A Simple Test to Assess Cerebrovascular Reserve Capacity Using Transcranial Doppler Sonography and Acetazolamide

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The goal of this study was the development of a simple bedside test to assess cerebrovascular reserve capacity using transcranial Doppler sonography. We studied 33 normal persons at rest and after stimulation of cerebral blood flow with 1 g acetazolamide. Their mean±SD increase in blood flow velocity in 54 middle cerebral arteries 10 minutes after stimulation was 24.4 ±9.2 cm/sec. We tried to validate the increase in blood flow velocity as cerebrovascular reserve capacity in 21 patients with obstructive carotid artery disease and symptoms of cerebral ischemia. The patients were studied using transcranial Doppler sonography and xenon-133 dynamic single-photon emission computed tomography after acetazolamide stimulation. Their increases in blood flow velocity (ΔFV) and increases in cerebral blood flow (ΔCBF) correlated significantly in both hemispheres (asymptomatic: \( Y=0.32X+10.65 \), \( r=0.45 \), \( p=0.04 \); symptomatic: \( Y=0.36X+2.28 \), \( r=0.59 \), \( p=0.004 \)). There was no significant difference between the slopes of the regression lines. Blood flow velocity and cerebral blood flow at rest were not correlated. The increase in blood flow velocity after acetazolamide stimulation offers a simple and reliable method for assessing cerebrovascular reserve capacity. (Stroke 1990;21:1306–1311)

In the etiology of cerebral ischemic events related to carotid artery occlusion, thromboembolic and hemodynamic mechanisms may be causative. Large studies indicate that embolic disease is best treated medically, a concept that might not be suitable in hemodynamic hypoperfusion.

Obstruction of a brain-supplying vessel is normally compensated for by collateral blood supply via the circle of Willis, leptomeningeal anastomoses, or natural anastomoses with the external circulation such as the ophthalmic artery. In patients with functionally insufficient natural collateral blood supplies, symptoms of cerebral ischemia will result. Angiography, computed tomography, or measurements of cerebral blood flow (CBF) at rest give little information on the collateral supply's ability to counteract sudden drops in perfusion pressure that might result in transient ischemic attacks (TIAs) or permanent neurologic deficits. Functional testing is possible with a vasodilatory stimulus such as acetazolamide, which should have no additional effect on CBF in an area of compensatory vasodilation. The combination of CBF measurements and induced vasodilation for assessing the cerebrovascular reserve capacity (CVRC) has been established and validated.1,2

With the new technique of transcranial Doppler sonography (TCD), changes in mean blood flow velocity (FV) in the basal cerebral arteries can be monitored noninvasively. Although FV does not reflect CBF quantitatively, changes in FV correspond to changes in CBF as long as the diameter of the insonated vessel remains constant.3,4 In patients with occlusive cerebrovascular disease, we used TCD to develop a simple method for assessing CVRC. The results were validated with xenon-133 dynamic single-photon emission computed tomography (D-SPECT).

Subjects and Methods

We studied FV in 33 controls without evidence of cerebrovascular disease. Each control had a normal medical history, took no medications, and had normal chest roentgenographic, electrocardiographic, and screening clinical laboratory results. In 12 controls (two women and 10 men aged 23–73 [mean±SD 47±15, median 54] years), mean FV in the left middle cerebral artery (MCA) was measured using TCD with a fixed monitoring probe; after establishing a baseline, 1 g i.v. acetazolamide was injected,
and FV was continuously measured for 30 minutes. In the other 21 controls (eight women and 13 men aged 21-78 [mean±SD 43±13, median 46] years) mean FV in the left and right MCA at rest and 15 minutes after the injection of 1 g i.v. acetazolamide was measured using TCD. The study protocol assured a supine position and no acoustic or visual distraction. Blood pressure was measured at rest and 15 minutes after injection of 1 g i.v. acetazolamide.

In 21 symptomatic patients (two women and 19 men aged 26-75 [mean±SD 58±13, median 59] years), angiography demonstrated an internal carotid artery (ICA) occlusion in 18 patients and a high-grade (>90%) ICA stenosis in two; in the remaining patient angiography revealed high-grade stenosis of an MCA. In the contralateral ICA a ≤50% stenosis was found in five patients and a ≤80% stenosis in another two. We calculated CVRC using D-SPECT and TCD measurements performed at least 24 hours apart to avoid potential addition of acetazolamide effects. After verifying that the time course of FV increases after acetazolamide injection in patients was the same as that in controls, TCD studies were performed according to the results obtained with the controls. Clinical data of the patients are summarized in Table 1.

Mean FV as centimeters per second was measured at rest and after the injection of 1 g i.v. acetazolamide with a transcranial Doppler unit (TC 2-64 Trans Scan, EME, Überlingen, FRG) described in detail elsewhere using a 2-MHz probe and insonation of the MCA's main trunk at a depth of 50-55 mm. We calculated CVRC as the absolute increase of mean FV above resting values (ΔFV) as centimeters per second.

