Effects of Catecholamine Infusions on Cerebral Blood Flow and Oxygen Consumption of the Isolated Perfused Dog Brain

BY R. ZIMMER, M.D., R. LANG, M.D., AND G. OBERDÖRSTER, M.D.

Abstract:
Effects of Catecholamine Infusions on Cerebral Blood Flow and Oxygen Consumption of the Isolated Perfused Dog Brain

Our earlier studies revealed a weak alpha-adrenergic and beta-adrenergic activity of the cerebral vessels of the isolated perfused dog brain. The present investigations were undertaken to determine whether vascular adjustments occur in the cerebral circulation during longer periods of catecholamine infusions. The experiments were performed on six isolated canine brains cross perfused from donor dogs. Norepinephrine (2 μg per minute), epinephrine (2 μg per minute), and isoprenaline (0.2 ng per minute) were applied intra-arterially (i.a.) for a period of ten minutes. Total venous outflow, perfusion pressure in the circle of Willis, and venous O₂ saturation were monitored continuously. Cerebral vascular resistance (CVR) and cerebral O₂ consumption (CMRO₂) were calculated. Based on the pressure-flow relationship tested in each brain, the indirect effects of catecholamines on CVR caused by autoregulatory influences were calculated and eliminated. During norepinephrine and epinephrine infusions cerebral blood flow (CBF) was found to be decreased by 10.2 ± 6.0% and 4.1 ± 3.3%, respectively, whereas during isoprenaline infusion CBF increased by 9.3 ± 3.6% (mean values ± SD). The maximal changes of CBF were reached in the first or second minute of catecholamine infusion and persisted up to the end of infusion (P > 0.05). After elimination of the indirect effects of catecholamines on CVR, the direct effects on CVR were reduced to about 50% of the original values and remained constant at the level reached during the whole period of infusion. CMRO₂ was not changed (P > 0.05) during infusion of the different catecholamines. Based on these investigations it is assumed that no pronounced vascular adjustments occur in the cerebral circulation during catecholamine infusions.

Additional Key Words
- epinephrine
cerebral circulation
- norepinephrine
vascular adjustments
- isoprenaline
cerebral metabolism

Exogenous catecholamines have pronounced effects on blood vessels in every region of the body except the brain, where their influence on the total cerebral blood flow is still controversial.¹ ² In accordance with the findings of other authors,³ ⁴ our earlier studies⁵ revealed a weak alpha-adrenergic and beta-adrenergic activity of the cerebral vessels of the isolated perfused dog brain. Since these investigations were obtained with injections of catecholamines, no conclusion could be made whether the vasoconstrictor response of cerebral vessels to norepinephrine or the vasodilator response to isoprenaline is followed by a secondary opposite phase of reaction. The latter is called either autoregulatory escape,⁶ vascular escape⁷ or vascular adjustment⁸ and is observed to an extreme extent in the circuit of the intestine,⁹ liver,¹⁰ and kidney¹¹ during longer infusions of catecholamines and/or sympathetic stimulation.

With respect to the cerebral circulation, however, it has not yet been investigated whether such vascular adjustments exist during infusion of catecholamines. One reason for this lack of information could be the fact that the nitrous oxide¹² or the radioactive clearance¹³ technique frequently used for measuring CBF does not allow detection of rapid transient flow changes.

The assumption that vascular adjustments might exist in the cerebral circulation is supported by the findings of Harper et al.¹⁴ According to them, vascular adjustments could occur during sympathetic stimulation and norepinephrine infusion by opposite reactions.
of two different vascular sections: the intracranial extracerebral arteries and the small arteries and arterioles being in direct contact with the brain parenchyma and controlled predominantly by the metabolic need of the tissue.

Since we have developed a method for continuous measuring of CBF, it seemed to be of considerable interest to us to investigate whether or not vascular adjustments in the cerebral circulation actually occur during catecholamine infusions.

