Cerebral Metabolic Changes During Treatment of Subacute Cerebral Infarction by Alpha and Beta Adrenergic Blockade With Phenoxybenzamine and Propranolol

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Abstract: Cerebral hemispheric blood flow (HBF) and metabolism were measured in 30 patients with acute and subacute cerebral infarction before and after intracarotid infusion of the alpha adrenergic blocking agent phenoxybenzamine (PBZ) or the beta adrenergic blocker propranolol (PPL) dissolved in saline. Following intracarotid injection of 7 μg per kilogram per minute PBZ, HBF showed no change but cerebral hemispheric oxygen consumption (HMIO2) and carbon dioxide production (HMICO2) decreased. Glucose consumption (HMIG1) was unchanged but the glucose to oxygen utilization ratio (HG:O) increased. Intracarotid injection of 1.45 μg per kilogram per minute PPL caused reduction of HBF, HMIO2, HMICO2, HMIG1 and HG:O. After PBZ infusion, mean systemic arterial blood pressure (MABP) decreased slightly, intracranial venous pressure (ICVP) and CSF pressure (CSFP) increased, and central venous pressure (CVP) remained unchanged. PPL infusion had no effect on intracranial dynamics. Possible mechanisms whereby PBZ and PPL influence cerebral metabolism and function were discussed. Inhibition of uncoupling of oxidative phosphorylation appeared to be the most likely explanation for the improvement in brain function and metabolic change associated with each of the drugs. These data support the concept that catecholamines released into brain tissue are a possible cause of uncoupled oxidative phosphorylation.

Presently available evidence suggests that adrenergic blocking agents warrant clinical evaluation in the treatment of acute cerebral ischemia, infarction, hemorrhage, and anoxia.

Introduction

The energy supplied by cerebral mitochondria to maintain normal function of the brain is primarily obtained from high energy phosphate bonds such as adenosine triphosphate (ATP), and creatine phosphate converted from adenosine diphosphate (ADP) or creatine, and inorganic phosphate (Pi) by means of tightly coupled oxidative phosphorylation which in turn derives energy from carbohydrate metabolism. There is a great deal of experimental biochemical, morphological and pathophysiological evidence to show that this source of energy is disturbed in ischemic and anoxic injury to the brain.1-7 It is well established that ischemia or anoxia of the brain results in depletion of tissue ATP and creatine phosphate with an increase in concentrations of ADP, creatine, and Pi and accelerated lactate production from anaerobic glycolysis.8-12 Since the central nervous system is extremely dependent upon oxygen utilization, ischemia results in rapid failure of cerebral function which becomes irreversible if allowed to persist.1

Along with these metabolic studies of the effect of ischemia on the brain has come recognition of the im-

Additional Key Words: cerebral metabolism, catecholamines, blood flow, uncoupled oxidative phosphorylation.

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Importance of the autonomic nervous system in controlling cerebral blood flow and metabolism, and knowledge that these autonomic components are themselves highly sensitive to anoxia with resulting derangement of both regulation of blood flow and metabolism of the brain.

In 1948, Ahlquist\(^6\) described two physiologically different types of adrenergic receptors present in the walls of the blood vessels, alpha adrenotropic receptors responding to stimulation by vasoconstriction and beta adrenotropic receptors responding with vasodilatation. Phenoxybenzamine (PBZ), a potent, long-acting adrenergic blocker, acts upon vessels by blocking their alpha adrenergic receptors, resulting in vasodilatation without altering the function of other sympathetic or parasympathetic receptors.\(^14\) The ability of a small amount of intra-arterially injected PBZ to produce regional adrenergic blockade limited to the vascular bed injected was then reported.\(^18\) Later, it was observed that PBZ protects the brain and the liver against ischemia and inhibits the usual depletion of high energy phosphates resulting from ischemia.\(^8,10\) Propranolol (PPL), a beta adrenergic blocker, was found to cause profound inhibition of the stimulating effect of catecholamines on carbohydrate and lipid metabolism.\(^20,24\)

The present investigation therefore was designed to evaluate any circulatory and metabolic effects of regional intracarotid injection of PBZ or PPL in patients suffering from acute cerebral ischemia.

**Methods**

**CLINICAL CASE MATERIAL**

Cerebral hemispheric blood flow (HBF) and metabolism were measured in 30 patients with acute and subacute cerebral ischemia and infarction confirmed by clinical, EEG, CSF, angiographical, and brain scan examinations. Age, sex, clinical diagnosis, severity, interval of time between the ischemic episode and the time of study, and associated diseases considered to be risk factors are summarized in table 1.