Regional CBF as milliliters per 100 g per minute was measured at rest and 15 minutes after the injection of 1 g i.v. acetazolamide using inhaled xenon-133 gas and D-SPECT, a rapidly rotating detector system with 64 separate NaI crystals (Tomatomatic 64, Medimatic, Copenhagen, Denmark) for tomographic recording of axial slices. Spatial resolution within a slice was 17 mm. CBF was quantified in three slices (2, 6, and 10 cm above the canthomeatal line). Each slice was divided into regions of interest by a special computer program. For comparison with the TCD results, only data from the second slice in a region of interest representing the perfusion territory of the MCA were analyzed. In the D-SPECT studies, we calculated CVRC as the absolute increase of regional CBF above resting values (ΔCBF) as milliliters per 100 g per minute based on our previously published protocol and nomogram. In 26 healthy normal subjects, a linear reciprocal relation (ΔCBF=−0.6×CBF\text{rest}+50, r=0.77) describes the proportionally greater increase of CBF after acetazolamide injection in individuals with a low CBF at rest and lesser increases in those with a high CBF at rest. In each D-SPECT study, we measured blood pressure at rest. In each D-SPECT study, we measured blood pressure at rest.
pressure, PaCO₂, and PaO₂ at rest and after acetazolamide injection.

Results are given as mean±SD unless stated otherwise. We used the Wilcoxon signed rank test to analyze differences between groups. A probability level of ≤0.05 was considered to indicate significant differences. In the patient group we compared TCD measurements of ΔFV with D-SPECT measurements of ∆CBF using linear regression analysis, and we compared slopes of the regression lines using Student’s t test.

Results

Figure 1 shows FV at rest and after acetazolamide injection in the 12 controls. In all controls, FV had increased significantly by the first minute (p=0.003) after injection and reached a plateau by the fifth minute (p=0.002); this plateau lasted at least 30 minutes. For standardization purposes, FV at 10 minutes after injection was chosen empirically as the value for calculating CVRC as ΔFV.

For all 33 controls, FV at rest in 54 MCAs was 60.9±10.7 (range 38–84) cm/sec and ΔFV was 24.4±9.2 (range 6–48, median 25) cm/sec. The normal range for FV at rest is 57.3±14.8 cm/sec. There was no correlation between FV and blood pressure (r=0.22), FV at rest (r=0.16), or age (r=0.2). There was an age-dependent decline in FV at rest (FVrest=-0.32×Age+75.21, r=0.41, p=0.002).

The results of all TCD and D-SPECT measurements in the patient group are given in Table 2. All but five patients (2, 6, 12, 20, and 21) had a normal FV at rest in the asymptomatic hemisphere. In the symptomatic hemisphere FV at rest was normal in eight, below normal in 11, and above normal in two patients. Mean FV at rest for the two hemispheres did not differ significantly (p=0.18). However, mean CBF in the symptomatic hemisphere was significantly lower (p=0.0001) than that in the asymptomatic hemisphere.

In the asymptomatic hemisphere, there was no ΔFV of <12 cm/sec, the maximum being 64 cm/sec (Table 2). In the symptomatic hemisphere, however, ΔFV was negative in five patients and zero in four. According to our normal range, ΔFV in the symptomatic hemisphere was pathologically low in 11 patients and borderline low (6–10 cm/sec) in three others. Mean ΔFV for the two hemispheres differed significantly (p<0.0001).

Based on our nomogram, ∆CBF in the asymptomatic hemisphere was normal in all but one patient (19) while that in the symptomatic hemisphere was normal in five patients (4, 9, 17, 18, and 21) and low in the other 16. Mean ∆CBF differed significantly (p=0.0001) between hemispheres (Table 2).

After acetazolamide injection, a decrease in CBF (the so-called “steal phenomenon”) occurred in the symptomatic hemisphere in seven patients (Table 2). Four of the five patients with a negative ΔFV had a steal phenomenon, and all seven patients with a steal phenomenon had a pathologically or borderline low ΔFV. In six instances (symptomatic hemisphere for patients 10, 13, 14, and 16; both hemispheres for patient 19) ΔFV was falsely negative, in 11 instances it was correctly positive, in 24 it was correctly negative, and in one (symptomatic hemisphere for patient 9) it was falsely positive. There was no correlation between FV at rest (AFV) and CBF (ACBF) (ACBF=0.01ΔFV+59.18, r=0.02 for asymptomatic hemisphere and ACBF=-0.07ΔFV+56.22, r=0.24 for symptomatic hemisphere). However, ΔFV and ∆CBF were linearly related in the asymptomatic (p=0.32ΔFV+10.65, r=0.45, p=0.04) as well as the symptomatic (ACBF=0.36ΔFV+2.28, r=0.59, p=0.004) hemispheres (Figure 2).

Discussion

Our results prove a linear relation between ΔFV and ∆CBF after acetazolamide injection and suggest that ΔFV can be used as an indicator of CVRC.
TABLE 2. Measurements for Calculating Cerebrovascular Reserve Capacity in 21 Patients With Occlusive Carotid Artery Disease

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<td>Mean ±SD</td>
<td>61±21</td>
<td>28±12</td>
<td>55±30</td>
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Pt, patient number; FV, mean blood flow velocity in middle cerebral artery; ΔFV, change in FV 10 minutes after injection of 1 g i.v. acetazolamide; CBF, cerebral blood flow in region of interest reflecting middle cerebral artery mainstem territory; ΔCBF, change in CBF 15 minutes after injection of 1 g acetazolamide.

