The Relationship of Regional Cerebrovascular $CO_2$ Reactivity to Blood Pressure and Regional Resting Flow

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Abstract:
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Cerebrovascular $CO_2$ reactivity (the change in cerebral blood flow per mm Hg change in $PaCO_2$) is shown to be directly related to resting flow and inversely related to blood pressure for regional as well as for mean CBF data. Both regional and mean $CO_2$ reactivity therefore are proportional to the ratio resting flow: blood pressure. This ratio is the reciprocal of resistance and may be called conductance. When regional $CO_2$ reactivity for 428 cerebral areas is plotted against an approximation of regional conductance, the data describe positive linear relationships similar to those found when mean $CO_2$ reactivity is plotted against mean conductance. These relationships can be demonstrated whether $CO_2$ reactivity is calculated with specific or percent change in flow. The way in which $CO_2$ reactivity relates to conductance, therefore, may provide a more reliable index of the integrity of the cerebrovascular $CO_2$ response than the CBF change per se. Analysis of $CO_2$ reactivity as a function of conductance may facilitate the interpretation of mean and regional $CO_2$ reactivity and may provide a more meaningful basis for comparison of the $CO_2$ response between individuals.

Additional Key Words: autoregulation, cerebral blood flow (CBF), conductance, $CO_2$ response, perfusion pressure, resistance, $^{133}Xenon$.

A prior report suggested that the change in mean cerebral blood flow (CBF) in response to a change in $PaCO_2$ is related to blood pressure and to mean resting CBF values. Analysis of $^{133}Xenon$ clearance data for 29 patients indicated that mean $CO_2$ reactivity (the mean change in CBF per millimeter Hg change in $PaCO_2$) is directly related to mean resting CBF and inversely related to mean arterial blood pressure (BP); i.e., mean $CO_2$ reactivity is proportional to the ratio mean resting CBF: mean arterial BP. This ratio is the reciprocal of cerebrovascular resistance and may be called conductance.

The previous report indicated a positive linear correlation between mean hemispheric $CO_2$ reactiv-
ity and mean hemispheric conductance over a wide range of conductance values, with different slopes being defined for normal and high blood pressure subjects. The correlations were demonstrated whether CO$_2$ reactivity was calculated with specific or percent flow change. This report will examine regional CO$_2$ reactivity as a function of conductance. Demonstrating a relationship between these parameters would provide a physiological basis for the analysis of regional CO$_2$ reactivity. Because regional arterial pressures are ordinarily unknown, true regional conductance cannot be calculated. However, a conductance value derived from regional resting CBF and mean arterial BP may be shown to provide a useful approximation. Regional CO$_2$ reactivity will be plotted against the ratio of regional resting CBF to mean arterial BP for 428 cerebral areas studied in 29 patients. The data points will be analyzed for linear correlation. As in the previous study, the analysis is based on cerebrovascular CO$_2$ reactivity occurring in response to induced hypocapnia.

**Methods**

**TERMINOLOGY**

**CO$_2$ Reactivity**

CO$_2$ reactivity will refer to the change in CBF per mm Hg change in Pa$_{CO_2}$. Percent change is the percentage difference in CBF between two studies as calculated by the formula

$$\frac{\text{CBF}_1 - \text{CBF}_2}{\text{CBF}_1} \times 100$$

and is a value uncorrected for change in Pa$_{CO_2}$. The absolute flow change in CBF per mm Hg change in Pa$_{CO_2}$ is the specific reactivity and the percent change in CBF per mm Hg in Pa$_{CO_2}$ is the percent reactivity. That these are different parameters is illustrated by the fact that for a drop of 20 from an initial value of 100 the percent change is 20%, but for the same drop from an initial value of 50 the percent change is 40%.

**Conductance**

This is the reciprocal of resistance. In precise terms it is the ratio of blood flow to perfusion pressure. In recumbent man the mean arterial pressure may be used as an estimate of cerebral perfusion pressure. Because alterations in Pa$_{CO_2}$ may change blood pressure, the denominator in the conductance ratio was calculated by taking the average of the mean blood pressure values for the two clearance studies. Blood pressure measurements were made from a catheter in the internal carotid artery.

**High Blood Pressure**

This refers to mean study blood pressures which have an average value of 120 mm Hg or more and does not necessarily connote an underlying disease state.

