Transcranial Doppler Is Valid for Determination of the Lower Limit of Cerebral Blood Flow Autoregulation

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Background and Purpose This study validates transcranial Doppler sonography (TCD) for determination of the lower limit of cerebral blood flow (CBF) autoregulation and establishes a relation between global CBF and mean flow velocity (Vmean) in the middle cerebral artery.

Methods Relative changes in CBF and in Vmean were compared in 12 normal volunteers (2 women and 10 men; median age, 30 years [range, 21 to 61 years]). Catheters were placed in the left radial artery and in the bulb of the right internal jugular vein, respectively. Baseline CBF was measured by single-photon emission computed tomography scanning; concomitantly, blood samples were drawn for calculation of the cerebral arteriovenous oxygen difference. Then changes in mean arterial pressure (MAP) were induced, and relative changes in global CBF were calculated according to Fick’s principle assuming a constant cerebral oxygen metabolism. MAP was increased 30 mm Hg by norepinephrine infusion and more or less implicitly assumed that changes in cerebral blood flow (MAP minus intracranial pressure) or by internal jugular venous oxygen content, where a constant cerebral oxygen consumption is assumed. Obviously, these invasive measures do not provide sufficient insight in cerebrovascular hemodynamics. Repeated measurements every day of CBF by, for example, 133Xe technique is a cumbersome and a more expensive method, and the patients are exposed to a prohibitive amount of radioactivity, which limits the number of studies that can be performed. Transcranial Doppler sonography (TCD) is a noninvasive technique that allows for constant monitoring of mean flow velocity (Vmean) in an intracerebral artery. Many studies have more or less implicitly assumed that changes in Vmean reflect changes in CBF, although the vessel diameter of the middle cerebral artery (MCA) may change. The relation between CBF and Vmean has been evaluated in a few studies but only within the limits of CBF autoregulation. As a measure of blood flow the relation between Vmean and CBF must be known, and this relation should be valid for a wide range of MAP values. By a well-established method we determined the autoregulation profile below the lower limit in healthy volunteers and compared the results obtained with those recorded by TCD at varying levels of MAP.

Subjects and Methods

Subjects

After approval of the Ethical Committee of Copenhagen (L-92103), two female and ten male healthy volunteers with a median age of 30 years (range, 21 to 61 years) were investigated after informed consent had been obtained (Table). The volunteers also served as controls in separate studies for evaluation of the lower limit of autoregulation after β-labetalol infusion and in patients with liver failure, and separate reports will be given for these studies.
Methods
Cerebral Blood Flow Measurements
Before the autoregulation study, regional CBF was measured by 133Xe inhalation and external registration of the uptake and washout from the brain by a brain dedicated single-photon emission computed tomography (SPECT) scanner (Tomomatic 64, Medimatic). Three tomographic pictures, each slice 2 cm thick, were obtained in each subject. Global CBF (milliliters per 100 g per minute) was calculated as the averaged CBF value. Relative changes in global CBF were calculated from the arteriovenous oxygen content differences according to Fick's principle (CBF\(_{\text{Fick}}\)).

Transcranial Doppler Measurements
V\(_{\text{mean}}\), in the MCA was determined by a 2-MHz pulsed Doppler probe (Multi Dop X, DWL). The TCD probe was maintained in the right temporal region by a headband with insonation through the posterior temporal window at a depth of 45 to 55 mm. V\(_{\text{mean}}\) was continuously calculated as the time-averaged maximum velocity over the cardiac cycle computed from the envelope of the maximum frequencies and displayed by the equipment.

Autoregulation Study
One catheter was inserted in the left radial artery for blood sampling and for continuous recording of MAP, and another was placed in a cubital vein for drug administration. After local anesthesia, a catheter was placed with the tip in the bulb of the right internal jugular vein by the Seldinger technique. A transparent plastic box connected to a vacuum pump enclosed the abdomen and legs.

One recording of CBF (SPECT) and one of MAP were performed before and during labetalol administration, respectively. To obtain a wide range of MAP values, a moderate and gradual increase in MAP to a level of 30 mm Hg above baseline was induced by an intravenous infusion of norepinephrine (2 mg·100 mL\(^{-1}\), 5 to 15 \(\mu\)g·min\(^{-1}\)). MAP was subsequently lowered by the combined effect of vacuum and labetalol infusions (2 mg·100 mL\(^{-1}\), 5 to 15 \(\mu\)g·min\(^{-1}\)). MAP indicates mean arterial blood pressure; CVR, cerebral vascular resistance; CBF, cerebral blood flow; and V\(_{\text{mean}}\), transcranial Doppler mean flow velocity. Values are median and (range). Lowest and highest values are significantly different from baseline values (\(P<.001\)).

Results
Baseline, maximum, and minimum values of MAP, CBF, cerebral vascular resistance (defined as MAP divided by CBF), V\(_{\text{mean}}\), and the lower limit of autoregulation identified by TCD and CBF\(_{\text{Fick}}\) are listed in the Table. A statistically significant difference was found between baseline and extreme values of MAP, CBF, V\(_{\text{mean}}\), and cerebral vascular resistance.

CBF\(_{\text{Fick}}\) identified the lower limit in all volunteers. In all but one volunteer the lower limit could be identified by V\(_{\text{mean}}\), which probably was due to a slight but steady change in the probe positioning. The lower limit of autoregulation as evaluated by Fick's method was 79 mm Hg (range, 53 to 113 mm Hg), which was not statistically significantly different from 91 mm Hg (range, 41 to 108 mm Hg), as estimated by V\(_{\text{mean}}\) (Fig 1).