There were 21 males and nine females ranging in age from 27 to 77 with the mean age being 57 years. The mean duration between the time of study and the onset of cerebral ischemia was 15 days. Twenty-one patients had cerebral hemispheric infarction, seven had brainstem ischemia or infarction, and two had ischemia referable to both carotid and vertebrobasilar systems.

The clinical course and severity of the stroke were graded into Grades 2 through 4\(^7\) as follows:

- **Grade 2**: Fourteen patients with reversible ischemic neurological deficits lasting 24 hours to three weeks in duration.
- **Grade 3**: Twelve patients with presumed cerebral infarction with moderate persistent disabilities.
- **Grade 4**: Four patients with presumed cerebral infarction with persistent severe neurological deficits.
- **Twenty-four patients** had associated hypertension and/or diabetes.

**METHODS FOR SELECTION OF PATIENTS AND OBTAINING INFORMED CONSENT**

Suitable patients were selected for admission to the study by two or more of the staff neurologists after review of the patients' records and exclusion of cases where there was some medical contraindication to the procedure. Each patient was seen in consultation by a cardiologist and was not admitted to the study unless he indicated in the record that there was no cardiological or general medical contraindication. The procedure was described to the patient or the responsible relative on two separate occasions, first by two staff neurologists and second by a specially trained registered nurse who later witnessed the signing of a standard consent form. The consent form included a description in simple terms of how the catheters are placed and stated that any further explanation would be provided on request and that the patient might withdraw from the procedure at any time.

**PREMEDICATION AND PLACEMENT OF CATHETERS**

A detailed description with citation of relevant references for the methods used in the present study has been reported previously.\(^19\) Premedication consisted of intramuscular injection of 50 mg meperidine hydrochloride. Local anesthesia was induced at all puncture sites by infiltration of 1% procaine hydrochloride. The catheters were inserted under fluoroscopic control via the antecubital veins into each cerebral transverse sinus to sample the cerebral venous blood and to measure intracranial venous pressure (ICVP).

Another catheter was placed into the superior vena cava for measuring central venous pressure (CVP). Catheters also were inserted into the brachial artery to sample arterial blood and record arterial blood pressure (BP). A lumbar puncture was performed and a catheter was inserted into the subarachnoid space to monitor intracranial pressure (ICP).

All pressures were continuously recorded with Statham pressure transducers.

**MEASUREMENT OF CEREBRAL CIRCULATION AND METABOLISM**

Arterial and cerebral venous oxygen tension (P\(_{\text{O}_2}\)), carbon dioxide tension (P\(_{\text{CO}_2}\)) and pH were measured by means of electrodes mounted in flow-through cuvettes, and oxygen saturation (S\(_{\text{O}_2}\)) was monitored with a refection oximeter. An infrared absorption CO\(_2\) gas analyzer was used to measure arterial and cerebral venous CO\(_2\) content,\(^28\) and glucose was measured continuously with the Technicon Auto-Analyzer.

Ten milligrams of phenoxybenzamine (PBZ) hydrochloride (Dibenzyline\(^\text{®}\)) at a rate of 7 \(\mu\)g per kilogram body weight per minute, or 2 mg of propranolol (PPL) hydrochloride (Inderal\(^\text{®}\)) 1.45 \(\mu\)g per kilogram body weight per minute, each diluted in 20 ml normal saline, was slowly injected into the carotid artery over an interval of 15 to 20 minutes.

A bolus of 8 to 10 ml of hydrogen-saturated saline was injected into the carotid artery and HBF was calculated from the clearance curve of hydrogen from the transverse sinus blood measured with a hydrogen electrode. Hemispheric metabolic indices for oxygen (HMIO\(_2\)), carbon dioxide (HMICO\(_2\)), glucose (HMIGI), and hemispheric glucose to oxygen utilization ratio (HG:O) were calculated using formulas reported previously.\(^29\) Calculations were based on HBF and the concentration difference between arterial and ipsilateral transverse sinus blood.

Measurements of HBF and metabolism were made in the steady state and after PBZ or PPL infusion, and in cases...
TABLE 1

Case Material

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Phenoxybenzamine Infusion

Propranolol Infusion

M = male, F = female, R = right, L = left.

with unilateral cerebral infarction the measurements were obtained from the diseased hemisphere. The steady state was achieved by having the patient lie comfortably on a tilting table for approximately 30 minutes until all the parameters (arterial and cerebral venous Po2, Pco2, pH, O2 saturation, CO2 content, ICVP, ICP, CVP and arterial BP) were noted to be stable on the continuous recordings.

Before and after the infusion to be tested, blood samples were drawn from the artery and transverse sinus in order to measure the concentrations of chemical substrates in arterial and cerebral venous blood. Free fatty acids (FFA) in the plasma were measured by means of a colorimetric method based on the formation of copper soaps with the fatty acids. The methodological error was less than 1.5% in the present study.

