
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<td>136/60</td>
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<tr>
<td>Mean</td>
<td>86.4</td>
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<tr>
<td>Changes</td>
<td>7%</td>
<td>33%</td>
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</table>

Mean MABP/HR changes indicate a decrease in blood pressure and heart rate post-ATP.
CVR:

- Cerebral Vascular Resistance (CVR) was calculated by dividing MABP with CBF.

- No changes in CVR were observed in pre and post ATP conditions.
# Changes in CVR (Pre & Post ATP)

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<th>1min post-ATP</th>
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<tbody>
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<td></td>
<td>CBF</td>
<td>MABP</td>
<td>CVR</td>
<td>CBF</td>
</tr>
<tr>
<td>1</td>
<td>53.09</td>
<td>94</td>
<td>1.8</td>
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<td>86.4</td>
<td>1.6</td>
<td>54.9</td>
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</table>
DISCUSSION:

- In a (Sollevi et al.) study intravenous adenosine was given at a dose of 0.2-0.5 mg/kg/min.
- In normo-ventilated cases there was an increase in mean CBF of 23-85% and decrease in mean CVR by 43-65%.
- In hyperventilated patient no significant effect was seen. It was suggested that hyperventilation counteracts cerebral vasodilatory effects of adenosine.

Another study (Ito et. al.) reported that CBF values decreased after dipyridamole stress.

It also caused a significant reduction in PaCO₂.

The decrease in CBF was due to decrease in PaCO₂ which was due to hyperventilation side effect of adenosine.

Ito H et. al. Stroke. 1999;30:1616-1620
In our study, there was no increase in the CBF after ATP, rather there was slight decrease, which was however non-significant. This finding goes in line with two other reported findings with adenosine. (Lagerkranser M et. al. Acta Anaesthesiol Scand 1989 Jan; 33(1):15-20. Stange K et. al. Acta Physiol Scand 1997 Jun; 160(2):117-22.)

All of our cases were normo-ventilated.

The decrease in PaCO₂ was also non-significant (41.6 vs. 39.6 mmHg).

The hyperventilation side effect reported previously was not observed.
**BBB:**

- Blood-Brain barrier is a unique protective device.
- It has been reported that adenosine is unable to cross blood-brain barrier.
- Sollevi *et. al.* commented that as the adenosine increased CBF, it has passed the blood-brain barrier to exert its effect.
- In our study we also did not see any evidence of ATP to cross the BBB as it failed to result in any significant action on the cerebral blood vessels.
It is reported, that there are fewer side effects with intravenous ATP than adenosine.

Although all side effects were well-tolerated and resolved spontaneously within 1 to 2 minutes after discontinuation of adenosine/ATP infusion.

Explanation for the fewer side effects with ATP is due to the breakdown time of ATP in plasma, as it is gradually degraded to adenosine en-route from the peripheral vein to coronary sinus.

- It is also reported that large dose of intravenous adenosine and dipyridamole can induce severe hypotension, severe enough to be out of the range of cerebral autoregulation and hence cause a decrease in CBF.

  (Kassell NF et. al. J Neurosurg 1983;58:69-76 18)

- In our study none showed any major fall of BP. There was only 7% and 6% reduction in MABP after 3 min and 1 min post ATP studies.
- Although we had some reduction in the MABP but there was simultaneously slight non-significant reduction in CBF, so eventually there was no change in CVR.
- The mild reduction in MABP did not show any effect in significant reduction of CBF due to cerebral autoregulation.
The fact that the CBF is maintained is of clinical significance, since this allows an adequate oxygen transport without major increase in intracerebral blood flow & volume (and hence intracranial pressure).
CONCLUSION:

- The study indicates that intravenous ATP administration results in non-significant change of CBF.

- Normal CBF is maintained in response to intravenous ATP.

- It may give solution to the previous conflicting reports with some of the reported findings of intravenous adenosine administration.
Thank you