Effects of Carbon Dioxide on Cerebral Hemodynamics in Normal Subjects and in Cerebrovascular Disease Studied by Carotid Injection of Radioalbumin

By Cesare Fieschi, M.D., Alessandro Agnoli, M.D., and Elda Galbo, M.D.

Research has provided ample evidence that the cerebral vascular system possesses a marked degree of autonomy and is largely unaffected by changes in the systemic circulation. This autonomy is made possible, first of all, by minimal effect on cerebral vessels of those factors which act on the general circulation, such as the autonomic innervation and, second, by the extreme sensitivity of cerebral vessels to intrinsic regulatory mechanisms which ensure a large margin of compensation for variations in arterial pressure or cardiac output. The stimuli which have proved most effective in eliciting vasoactive responses are: 1) variations in the blood levels of oxygen and, particularly, of carbon dioxide; and 2) changes of perfusion pressure.

The action of CO₂ on cerebral circulation appears to involve an active vasodilatation which reduces the cerebrovascular resistance to blood flow. CO₂ concentrations of 5% to 7% in inspired air produce peripheral vasoconstriction and a slight increase of arterial pressure. As a result of this combined action (cerebral vasodilatation and increase of perfusion pressure), cardiac output is redistributed in favor of the brain. Cerebral blood flow increases by about 54% in normal young subjects during inhalation of 5% CO₂. Cardiac output itself is changed very little, and cerebral oxygen consumption does not show any significant change.

Quantitative data obtained with inert gas methods for measuring cerebral blood flow (CBF) have been reviewed by Kety and other workers from the same laboratory. At a concentration of 2.5% in inspired air, the action of CO₂ is nil, while at a concentration of 3.5% a significant effect is noted. At 7% the response is far greater than at 5%. The effect of higher concentrations of CO₂ has not been investigated quantitatively. The increase of blood flow also varies among the different structures of the central nervous system. Freygang and Sokoloff report that in the cat the increase is higher in the gray than in the white matter (67% and 54% respectively) with 5% CO₂; regional differences within gray and white matter may also be relevant.

Response of cerebral circulation to CO₂ in pathological conditions has been studied in great detail. Most of the evidence suggests that inhalation of 5% CO₂ can dilate the cerebral vessels and can increase cerebral blood flow even in the presence of vascular disease. Novack et al. have, for example, recorded a normal hemodynamic response to 5% CO₂ in essential hypertension and in hypertension associated with cerebral arteriosclerosis. In normotensive arteriosclerotic patients, on the other hand, they were unable to provoke any significant variation in blood flow or resistance. These findings are not confirmed by Pazekas et al. who report a clear

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response to 5% CO₂ both in normotensive and hypertensive patients with cerebral arteriosclerosis and/or focal cerebrovascular disease, the response being less marked in hypertensive patients.

Schieve and Wilson in a similar study calculated the variations of CBF from the reduction of arteriovenous oxygen difference after four minutes of CO₂ inhalation, assuming the cerebral oxygen consumption constant. They found that in normal subjects the cerebral hemodynamic response to 5% CO₂ decreased slightly with age; this effect was less marked with 7% CO₂. In patients with cerebrovascular diseases the absolute increase of CBF was considerably lower than in normal subjects of the same age group; consequently the authors proposed this test to differentiate senile dementia from that caused by arteriosclerosis. This last point, however, has been disputed.

Concluding his review of the literature, Sokoloff wrote: "even though there may be sufficient disease in the cerebral vessels to raise cerebrovascular resistance and reduce blood flow markedly, there still remains a considerable degree of labile tone which can be reduced by carbon dioxide. There is evidence that the degree of reactivity is somewhat reduced, particularly when the disease is organic and associated with old age, but the change in reactivity does not appear to be sufficiently pronounced or uniform to form the basis of a reliable test for organic cerebrovascular diseases."