Inorganic phosphate was measured by modification of the semiautomated colorimetric method adapted for the Technicon Auto-Analyzer. The methodological error in the measurement of serum Pi was in the range of 0.01 mg/dl and the reproducibility for the method was within 0.5% in the physiological range. Triglycerides were measured using a semiautomated fluorometric method based on the Hantzsch condensation reaction between an amine, beta-diketone and aldehyde. L-glutamate was measured by the enzymatic method of Bernt and Bergmeyer. Statistical analysis of the mean data was performed by applying the t-test of the significance between the sample mean for paired values. Results were regarded to be significant when they reached the 5% level of confidence. Thus, the conclusions drawn in this study are based on changes in mean values for the entire study.
CEREBRAL METABOLIC CHANGES DURING ADRENERGIC BLOCKADE

EFFECT OF PHENOXYBENZAMINE INFUSION ON OTHER METABOLITES

FREE FATTY ACIDS

INORGANIC PHOSPHATE

TRIGLYCERIDE

GLUTAMATE

Figure 1

To show the effect of intracarotid injection of 10 mg phenoxybenzamine (PBZ) on cerebral hemispheric blood flow (HBF) and metabolic indices in stroke. Mean changes are calculated from the steady state values ($\Delta$) after the PBZ infusion. The mean values (±SD) in the steady state are shown parenthetically. Statistically significant changes are shown by an asterisk (*). Following the infusion, the changes were measured twice: at intervals of 15 minutes (measurement No. 1) and 70 minutes (measurement No. 2). $\Delta$ HMIO$_2$ and $\Delta$ HMICO$_2$ significantly decreased, and $\Delta$ HG:O increased. These changes were sustained throughout the study. N means the number of measurements and the small vertical bars represent standard deviations.

Results

EFFECT OF PHENOXYBENZAMINE AND PROPRANOLOL ON HEMISPHERIC BLOOD FLOW AND METABOLISM

Hemispheric blood flow and metabolic indices for each patient in the steady state and following the infusion of an adrenergic blocking agent, PBZ or PPL, are listed in tables 2 and 3. Since each measurement of HBF requires ten minutes, the metabolic indices were calculated from the mean of minute-to-minute values obtained from the continuous records of the metabolic parameters sampled over the same ten-minute interval. Mean changes from the steady state values of cerebral hemispheric blood flow and metabolic indices ($\Delta$ HBF, $\Delta$ HM1) are graphically illustrated in figures 3 and 4. The changes in HBF and metabolism were calculated for the intervals of 15 minutes after the cessation of infusion in all patients (No. 1) and 70 minutes after the infusion in 23 patients (No. 2).

A typical recording of cerebral arteriovenous blood gases and pH together with intracranial and systemic pressures measured during the infusion of phenoxybenzamine are illustrated along with EEG samples in figure 5.

Following the PBZ infusion, HBF did not change significantly. Cerebral oxygen consumption (HMIO$_2$) and carbon dioxide production (HMICO$_2$) decreased significantly 15 minutes after the infusion and thereafter had a tendency to decrease further. However, later values were not significantly reduced 70 minutes after the infusion because of the smaller number of measurements (N = 9) and hence a larger standard deviation. It was noted that the patients with less severe ischemic neurological deficits referable to carotid and/or verteobasilar systems showed smaller changes in the metabolic indices than patients with more massive cerebral hemispheric infarction. Cerebral glucose consumption (HMIG1) showed no significant change. The mean increase in the hemispheric glucose to oxygen ratio (HG:O) was statistically significant and was sustained through completion of the measurements.

After PPL infusion, HBF and the metabolic indices HMIO$_2$, HMICO$_2$, HMIG1 and HG:O all showed statistically significant reduction. Hemispheric metabolic index for lactate, measured in nine cases, decreased from 0.90 ± 0.60 to 0.46 ± 0.22 ml/100 gm brain per minute, but this reduction did not reach the level of statistical significance (0.05 < P < 0.1).
EFFECT OF PROPRANOLOL INFUSION ON OTHER METABOLITES

FREE FATTY ACIDS

INORGANIC PHOSPHATE

TRIGLYCERIDE

\[ A-V \] mMol/L

\[ A-V \] Mg/dl

\[ A-V \] Mg/dl

\[ A-V = \text{Arterio-Cerebral Venous Difference} \]

**FIGURE 2**

To show the effect of intracarotid injection of 2 mg propranolol (PPL) on cerebral hemispheric blood flow (HBF) and metabolic indices in stroke. Fifteen minutes after the infusion, \( \Delta \text{HBF}, \Delta \text{HMI02}, \Delta \text{HMIco2}, \Delta \text{HMGI}, \) and \( \Delta \text{HG:O} \) decreased significantly. These changes were sustained throughout the study except in \( \Delta \text{HMI02} \) and \( \Delta \text{HG:O} \).

