Effect of Beta-Adrenergic Blockade With Propranolol on Cerebral Blood Flow, Autoregulation and CO₂ Responsiveness

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SUMMARY Cerebral autoregulation and vasomotor responsiveness to carbon dioxide were measured quantitatively in normal baboons before and after intravertrbral or intravenous infusion of the beta-adrenergic blocking agent, propranolol hydrochloride (Inderal®). Continuous measurements were made of cerebral blood flow (CBF; measured as bilateral internal jugular venous outflow using an electromagnetic flowmeter), cerebral perfusion pressure (CPP), arterial Po₂ and Pco₂ and venous Po₂, cerebral arteriovenous oxygen difference and endotracheal Pco₂. The autoregulation index (A.I. = ΔCBF/ΔCPP) and the chemical index (C.I. = ΔCBF/ΔPacO₂) were used as quantitative measures.

The effect of intravertrbral infusion of propranolol (0.01 mg per kilogram of body weight) was compared to intravenous infusion of identical doses of propranolol so that any specific action of the drug on a possible vasomotor center in the brain stem may be assessed. Significant reductions (−25%) in CBF and CPP followed both intravertrbral and intravenous infusion of propranolol. Cerebral metabolic rate for oxygen (CMRO₂) decreased significantly (−18%) and cerebrovascular resistance (CVR) increased significantly (+19%) after intravertrbral infusion of propranolol while less significant changes ensued following intravenous infusion of propranolol. Cerebral autoregulatory vasodilatation during increases in CPP was significantly enhanced following both intravertrbral and intravenous propranolol. Cerebral autoregulatory vasodilatation during decrease in CPP was not influenced by propranolol. Cerebral vasodilatory responsiveness to CO₂ inhalation was significantly inhibited following intravertrbral propranolol while no significant change resulted from intravenous propranolol. Cerebral vasoconstrictive responsiveness to hyperventilation was not influenced by propranolol.

These results indicate that the CBF and CMRO₂ are reduced by a pharmacological beta adrenergic blockade with propranolol hydrochloride.

RECENTLY EVIDENCE has accumulated indicating that the cerebral blood vessels are supplied by adrenergic as well as cholinergic nerves. Histochemical and electron microscopic studies have demonstrated that the density of adrenergic innervation of the cerebral vessels gradually decreases from proximal to distal parts of the vascular tree and that the extracerebral vessels receive greater innervation. These studies provide a morphological basis for the neurogenic control of cerebral circulation.

The functional significance of adrenergic control of cerebral blood flow (CBF) has been indicated from physiological and pharmacological studies. It has been shown that CBF may be increased or decreased by procedures such as electrical stimulation of the sympathetic nerves, administration of neurotransmitters and alpha or beta adrenergic blockers.

It has also been shown that CBF is influenced by ablation or stimulation of brain stem structures. Impairment of autonomic reflex activity in the Shy-Drager syndrome is accompanied by some patients by cerebral dysautoregulation. Furthermore, it was also shown in patients with cerebrovascular disease that impaired neurogenic cerebrovascular control and dysautoregulation followed cerebral ischemia and infarction, particularly in a series of cases with brain stem lesions. These findings suggest a possible functional role of central neurogenic control of the cerebral circulation mediated by the autonomic pathways from the brain stem centers. However, a precise functional mechanism of the central beta-adrenergic system influencing cerebrovascular control has yet to be established. Recent data obtained in this laboratory imply that CBF is controlled by dynamic interactions between adrenergic and cholinergic as well as other monoaminergic systems and that a dynamic balance in autonomic nervous activities is essential for normal cerebral autoregulation as well as cerebrovascular responsiveness to CO₂.

The present study was designed to elucidate a possible role of beta-adrenergic mechanisms involving cerebrovascular autoregulatory and chemical vasomotor reactivity in the baboon.