The inert gas methods employed in these researches permit the measurement of the steady state value for CBF during the 10-minute test period. The test is started after 5 to 20 minutes of equilibration with the hypercapnic mixture, and only the maximum effect of any given concentration of CO₂ is measured. It is therefore impossible with these methods to determine the early time course of the response. The only information on the characteristics of the early portion of the response has been obtained in two cases studied with Kr by Lewis et al. They have shown that the increase of CBF in response to 7% CO₂ inhalation sets in at a fairly constant rate during the first four minutes.

The object of the present investigation of which the preliminary results have already been communicated, is to evaluate, by means of carotid radioisotope rheoencephalography, the degree and time pattern of the cerebral hemodynamic response to the inhalation of 5% CO₂ in aged subjects without vascular diseases, and in patients with cerebral vascular lesions, the degree of hypercapnia being measured by the analysis of arterial blood samples taken during the test.

**Methods**

We have studied 37 subjects with ages of 50 or more years. The subjects of the control group (9 men and 2 women, mean age 58 years) were in the hospital for minor organic diseases. Only those patients were selected who had: 1) no neurologic or psychiatric evidence of brain disease; 2) no clinical evidence of cardiovascular or respiratory diseases; 3) blood pressure, standard blood and urine laboratory tests, plain X-rays of chest and skull, EEG and ECG within normal limits.

The patients of the cerebrovascular disease group (13 men and 13 women, mean age 62 years) had each suffered a major stroke, clinically diagnosed as infarct, from a minimum of one month to a maximum of two years, preceding the study. The study was carried out after the termination of the acute phase of the illness, and no alterations in the state of consciousness were present at the time. No patients showed signs of respiratory insufficiency and/or pulmonary disease. Several had fundoscopic, electrocardiographic and other signs of cardiovascular diseases; the average blood pressure in the group was 171/97 mm Hg.

Unilateral or bilateral carotid angiography was performed in nineteen patients, showing various degrees of localized or diffuse cerebral atherosclerosis and, in two cases, an occlusion of the internal carotid. In the remaining seven patients this diagnosis appeared unlikely on the basis of the EEG recorded during digital carotid compression, and of the isotopic curves.

The subjects were not fasted and for the procedure were placed in the supine position. No specific premedication was employed, but no attempt was made to control other drugs which the patient might have been receiving.

A mixture of 5% CO₂ and 95% O₂ was administered to the patient through an anaesthetic bag and mask. Before beginning the inhalation, a bilateral study of the carotid circulation was made employing radioisotope rheoencephalography.
Normal radionuclide rheoencephalographic curves (REG). Curves of radioactivity recorded over the ipsilateral parieto-temporal region (upper) and over the ipsilateral mastoid region (lower) after injection of a single bolus of radioalbumin into the common carotid artery. The abscissa represents time in seconds, the ordinate represents deflection in mm. Full scale deflection (100 mm) corresponds to 100,000 counts/min. Arrows show the graphic features whose duration is measured. To the right, the cerebral curve is plotted on semilogarithmic scale.

To evaluate the condition of the cerebral circulation, the following features of the curves were considered (fig. 1): in the mastoid curve: the time of increment in the carotid wave ($T_{inc}$), the interval between the apex of the carotid curve and that of the jugular curve ($C-J$), and the length of the jugular wave ($J$ time); in the cerebral curve: the time of increment ($T_{inc}$), the plateau or time of stasis ($T_{sta}$), the time of decrement ($T_{dec}$), the interval between upstroke and downstroke halfway from the maximum height ($T_{max}$), and the slope "r" of the downstroke.

The downstroke of cerebral curve corresponds to the phase of washout of the cerebral vessels. When plotted on a semilogarithmic scale it shows...
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a linear slope. Only at very low values of activity (about 10% of the maximum) the slope becomes less regular, and the curve tends to flatten out. Let us now assume the cerebral vascular area perfused by the carotid artery as a mixing volume through which the blood flows at a constant rate. The indicator introduced by a single injection into the afferent artery reaches a maximal concentration in the system, followed by a progressive decrease of concentration during the washout phase. Before recirculation ensues, the change in the amount of indicator in the system $(dQ)$ during a time interval of the washout phase $(dt)$ is described by a differential equation:

$$\frac{dQ}{dt} = -F \times c(t)$$  \hspace{1cm} (1)