Methods

Fifteen experiments were performed on six isolated perfused brains with an average weight of 58 grams. The brains were perfused by donor dogs (body weight, 28 ± 3 kg), which were intravenously anaesthetized with a mixture of allobarbital (50 mg per kilogram), urethane (100 mg per kilogram), and ethylene urea (100 mg per kilogram). After hepianization (Vetren®, 20 mg per kilogram) and curarization (Succinyl-"Asta", 2 mg per kilogram), the donor dogs were ventilated artificially by an Engström respirator so that arterial PO2 and PCO2 were kept constant at a level of 100 to 120 mm Hg and 38 to 40 mm Hg, respectively. The values were controlled with a Pt-electrode and a glass electrode (Fa. Eschweiler & Co., Kiel, Germany) every 20 minutes. Furthermore, the arterial pH was measured by a glass electrode (Fa. Ingold, Ingelheim, Germany) and kept constant at 7.36 to 7.40 by infusion of NaHCO3 solution.

A schematic drawing of the experimental set-up is given elsewhere.3 To achieve complete isolation of the cerebral circulation, all extracranial tissue was dissected. The neurocranium and the dura mater, however, had to remain intact for technical reasons. Before dissection of the extracranial tissue, the following arteries had to be ligated:16 18 the pharyngeal ascendens artery (including the anastomosis with the internal carotid artery), the external carotid artery with its branches, the internal carotid artery, the internal and external ophthalmic arteries, and the external ethmoidal artery. The ethmoidal artery was occluded indirectly by sealing the dissection surface, which was caused by cutting off the facial bone in the plane of the upper fourth premolar tooth. After decapitation of the head from the trunk between the occipital hole and the first cervical vertebra, the basilar artery was occluded. The brains were perfused bilaterally by an anastomosis between the femoral artery of the donor and the internal maxillary artery of the perfused brain, from which on both sides the blood passed through the anastomotic artery from the external ophthalmic artery and the anastomotic ramus of the middle meningeal artery into the circle of Willis.

The blood pressure in the circle of Willis was measured by a pressure transducer (Statham 23Db) via a cannula inserted into the basilar artery; by two additional pressure transducers the perfusion pressure in the internal maxillary artery and the mean arterial blood pressure of the donor were recorded. At the beginning of each experiment the perfusion pressure in the circle of Willis was adjusted to 80 mm Hg. To obtain this perfusion pressure in the circle of Willis, a perfusion pressure of 120 to 160 mm Hg in the internal maxillary artery was necessary. The reasons for this high pressure drop in our experiments are the small unavoidable arterial bleedings and the small number of anastomoses left for perfusion compared with the normal anatomy of the intact animal. The high perfusion pressure in our experiments was obtained by a hydrostatic pressure difference between the donor dog and the perfused brain.

CBF was measured continuously as total venous outflow of the confluence of sinuses with a photoelectric drop recorder adjusted to an integrator unit. To avoid outflow of other veins, the venous outflow was sucked off with a pressure of -2 to -3 cm H2O and, in addition, the oesophageal venous confluence sinus had to be closed. The blood from the confluence of sinuses and the blood dropping from the small arterial bleedings (on average the same amount as CBF) were reinfused in the femoral vein of the donor by a speed-controlled roller pump.

In a small venous bypass the venous O2 saturation was monitored continuously with an Oxymeter (Atlas-Elektronik, Bremen, Germany). The ECoG, recorded from bone screws in the frontal and occipital region of the skull, was monitored with an electroencephalograph (Fa. Schwarzer, München, Germany).

The following drugs were used: L-adrenalin-hydrogen-L-tartrate, L-noradrenalin-L-tartrate and N-isopropyl-DL-noradrenalin-HCl (Schuchardt-GmbH, München, Ger-
EFFECTS OF CATECHOLAMINE INFUSIONS

TABLE 1 (Cont'd)