Methods

Twelve baboons (Papio anubis) of either sex weighing 4 to 11 kg were anesthetized with intravenous pentobarbital sodium 20 mg per kilogram of body weight. Constant anesthesia was maintained by supplemental pentobarbital at a rate of 3 mg per kilogram per hour. The trachea was intubated. The animal was paralyzed with gallamine triethiodide (Flaxedil®) and respiration was controlled with a Harvard mechanical respirator. Continuous measurements were made of end-tidal CO₂, systemic arterial blood pressure, intracranial venous pressure (ICVP) measured as the superior sagittal sinus wedge pressure, arterial blood gases (Po₂, Pco₂ and cerebral venous Po₂) and cerebral arteriovenous oxygen difference (A-VO₂) in the same manner as described elsewhere. The EEG and EKG were also monitored. CBF was measured as cerebral venous outflow using electromagnetic flowmeters as described previously.
Cerebral metabolic rate for oxygen (CMRO₂), cerebral perfusion pressure (CPP), mean arterial blood pressure (MABP) and cerebrovascular resistance (CVR) were computed in the usual fashion using the following formulas: 

\[
\text{CMRO}_2 = \text{CBF} \cdot (A-\text{VO}_2) \quad (1)
\]

\[
\text{CPP} = \text{MABP} - \text{ICVP} \quad (\text{mm Hg}) \quad (2)
\]

\[
\text{CVR} = \frac{\text{CPP}}{\text{CBF}} \quad (\text{mm Hg/ml/100 gm brain/min}) \quad (3)
\]

All parameters were recorded on a Grass Model 7 polygraph.

Cerebral autoregulation was estimated quantitatively by means of an autoregulation index (A.I.)\(^5\)\(^-\)\(^8\)\(^-\)\(^9\)\(^-\)\(^10\) using the following formula:

\[
\text{A.I.} = \frac{\Delta\text{CBF}}{\Delta\text{CPP}} \quad (\text{ml/100 gm brain/min/mm Hg}) \quad (4)
\]

where \(\Delta\text{CBF}\) equals the change in CBF and \(\Delta\text{CPP}\) equals the induced change in CPP from the steady state level. Theoretically, when A.I. equals zero there is perfect autoregulation and the value of A.I. is directly proportional to the degree of dysautoregulation. CPP was changed by inverting or deflating an intra-aortic balloon inserted into the thoracic aorta as described elsewhere.\(^9\)\(^-\)\(^10\) Measurements were made during the five-minute interval following induced hypertension and during another five-minute interval during hypotension, that followed the deflation of the intra-aortic balloon. Both values during hypertension and hypotension were compared with steady state values before inflation of the intra-aortic balloon. Arterial Pco₂ (Paco₂) was controlled between 36 and 45 mm Hg.

The cerebral vasomotor responsiveness to CO₂ was tested by subjecting the animal to inhalation of 3% CO₂ in air or mechanical hyperventilation (room air) by changing the speed of the respirator for five minutes. Quantitative assessment of cerebral vasomotor responsiveness to CO₂ was made by using a chemical index (C.I.) as defined by the following formula:

\[
\text{C.I.} = \frac{\Delta\text{CBF}}{\Delta\text{Paco}_2} \quad (\text{ml/100 gm brain/min/mm Hg}) \quad (5)
\]

where \(\Delta\text{Paco}_2\) equals the induced change in Paco₂ and \(\Delta\text{CBF}\) equals the observed change in CBF from the steady state level.

The CBF values were adjusted for concurrent changes in Paco₂, if any, for computation of A.I., while CBF values were adjusted for any concurrent change in CPP for computation of C.I. as described elsewhere,\(^9\)\(^-\)\(^10\) depending upon the particular animal’s autoregulatory and CBF/CO₂ response. In a series of pilot studies of four baboons where the Paco₂ was adjusted actually in vivo by changing the Pco₂ of the inspired air during elevation of CPP, the mean value of the correction factor was found to be 0.28 \(\times\) C.I. (ml/100 gm brain/min/mm Hg) at five minutes after CO₂ inhalation. The same correction factor was applied to adjust CBF to any change in Paco₂. In the test for CO₂ responsiveness, CBF values were adjusted to any change of CPP assuming the individual CVR to be dependent upon Paco₂. To reestablish a steady state with normal CPP and Paco₂, a 15 to 30-minute interval was interposed between each procedure.

Propranolol hydrochloride (Inderal®), a beta-adrenergic blocking agent, was diluted in saline solution and infused into the vertebral artery or femoral vein at a constant rate of 1.03 ml per minute using a Harvard syringe infusion pump. The drug was infused at a dose of 0.09 mg per kilogram of body weight. The measurements of cerebral autoregulatory responsiveness and vasomotor reactivity to CO₂ were performed serially before and after propranolol (PPL) administration. The animals were divided into two groups, so that the effect of intravertebral infusion was tested in seven animals and that of intravenous infusion was tested in five animals. At the end of each experiment, trypan blue solution was infused in the same manner as drug infusion and the brain was then removed, weighed and inspected. The territory perfused with intravertebral dye was identified and compared with that of intravenous administration of dye.