EFFECT OF PHENOXYBENZAMINE AND PROPRANOLOL ON CEREBRAL VENOUS AND ARTERIAL GASES, GLUCOSE AND pH

The mean change of cerebral arteriovenous blood gases, glucose and pH after the PBZ or PPL infusion compared to the steady state values is shown in figures 6 and 7.

The only significant changes in the arterial blood after the PBZ infusion were a decrease in carbon dioxide content (\( \text{aCO2} \)) and an increase in glucose concentrations (\( \text{aGl} \)). Metabolic changes in arterial blood were slight, but those in the cerebral venous blood were marked and significant. Cerebral venous \( \text{Pao2}, \text{Sao2}, \) pH and glucose increased, indicating a decrease in cerebral metabolism since HBF was unchanged.

Following the PPL infusion, glucose showed a marked increase which was the most noticeable change that occurred in the cerebral venous and arterial blood. Changes in cerebral venous and arterial gases and pH were small and not significant.

EFFECT OF PHENOXYBENZAMINE AND PROPRANOLOL ON INTRACRANIAL DYNAMICS

The changes from the steady state in mean intracranial venous pressure (MICVP), mean central venous pressure (MCVP), and mean arterial pressure (MABP) are shown in figures 8 and 9.

Following the PBZ infusion, MICVP and MICP increased significantly and remained so, indicating that PBZ increased cerebral blood volume due to vasodilatation and relocation of blood since HBF did not increase. MCVP did not change. MABP decreased slightly but significantly, indicating that locally injected PBZ recirculates to some degree and also affects other systemic vascular beds.

After the PPL infusion, MICVP, MICP, MCVP and MABP did not show any statistically significant change during the measurements.

EFFECT OF PHENOXYBENZAMINE AND PROPRANOLOL ON CEREBRAL METABOLITES

The mean arterial concentrations of free fatty acids, inorganic phosphate, triglycerides and glutamate in the steady state and after the infusion are listed in table 4. The cerebral arteriovenous (A-V) differences for each substrate are illustrated in figures 1 and 2. Arterial and cerebral venous blood was sampled in the...
### TABLE 2

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<th>HBF After infusion SD</th>
<th>HMO Steady state</th>
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<th>HMCO Steady state</th>
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<td>1.95</td>
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*Significant as compared with steady state values.

HBF = hemispheric blood flow.

HMIBF = hemispheric metabolic index for brain.

HMICO = hemispheric metabolic index for carbon dioxide.

HMIG = hemispheric metabolic index for glucose.

HG:O = hemispheric glucose:oxgen utilization ratio.
<table>
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<th>Case no.</th>
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<th>HMI O₂ (ml/100 gm brain/min)</th>
<th>HMI CO₂ (ml/100 gm brain/min)</th>
<th>HMI Gl (mg/100 gm brain/min)</th>
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*Significant as compared with steady state values.

HBF = hemispheric blood flow.
HMIO₂ = hemispheric metabolic index for oxygen.
HMICO₂ = hemispheric metabolic index for carbon dioxide.
HMIG = hemispheric metabolic index for glucose.
HG:O = hemispheric glucose:oxygen utilization ratio.
CEREBRAL METABOLIC CHANGES DURING ADRENERGIC BLOCKADE

EFFECT OF PHENOXYBENZAMINE INFUSION ON HEMISPHERIC BLOOD FLOW AND METABOLISM

Typical recordings of cerebral venous and arterial blood gases, pH, central venous pressure (CVP), intracranial pressure (ICP) and systemic arterial pressure (BP) with EEG tracings before, during, and after PBZ injection. Note the rise in cerebral venous oxygen tension (CVP\textsubscript{O\textsubscript{2}}) and saturation (CVP\textsubscript{SO\textsubscript{2}}). The respiration (Resp) was of Cheyne-Stokes type and changed to more regular breathing after PBZ injection. There also was increase in the EEG frequency during and after the infusion.

steady state and 70 to 90 minutes after cessation of the infusion.

The mean arterial concentrations for all four of these chemical substrates showed no significant change after the infusion of PBZ, but following PPL infusion the mean arterial concentrations for FFA and triglycerides decreased and those for Pi increased significantly. The elevated concentration of free fatty acids in the steady state occurred because two-thirds of the patients studied suffered from diabetes mellitus (table 1).