\[
\begin{array}{cccccc}
\text{min} & \text{8} & \text{10} & \text{12} & \text{16} & \text{20 min} \\
-10.2 & 6.4^* & -11.2 & 5.7^* & -0.7 & 4.3 & -0.9 & 4.0 & -1.2 & 3.1 \\
+38.4 & 13.5^* & +42.5 & 14.5^* & +15.6 & 16.6 & +9.9 & 7.3 & +9.9 & 6.2 \\
+18.6 & 6.2^* & +21.2 & 4.6^* & +4.1 & 5.7 & +0 & 6.8 & +2.7 & 6.2 \\
-3.3 & 2.4^* & -3.3 & 2.1^* & +5.0 & 5.0 & +3.3 & 5.5 & +1.2 & 4.8 \\
+36.1 & 20.3^* & +39.1 & 21.8^* & +13.4 & 21.8 & +3.0 & 18.5 & -0.9 & 4.9 \\
+13.8 & 9.9^* & +15.3 & 9.9^* & -7.9 & 11.9 & -1.0 & 8.4 & +0 & 3.5 \\
+10.2 & 3.9^* & +10.8 & 4.1^* & +3.5 & 23.3^* & +0.5 & 0.8 & -0.5 & 0.5 \\
-23.0 & 4.8^* & -24.6 & 4.8^* & -11.6 & 1.9^* & -5.9 & 3.1 & -2.4 & 2.4 \\
-9.2 & 3.4^* & -9.2 & 3.4^* & -3.9 & 2.4^* & -1.0 & 1.0 & +1.4 & 3.4 \\
\end{array}
\]

The drugs were dissolved in distilled water. The dose of each catecholamine refers to the base. The dose per brain was 2.0 \( \mu \text{g} \) per minute of epinephrine and norepinephrine, and 0.2 \( \mu \text{g} \) per minute of isoprenaline during ten minutes. The drugs were infused intra-arterially by an infusor (Braun, Melsungen) into the anastomosis between the donor and the brain so that 30 seconds were needed to reach the brain. By this, a complete mixture with the arterial blood was achieved. For the calculation of the dosages, the blood from the arterial bleedings was taken into account. In any case, the volume of application was 0.2 ml per minute. Control infusions of 0.2 ml per minute in distilled water showed no effect. In each experiment two to three infusions were made. The order of administration of the three drugs was randomized. When CBF and perfusion pressure had returned to baseline, the next perfusion was performed. Tachyphylaxis could not be observed.

The pressure-flow relationship in each brain was investigated 30 minutes after application of the drugs. Based on the calculated pressure-resistance diagram, the indirect effects of catecholamines on CVR caused by autoregulatory influences were eliminated. In addition, in three experiments, the reactivity of the cerebral vessels to increased arterial \( P_{\text{CO}_2} \) was determined. The results, which are represented as mean differences from control, were statistically compared by means of the \( t \)-test of paired data.

**Results**

During the period of the experiments the mean control values and SD of CBF were 40.2 ± 3.4 ml \( \times \) 100 g \( ^{-1} \) \( \times \) min \( ^{-1} \), of CVR were 2.01 ± 0.15 mm Hg \( \times \) 100 g \( ^{-1} \) \( \times \) min \( ^{-1} \), of oxygen consumption were 2.90 ± 0.20 ml \( \times \) 100 g \( ^{-1} \) \( \times \) min \( ^{-1} \), of pressure in the circle of Willis were 80 ± 2 mm Hg, of mean arterial blood pressure of the donor were 111 ± 18 mm Hg, and of hematocrit were 38 ± 5%. During an arterial \( P_{\text{CO}_2} \) level of about 80 mm Hg, CBF was found to be increased at a perfusion pressure of 75 mm Hg by 104 ± 15%. As it is demonstrated in figure 1, the pronounced ability of the cerebral vessels to autoregulate was maintained. The time course of autoregulation was found to last up to three minutes. However, ten seconds after the induced pressure changes, 74% of the autoregulatory changes of vascular resistance were performed. The ECoG of the isolated perfused brains did not show pathologically changed patterns up to four hours of perfusion. As is shown by these data, the function of the brain and the reactivity of the cerebral vessels, so far as detectable with the measured parameters, are intact in spite of the long-lasting operative procedure.

During infusion of norepinephrine (fig. 2, table 1), CBF was maximally decreased (\( P < 0.02 \)) in the

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**FIGURE 1**

Pressure-flow and pressure-resistance diagram (steady-state values) of six isolated perfused brains.
TABLE 2
Changes of Pressure Differences of the Extracerebral Arteries Leading Blood to the Brain in Our Preparation and Mean Arterial Blood Pressure of the Donor During I.A. Infusion of Norepinephrine (2.0 μg/min), Epinephrine (2.0 μg/min) and Isoprenaline (0.2 μg/min)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Time of Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
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<tr>
<td>Norepinephrine</td>
<td>+7.6 ± 3.0*</td>
</tr>
<tr>
<td>MABP</td>
<td>118.6</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>+12.3 ± 3.1*</td>
</tr>
<tr>
<td>MABP</td>
<td>116.8</td>
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<tr>
<td>Isoprenaline</td>
<td>0 ± 2.3</td>
</tr>
<tr>
<td>MABP</td>
<td>108.6</td>
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</table>

P = pressure difference of the extracerebral arteries (mm Hg); MABP = mean arterial blood pressure (mm Hg). Values listed are means ± standard deviation.

