Effect of labetalol on cerebral blood flow, oxygen metabolism and autoregulation in healthy humans

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Summary
We have studied the effects of labetalol on cerebral blood flow (CBF) and cerebral oxygen metabolism (CMRO2) in eight healthy volunteers. CBF was measured by single photon emission computerized tomography before and during infusion of labetalol. CMRO2 was calculated as CBF × cerebral arteriovenous oxygen content difference (CAO₂ – CVO₂). CBF autoregulation was tested during infusion of labetalol by changing arterial pressure and estimating relative changes in global CBF from changes in MAP. The lower limit of CBF autoregulation was 88 mm Hg (94% of baseline mean arterial pressure). We conclude that labetalol did not influence global or regional CBF, or CMRO2, and CBF autoregulation was preserved.

Key words

Labetalol has been recommended for acute treatment of hypertension [1–5]. It has been used also to induce hypotension during anaesthesia [6, 7]. In these situations the haemodynamic and metabolic effects on the human brain may be important but there is little information with regard to labetalol. Thus the aim of the present study was to evaluate the effect of labetalol on cerebral blood flow (CBF), cerebral oxygen metabolism (CMRO2) and CBF autoregulation.

Subjects and methods
We studied eight healthy normotensive volunteers (seven males), mean age 23 (range 20–28) yr. All fasted and did not smoke for at least 12 h before the study, which was approved by the Scientific Ethics Committee of Copenhagen. Informed consent, according to the Helsinki II declaration, was obtained from all participants.

STUDY DESIGN
Absolute regional CBF (rCBF), using single photon emission computerized tomography (SPECT), was measured before and during administration of labetalol (Trandate, Glaxo, Denmark). CBF autoregulation was tested during continued infusion of labetalol. The lower limit of CBF autoregulation (LL) and the effect of labetalol on CBF and CMRO2 were calculated.

CATHETERIZATION, MONITORING AND (CAO₂ – CVO₂) MEASUREMENT
Under local anaesthesia, a catheter was introduced into the left radial artery and another catheter was placed in the right internal jugular vein with the tip in the jugular bulb. The position of the catheter was confirmed by injecting isotonic saline into the catheter and confirmed by a typical murmur in the subject’s ear [8]. An i.v. catheter was placed in the brachial vein for infusions.

Mean arterial pressure (MAP) was measured continuously via a radial artery cannula. The transducer was placed at the mid-axillary level. During the study ECG and heart rate were monitored also.

Sets of blood samples consisted of one arterial and two venous samples, which were obtained simultaneously from the radial artery catheter and jugular catheter, respectively. The mean value of the two venous samples was used. Blood was analyzed immediately for haemoglobin concentration, oxygen saturation (SO₂) (OSM3 Hemoximeter, Radiometer, Copenhagen), oxygen tension (PO₂), arterial carbon dioxide tension (PAO₂) and pH (ABL3, Radiometer, Copenhagen). (CAO₂ – CVO₂) was calculated as the difference between arterial and venous oxygen content [(SO₂ × 1.34 × Hb) + (PAO₂ × 0.003)] for arterial and venous blood, respectively.

MEASUREMENT OF GLOBAL AND REGIONAL CBF
During CBF measurements, the participants rested in quiet surroundings in the supine position with the eyes closed. After xenon-133 inhalation, a SPECT scanning (Tomomatic 64, Medimatic, Hellerup, Denmark) of the brain was used for measurement of
CBF. For estimation of arterial xenon-133 concentration, a detector was placed over the apex of the right lung. The scanner yielded three parallel slices at 1, 5 and 9 cm above the orbitomeatal (OM) plane [9, 10]. Global CBF was estimated from the OM 5 plane as the mean of all brain pixel values [11]. rCBF was estimated by a standardized set of symmetrically placed regions of interest. A side-to-side asymmetry ratio less than 10 % was considered normal [12]. After the first CBF measurement (baseline), the labetalol group received a bolus dose of labetalol 1 mg kg\(^{-1}\) followed by an infusion of 2 mg min\(^{-1}\). Thirty minutes after the start of the infusion the SPECT measurement was repeated. If necessary MAP was maintained unchanged by infusion of angiotensin, which does not influence CBF [13]. The second CBF value was corrected for any differences in \(P_{\text{CO}_2}\) from the first measurement using reactivity of CBF to changes in \(P_{\text{CO}_2}\) (carbon dioxide reactivity) of 30 % kPa\(^{-1}\) [14]. It has been shown that labetalol does not influence carbon dioxide reactivity [15].

**CALCULATION OF CMRO\(_2\)**

During each SPECT measurement, one set of blood samples was obtained for measurement of \((C_{\text{a,O}_2} - C_{\text{v,O}_2})\) and \(P_{\text{a,CO}_2}\). CMRO\(_2\) was calculated as CBF×\((C_{\text{a,O}_2} - C_{\text{v,O}_2})\). For calculation of CMRO\(_2\) during administration of labetalol the CBF values corrected for changes in \(P_{\text{CO}_2}\) were used.

