Cerebral Blood Flow Regulation: Vascular Resistance Adjustments in the Circle of Willis

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SUMMARY Continuous measurements of systemic blood pressure (BP), cerebral perfusion pressure and CBF were accomplished in the cat during transient hypertension, hypercapnia and bilateral carotid artery occlusion. From these measurements resistance values in the circle of Willis and in the cerebral arteries distal to the circle were calculated. The results indicate that the arteries of the circle of Willis and the arteries distal to the circle of Willis dilate and contract independently.

Ric = \( \frac{CPP}{CBF \text{ caudate}} \)

Rec = \( \frac{BP \text{ systemic} - CPP}{CBF \text{ caudate} + \text{ext. carotid flow}} \)

CBF measurements by the thermal diffusion method are affected by heat exchange between brain and environment as well as between brain and blood. When temperature gradients are allowed to develop independent of blood flow, an error in flow calculation is introduced. The magnitude of this potential error has been measured in vitro. Each experimental preparation is tested for the source of error.

The response time of the heated probe is almost immediate when flow increases, but when flow decreases tissue heat loss lags, with a maximum delay at zero flow. A calibration slope at zero flow is obtained at termination of the experiment. The comparison of the negative flow changes with the slope at zero flow provides a quantitative estimate of flow change during periods of reduced flow. Formulas for slope correction are as follows:

1. Flow increase \( F(t) = F(t) - F(t) \frac{dF(t)}{dt} \)

2. Flow decrease \( F(t) = F(t) \frac{K}{\max df \text{ at zero flow} dt} \)

When a zero flow level is established, increases in flow can be calculated as a function of increases above average flow.

Procedure

Under light nembutal anesthesia (30 mg per kilogram), a cannula was threaded into the inferior vena cava for instillation.

*The calculation does not include external carotid flow since it represents a small proportion of total common carotid flow.

†Thermocouple probes were placed in 10% gelatin, heated to 40°C and allowed to cool at room temperature. The temperature difference between thermal junctions was measured without heating current; then the power required to maintain \( \Delta T \) at 1.5°C and 2.5°C was determined. The differences between the power required to maintain the selected \( \Delta T \) when both thermal junctions were equal and at unequal environmental temperatures were plotted as a percentage of the total current used to maintain the selected \( \Delta T \) (fig. 1).

During in vivo application, the experimental preparation is enclosed in a plastic hood to maintain stable temperature relationships. This can be verified by applying the experimental condition with probes in place, unheated. If during induced blood flow change the thermocouple indicates no gradient between junctions, the experiment is continued. Subsequently, absolute brain temperature is constantly monitored at the reference thermal junction as an index of ambient brain temperature. When this precaution is maintained, the heating current parallels blood flow. Results under these conditions show complete reproducibility from one test animal to another.

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tion of medication. Systemic arterial pressure was monitored by a catheter threaded into the descending aorta from the femoral artery and connected to a Grass resistance bridge pressure transducer. A tracheostomy was then performed to measure expired CO₂ and respiratory rate by a Beckman gas analyzer. Each common carotid artery was exposed and dissected free by blunt dissection. A small catheter then was threaded into a lingual artery, or distally in the carotid artery. A pneumatic occluding cuff was placed around both common carotid arteries or the remaining patent artery. The head was placed in a stereotaxic frame for introduction stereotactically of the thermal diffusion probes into the caudate nuclei bilaterally with reference probes in the ipsilateral thalamus. The active thermal diffusion probe had a platinum electrode attached to measure tissue oxygen content by polarographic methods. An additional thermocouple with ice water reference was attached to the thalamus reference electrode to monitor absolute brain temperature. The EEG was monitored from the electrode shafts in bipolar montage. The heart rate was measured from the pulses of arterial pressure by a cardiotachometer.

All parameters were recorded on a Grass Model 7B oscillograph with simultaneous recording on a Tandberg four-channel FM tape recorder through a time division multiplexer. The analogue data were digitized at 255 points in five-minute epochs and calculations and graphing of resistance values were done by a digital computer.

Each animal was killed at the end of the experiment to obtain zero and calibration values for the thermal diffusion probes. The brain was fixed in situ, with intra-arterial formalin for histological verification of probe location.

The parameters measured in each animal included: bilateral reference probe absolute temperature, bilateral tissue oxygen saturation, cardiotachometer and distal carotid wedge pressure, or lingual artery pressure as a measure of intracranial-extracerebral supply pressure. These measurements were in addition to measurements of bilateral local CBF, bilateral EEGs, expired CO₂, and BP.

Results

RESPONSE TO CO₂

The increase in CBF during CO₂ inhalation occurs as a result of dilation of cerebral arteries, i.e., there is a marked reduction of Ric while Rec remains stable (fig. 2).

RESPONSES TO DRUG-INDUCED HYPERTENSION

Each of three agents (epinephrine, norepinephrine and angiotensin) were given intravenously in a single bolus to produce transient 50% increase in systemic BP. The patterns of pressor response to each were not alike. Maximum response to angiotensin occurred more gradually than the response to either epinephrine or norepinephrine, and was persistent for four to five minutes. BP elevation after a single injection of norepinephrine dissipated in one to two minutes and gradually reached control level. BP elevation after a
Infusion of epinephrine. A brief period of hypertension was followed by relative hypotension. Brain resistance increased with systemic hypertension. Collateral vascular resistance rise peaked when brain resistance was decreasing.