*P < 0.05.

first minute of infusion and persisted on the level reached (P > 0.24) up to the end of infusion. The perfusion pressure in the circle of Willis increased correspondingly, showing, however, an additional increase (P < 0.05) between the second and tenth minute of infusion.

The maximal decrease of CBF (P < 0.01) during infusion of epinephrine (fig. 3, table 1) was observed in the second minute of infusion. As during norepinephrine infusion, the decrease of CBF remained constant (P > 0.05) between the second and tenth minute of infusion. After the end of infusion, CBF increased before returning to control value. This increase of CBF did reach the level of statistical significance, if the maximal increase of CBF after the end of infusion was compared with the control value in each experiment. Compared with norepinephrine infusion, the increase of perfusion pressure in the circle of Willis was more pronounced, if one takes into account the smaller flow changes during epinephrine infusion.

During infusion of isoprenaline (fig. 4, table 1), CBF was maximally increased (P < 0.01) in the second minute of infusion. The increase of CBF did not change (P > 0.05) up to the end of infusion. The perfusion pressure in the circle of Willis decreased correspondingly.

The changes of CVR during infusion of catecholamines (calculated from CBF and the perfusion pressure in the circle of Willis) are represented in table 1. As the discrepancies between flow changes and perfusion pressure show (figs. 2 to 4), the pressure changes in the circle of Willis must be influenced by secondary factors: (1) the pressure changes per se lead to autoregulatory reactions tending to compensate the effects of pressure changes on CBF; and (2) the changes of perfusion pressure in the circle of Willis are influenced by changes of the pressure difference of the extracerebral arteries leading blood to the circle of Willis in our preparation (table 2), by changes of the mean arterial blood pressure of the donor (table 2), and by changes of the technically unavoidable small arterial bleedings during catecholamine infusion. Preliminary measurements of these arterial bleedings showed a decrease of 30% to 50% during epinephrine and norepinephrine infusion and an increase of 15% to 20% during isoprenaline infusion.

For these reasons it was necessary to exclude the indirect effects of catecholamines upon CVR in our experiments by comparing the CVR values taken from the pressure-resistance diagram at the cor-
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TABLE 1 (Cont’d)

<table>
<thead>
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<th>14</th>
<th>20 min</th>
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<td>1</td>
<td>+ 5.2 ± 7.3*</td>
<td>+ 14.0 ± 6.5*</td>
<td>+ 5.2 ± 2.1*</td>
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<td>123.6*</td>
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<tr>
<td>108.4</td>
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<td>+ 1.0 ± 2.0</td>
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<td>108.2</td>
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responding pressure and at the corresponding time with the CVR values during catecholamine infusion. The difference was expressed in percent of control values. As shown in table 1, the original CVR values are reduced to about 50% by elimination of the secondary autoregulatory effects.

The venous O₂ saturation was decreased during epinephrine and norepinephrine infusions and increased during isoprenaline infusion, whereas no change in CMRO₂ was found (table 3) during infusion of the different catecholamines.

Discussion

With respect to the effects of circulating catecholamines on cerebral vessels, recent studies have revealed as conflicting results as the earlier investigations. Thus it has been reported by Lluch et al. that an i.a. injection of 5 µg norepinephrine and epinephrine in the goat led to a decrease of 55% in CBF, and of 1 µg isoproterenol to an increase of 75%; on the other hand, Olesen demonstrated that an i.a. infusion of 2 µg per minute of epinephrine and norepinephrine has no significant effect at all on CBF in man. Our earlier studies as well as the present investigations provide evidence that a weak alpha-
TABLE 3
Changes of Venous O₂ Saturation and O₂ Consumption During I.A. Infusion of Norepinephrine (2.0 μg/min), Epinephrine (2.6 μg/min), and Isoprenaline (0.2 μg/min)