Below the lower limit of autoregulation a significant correlation between CBF\(_{\text{Fick}}\) and V\(_{\text{mean}}\) was found (\(R^2=.73, P<.001\); CBF\(_{\text{Fick}}\) = -6.3+1.0·V\(_{\text{mean}}\)) (Fig 2). As expected, CBF and V\(_{\text{mean}}\) remained unchanged at the autoregulation plateau. The interindividual variation in intercept was considerable at -6.3 (range, -39.8 to +10.9), whereas the slope was close to 1.0 (1.01 [range, 0.99-1.03]).

Statistical Analysis
For statistical comparison of baseline values, the nonparametric Mann-Whitney test was used with a significance level of \(P<.05\). Values are presented as median and range. The lower limits of autoregulation, as obtained by the two methods, were compared by the nonparametric Wilcoxon's test for paired samples. CBF\(_{\text{Fick}}\) and V\(_{\text{mean}}\) were plotted against the corresponding MAP, and the lower limit of autoregulation was computed by the least-squares method by repeatedly fitting the data to two linear regression lines: a horizontal and an oblique line where the crossover point defines the lower limit. The following criteria had to be fulfilled to establish the lower limit of the autoregulation: (1) The squared sum of differences between the calculated autoregulation curve and the measured points should not exceed that of a straight line and (2) the calculated lower limit should be within physiologically meaningful limits, ie, between 50 mm Hg and 110 mm Hg, and it should be determined with a mean error of less than 25% of the calculated value.
to an autoregulatory dilation of the smaller resistance vessels.

The lower limit of autoregulation was statistically identified in all subjects by the CBF$_{\text{max}}$ method, but only in 11 of 12 subjects by TCD. Both methods yielded similar values for the lower limit, although a tendency toward higher values was found with TCD. This, as well as the lack of identification of a lower limit in one subject, may have been caused by a slight and steady change in probe positioning, which would tend to decrease the measured V$_{\text{mean}}$ in the course of the experiment as the vessel is no longer in the center of the ultrasound beam. Fixation of the probe with a headband as well as fixation gel may reduce this error in future studies.

Our findings disagree to some extent with a previous study in which V$_{\text{mean}}$ decreased significantly and CBF remained constant in patients with autonomic failure and orthostatic hypotension who had a decrease in MAP of approximately 20 mm Hg. This discrepancy was explained by the authors as a possible physiological reactive dilatation of the MCA in hypotension. This explanation is not supported by our results, and autoregulation may actually have been lost. In their study, a stationary detector system with intravenous $^{133}$Xe injection was applied for repeated CBF measurement, and only 6 to 8 mCi $^{133}$Xe was injected, which may induce significant scatter of the results. We believe that this method might have been too insensitive for minor changes in CBF, and it would be desirable to reinvestigate the possible absence of autoregulation in autonomic failure within a larger blood pressure range and with more sensitive methods.

Below the lower limit of autoregulation, V$_{\text{mean}}$ correlated significantly with changes in global CBF. As previously pointed out, V$_{\text{mean}}$ as a measure of CBF assumes a linear relation between normalized CBF and V$_{\text{mean}}$ values where the slope is 1 and the intercept 0.23 Indeed, these criteria were met in our study below the lower limit of autoregulation.

Lindegaard et al$^{14}$ and Newell et al$^{16}$ investigated V$_{\text{max}}$ in the MCA in seven patients who underwent carotid endarterectomy. Normalized changes in V$_{\text{max}}$ (V') were related to normalized changes in blood flow volume in the ipsilateral extracranial part of the internal carotid artery (Q') at varying blood flow and MAP values, and a composite analysis of data from all patients showed a significant linear relation between these two variables: $Q' = 5.6 + 0.94 \cdot V'$. This relation is close to the one we found even though most of their patients hardly reached the lower limit of autoregulation.

Considerable interindividual variations in the relation between absolute blood volume and V$_{\text{mean}}$ were found in the study of Lindegaard et al$^{14}$ which is confirmed by our study. This is most likely caused by interindividual differences in the diameter of the MCA and in hematocrit, which totally hamper the validity of the TCD measurements for evaluation of absolute CBF values.

Severe diseases, eg, acute liver failure and subarachnoid hemorrhage, are frequently associated with cardiovascular instability and decreased cerebral perfusion pressure. Since CBF autoregulation may be disturbed in these conditions,$^{2,8}$ a close monitoring of cerebral perfusion is desirable. Oxygen saturation levels measured in the bulb of the internal jugular vein may be indicative...
of CBF changes, but changes in cerebral oxygen consumption are likely to occur, induced either by drugs or by spontaneous fluctuation in the disease. Under these conditions, changes in oxygen saturation no longer reflect CBF. Changes in vessel diameter will, on the other hand, disturb the evaluation by \( V_{\text{mean}} \), and it remains to be investigated in which condition alterations of the MCA diameter occur.

In conclusion, the lower limit of CBF autoregulation can be determined by TCD because there is a good correlation between CBF and \( V_{\text{mean}} \) in the MCA below the lower limit of autoregulation. In future studies, TCD may be suitable for measurements of autoregulation limits in normal brain and also under conditions in which changes in cerebral oxygen metabolism are likely to occur. Conversely, in studies in which diameter changes of the MCA may take place, replacement of the "classic" method for evaluation of autoregulation is recommended or should at least be evaluated before investigation. If it should be established that autoregulation is absent, the combination of the two methods would certainly increase the reliability of the findings.

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