Previous studies in normal subjects, in patients without metabolic disorders, and in those with chronic cerebral arteriosclerosis have not shown any uptake or release of free fatty acids, inorganic phosphate or triglycerides. In the present study, measurements made in patients with recent cerebral ischemic episodes showed a significant release of free fatty acids into the cerebral venous blood from the ischemic brain, since the cerebral venous values were higher than those of the cerebral arterial blood. Inorganic phosphate also was released from the ischemic brain in the majority of patients, although the mean value was not significant in the group of patients treated with PBZ since the patients with mild attacks of brainstem ischemia or infarction displayed either positive or low negative values.

Following PBZ infusion, the release of free fatty acids and inorganic phosphate from the ischemic brain was reversed and both were taken up by the brain along with triglycerides. The positive (A-V) difference for glutamate after PBZ infusion was not a significant change from the control value.

After the infusion of PPL, the release of both free fatty acids and inorganic phosphate was reduced and triglycerides were significantly taken up by the brain.

Discussion
The present measurements were undertaken in patients with acute and subacute cerebral ischemia
EFFECT OF PROPRANOLOL INFUSION ON HEMISPHERIC BLOOD FLOW AND METABOLISM

\[ \Delta \text{HBF (ml/100gm brain/min)} \]
\[ \Delta \text{HMI-O}_2 \text{(ml/100gm brain/min)} \]
\[ \Delta \text{HMI-CO}_2 \text{(ml/100gm brain/min)} \]
\[ \Delta \text{HMI-GI (mg/100gm brain/min)} \]
\[ \Delta \text{H-G/O} \]

TABLE 4

Effect of Phenoxybenzamine and Propranolol Infusion on Cerebral Metabolites

<table>
<thead>
<tr>
<th></th>
<th>Steady state</th>
<th>After Infusion</th>
<th>Steady state</th>
<th>After Infusion</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Arterial concentrations</td>
<td>Arterial concentrations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free fatty acids (mmol/1)</td>
<td>1.00 ± 0.56  (N = 12)</td>
<td>1.12 ± 0.59</td>
<td>0.86 ± 0.69  (N = 7)</td>
<td>0.66 ± 0.48*</td>
</tr>
<tr>
<td>Inorganic phosphate (mg/dl)</td>
<td>2.47 ± 0.58  (N = 15)</td>
<td>2.63 ± 0.46</td>
<td>2.23 ± 0.48  (N = 10)</td>
<td>2.34 ± 0.57*</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>76.8 ± 27.4  (N = 14)</td>
<td>69.5 ± 26.0</td>
<td>85.4 ± 42.2  (N = 12)</td>
<td>63.6 ± 30.8*</td>
</tr>
<tr>
<td>Glutamate (mg/dl)</td>
<td>3.84 ± 0.97  (N = 13)</td>
<td>3.70 ± 0.98</td>
<td>—</td>
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</tbody>
</table>

Values = mean ± SD. 
N = Number of measurements. 
* = Statistically significant difference compared to steady state values.

To show the effect of PBZ on cerebral venous and arterial blood gases, glucose and pH. Differences from the steady state (Δ) are illustrated. The mean values (± SD) of the individual parameters in the steady state are shown parenthetically. Significant changes were seen in all cerebral venous parameters and were sustained following the PBZ infusion. The only significant changes in the arterial values were a fall in carbon dioxide content (aCO2) and a rise in glucose concentrations (aGI).
CEREBRAL METABOLIC CHANGES DURING ADRENERGIC BLOCKADE

EFFECT OF 10mg PHENOXYBENZAMINE
(Intra-carotid Injection)

FIGURE 5

To show the effect of PPL on cerebral venous and arterial blood gases, glucose and pH. The only significant changes in both arterial and cerebral venous values were a conspicuous rise in glucose concentrations following the infusion.

and infarction in the hope of defining changes in cerebral metabolic and intracranial dynamics that might be improved or alleviated by medical treatment. Recently, it has been demonstrated in experimental trauma and ischemia of the brain and spinal cord that neurotransmitters are released into the central nervous system parenchyma, adversely affecting its structure, energy metabolism and blood flow, and that such neurotransmitters exert part of this deleterious effect by their action on the autonomic innervator and receptor sites.16-18,36,39 The functional significance of both alpha and beta adrenergic receptors in the cerebrovascular system has recently been established.27-36,41 We have shown in this Center that norepinephrine is increased in the cerebrospinal fluid of patients with stroke37 and that concentrations of total catecholamines in CSF correlate with enhanced cerebral oxygen consumption, suggesting the possibility of impaired oxidative phosphorylation in acute stroke patients.42