**FIGURE 1**

The topographical relation of the 16 detectors to the brain. The numbers are those designated for the area of cerebral tissue monitored by each detector.
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CBF DETERMINATION
A regional 133Xenon clearance method was employed. CBF values were derived from the first two minutes of the semilogarithmically displayed clearance curve, a value known as flow initial (F_initial), and are in units of milliliters per 100 gm of cerebral tissue per minute. 133Xenon dissolved in saline was injected as a bolus into the internal carotid artery and the rate of clearance monitored from 11 to 16 (mean 15) regions of the brain by detectors placed at the lateral surface of the head. The approximate topographical position of the detectors in relation to the convexity of the cerebral hemisphere is shown in figure 1, as well as the numerical designation for the cerebral region monitored by each detector. To test CO₂ reactivity each patient had two consecutive CBF studies, the first at normocapnia and the second with the PaCO₂ lowered by hyperventilation or by a change in the inspired CO₂ content. Approximately 15 to 30 minutes elapsed between the two measurements. An arteriogram was made immediately following the second measurement. The mean hemispheric flow values used in this paper are derived by taking the average of the regional flow data for each hemisphere.

PATIENTS
Details of the 29 cases to be reviewed were given in the report on mean reactivity/conductance analysis. They were selected from the CBF records of the National Hospitals for Nervous Diseases, London, England, on the basis of the following criteria: (1) having had a PaCO₂ drop of at least 10 mm Hg between two consecutive CBF studies, and (2) not having been known to have a cerebral tumor, hemorrhage or dementia. Of the 29 patients, one each had a pituitary adenoma and optic atrophy, one was referred for temporal lobe epilepsy, nine for transient ischemic attacks, and 17 with completed strokes. Because impairment of vasomotor reactivity is a transient phenomenon following an acute insult, it may be pertinent that one of the 29 patients was studied two days after a stroke and one six days afterward, but all the others had an interval of at least two weeks between a neurological event and blood flow study, and 15 patients had at least one month elapse.

The mean CO₂ reactivity data for the 29 cases were found to describe linear relationships with mean conductance. The correlation coefficient (r) for this relationship was +0.735 and +0.637 for specific and percent reactivity, respectively. Each correlation was
statistically significant with a P value of less than 0.001. Two subgroups with different regression lines were recognized. One consisted of 22 normal blood pressure patients with mean conductance values below 0.80 ($r = +0.896$ and $+0.795$ for specific and percent reactivity, respectively) and the other consisted of four of the five high blood pressure cases ($r = +0.981$ and $+0.984$, respectively).

**Results**

The regional data points for the 29 cases (428 areas) describe a statistically significant linear relationship with an approximation of regional conductance:

$$\frac{\text{regional resting CBF}}{\text{mean arterial BP}}$$

For specific and percent reactivity the correlation coefficients are $+0.758$ and $+0.556$, respectively. The respective correlation coefficients for the 22 normal blood pressure cases (319 areas) are $+0.866$ and $+0.663$ and for the four high blood pressure patients (62 areas) $+0.827$ and $+0.708$. Each of the six correlation coefficients is statistically significant with a P value of less than 0.001. The regional data points for the 22 normal blood pressure cases are plotted in figures 2 and 3 and for the four high blood pressure cases in figures 4 and 5.

**Discussion**

That blood pressure and resting CBF levels may modulate CO$_2$ reactivity may explain the variability found when CO$_2$ reactivity is analyzed independently. For six normal young males Kety reported active and passive hyperventilation data from which may be calculated specific reactivities ranging from 0.71 to 2.28 and percent reactivities ranging from 1.19 to 3.07. Data from Fazekas and Olesen show considerable variability among a group of normals and a group of neurological patients without focal flow abnormalities, respectively (table 1).

Examination of the pooled regional CBF data for the 29 National Hospital cases indicates that over a wide range of conductance values a positive linear relationship exists between regional CO$_2$ reactivity and an approximation of regional conductance at two blood pressure levels, similar to that found with mean reactivity/conductance analysis.