<table>
<thead>
<tr>
<th>Drug</th>
<th>v.O₂ sat.</th>
<th>ΔCMRO₂</th>
<th>Time of Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>-2.4 ± 1.2</td>
<td>-2.5 ± 1.3</td>
<td>-2.4 ± 1.3</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>-0.10 ± 0.19</td>
<td>-0.13 ± 0.19</td>
<td>-0.14 ± 0.20</td>
</tr>
<tr>
<td>Isoprenaline</td>
<td>-0.04 ± 0.10</td>
<td>-0.05 ± 0.14</td>
<td>-0.03 ± 0.15</td>
</tr>
<tr>
<td>v.O₂ sat.</td>
<td>+ 1.8 ± 0.9</td>
<td>+ 2.2 ± 1.1</td>
<td>+ 2.5 ± 1.1</td>
</tr>
<tr>
<td>ΔCMRO₂</td>
<td>-0.01 ± 0.11</td>
<td>+ 0.03 ± 0.14</td>
<td>+ 0.03 ± 0.13</td>
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</tbody>
</table>

v.O₂ sat. = changes of venous O₂ saturation (%); ΔCMRO₂ = changes of cerebral O₂ consumption (ml · 100 g⁻¹ · min⁻¹)

Values listed are means ± standard deviation.

*P > 0.05.

Norepinephrine and beta-adrenergic activity is detectable in the cerebral circulation of the dog. This finding is in accordance with the reports of other authors. Furthermore, the present investigations reveal that during infusion of catecholamines the decrease of CBF during epinephrine and norepinephrine infusion and the increase of CBF during isoprenaline infusion persist on the same level after having reached a steady state in the first or second minute of infusion. This observation indicates that no pronounced vascular adjustments as observed in other organs occur in the cerebral circulation during catecholamine infusion.

First of all methodical reasons, which might be responsible for the lack of vascular adjustments during catecholamine infusion in our experiments, must be excluded. Since the drugs have been infused with constant speed, the drug concentration in the arterial blood perfusing the brain has changed depending on CBF changes. As has been calculated, however, from the dose response curves obtained in our earlier investigations, the changes in drug concentration caused by changes of CBF can be neglected. Furthermore, preceding experiments have shown that infusion of 2.0 μg per minute of epinephrine and 0.2 μg per minute of isoprenaline into the venous system of the extracorporeal circulation for ten minutes does not show any effect on CBF, whereas during 2.0 μg per minute of norepinephrine infusion in the eighth minute of infusion, a very small effect on CBF and CVR has been observed (tables 1 and 2). At this time, however, it is improbable that vascular adjustments begin to occur.

Another methodical reason for the apparent lack of vascular adjustments may be an impairment of autoregulation in our preparation, since it has been shown by Folkow et al. and Richardson et al. that vascular adjustments can be correlated to a certain extent with the degree of autoregulatory reactions. That the surgical trauma could be responsible for the lack of autoregulation in the isolated perfused brain has been suggested by the findings of Sagawa et al.

In contrast, our findings (fig. 1), as well as those of White, clearly show that autoregulation is maintained in the isolated perfused brain independent of sympathetic or other peripheral influences. Concerning the range of autoregulation in our investigations, it must be noted that in contrast to other investigations not the mean arterial blood pressure but the pressure in the circle of Willis has been measured. According to the findings of Kanzow et al., a pressure drop of 20% can be supposed between the common carotid artery and the branches of the circle of Willis; thus, the upper limit for complete autoregulation related to mean arterial blood pressure would be about 140 mm Hg. This is in accordance with the findings of other authors. Based on our earlier findings and those of Häggedal et al., it can be assumed, furthermore, that autoregulation is maintained even during catecholamine infusion. This assumption is supported by the discrepancies of pressure and CBF (figs. 2 to 4), which indicate that autoregulatory reactions must have occurred.

