Autoregulation and Hyperemia of Cerebral Blood Flow as Evaluated by Thermal Diffusion

BY L. PHILIP CARTER, M.D.,
AND JAMES R. ATKINSON, M.D.

Abstract:
A thermal diffusion flow probe gave a quantitative dynamic recording of cerebral blood flow (CBF) during bleeding and transfusion in experimental animals. Autoregulation was readily demonstrated in nine of 12 animals and was found only with gradual hypotension. After autoregulation was lost, no increase in CBF could be obtained with carbon dioxide inhalation. Reactive hyperemia was demonstrated consistently following compromised CBF and, again, no increase in CBF with hypercarbia could be obtained until the hyperemia had subsided. Once hyperemia ceased, autoregulation could be demonstrated again in the same animal.

Introduction

Autoregulation, the mechanism which maintains a relatively constant cerebral blood flow (CBF) during variations in cerebral perfusion pressure, was first demonstrated by Fog in 1934. Using the cranial window technique demonstrated by Forbes and Wolff in 1928, he was able to observe dilatation during hypotension and constriction during hypertension of the pial vessels. In 1959, Lassen compiled data to demonstrate constant CBF when blood pressure ranged from 175 to 50 mm Hg and popularized the idea of cerebral autoregulation. Further evaluation of this phenomenon has been primarily with radioactive diffusion washout techniques.

Hyperemia or luxury perfusion is a supranormal flow and has been demonstrated by Haggendal et al. to follow reduced perfusion pressure induced by changes in cerebrospinal fluid pressure. Ingvar has pointed out that the same pattern follows all forms of cerebral hypoxia.

Since vasomotor phenomena are altered by many common neurological diseases such as neoplasms, ischemia, and subarachnoid hemorrhage, further evaluation of autoregulation and hyperemia may lead to better understanding of the pathophysiology of these neurological diseases.

Four theories of the autoregulation mechanism are commonly considered:

1. The myogenic or Bayliss effect proposes that the precapillary arteriole wall muscle responds to changes in pressure and therefore is responsible for altering flow.
2. The tissue pressure theory states that egress of fluid from capillaries is dependent upon perfusion pressure. This egress alters the tissue pressure which affects the thin-walled veins and capillaries and in turn their vascular resistance.
3. The metabolic theory (Berne 1964) suggests that flow changes with pressure initially, and that the altered tissue metabolic conditions are then subsequently responsible for the changes in vascular resistance.
4. The neurogenic theory proposes that nerve fibers terminating in cerebral vessels control the vascular resistance and subsequent flow through these vessels.

The extent each of these mechanisms contributes to overall control of cerebral autoregulation remains unclear. Harper and Haggendal have proposed that the primary control is myogenic because of supposed flow stability during pressure changes, but that present methods of measuring local flow have been unable to clarify whether the flow is indeed constant with pressure changes.

The Peltier thermal diffusion flow probe can give an accurate quantitative dynamic assessment of local cortical blood flow (Carter and Atkinson, 1973). It has advantages over the radioactive gas diffusion techniques in that a continuous record can be obtained and CBF does not have to be constant. In addition, at low perfusion rates the radioactive washout technique may be unreliable since a smaller amount of radioactive gas is carried to the tissue initially. On the other hand, the thermal diffusion probe applies its diffusible tracer (i.e., the thermal
gradient) directly to the cortex and is dependent upon flow only for dissipation of the tracer.

It was the purpose of this study to evaluate the dynamics of CBF with the Peltier thermal diffusion flow probe.

**Methods**

Twelve mongrel cats were anesthetized with intraperitoneal pentobarbital (30 mg per kilogram). Tracheostomy, bilateral femoral artery, and unilateral femoral vein cut downs were performed. The animals were placed in a head holder, connected to a positive pressure respirator, and paralyzed with gallamine triethiodide (5 mg per kilogram). Small additional doses of gallamine were used to keep the animal flaccid. A small left parietal craniectomy was carried out and a Peltier thermal diffusion flow probe was placed on the cortex. The cortex and probe were covered. During surgery the animals received 50 cc of 5% dextrose and water plus 9 mEq NaHCO₃ intravenously to correct any slight ketosis since the animals were fasting the night before surgery.