BP rise induced by norepinephrine infusion persisted for one minute and was not followed by hypotensive interval. Brain resistance paralleled systemic BP change. Collateral resistance remained unchanged.

A marked increase in Ric occurred almost simultaneously with the elevation of systemic BP and CPP following angiotensin infusion. This limited the increase in CBF. Rec remained unchanged (fig. 3). BP and CPP were maintained at maximum for approximately 45 seconds, then there was a gradual return to baseline during the next three minutes. The small increase in CBF caudate began to decline as peak BP rise receded. During the three-minute interval when systemic and perfusion pressures were greater than control levels, CBF caudate fell below control value as a result of residual increase in Ric.

There was minimal change in CBF after a single injection of epinephrine (fig. 4). The rise in systemic BP caused an immediate and a marked increase in Ric; it peaked in eight to ten seconds. There was also a slight rise in Rec with a maximum increase at 15 seconds. This peak of Rec increment occurred after Ric had begun to fall and had dropped below control levels. Both Ric and Rec then remained below control levels for two minutes. During this interval when BP and CPP remained below control levels, CBF was stable, since the reduced level of resistance offset the effect of relative hypotension.

Pressure increase after single injection of norepinephrine resulted in prompt increase in Ric. CBF rose slightly during the hypertensive period. Increased Ric began to dissipate in less than 30 seconds and resistance reached control levels in one minute but did not fall below control levels as it did after epinephrine. Rec was not affected by norepinephrine (fig. 5).

The initial regulatory responses to induced transient hypertension were simultaneous with a pressure increase induced by all three agents. Vasocostriction of brain arteries persisted following peak BP rise, with angiotensin for three minutes, with norepinephrine for 50 to 60 seconds, and with epinephrine for only 15 seconds. The changes in brain resistance (Ric) paralleled each of the systemic BP responses. The increase in Ric was a nonspecific response to hypertension. This had been demonstrated in the cat and monkey and in human studies. The additional vasodilator effect of epinephrine which occurs in the brain may be explained by either its metabolic action or directly as a result of β-receptor response.

Pharmacological effects on resistance measurements are summarized in table 1.

The vasodilating effect of CO₂ inhalation was reversed during epinephrine-induced or norepinephrine-induced hypertension. When epinephrine or norepinephrine was given during a period of hypercapnic vasodilation, the Ric and Rec responses remained as in a normocapnic state (figs. 6 and 7).

**Response to Bilateral Carotid Occlusion**

Bilateral common carotid artery occlusion initiated a series of changes in CBF, systemic BP, brain perfusion pressure and vascular resistance.

The immediate effects were an abrupt and marked increase in vascular resistance in the perfusing arteries (Rec), an immediate reduction in CBF caudate, usually in excess of 30%, and a decrease concurrently with flow reduction in brain vascular resistance (Ric). At the same time systemic BP rose. As these changes occurred, there was vasodilation of the circle of Willis and the CBF caudate began to be restored within ten seconds, systemic BP remained stable, and resistance in perfusing vessels (Rec) continued to decline. The increase in CBF caudate was accomplished by this lowered resistance in Rec. After 30 to 40 seconds a small increase in CBF began to decline as peak BP rise receded.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Immediate response (≤20 seconds)</th>
<th>Late response (&gt;20 seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin</td>
<td>Ric +</td>
<td>Ric +</td>
</tr>
<tr>
<td></td>
<td>Rec 0</td>
<td>Rec 0</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Ric +</td>
<td>Ric -</td>
</tr>
<tr>
<td></td>
<td>Rec +</td>
<td>Rec 0</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Ric +</td>
<td>Ric +</td>
</tr>
<tr>
<td></td>
<td>Rec 0</td>
<td>Rec 0</td>
</tr>
</tbody>
</table>

+ = increase, − = decrease, and 0 = no change.
steady state was maintained; CBF caudate sometimes remained slightly below the control level, systemic BP remained elevated, Ric increased slightly or remained stable, and Rec decreased slowly. Upon release of occlusion, systemic BP promptly fell back to the control level, and collateral (CPP) artery pressure was restored. Vascular resistance in perfusing arteries (Rec) reached the pre-occlusion level in ten seconds. However, brain vascular resistance (Ric) rose slowly and, until it reached control level, CBF caudate sometimes exceeded pre-occlusion levels. A gradual return to baseline values occurred within one to two minutes of release of occlusion (fig. 8).

The immediate response to bilateral carotid occlusion was the opening of collateral channels including the circle of Willis. This partially restored CBF. Additional increases in CBF occurred as Rec was further reduced in spite of a slight increase in Ric.

Conclusion

The arteries in the brain contract and dilate independently of the arteries of the circle of Willis and its supply channels.

References

Cerebral blood flow regulation: vascular resistance adjustments in the circle of Willis.
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