Statistical significance was estimated by means of Student’s t-test or the paired t-test at a level of confidence above 95% (\(P < 0.05\)).

**Results**

**Changes in Cerebral Hemodynamics and CMRO₂**

During and After Infusion of PPL

Results obtained are summarized in table 1. During both intravertebral and intravenous infusions of PPL, CBF decreased significantly while no significant change was observed in CMRO₂, CPP or CVR. The decrease in CBF occurred within three minutes of initiation of infusion of the drug.

At five minutes after ceasing either intravertebral or intravenous administration of PPL, significant progressive decreases in CBF were accompanied by a significant reduction in CPP. CMRO₂ decreased significantly and CVR increased significantly following intravertebral infusion of PPL while less or no significant change was observed in both CMRO₂ and CVR following intravenous infusion of PPL. Bradycardia was also observed. Intravertebral PPL always produced more significant changes than those following intravenous PPL.

**Effects of PPL on Cerebral Autoregulation**

Results are summarized in figure 1. Changes in A.I. during induced hypertension before and after PPL were compared. Following elevation of CPP in the control experiments, A.I. showed an immediate stepwise increase, reached peak value and then decreased progressively toward zero. Following both intravertebral and intravenous PPL, marked decreases in A.I. were observed at all time intervals. At the end of the five-minute interval during elevation of CPP, marked decreases in A.I. were observed at all time intervals. At the end of the five-minute interval during elevation of CPP, marked decreases in A.I. were observed at all time intervals.

![FIGURE 1. Effect of propranolol (PPL) on cerebral autoregulation.](http://stroke.ahajournals.org/DownloadedFrom/http://stroke.ahajournals.org)
TABLE 1  Effect of Propranolol (PPL) on Cerebral Hemodynamics and CMRO2

<table>
<thead>
<tr>
<th></th>
<th>Steady state value before PPL (mean ± SD)</th>
<th>During infusion (mean ± SD)</th>
<th>Percent change 5 minutes after PPL (mean ± SD)</th>
<th>60 minutes after PPL (mean ± SD)</th>
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<tbody>
<tr>
<td>CBF (ml/100 gm brain/min)</td>
<td></td>
<td></td>
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<tr>
<td>Vt</td>
<td>45.6 ± 6.2</td>
<td>-15.4 ± 6.2*</td>
<td>-30.9 ± 14.1*</td>
<td>-29.3 ± 7.8*</td>
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<td>V</td>
<td>44.5 ± 2.8</td>
<td>-14.1 ± 7.1*</td>
<td>-25.5 ± 13.1*</td>
<td>-22.8 ± 5.9*</td>
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<td>CPP (mm Hg)</td>
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<td></td>
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<tr>
<td>Vt</td>
<td>74.0 ± 7.8</td>
<td>-3.4 ± 9.2</td>
<td>-18.7 ± 3.6*</td>
<td>-20.1 ± 7.6†</td>
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<td>V</td>
<td>76.0 ± 9.9</td>
<td>-6.2 ± 8.4</td>
<td>-16.9 ± 4.5*</td>
<td>-18.5 ± 8.9†</td>
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<td>CVR (mm Hg/ml/100 gm brain/min)</td>
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<td></td>
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<tr>
<td>Vt</td>
<td>1.64 ± 0.40</td>
<td>+5.0 ± 12.4</td>
<td>+18.8 ± 14.3*</td>
<td>+11.3 ± 11.5*</td>
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<tr>
<td>V</td>
<td>1.72 ± 0.26</td>
<td>+6.8 ± 10.4</td>
<td>+12.2 ± 11.7†</td>
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<td>CMRO2 (ml/100 gm brain/min)</td>
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<tr>
<td>Vt</td>
<td>2.87 ± 0.58</td>
<td>-4.4 ± 9.7</td>
<td>-17.6 ± 13.5*</td>
<td>-19.2 ± 7.7*</td>
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<td>V</td>
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<td>-10.6 ± 12.5</td>
<td>-20.5 ± 7.3*</td>
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<td>HR (beats/min)</td>
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<tr>
<td>Vt</td>
<td>140 ± 17</td>
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<td>-36.2 ± 9.2*</td>
<td>-23.6 ± 14.0*</td>
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<tr>
<td>V</td>
<td>149 ± 12</td>
<td>-19.6 ± 10.8*</td>
<td>-35.2 ± 5.4*</td>
<td>-21.2 ± 8.0*</td>
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<td>Paco2 (mm Hg)</td>
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<tr>
<td>Vt</td>
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<td>-1.3 ± 2.7</td>
<td>-1.4 ± 3.0</td>
<td>-1.2 ± 2.4</td>
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<tr>
<td>V</td>
<td>39.5 ± 2.6</td>
<td>-1.4 ± 3.1</td>
<td>-1.4 ± 2.8</td>
<td>-1.2 ± 1.8</td>
</tr>
</tbody>
</table>