These morphological, pharmacological and biochemical findings led us to examine the possible therapeutic usefulness of adrenergic blocking agents in the treatment of cerebrovascular disease. It has been shown that PBZ protects the brain against ischemia in the treatment of hemorrhagic shock16-18 and that the neurological deficits of patients with cerebral ischemia from vasospasm accompanying a ruptured aneurysm are improved by intracarotid infusion of PBZ.43 It also has been shown that intracarotid PBZ relieves spasm in patients with subarachnoid hemorrhage and in some cases increases CBF.44

Other investigators have shown that intra-arterial injection of PBZ has a regional effect on the arterial territory of supply, becoming rapidly taken up by the receptor sites and causing regional dilatation of the vessels supplying the organ injected.16,45,46 Local injection of PBZ into the cerebral arteries enhances regional cerebral blood flow (rCBF) and abolishes cerebral vasoconstriction induced by the prior injection of norepinephrine.47 Furthermore, we have shown that administration of alpha-methyldopa to hypertensive patients with stroke increased CBF and have hypothesized that this drug might decrease the vasoconstrictive effect of catecholamines acting on the cerebral vessels.48

In the present study, although hemispheric blood flow (HBF) did not increase after PBZ infusion, intracranial venous pressure and cerebrospinal fluid pressure increased, compatible with an increase in cerebral blood volume due to cerebral vasodilatation. This was confirmed by measurement of regional
EFFECT OF PHENOXYBENZAMINE INFUSION ON CEREBRAL VENOUS AND ARTERIAL BLOOD GASES, GLUCOSE AND pH

To show the effect of PBZ on cerebral dynamics. Note the significant and sustained increase in intracranial venous pressure (ICVP) and intracranial pressure (ICP) accompanied by a decrease in arterial blood pressure (MABP), compatible with an increase in cerebral blood volume.

Cerebral blood flow (rCBF) and blood volume (rCBV) using $^{133}$Xe and $^{99m}$Tc clearance, respectively, in many of these patients performed before and after the infusion of PBZ into the carotid artery. These concurrent measurements of rCBF and rCBV also showed an increase of rCBF and regional cerebral blood volume in the ischemic regions. Regional increases in CBF may occur in the absence of significant changes of HBF if there is relocation of blood or an increase in cerebral blood volume or both. However, there were two other competing factors tending to minimize any increase in HBF induced by PBZ: (1) the small but significant reduction in blood pressure in the presence of impaired autoregulation which was shown to be present in all these patients, and (2) the decrease in cerebral metabolism with reduced CO$_2$ production.

When administered in combination with PBZ, the beta adrenergic blocking agent propranolol reduces lactic acidosis, improves microcirculatory failure, and enhances tolerance to shock or hemorrhage, whereas PPL alone may decrease blood supply to the tissue by blocking the vasodilator effect of isoprenaline, epinephrine or norepinephrine on beta adrenergic receptors. In our patients, intracarotid administration of propranolol reduced cerebral glucose consumption, CO$_2$ production and oxygen consumption as well as hemispheric blood flow. The present result was in good agreement with the observation that PPL caused a slight fall in CBF.
CEREBRAL METABOLIC CHANGES DURING ADRENERGIC BLOCKADE

EFFECT OF PROPRANOLOL ON CEREBRAL VENOUS AND ARTERIAL BLOOD GASES, pH AND GLUCOSE

CEREBRAL VENOUS BLOOD

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<td>NO. 1</td>
<td>NO. 2</td>
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</table>

| Δ P0₂ (mm Hg) | 10.0 ± 2.6 ± 4.0 | 0 ± 1.0 ± 0.8 |
| Δ SO₂ (%)     | 0.0 ± 0.2 ± 0.4  | 0 ± 0.1 ± 0.2 |
| Δ PCO₂ (mm Hg)| -2.0 ± 0.8 ± 0.4 | 0 ± 0.4 ± 0.2 |
| Δ pH          | -0.3 ± 0.2 ± 0.4 | 0 ± 0.1 ± 0.2 |
| Δ GI (mg/dl)  | 15.0 ± 3.4 ± 3.2 | 0 ± 1.0 ± 0.8 |

N=14

ARTERIAL BLOOD

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<td>NO. 1</td>
<td>NO. 2</td>
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</table>

| 10.0 ± 2.6 ± 4.0 | 0 ± 1.0 ± 0.8 |
| 0.0 ± 0.2 ± 0.4  | 0 ± 0.1 ± 0.2 |
| -2.0 ± 0.8 ± 0.4 | 0 ± 0.4 ± 0.2 |
| -0.3 ± 0.2 ± 0.4 | 0 ± 0.1 ± 0.2 |
| 15.0 ± 3.4 ± 3.2 | 0 ± 1.0 ± 0.8 |

N=14

To show the effect of PPL on cerebral dynamics. There was no significant change observed in MICVP, MICP, MCVP, and MABP following the infusion.

and oxygen consumption and a greater fall in glucose consumption in the canine brain.