where $c(t)$ is the concentration of indicator at time $(t)$, and $F$ is the turnover rate (in this case blood flow). Since we are concerned with a radioactive tracer and our measurements are measurements of radioactivity, change in total activity $dx$ can be substituted for $dQ$, and specific activity $a(t)$ for concentration $c(t)$. But the specific activity $a(t) = x(t)/N$, in which $N$ is the volume of the system. Thus equation 1 is changed to:

$$\frac{dx}{dt} = -\frac{F}{N} \times x(t)$$  \hspace{1cm} (2)

where $\frac{F}{N} = R$, the fractional turnover rate of blood in the system. When integrated between the limits of zero time and time $t$, it becomes a monoeponential equation

$$x(t) = x(0) e^{-R t}$$  \hspace{1cm} (3)

in which the logarithm of the activity decreases linearly with time. Equation 3 can be solved for $R$:

$$R = -\frac{\ln x(t)/x(0)}{t}$$  \hspace{1cm} (4)

If we choose a time $T_Y$ during which the activity $x(t)$ is reduced by 50%, it becomes

$$R = -\frac{\ln 0.5}{T_Y} = \frac{0.693}{T_Y}$$

From the linear slope of the cerebral curve plotted on semilogarithmic scale, we measure a factor $r = \frac{0.693}{T_Y}$.

The problem which arises deals with the relationships that exist between the theoretical $R = F/N$, and our experimental "$r."$ At least two sources of error may be found in our method. First, the cerebral vessels are not a true mixing volume; different rates of flow may be present in different areas, and laminar flow can occur. The second source of error derives from limitations of external counting. As in other similar methods, such limitations are due to: 1) presence of tracer in the portion of extracerebral circulation seen by the detectors; 2) effects of scattered radiations; 3) effects of uneven spatial distribution of radioactive tracer within the brain. Here, self absorption, inverse square law and geometrical characteristics of the collimators present complications. From the above statements it follows that the "slope" $r$ differs from the $R$ of the equation $R = F/N$ by some unknown factors, which may differ from patient to patient. Furthermore cerebral blood volume $N$ cannot be assumed to be a constant. With these limitations "$r"$ can be accepted as a nonlinear and approximate index of blood flow in the area studied.

The reliability of this index, empirically tested, proved to be satisfactory. Some of the described limitations probably can be overcome by using a detecting system in which isoefficiency could be obtained, and by direct injection of the tracer into the internal carotid artery.

After beginning the CO$_2$ inhalation, injections of a radioactive bolus were made at regular intervals of 1, 2, 3 or 4, 5, and 6 or 7 minutes through the same needle left in situ. Tests were done on one side only, the choice being arbitrary in the case of the healthy subjects. In patients with history of apoplexy the side chosen corresponded to the hemisphere involved by the disease, with the exception of the two cases of internal carotid thrombosis, in which the examination was made on the opposite side.

In the resting state and at one minute and five

![FIGURE 2](changes in arterial CO$_2$ and O$_2$ content and mean arterial pressure during inhalation of 3% CO$_2$ and 95% O$_2$ in 37 cases. The mean arterial pressure has been calculated by adding one-third of the pulse pressure to the diastolic pressure. The oxygen content at one minute has been measured in five cases only.)
Curves of radioactivity recorded over the ipsilateral parietotemporal region (upper) and over the ipsilateral mastoid region (lower) after the injection of a single dose of radioalbumin into the common carotid artery in a normal subject. From left to right are shown the curves recorded in the resting state, after one minute of 5% CO₂ inhalation, and after five minutes of inhalation. The ordinate represents the deflection in mm, the abscissa represents time in seconds. The numerical values of the "intermediate time," of the "carotid-jugular interval" and of the semilogarithmic slope \( (r = 0.693/T_{1/2}) \) are presented on the curves. Recordings of the pulse rate and of respiration are presented in the two lower tracings, with the numerical values of arterial pressure and arterial CO₂ and O₂ content in volume per cent.