*Percent change indicates change in percent compared to steady state value.
†Statistical significance of change: \( p < 0.01 \), \( p < 0.005 \), \( p < 0.001 \).

Results obtained are summarized in figure 2. The values of C.I. were always greater during CO2 inhalation than during hyperventilation. During induced hypercapnia, C.I. decreased significantly following intrathecal PPL, while no significant change in C.I. was observed after intravenous PPL. During induced hypocapnia, no significant change in C.I. was observed following both intrathecal and intravenous PPL.

![Figure 2. Effect of PPL on cerebral chemical vasomotor reactivity.](https://example.com/figure2.png)

**Discussion**

**The Validity of the Experimental Model**

The method for measuring CBF using electromagnetic measurement of internal jugular venous outflow has been validated and compares well to concurrent measurements made by intracarotid bolus of Argon gas using mass spectrometry. The general surgical preparation was accomplished with minimal blood loss and without shock as judged from the blood pressure, heart rate and hematocrit levels determined repeatedly throughout the experimental procedure. Meticulous care was taken for preservation of the carotid arteries, vagus nerves and sympathetic chains. Anesthesia was carefully maintained constant. The technique of intraveebral balloon to produce acute changes in CPP is relativelyatraumatic and is more reproducible when compared with other non-pharmacological methods such as clamping of the aorta. The experimental model using intrathecal infusion to study the effects of pharmacological agents has been discussed in detail elsewhere. No appreciable anatomical anomaly of the cervical and cerebral vessels was encountered in the present series of animals. One of the essential pharmacological actions of propranolol hydrochloride is its potency to inhibit selectively the beta-adrenergic receptors with little effect on the alpha-adrenergic receptors. Vasodilatation produced by histamine, acetylcholine (Ach) and nitroglycerin is unaffected by PPL. The hypotensive effect of 5-hydroxytryptamine in atropinized rats is not inhibited by PPL. It has been shown in mice, rats, dogs and monkeys that propranolol hydrochloride crosses the blood-brain barrier rapidly and remains concentrated within the brain tissue over two or three hours, at least, following intravenous injection of the drug at a dose of 0.1 mg per kilogram.

**Effect of PPL on Cerebral Circulation and CMRO2**

It has been demonstrated that intravenous administration of the beta-adrenergic blocker, propranolol, reduces CBF, CMRO2 and CMR glucose. These findings have been interpreted with the view that PPL influences cerebral metabolism primarily and reduces CBF secondarily. Meyer et al. have recently shown in patients with stroke a...
similar effect of PPL on CBF, CMRO₂, and CMR glucose, and have suggested that beta-adrenergic innervation may influence cerebral vasodilator tonus as well as cerebral metabolism.

The present study demonstrated significant decreases in CBF occurring immediately following either intravertebral or intravenous infusion of PPL. This immediate decrease in CBF may be mediated by direct beta-adrenergic blockade in the diencephalic (hypothalamic) and the peripheral receptor sites of cerebrovascular innervation, since CMRO₂ and CPP did not change significantly during these infusions. This delay between the CBF change and the change in CMRO₂ would suggest that at least part of the change in CBF is due to a direct beta-adrenergic blockade (neurogenic) and is not secondary to the metabolic change. This view also is supported by the findings that intravertebral infusion of PPL produced more marked vasoconstrictor responses than intravenous infusion of PPL.