Recent animal studies lend support to the concept that CO$_2$ reactivity is related to conductance...
and its parameters, blood pressure and flow. Myers and Honig\textsuperscript{8} report that the magnitude of a vasoconstrictor response in the femoral artery of dogs is inversely related to resting resistance. Therefore, the amount that luminal size decreases and flow falls would be directly related to conductance, the reciprocal of resistance. Davis and Dow\textsuperscript{10} report that in response to a standard vasoconstrictor stimulus the increase in resistance in the dorsal pedal artery in dogs is inversely related to intraluminal pressure. They suggest, therefore, that as resting pressures rise a smaller change in flow might occur in response to a given vasoconstrictor stimulus.

\begin{table}
\centering
\caption{Specific and Percent Reactivity Calculated from Mean CBF Data Reported from Several Laboratories}
\begin{tabular}{|c|c|c|c|c|c|c|c|c|}
\hline
Source & No. of trials & Range & Mean & SD & CV, \% & Range & Mean & SD & CV, \% \\
\hline
Kety \& Schmidt, 1946\textsuperscript{6} & 11 & 0.71-2.28 & 1.35 & ±0.51 & 38 & 1.19-3.07 & 1.95 & ±0.58 & 30 \\
Fazekas et al., 1961\textsuperscript{7} & 9 & 1.00-3.00 & 3.27 & ±1.95 & 59 & 1.67-8.83 & 5.12 & ±2.17 & 42 \\
Olesen et al., 1971\textsuperscript{9} & 14 & 0.75-3.32 & 1.68 & ±0.64 & 38 & 1.97-3.64 & 2.86 & ±0.57 & 20 \\
Ackerman et al., 1972\textsuperscript{1} & 29 & 0.38-2.67 & 1.45 & ±0.58 & 40 & 0.97-4.83 & 2.66 & ±0.90 & 34 \\
\hline
\end{tabular}
\end{table}

SD = standard deviation.
CV = coefficient of variation.
Since hypocapnia can be considered a vasoconstrictor stimulus the observations of Myers and Honig and of Davis and Dow on vasoconstrictor responses in the hindlimb of the dog are parallel to those noted here for the human cerebrum, namely, that the magnitude of a change in flow in response to hypocapnia would be proportional to conductance and inversely related to blood pressure.

Flohr et al.\textsuperscript{11} report a relationship between resting flow values and CO\textsubscript{2} reactivity. They found significantly different CO\textsubscript{2} reactivities at various levels of the neuraxis of the cat and suggest that these differences are directly related to the resting flows. The concept of CO\textsubscript{2} reactivity being related to resting flow would be consistent with Wilder's Law of Initial Value, which states, in part, that the lower the initial value of a physiological function, the smaller is the response to a function-depressing stimulus.\textsuperscript{12}

The hypothesis that CO\textsubscript{2} reactivity may be related to conductance is a new concept which requires further evaluation. Its broad implication is that under physiological as well as stress conditions\textsuperscript{13-16} CO\textsubscript{2} reactivity is dependent on the basal tone of the cerebrovascular bed. The cerebral vessels have the capacity to autoregulate, i.e., to change resistance in the direction of a change in BP in order to maintain constant CBF. A corollary of the reactivity/conductance hypothesis hence might be that autoregulatory responses, by their role in helping to determine the tone of the cerebrovascular bed, interrelate with the CO\textsubscript{2} response even under normal circumstances.

The possibility that regional and mean CO\textsubscript{2} reactivity may be functions of conductance suggests important considerations in the interpretation of the CO\textsubscript{2} response: (1) The way in which specific and percent reactivity relate to conductance may be a more reliable index of the integrity of the...
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cerebrovascular CO₂ response than the magnitude of the specific or percent change per se. In some instances small flow changes may represent normal CO₂ reactivity when related to the conductance at which they were measured and ostensibly large flow changes may represent impaired CO₂ reactivity. (2) For the conditions of study the data points of patients with intact CO₂ reactivity may define a statistically meaningful “normal” line for the regression of reactivity on conductance. Reactivity/conductance analysis thus may provide a more physiological basis for the comparison of the CO₂ response between cerebral regions in the same or different individuals. (3) By demonstrating the displacement of data points from an appropriate mean regression line, regional reactivity/conductance analysis may help localize areas of acutely disordered vascular physiology when they are accompanied by relative CO₂ vasoparalysis.

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