Results

CHANGES IN BLOOD O₂ AND CO₂, PULSE RATE, RESPIRATION RATE, AND ARTERIAL PRESSURE

No noticeable differences were found between the control and patient groups, as previously reported, but some significant individual variation was observed within each group. The mean values after five minutes of inhalation (table 1 and fig. 2) are in agreement with the findings reported in the literature. Pulse rate increased slightly, while systolic and diastolic arterial pressure increased by 17% and 14%. In a few hypertensive patients this increase was appreciably greater, suggesting a heightened vascular reactivity.

Respiration generally became deeper and only slightly more rapid (fig. 3). Arterial O₂ content increased by 1.94 vol % and CO₂ con-

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tent rose by 4.6 vol%. The control CO₂ values (43.5 vol%) suggested the existence of a moderate degree of hypoxia, probably due to emotional hyperpnea. These changes set in sharply in the first minute but continued more gradually in successive periods (fig. 2).

CHANGES IN THE RADIOENCEPHALOGRAPHIC CURVES IN RESPONSE TO CO₂ INHALATION

Under basal conditions the mean values in normal elderly subjects (table 2a) were slightly different from those in normal young subjects. This indicates the change which hemodynamic values undergo with advancing age and which may be related to chronological age per se or, as recently suggested, to minimal degrees of arteriosclerosis. The mean values recorded from patients in the present investigation (table 2a) are considerably altered, which confirms the findings obtained in a larger series. Significant differences from findings in normal elderly subjects were found with regard to several portions of the curves recorded (table 2; columns with headings T stasis, T intermediate, semilog slope, T decrement, C-J interval).

The characteristics of the radioencephalographic curves recorded in normal subjects at times of 1, 2, 3 to 4, 5, and 6 to 7 minutes after inhalation of CO₂ are shown in tables 2b-f and in figures 4 to 7. In the latter only
### Table 3

**Time Course (in Minutes, Mean ± snj of Radioisotope Rhoeencephalogr aphic Curves During Inhalation of 5% CO₂)**

<table>
<thead>
<tr>
<th></th>
<th>Cerebral curve</th>
<th>Mantled curve</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T increment</td>
<td>T steady</td>
</tr>
<tr>
<td><strong>a) Resting state</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1.4 ± 0.73</td>
<td>2.1 ± 0.56</td>
</tr>
<tr>
<td>20 injections</td>
<td>(P &lt; 0.001)</td>
<td>(P &lt; 0.001)</td>
</tr>
<tr>
<td>CV lesions†</td>
<td>1.7 ± 0.28</td>
<td>2.5 ± 1.18</td>
</tr>
<tr>
<td>30 injections</td>
<td>(P &lt; 0.001)</td>
<td>(P &lt; 0.001)</td>
</tr>
<tr>
<td><strong>b) after 1 min inhalation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1.2 ± 0.19</td>
<td>1.2 ± 0.23</td>
</tr>
<tr>
<td>8 injections</td>
<td>(P &lt; 0.001)</td>
<td>(P &lt; 0.001)</td>
</tr>
<tr>
<td>CV lesions</td>
<td>1.4 ± 0.33</td>
<td>1.5 ± 0.68</td>
</tr>
<tr>
<td>19 injections</td>
<td>(P &lt; 0.001)</td>
<td>(P &lt; 0.001)</td>
</tr>
<tr>
<td><strong>c) after 2 min inhalation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1.2 ± 0.29</td>
<td>1.3 ± 0.16</td>
</tr>
<tr>
<td>8 injections</td>
<td>(P &lt; 0.001)</td>
<td>(P &lt; 0.001)</td>
</tr>
<tr>
<td>CV lesions</td>
<td>1.4 ± 0.47</td>
<td>1.5 ± 0.74</td>
</tr>
<tr>
<td>17 injections</td>
<td>(P &lt; 0.001)</td>
<td>(P &lt; 0.001)</td>
</tr>
<tr>
<td><strong>d) after 3-4 min inhalation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1.2 ± 0.38</td>
<td>1.5 ± 0.52</td>
</tr>
<tr>
<td>5 injections</td>
<td>(P &lt; 0.001)</td>
<td>(P &lt; 0.001)</td>
</tr>
<tr>
<td>CV lesions</td>
<td>1.3 ± 0.24</td>
<td>1.7 ± 0.1</td>
</tr>
<tr>
<td>16 injections</td>
<td>(P &lt; 0.001)</td>
<td>(P &lt; 0.001)</td>
</tr>
<tr>
<td><strong>e) after 5 min inhalation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1.2 ± 0.27</td>
<td>1.1 ± 0.24</td>
</tr>
<tr>
<td>9 injections</td>
<td>(P &lt; 0.001)</td>
<td>(P &lt; 0.001)</td>
</tr>
<tr>
<td>CV lesions</td>
<td>1.3 ± 0.21</td>
<td>1.7 ± 0.88</td>
</tr>
<tr>
<td>15 injections</td>
<td>(P &lt; 0.001)</td>
<td>(P &lt; 0.001)</td>
</tr>
<tr>
<td><strong>f) after 6-7 min inhalation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1.1 ± 0.19</td>
<td>1 ± 0.33</td>
</tr>
<tr>
<td>15 injections</td>
<td>(P &lt; 0.001)</td>
<td>(P &lt; 0.001)</td>
</tr>
<tr>
<td>CV lesions</td>
<td>1.3 ± 0.12</td>
<td>1.4 ± 0.63</td>
</tr>
<tr>
<td>12 injections</td>
<td>(P &lt; 0.001)</td>
<td>(P &lt; 0.001)</td>
</tr>
</tbody>
</table>