Various factors as redistribution of flow, "autoregulatory" reactions on a metabolic basis, beta-adrenergic receptors or autonomic dilatory reactions of vascular smooth muscle have been considered to be responsible for vascular adjustments during catecholamine infusion or sympathetic stimulation. In the brain, "autoregulatory" adjustments on the metabolic basis during norepinephrine infusion and sympathetic stimulation are supposed by Harper. Recent investigations of Nelson et al. and Falck et al. have shown a rich adrenergic nerve supply of the intracranial extracerebral arteries and only a scanty sympathetic innervation of the intraparenchymal arteries and arterioles. Thus, Harper has assumed a dual sympathetic and metabolic control system of the cerebral circulation. This assumption has been supported by his findings that during moderate hypotension and hypercapnia, which lead to an impairment of autoregulation, an i.a. infusion of norepinephrine has caused a significant decrease of CBF, whereas in normotensive and normocapnic...
EFFECTS OF CATECHOLAMINE INFUSIONS

TABLE 3 (Cont'd)

<table>
<thead>
<tr>
<th></th>
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animals no effect of norepinephrine on CBF has been observed.

Since the findings of Harper indicate that vascular adjustments during norepinephrine infusion can occur in the cerebral circulation, the question arises whether the vascular adjustments are of such a short duration that they have taken place before steady state values of CBF in the present investigations have been reached. To investigate this possibility the effect of catecholamines during hypercapnia has been tested in experiments which will be published elsewhere. The effect of catecholamines under these conditions of impaired autoregulation, however, has not been augmented but has been decreased, probably due to the lowered arterial pH. This is in contrast to the findings of Harper and James et al. The latter author has found a striking constrictory effect on the cerebral vessels during sympathetic stimulation when arterial Pco2 was elevated. Since the CO2 reactivity of the cerebral vessels in our investigations corresponds with that reported by Reivich, a normal CO2 reactivity of the cerebral vessels can be assumed. Therefore, on the basis of the concept of a dual sympathetic and metabolic control system, the occurrence of vascular adjustments during catecholamine infusion cannot be confirmed in our investigations.

Provided a direct or indirect effect of catecholamines on cerebral metabolism can be excluded, cerebral O2 consumption, in addition, could give a hint for the occurrence of vascular adjustments. In the brain the influence of catecholamines on cerebral metabolism is restricted for the following reasons: a direct significant effect of catecholamines on cerebral metabolism seems improbable because of the blood-brain barrier to catecholamines. Direct central effects, which could be caused by the lack of the blood-brain barrier in the hypothalamic area and which could lead to changes in cerebral metabolism by changes in cerebral activity, have been observed only during special experimental conditions without anesthesia. Indirect central effects leading to a change in the activity of the reticular system have been shown to be related to the increase of baroreceptor activity during administration of catecholamines. Since, in our investigations, anesthesia was used and peripheral receptors were eliminated by isolation of the brain, direct or indirect effects of catecholamines can be excluded. Actually, the lack of an increase in cerebral O2 consumption in the present investigations might support this assumption.

According to the different experimental conditions influencing the effects of catecholamines on the brain, the findings available in the literature differ partially. King et al. have shown an increase in cerebral O2 consumption and CBF during epinephrine infusion in the conscious man, whereas Fazekas et al., Sensenbach et al. and Gottstein have not found any effect of epinephrine on cerebral metabolism. No change in cerebral O2 consumption has been observed during norepinephrine infusion. Recently, however, Laubie et al. and Xanalatos et al. have shown different methods an increase in cerebral O2 consumption during isoprenaline infusion in the anesthetized dog. We assume that the findings of these authors could be caused by the influence of peripheral systems on the brain, as mentioned above, which are excluded in our preparation.

Furthermore, it must be noted that the changes in venous O2 saturation (table 3) could be influenced by contamination of venous blood drained from the dura and the neurocranium in our preparation. On the basis of preceding experiments, however, it is felt that these possible influences are negligible. Therefore, the changes in venous O2 saturation are supported to be predominantly due to the changes of CBF during unchanged metabolic demand of the cerebral tissue. Based on this assumption, the decrease of venous O2 saturation during epinephrine and norepinephrine infusions could be regarded as compensatory mechanism for the decrease of CBF probably due to dilatation of the precapillary arterioles. Further investigations, however, are necessary to support this assumption.

On the basis of our findings, it does not seem reasonable to assume that pronounced vascular ad-
justments caused by the metabolic need of the tissue occur in the cerebral circulation during catecholamine infusion.

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References

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