The Peltier thermal diffusion flow probe was fully described by Brawley in 1968 and calibrated by us. It has two contact plates with the cortex, one heated and one cooled. The temperature difference between these two plates is recorded as voltage by attached thermocouples connected back to back. Peltier probe flow has been found linearly related to CBF as measured by 133Xe diffusion washout.

Respirations were monitored on a Statham strain gauge. Arterial blood gases were drawn after the animal had been on the respirator for 30 minutes and if necessary the respirator was adjusted and repeat blood gases obtained.

Blood pressure (BP) was monitored from the cannula in one femoral artery via a Statham transducer. Mean blood pressure (BP) was obtained by electrical integration. CBF, respirations, BP, BP, and time all were recorded on a Grass Model 7 polygraph.

Prior to bleeding, the animals were heparinized. When the experimental specimen appeared stable, the remaining femoral artery cannula was connected to a Holter pump and slow arterial bleeding was carried out. We had previously noted that rapid reduction in BP (less than one minute) produced by bleeding consistently reduced CBF concomitantly with BP (fig. 1), as previously reported by Noell and Schneider. When CBF showed a significant reduction, the animal was transfused with Ringer’s solution and autogenous blood at 37°C over a short time period (five to ten minutes). The specimen was allowed to stabilize, and the procedure then was repeated.

Carbon dioxide reactivity of the cerebral vessels was tested by connecting the respirator intake to a 10% CO₂ and 90% O₂ gas mixture (fig. 2). This was carried out at various stages of the hypotensive-hyperemic cycle.

At the end of each experiment a bolus of intravenous potassium chloride was used to create cardiac arrest. The dead brain value for the thermal diffusion probe then was obtained.

The experimental data were analyzed with the aid of the PDP 12 computer.

**Results**

Autoregulation was demonstrated 14 times in nine of 12 animals (fig. 3), and up to four times in the same animal. An example of autoregulation is seen in figure 4. There was no significant difference in pH, PaO₂, O₂ saturation, initial CBF, and initial BP between those animals that did and those that did not autoregulate (fig. 5). Of the three animals that did not autoregulate, two were felt possibly to be in a hyperemic phase immediately prior to bleeding (note the increased CBF in those that did not autoregulate), and no apparent cause was found for the third.

In the animals that did autoregulate the BP was dropped slowly over five to 167 minutes and the BP, when the CBF showed a 25% reduction, was 39.7 ± 8.7 mm Hg.*

*Standard deviations.
AUTOREGULATION AND HYPEREMIA

All animals, including the animals that did not autoregulate, demonstrated hyperemia upon transfusion which lasted for ten to 24 minutes. Upon transfusion when the peak BP was reached the CBF was 21.69 ± 9.85 cc/100 gm per minute* greater than for the same blood pressure prior to hypotension.

Carbon dioxide reactivity was present in all seven animals tested prior to bleeding, including two that did not autoregulate. Of seven attempts during hypotensive loss of autoregulation and hyperemia, no carbon dioxide reactivity could be demonstrated (figs. 6 and 7). Carbon dioxide reactivity could be demonstrated but was attenuated in all four animals tested following recovery from hyperemia.

Autoregulation was easily demonstrated with gradual but not with abrupt hypotension. Hyperemia consistently followed reduced tissue perfusion and

---

FIGURE 2
Normal response to 10% CO₂ inhalation for one minute. Event markers delineate the time the animal was breathing CO₂. Note: No change in respirations. Paper speed was increased after probe check.

FIGURE 3
Plot of BP versus CBF in animals that did demonstrate autoregulation. Note: The CBF was maintained until BP fell between 35 and 60 mm Hg.
subsided spontaneously. Increased CBF with carbon dioxide, present before and after hypotension and hyperemia, could not be demonstrated once autoregulation had been lost until hyperemia had subsided, probably an indication of maximal vascular dilatation. Autoregulation could be demonstrated repeatedly in the same animal if hyperemia was allowed to subside before retesting.

**Discussion**

Most data on cerebral autoregulation have been accumulated through the use of radioactive gas diffusion techniques; however, in a changing situation when one cannot presume constant CBF, a thermal diffusion probe such as used in these experiments has the advantage of a continuous dynamic recording. The data we obtained during autoregulation are comparable to those obtained by Lassen,

\[3\] demonstrating preservation of CBF to a BP of 50 mm Hg. Carlyle and Grayson\n
\[11\] demonstrated cerebral autoregulation by thermal diffusion qualitatively in a BP range of 150 to 30 mm Hg.