*For meanings of headings of columns (T increment, etc.) see figure 1.

†Normal = normal subjects.
†CV lesions = patients with cerebrovascular disease.
Increase of the semilogarithmic slope of the parietotemporal curve in elderly normal subjects and in patients with cerebrovascular disease during inhalation of 5% CO₂ in O₂. The ordinate represents the values of the slope ($r = \frac{0.693}{T}$); the abscissa represents minutes of inhalation. The patients are divided in four groups according to the hemodynamic conditions existing in the resting state (slope $0.30 = $ normal values, slope $0.20$ to $0.30 = $ slight alterations, slope $0.20 = $ marked alterations) and according to the presence of thrombosis of the contralateral internal carotid.

All the times decreased rapidly in the first minute. Most of them remained at their new level throughout the inhalation (fig. 7) or underwent a moderate progressive decrease to the end of the procedure (fig. 6). The decrement time and the J time showed a greater decrease after the first minute (table 2). The semilog slope increased markedly in the first minute, and at a slower but consistent rate throughout the inhalation (fig. 5).

The maximal percentage reduction from base values was about 20% for the increment times, 30% for the carotid-jugular interval and decrement times, and 40 to 50% for the static and intermediate times. An increase of 72% was recorded for the slope $r$.

The response in patients with history of apoplexy was similar to that obtained in normal subjects (table 2). On the whole, the maximal changes of the times in patients were greater than those found in normal subjects, although, because the starting values were higher in the former, the percentage reduction is the same in the two groups.

On the other hand, the $r$ slope exhibited a smaller absolute increase but a greater percentage increase in the patients (by reason of the reduced base value). The rise of the slope was more gradual and progressive in patients than in normal subjects. From a percentage point of view, the change of slope in the group of patients with history of apoplexy was 44% at the first minute, 69% at the second minute, and 95% at the sixth to seventh minute (compared with 44%, 55%, and 72% in the normal subjects). Even after six minutes of CO₂ inhalation, statistically significant differences could be seen between the mean values of the two groups (table 2).
In some patients the hemodynamic response was extremely poor, or at any rate considerably slower than in others (fig. 4). This finding did not appear correlated with a delay of the arterial CO₂ increase. Also, it was difficult to find definite clinical features common to all these cases and at the same time absent from the remaining ones. However, on the basis of the hemodynamic changes recorded by radioencephalography in the resting state, we were able to distinguish three subgroups within the group of patients with cerebrovascular lesions. In these subgroups, the response to CO₂ registered in the main REG findings is compared with that found in the normal subjects and shown graphically in figures 5 to 7.