There are several previous studies indicating that PBZ and PPL, apart from their vascular properties as blockers of adrenergic receptors, also change cerebral metabolism, presumably by passing the blood-brain barrier. Although PPL has been reported to cross the blood-brain barrier rapidly, it has been assumed that alpha adrenergic blocking agents do not cross the blood-brain barrier. The present metabolic changes were measured within 15 minutes of completing the PBZ injection, which suggests that PBZ does cross the barrier in patients with infarction, possibly due to damage to the barrier which is known to occur following ischemia.

The results of the present observations following administration of adrenergic blocking agents to these patients with acute and subacute cerebral infarction are taken to indicate recoupling of oxidative phosphorylation since (1) inorganic phosphate moved into the brain, (2) the release of free fatty acids, which are known to cause uncoupling, from the brain tissue was reduced, and (3) the level of cerebral oxygen consumption and CO₂ production were reduced.

The EEG and records of respiration also improved after PBZ administration in much the same manner as reported by Kovach et al., whose animals were protected by PBZ from the effects of cerebral ischemia with inhibition of uncoupling of oxidative phosphorylation and EEG slowing. The effect of these adrenergic blocking agents on cerebral metabolism also was similar to that previously reported when intravenous glycerol was administered to patients with acute cerebral infarction.

Uncoupling of oxidative phosphorylation as a result of ischemia of the brain has been reported by a number of laboratories, the brain showing more rapid and severe uncoupling than tissues from other organs. Previous investigations also have shown that metabolic changes induced by 2, 4-dinitrophenol (DNP), a specific uncoupling agent of oxidative phosphorylation, are similar to those seen after cerebral ischemia. For example, administration of 2, 4-DNP, like ischemia of the brain, produces increased oxygen consumption, cerebral edema, and slowing and flattening of the EEG. Furthermore, if the brain is rendered edematous by ischemia and anoxia prior to the administration of 2, 4-DNP, its uncoupling effect is reduced, providing further evidence that ischemia of the brain produces uncoupling. Indeed, postanoxic uncoupling of oxidative phosphorylation has been listed as a primary...
Effect of Phenoxybenzamine Infusion on Intracranial Dynamics

To show the effect of PBZ on the arteriovenous (A-V) difference for concentrations of free fatty acids, inorganic phosphate, triglycerides and glutamate in patients with acute stroke. Note significant reversal of the loss or increased uptake by ischemic brain of free fatty acids and inorganic phosphate, and the significant increase in triglyceride consumption following the infusion. Glutamate consumption was not further increased by PBZ infusion. Asterisks indicate a statistically significant difference from zero.

Metabolic disturbance accompanying the other well-known effects of ischemic anoxia on cerebral metabolism.

Other possible explanations for the metabolic changes following PBZ and PPL administration have been considered but seem unlikely. For instance, we reject the “Crabtree effect” which is inhibition of cellular oxidation by high concentrations of glucose with increased anaerobic glycolysis whereby cerebral oxygen consumption is reduced, since reduction of oxygen consumption (HMIO$_2$) and CO$_2$ production (HMICO$_2$) induced by PBZ and PPL occurred not only in patients with elevated glucose concentrations but also in those with normal and even low blood sugar levels. The elevated blood glucose concentrations resulting from PBZ and PPL administration were not considered to exert a “Crabtree effect” since cerebral glucose consumption (HMI Gl) was monitored and did not increase after the infusion.

It also seems unlikely that reestablishment of flow through non-metabolizing brain accounts for the depression of HMIO$_2$ and HMICO$_2$ induced by PBZ, since measurements of rCBF after the PBZ injection showed small increases of flow in areas of ischemia and values of rCBF in zones of ischemia prior to injection were not close to zero. Furthermore, the simultaneous measurements of HBF did not change, and in any event improvement in the EEG and respiration could not be attributed to restoration of flow in non-metabolizing zones of brain.

The increase in arterial and cerebral venous blood glucose after PBZ or PPL injection, without any increase in cerebral glucose consumption, requires comment. Increased arterial glucose levels have been noted by other workers after large amounts of PBZ were administered. They assumed that it resulted from an accumulation of circulating catecholamines as a result of alpha adrenergic blockade at many receptor sites.
CEREBRAL METABOLIC CHANGES DURING ADRENERGIC BLOCKADE

EFFECT OF PROPRANOLOL INFUSION ON INTRACRANIAL DYNAMICS

To show the effect of PPL on arteriovenous (A-V) differences for concentrations of free fatty acids, inorganic phosphate and triglycerides in patients with acute cerebral ischemia. Note the significant reduction of the loss or increased uptake by ischemic brain of free fatty acids and inorganic phosphate, and the significant increase in triglyceride consumption following the infusion. Asterisks indicate a statistically significant difference from zero.

sites. This was apparently not the explanation in the present study since a small amount of PBZ was injected into the carotid artery.