Rapela and Green\n
\[12\] measured cerebral venous outflow in the dog and demonstrated autoregulation which could be abolished by continuous inhalation of 10% CO\(_2\) in O\(_2\).

When autoregulation was lost, we found an absence of CBF response to CO\(_2\) in agreement with Harper’s data\n
\[1\] but contrary to evidence cited by Ekström-Jodal et al.\n
\[14\] Symon et al.\n
\[15\] by observing

<table>
<thead>
<tr>
<th>pH</th>
<th>pCO(_2)</th>
<th>O(_2) Sat.</th>
<th>CBF</th>
<th>(\overline{BP})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoregulated</td>
<td>7.37 ± 0.08*</td>
<td>31.6 ± 5.9</td>
<td>97.1 ± 2.8</td>
<td>41.3 ± 9.6</td>
</tr>
<tr>
<td>No Autoregulation</td>
<td>7.35 ± 0.08</td>
<td>33.0 ± 4.6</td>
<td>97.5 ± 0.9</td>
<td>53.7 ± 8.5</td>
</tr>
<tr>
<td>Significant Difference</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Standard deviation

**FIGURE 5**

Table showing control values in animals that did and did not autoregulate. No significant differences were found between the two groups.
AUTOREGULATION AND HYPEREMIA

**CO₂ IN HYPOTENSION**

Demonstration of lack of CO₂ reactivity during hypotensive loss of autoregulation. Note: The CBF following transfusion is greatly increased compared to same BP during bleeding.

venous and arterial pulse height ratios, concluded that a reduced response to CO₂ does exist in hyperemia; however, in our experiments, CO₂ unresponsiveness persisted through the hyperemic phase. One might postulate that metabolites have accumulated during the episode of hypotension and that hyperemia represents persistent vasomotor paralysis before these metabolites have been washed from the system by adequate perfusion. The period of hyperemia in these experiments was shorter than that described by Häggendal et al.; however, the time of reduced tissue perfusion also was shorter. Betz and Heuser in 1967 demonstrated that the extracellular hydrogen ion concentration correlates quite well with cortical flow and may represent an important accumulated metabolite.

It appears likely that as perfusion pressure decreases, vascular resistance decreases and maintains constant flow. This appears to be a slow process requiring minutes to occur. Once maximal dilation has occurred, the flow cannot be maintained with further drop in perfusion pressure, and autoregulation is lost. We have been unable to demonstrate further increase in flow with carbon dioxide inhalation once autoregulation has been lost, although those proposing a myogenic mechanism of autoregulation, Ekström-Jodal et al., state this does occur. Furthermore, following elevation of BP by transfusion in the hyperemic phase, we found the vasculature was still unresponsive to carbon dioxide, indicating continued maximal dilatation.

Finding CO₂ reactivity before hypotension and hyperemia after hypotension in animals that did not autoregulate implies that the vascular reactivity was intact, but the sensing mechanism which detects the stimulus (i.e., reduced perfusion pressure) was not functioning efficiently.

The clinical implications of these findings are readily apparent. Abrupt hypotension is more dangerous than gradual hypotension since the autoregulatory system requires a brief time (one to five minutes) to function maximally. Once autoregulation has failed, attempts at increasing flow with CO₂ are unsuccessful. The absolute CBF at any given time is of no value in predicting vasomotor activity since in a relatively hyperemic phase autoregulation and CO₂ reactivity cannot be demonstrated. Finally, once autoregulation has been lost, it can be regained after a period of adequate tissue perfusion.

**CO₂ IN HYPEREMIA**

Demonstration of lack of CO₂ reactivity during hyperemic phase following transfusion.
References

1. Fog M: Om Piaorterierernes Vasomotoriske Reaktioner. Copenhagen, Lerih and Munksgaard, p 183, 1934
Autoregulation and Hyperemia of Cerebral Blood Flow as Evaluated by Thermal Diffusion
L. PHILIP CARTER and JAMES R. ATKINSON

Stroke. 1973;4:917-922
doi: 10.1161/01.STR.4.6.917

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1973 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/4/6/917

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/