Our observations can be summarized as follows: 1) In four patients with basal hemodynamic values within normal limits (semilogarithmic slope 0.30 or more), the response to hypercapnia did not differ noticeably from that found in the control group. The average blood pressure was 166/101 mm Hg. In three of these the morphology revealed by angiography pointed to the existence of vascular sclerosis without any change in the caliber of the large arteries. 2) In thirteen patients with slight or moderate basal alterations (slope between 0.23 and 0.29) there was, on the average, a certain delay in the hemodynamic response to hypercapnia. The blood pressure was 177/98 mm Hg. Angiography revealed diffuse angiosclerosis (three cases), deficient parietal filling to the extent of a carotid substenosis (four cases), and a less extensive sclerosis (three cases). 3) In seven cases the seriousness of the hemodynamic deficit was revealed by low REG values recorded in basal conditions (slope 0.20 or less) and confirmed by angiographic evidence of stenosis of the common carotid (one case), subocclusion of the middle cerebral artery (one case), and dilatation and deficient parietal filling of the internal carotid artery (two cases). The frequency of cardiac dysfunction (atrial fibrillation, and electrocardiographic evidence of myocardial ischemia and ventricular overload) was also higher than in the preceding groups. The average blood pressure was 169/103 mm Hg.

In these cases, within the first minute, the semilogarithmic slope rose only 24%, despite a very low base value (fig. 5). After two minutes of inhalation, a 47% increase was recorded, which was still lower than the normal response. By the end of the procedure (after six to seven minutes of inhalation) the percentage increase (98%) exceeded the normal one. Nevertheless, the absolute difference from normal was greater than that recorded in the resting state. The curves showing intermediate time paralleled those of the normal cases; the percentage variations were comparable in the two groups (fig. 6). This means that, owing to the higher basal value, the absolute reduction in the patients with cerebrovascular disease was greater, and the absolute difference
between the groups was diminished at the end of the procedure. This is even clearer for the carotid-jugular interval, reduction of which was very marked in the first minute (fig. 7). After that, the difference between this group and the normal group was much less than in the resting state, and their final values were almost identical.

In the two cases of occlusion of the internal carotid artery, the examination was carried out on the side contralateral to the thrombosis. The data recorded at the first and second minutes of hypercapnia indicated a normal response in circulation time and a greatly delayed response in the slope (figs. 5 to 7).

Discussion

Inhalation of 5% CO₂ gave rise to hypercapnia, an increase in arterial oxygen saturation, moderate hypertension, and very slight changes in pulse and respiration rate. These changes appeared rapidly (almost within the first minute of inhalation) and affected normal subjects and patients with cerebral vascular disease in the same way. The degree of hypercapnia and of the other changes varied from case to case. This suggests that the examination cannot be considered by itself a strictly standard test.

The radioisotope curves, which we used for the purpose of assessing cerebral hemodynamic response, showed marked changes in the first minute, followed by more gradual changes, consisting (in normal elderly subjects) of a 30% reduction in circulation time (C-J interval) and a 72% increase of the semilogarithmic slope. It is not possible to measure exactly the variation in blood supply on the basis of the above-mentioned changes, because the semilogarithmic slope r is only an approximate index of blood flow (see Methods). However, our data seem to agree with those quoted in the literature indicating that the increase in cerebral blood flow induced by 5% CO₂ inhalation is approximately 60% of the base value in normal subjects. The examination of patients with history of apoplexy and under basal conditions revealed hemodynamic alterations varying in degree from case to case. A significant increase of times and decrease of slope were present in the whole group.

During CO₂ inhalation the percentage changes of the elements of the radioencephalograms were equal to or higher than normal. It can therefore be stated that inhalation of CO₂ at 5% concentration increased the caliber of cerebral vessels and cerebral blood flow even in cases of cerebral vascular disease. On the other hand great variability from case to case could be observed. The most useful RVE elements for differentiating the response to CO₂ in single cases were: a) the intermediate time (Tᵢ) and b) the semilogarithmic slope. The most prominent abnormality was a clear-cut delay. The response was almost absent at one minute, starting only at two minutes of inhalation. The C-J interval and the remaining time elements of the curves did not prove valuable for this purpose, because of their more uniform response.