We consider a more likely explanation for the increase of blood glucose after PBZ administration to be mobilization of muscle glycogen and inactivation of hepatic phosphorylase. Propranolol has been observed to raise blood glucose levels by stimulating glycogenolysis and glycolysis in the liver, whereas it raised the glycogen contents of muscle and brain by depressing phosphorylase activity and reduced the pyruvate and lactate contents as a result of blocking beta adrenergic receptors which are mediated by the adenyl cyclase-cyclic AMP system.

Under usual conditions, increasing the blood glucose levels enhances cerebral glucose consumption. The fact that this did not happen after the administration of PBZ or PPL is thought to be due to blocking of the stimulating effect of catecholamines on glucose consumption or to recoupling of oxidative phosphorylation since uncoupling enhances glucose consumption (and CO₂ production) without producing effective energy metabolism.

The present measurements suggest that cerebral lipid metabolism was improved by both PBZ and PPL administration. It is known that the mobilization of free fatty acids is influenced by the autonomic nervous system. The level of phosphate in the blood also is assumed to be mediated by beta adrenergic receptors since PPL completely blocks adrenaline-induced hypophosphatemia. In the present study, PPL caused significant reduction of plasma free fatty acids, suggesting suppressed lipolysis and significant increase of serum phosphate which was mainly due to the block of beta adrenergic receptors and in part due to the reduced incorporation of phosphate into the tissue in relation to the depressed utilization of glucose.

Reference has already been made to the fact that the PBZ and PPL infusions each reversed the negative
cerebral arteriovenous differences for free fatty acids and inorganic phosphate to the positive, and this was taken as further evidence of recoupling of oxidative phosphorylation. It has been shown experimentally that in the acute stage of cerebral ischemia there is a progressive decrease in oxidative phosphorylation with an accumulation of free fatty acids.5-8 This has been presumed to result from increased breakdown of lipids, diminished lipid synthesis and/or decreased utilization of free fatty acids. The data obtained from our patients wherein the negative A-V differences for free fatty acids and Pi were converted to the positive by PBZ and PPL injections suggest an uptake by the brain of free fatty acids and Pi for lipid and phospholipid synthesis to repair damaged brain tissue. Likewise, the reversal or increase of the cerebral A-V difference for triglycerides after PBZ and PPL injections suggests restoration of lipid synthesis by the brain.

It is also well known that ischemia to the brain decreases cerebral production of high energy phosphate compounds. Consequently, adenosine diphosphate and inorganic phosphate become increased, resulting in a release of the degradation products of adenosine triphosphate into the cerebral venous blood.9-12 The reversal or narrowing of the negative A-V differences for inorganic phosphate observed after PBZ or PPL administration is believed to indicate their incorporation into high energy phosphate compounds as well as phospholipids.12 For example, it has been shown that ethylenediaminetetraacetic acid (EDTA), which is known to restore phosphate bonds in traumatized brain mitochondria,6-9,12 the reversal or narrowing of the negative A-V differences for inorganic phosphate observed after PBZ or PPL administration is believed to indicate their incorporation into high energy phosphate compounds as well as phospholipids.12

In conclusion, intracarotid injection of PBZ increases cerebral blood volume whereas intracarotid PPL decreases cerebral blood flow. However, both PBZ and PPL improve cerebral oxidative phosphorylation, energy production, lipid synthesis and brain function by blocking adrenergic receptor sites in the cerebral vessels and by reversing the deleterious metabolic effects of catecholamines released into ischemic brain tissue.10

Available evidence suggests that adrenergic blocking agents warrant further clinical evaluation in the treatment of acute and subacute cerebral ischemia, infarction, hemorrhage and anoxia.

Acknowledgments
The authors’ appreciation is expressed to Mrs. Susan Kwant and Mr. Peter Miller for their valuable technical assistance.

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Stroke, Vol. 5, March-April 1974
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Cerebral Metabolic Changes During Treatment of Subacute Cerebral Infarction by Alpha and Beta Adrenergic Blockade With Phenoxybenzamine and Propranolol

JOHN STIRLING, MEYER, SHIGEMICHI OKAMOTO, KUNIO SHIMAZU, ATSUO KOTO, TADAO OHUCHI, ATSUO SARI and ARTHUR DALE ERICSSON

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