**CALCULATION OF RELATIVE GLOBAL CBF**

Three sets of blood samples were obtained immediately before the first SPECT measurement. Relative CBF \(1/(C_{\text{a,O}_2} - C_{\text{v,O}_2})\), calculated from the mean of three \(1/(C_{\text{a,O}_2} - C_{\text{v,O}_2})\) values, was expressed as 100 % and was compared with the mean \(1/(C_{\text{a,O}_2} - C_{\text{v,O}_2})\) value immediately before the second SPECT measurement.

**TEST OF AUTOREGULATION**

Assuming a constant CMR\(_{\text{O}_2}\) changes in \(1/(C_{\text{a,O}_2} - C_{\text{v,O}_2})\) give a good estimate of changes in global CBF [16]. The mean \(1/(C_{\text{a,O}_2} - C_{\text{v,O}_2})\) value measured just before the last SPECT measurement was used as baseline for the autoregulation study.

Relative changes in global CBF compared with baseline values were estimated from measurements of \(1/(C_{\text{a,O}_2} - C_{\text{v,O}_2})\) during: (1) administration of labetalol and unchanged MAP (three sets); (2) administration of labetalol and increasing MAP (one set for each 5 mm Hg); and (3) administration of labetalol and decreasing MAP (one set for each 5 mm Hg).

After the second SPECT measurement, MAP was gradually increased by up to 30 mm Hg from baseline by an infusion of angiotensin in order to define the plateau of CBF autoregulation. To allow for elimination of angiotensin, a resting period of 10 min followed the infusion. MAP was decreased gradually by the combined effect of the labetalol infusion and vacuum applied over the legs and lower part of the body. The negative pressure was increased slowly until a reduction in resting MAP of 50 % was achieved.

If the subjects wanted the hypotension to be discontinued (e.g. because of symptoms of cerebral ischaemia such as dizziness or nausea), the vacuum was released immediately.

LL was computed by fitting repeatedly, using the least-square approach, the values of relative CBF \(1/(C_{\text{a,O}_2} - C_{\text{v,O}_2})\) and MAP to two linear regression lines, a horizontal and an oblique line, where the crossover point defines LL. The method has been described in detail elsewhere [17]. All values of relative CBF, except those obtained at MAP values <20 % below baseline MAP, were corrected for changes in \(P_{\text{CO}_2}\) [14]. To find the best autoregulation curve fit, the effect of changing the carbon dioxide correcting factor (from 0 to 5 % in CBF per 0.1 kPa change in \(P_{\text{CO}_2}\)) was tested by computer program. The best autoregulation curve fit was calculated as the minimum sum of squares for the two lines. CBF was defined as preserved if the minimum sum of squares for the two lines was less than that of a straight regression line through all data sets.

**STATISTICAL ANALYSES**

The Student’s \(t\) test for paired data was used. Differences were considered statistically significant when \(P < 0.05\). The results are presented as mean (SD).

**Results**

Global and regional CBF and CMR\(_{\text{O}_2}\) were normal in all subjects, with no significant side-to-side asymmetry. No changes were observed after infusion of labetalol (tables 1, 2). MAP, heart rate and \(P_{\text{a,CO}_2}\) did not differ between the two SPECT measure-
Table 2 Cerebral blood flow (ml/100 g min⁻¹) measured in symmetrically placed regions of interest before (baseline) and during infusion of labetalol (mean (sd)). The values for CBF during infusion of labetalol were corrected for changes in $P_{cO_2}$ from baseline by 30 % kPa⁻¹. Superior frontal (s. fr.), middle and inferior frontal (Mid.inf.fr.), superior temporal (Sup.fr.), middle and inferior temporal (Mid.inf.tp.), occipital lobe (Occp.) and basal ganglia (Bas.gangl.) were the regions measured. There was no difference between values measured before and during infusion of labetalol.

<table>
<thead>
<tr>
<th>Region</th>
<th>Baseline Left</th>
<th>Baseline Right</th>
<th>Labetalol infusion Left</th>
<th>Labetalol infusion Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.fr.</td>
<td>65 (12)</td>
<td>65 (12)</td>
<td>65 (12)</td>
<td>62 (11)</td>
</tr>
<tr>
<td>Mid.inf.fr.</td>
<td>66 (13)</td>
<td>68 (13)</td>
<td>64 (10)</td>
<td>67 (13)</td>
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<td>Sup.fr.</td>
<td>76 (17)</td>
<td>76 (16)</td>
<td>73 (12)</td>
<td>71 (11)</td>
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<tr>
<td>Mid.inf.tp.</td>
<td>59 (11)</td>
<td>57 (12)</td>
<td>58 (11)</td>
<td>55 (9)</td>
</tr>
<tr>
<td>Occp.</td>
<td>68 (14)</td>
<td>72 (15)</td>
<td>67 (7)</td>
<td>69 (9)</td>
</tr>
<tr>
<td>Bas.gangl.</td>
<td>72 (15)</td>
<td>75 (15)</td>
<td>69 (11)</td>
<td>73 (14)</td>
</tr>
</tbody>
</table>

Table 3 Lower limit of cerebral blood flow autoregulation (LL) measured during infusion of labetalol. Baseline mean arterial pressure (MAP), LL as a percentage of baseline MAP (%), and the carbon dioxide correction factor (corr. factor) used to obtain the best fit for the regression lines (for calculation of LL) are shown.