It may be asked whether the rate of increase in arterial CO₂ itself could be the limiting factor, being slower in some patients with slower respiratory exchanges. A continuous recording of CO₂ tension would be necessary to give a conclusive answer. However, the determinations made on blood samples after one and five minutes of inhalation indicate that the different groups had a comparable degree of hypercapnia, at least at the times measured. Therefore, the delayed hemodynamic response seems to reflect some intrinsic change in the responsiveness of the cerebral vasculature to CO₂. This abnormality could act through one of the following hypothetical mechanisms: 1) The rigid cerebral vessels are no longer capable of responding to any kind of stimulus through modifications of their caliber. 2) The sclerotic arterial vessels do not respond to the specific vasodilator stimulus provided by the increase in arterial CO₂. 3) The vessels are already dilated to compensate for the reduction in blood supply due to the existing vascular disease so that the possibility of a further response by dilatation is diminished. No definite proof exists
that one of these mechanisms is in fact responsible for an abnormal response to CO2.

In this study, the patients with reduced and/or delayed response were those with more abnormal REG findings in basal conditions and with more prominent angiographic abnormalities. Taking into consideration the angiographic findings, it appears that the delayed response could be the result either of a widespread alteration of the vessels, which thus lose their normal capacity for rapid dilatation; or of a reduction in caliber of the afferent arteries (as in the cases of carotid stenosis), which thus renders the response less effective in the more peripheral cerebral vessels.

Some relationship between degree of vascular reactivity to CO2 and blood pressure had been suggested in preceding researches. Normotensive arteriosclerotics or hypertensives were found to be less responsive. Our results fail to show any correlation between blood pressure and rate of hemodynamic response to CO2.

From a practical standpoint, certain conclusions can be stated. a) The response of the cerebral circulation to CO2 was far from uniform in patients with ischemic brain lesions due to vascular disease. Indeed, the response was practically normal in over half of the cases. This confirms an earlier conclusion that procedures based on CO2 inhalation cannot provide a reliable test for organic cerebral vascular diseases. b) In about one-third of the patients with cerebral vascular disease, the response to CO2 was definitely abnormal. This abnormality consisted not so much of an absolute diminution, but rather of a slower rate of response. This could account for the inconclusive results obtained with the quantitative inert gas methods, which take into account only the maximal responses.

c) In view of the lack of metabolic reserves of the brain and its extreme sensitivity to hypoxia, it is most important that the cerebral circulation should remain able to adapt promptly to sudden circulatory changes. This being the case, the finding of a poor or delayed response to a physiological stimulus such as CO2 can be regarded as suggestive of a serious alteration, perhaps justifying an equally serious prognosis.

d) A study of the functional characteristics of the cerebral circulation by means of radioencephalography has made it possible to identify variations of degree and extent in the hemodynamic disturbances in patients with cerebral vascular disease. By means of the CO2 test which, for the purposes of dynamic evaluation, is comparable to the functional tests commonly applied to other circulatory regions, the cerebral circulation of each individual patient can be studied in greater detail and its adaptability to emergencies and scope for compensation assessed on the basis of recorded data.

Summary

A study has been made in 11 normal elderly subjects and 26 patients suffering from the sequelae of cerebral apoplexy on the effects of the inhalation of a hypercapnic mixture on pulse rate, arterial pressure, arterial O2 and CO2 and the radioencephalographic curves recorded during injection of radioactive albumin into the carotid artery.

The hemodynamic response of the cerebral circulation to hypercapnia was very rapid and intense in normal subjects and in a number of patients with history of apoplexy. In a number of patients with vascular disease, on the other hand, the response was considerably delayed in time, more so than reduced in intensity.

Taking into account the early time course of the response, this hypercapnia test may provide a dynamic basis for evaluating severe degrees of reduced hemodynamic adaptability of the cerebral circulation.

References

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