Both CBF and CPP showed significant reductions five minutes after termination of the PPL infusion. It should be noted that these changes were accompanied by a mild persistent bradycardia and a significant reduction in CMRO₂ only on intravertebral infusion, but not on intravenous infusion. A possible explanation for this observation is that cerebral vasodilator tonus is directly inhibited by beta-adrenergic blockade and CBF is not adjusted properly in response to decreased CPP. It is also consonant with observations reported from this laboratory that alpha-adrenergic blockade with intracarotid phenoxybenzamine reduces the cerebral vascular tonus while beta-adrenergic blockade with intracarotid PPL inhibits cerebral vasodilator responses in patients with stroke. Luch et al. have revealed evidence in favor of the direct effect of alpha-adrenergic and beta-adrenergic agonists and antagonists on the cerebrovascular bed of the goat.

Specific cerebral effects of PPL on the cardiovascular system have been documented including hypotension and bradycardia. Kelliher and Buckley have demonstrated in cats that intraventricular PPL produced increases in epinephrine along with minor reductions in norepinephrine within the medulla and pons with less marked increases in both epinephrine and norepinephrine within the telencephalon. It is of interest that these changes were associated with hypotension and were shown to be independent of the beta-adrenergic blocking property. In contrast, it has been shown that the central bradycardic effect of PPL is correlated with its beta-adrenergic blocking action or, at least, with an antagonistic effect of PPL on the catecholamines within the central nervous system (CNS). It also has been well documented by several authors that some beta-adrenergic activity may participate in the central mechanisms of cardiovascular regulation and the effect of PPL may be derived from blockade of central beta-adrenoceptors.

The present results show that intravertebral PPL produced more significant reductions in CBF, CPP, heart rate and CMRO₂ five minutes after infusion of the drug by this route than when given intravenously. This observation supports the view that vasomotor centers presumably located within the hypothalamus and brain stem participate in the autonomic regulation of cerebral circulation and are influenced by PPL. The concurrently observed reduction in CMRO₂ is of interest, since it is possible that CBF might be reduced secondarily to change in CMRO₂. However, in the present study, a significant decrease in CBF occurred first during the intravertebral infusion of PPL followed later by a reduction in CPP and the decrease in CMRO₂. Further, marked bradycardia was concurrently observed indicating specific blockade of beta-adrenoceptors.

Effect of PPL on Cerebral Autoregulation and Chemical Vasomotor Reactivity

Results from the present study indicate that beta-adrenergic blockade enhances the cerebral autoregulatory vasoconstriction during induced hypertension, while it does not alter significantly the autoregulatory vasodilatation during induced hypotension. Thus, beta-adrenergic blockade with PPL appears to be opposite to alpha-adrenergic blockade with phenoxybenzamine in the pharmacological effects on the cerebral autoregulatory response. This observation appears to be in good agreement with the previous observation by Meyer et al. In patients with cerebral stroke. Furthermore, it is of interest that beta-adrenergic blockade with intravertebral PPL influences the cerebral autoregulatory mechanism in just the opposite direction of cholinergic activation mediated by intravertebral neostigmine. Likewise, the present results indicate that beta-adrenergic blockade with intravertebral PPL inhibits the cerebral vasodilatory responsiveness to hypercapnia in contrast to alpha-adrenergic blockade with phenoxybenzamine as well as cholinergic activation with intravertebral neostigmine, and similar to cholinergic blockade with intravertebral atropine.

The present results also are consistent with the dual control mechanism of CBF originally proposed by Deshmukh and Harper et al., in which the extraparenchymal vascular system is controlled primarily by the autonomc nervous system while the intraparenchymal arterioles are controlled primarily by an intrinsic metabolic activity and the metabolic products counteract the extraparenchymal vasomotor changes. Gotoh et al. have also shown evidence for a dual control system for CBF, measuring pial vasomotor alterations. Recently, Stoca et al. and Aoyagi et al. have demonstrated evidence that central cholinergic mechanisms, presumably located within the brain stem, may participate functionally in the dual control mechanisms of CBF. Meyer et al. have demonstrated functional participation of the double cholinergic and adrenergic neurogenic mechanisms in the control of CBF as well as cerebral autoregulatory and chemical vasomotor responsiveness.

References

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