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>LL (mm Hg)</th>
<th>Baseline MAP (mm Hg)</th>
<th>LL (%)</th>
<th>Corr. Factor (% kPa⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>77</td>
<td>96</td>
<td>80</td>
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<tr>
<td>8</td>
<td>86</td>
<td>90</td>
<td>96</td>
<td>27</td>
</tr>
<tr>
<td>Mean (sd)</td>
<td>88 (10)</td>
<td>94 (5)</td>
<td>94 (8)</td>
<td>14 (12)</td>
</tr>
</tbody>
</table>

Figure 1 Relative cerebral blood flow $\left(\frac{1}{(C_{aO_2}-C_{vO_2})}\right)$ vs arterial pressure (MAP) and the resulting regression curves for one of the volunteers.

Figure 2 Autoregulation curves of all volunteers for relative cerebral blood flow $\left(\frac{1}{(C_{aO_2}-C_{vO_2})}\right)$ vs mean arterial pressure (MAP).

The values for relative CBF plotted against MAP and the calculated regression lines for one of the volunteers are shown in figure 1 and the autoregulation curves for all volunteers in figure 2.

Discussion

The results of the present study showed that labetalol did not influence global CBF, rCBF or CMRO₂. This is in accordance with studies on global CBF, in which xenon-133 inhalation and stationary detectors [15, 18] or transcranial Doppler [15] were used for measurement of CBF. The effect of labetalol on rCBF or CBF autoregulation has not been studied previously in humans.

Our clinical impression was that most of the volunteers tolerated only small decreases from baseline MAP before symptoms such as yawning, sweating, pallor or nausea developed. This impression corresponded to the results presented in table 3, showing that LL was only 94 % of the baseline MAP level. However, comparing this with results obtained from comparable controls (healthy volunteers of similar age and baseline MAP) from other studies in our laboratory (using trimetaphan camsylate (Arfonad) combined with vacuum to decrease arterial pressure), there was no statistically significant difference in LL or LL as a percentage of baseline MAP [17, 19]. The somewhat higher LL found in the present study compared with the often quoted lower level of LL of 60 mm Hg probably reflects the different methods of measurement [17]. In earlier studies a visual approach was used to estimate a point on the downslope of the autoregulation curve where flow had decreased by 10 %.

In contrast, we used computer-generated calculations of the breakpoint between the slope and the horizontal line.

The method of estimating changes in global CBF from changes in $(C_{aO_2}-C_{vO_2})$, assuming constant cerebral metabolism is well established [16]. The validity of the $(C_{aO_2}-C_{vO_2})$ method used in the present study implies that CMRO₂ should be constant during induced hypotension, which has been shown in several other studies, as described by Lassen [16]. A degree of hyperventilation followed...
induction of hypotension in the present study. However, hyperventilation does not influence cerebral metabolism [20]. During increasing hypotension, carbon dioxide reactivity of the cerebral resistance vessels is reduced gradually and eventually abolished completely [14, 21]. We therefore applied the best fitting correction factor until a cut-off point, arbitrarily chosen as 20 mm Hg below baseline MAP.

The reproducibility of the SPECT scannings was studied in healthy volunteers with one CBF measurement and three re-measurements within 1 day. No significant CBF fluctuations occurred during the 3-h observation period [22].

The dose of labetalol used in the present study was rather high, although within the maximum recommended dose, and thus could be clinically relevant. The effects of labetalol on arterial pressure and heart rate in these doses in healthy subjects have shown some variations between studies. Generally, a greater reduction in arterial pressure occurs when the subject is standing, while little or no reduction in arterial pressure or heart rate takes place when the subject is supine [3]. This minor effect, which is in agreement with our results, could be caused by a direct sympathomimetic action of labetalol [3].

As the dose used in the present study has no effect on CBF or CMRO$_2$ and CBF autoregulation was preserved, we have no reservations in using labetalol to treat hypertension. However, the cerebral effect of labetalol in situations where CBF autoregulation may not be preserved, such as in patients with intracranial pathology, may be difficult to predict. In these situations one could speculate that hypotension could be more safely induced by using a hypotensive agent with cerebral vasodilating properties such as isoflurane, nitroglycerin or nitroprusside as these drugs might lower the threshold at which cerebral ischaemia occurs. On the other hand, each of these cerebral vasodilators has adverse effects, including an increase in intracranial blood volume. A possible role of labetalol could be to supplement these drugs, reducing the dose needed and thus partly diminishing their adverse effects.

Acknowledgements

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References