* Decrease in cerebrovascular reserve capacity according to Kreisig et al.6

† p<0.0001 different from asymptomatic by Wilcoxon signed rank test.

However, there is no correlation between CBF and FV at rest.

We used D-SPECT to validate our TCD results. Based on the Kanno/Lassen21 algorithm, D-SPECT allows calculation of regional CBF from the xenon-133 clearance. Emission computed tomography is used, giving the advantage of three-dimensionality over stationary detectors. With standardized region-of-interest software,7 the accuracy of D-SPECT for quantified CBF is high with satisfactory spatial resolution.

In recent studies,4-8 a positive correlation between CBF and FV was proven. TCD is a simple method of monitoring FV in the basal cerebral arteries. In contrast to other methods based on ultrasonography, TCD has a low emission frequency of 2 MHz. No imaging is possible, and vessel identification depends on anatomic characteristics, the examiner, and experience. This represents the method's main source of error. In a large series of 1,039 patients, Grolimund et al5 could insonate the MCA in all but 28 patients (2.7%). Our findings in controls are within the range of these authors' normal values. Measured FV is influenced by the angle of insonation, blood viscosity,
and vessel diameter. Aaslid\textsuperscript{10} described the accuracy of measured FV as a cosine function of the angle between the flow vector and the observation direction, that is, the direction of the ultrasonic beam. For the MCA, measured FV should therefore represent true velocity with an error of $<15\%$ with an insonation angle in the range 0°–30°. Changes of hematocrit influence changes of blood viscosity,\textsuperscript{11} resulting in changes of vessel diameter. Furthermore, different hematocrits cause different sound transmission times in blood, which are negligible on TCD.\textsuperscript{12} Applying the law of Hagen-Poiseulle, CBF depends on vessel radius raised to the fourth power. A dilatation of 20% thus doubles CBF without necessarily changing FV. To compare FV with actual CBF, it is therefore important to assure steady-state conditions. Changes in systemic arterial blood pressure influence vessel diameter and result in inaccurate Doppler measurements, as stressed by Kontos.\textsuperscript{13} His group demonstrated adaptive changes in vessel diameter of up to 10% with mild changes in blood pressure.\textsuperscript{14} There are no reports on an effect of acetazolamide on the diameter of basal cerebral arteries. The only known effect of acetazolamide is reversible inhibition of carbonic anhydrase.\textsuperscript{15} Acetazolamide increases CBF by mechanisms not yet fully explained. Recently, extracellular acidosis as a potential mediator was reported by Bickler et al.\textsuperscript{16}

The combination of D-SPECT with acetazolamide injection for assessing CVRC was introduced by Vorstrup et al\textsuperscript{17} in 1984. Our findings of CVRC in patients are interpreted on the basis of a nomogram, reported previously for 26 healthy normal subjects\textsuperscript{6}; $\Delta$CBF shows a linear reciprocal dependency on CBF at rest. As stated recently, Borgsrud et al\textsuperscript{18} could not prove this dependency in 12 normal subjects. In that series, CBF at rest ranged from 46 to 65.9 ml/100 g/min,\textsuperscript{19} compared with a range of 45–75 ml/100 g/min (hemispheral blood flow) in our control group. These differences in distribution might be responsible for the divergent findings.

The use of acetazolamide injection combined with xenon-133 inhalation for assessing CVRC in patients with carotid artery occlusion is reported by several groups. In a study including 72 patients with ICA occlusion symptomatic for TIAs, reversible ischemic neurologic deficit, or stroke, Derlon et al\textsuperscript{20} found a normal or slightly decreased CVRC in the contralateral, asymptomatic hemisphere and a permanently decreased CVRC in the ipsilateral, symptomatic hemisphere in 32% of the patients. In seven patients, these authors noted a spontaneous normalization of CVRC. The constellation of carotid artery occlusion and normal CVRC is not necessarily coupled with collateral vessels seen on angiography.

In D-SPECT measurements, the Kanno/Lassen\textsuperscript{21} algorithm does not differentiate gray from white matter nor pathologically changed (e.g., ischemic) from normal tissue. Four of our 21 patients had small territorial infarcts in the analyzed regions. In three of these four, $\Delta$CBF was pathologically low, whereas $\Delta$FV reflected normal to borderline CVRC.

Using the widely accepted D-SPECT method, our previous findings in a large group of normal persons suggested that $\Delta$FV depends on FV at rest. Although in all controls FV increased significantly after acetazolamide injection, we were unable to demonstrate the expected relation. Even with high FV at rest, a high $\Delta$FV was possible, thus providing further evidence that FV does not represent true CBF. Adaptive changes in vessel diameter might be responsible for this divergence.

In the only available study concerning the influence of acetazolamide on FV, Hauge et al\textsuperscript{22} reported an increase after 2 minutes and a maximum increase after 25 minutes. However, these authors insonated the extracranial ICA and, more importantly, they used 500 mg acetazolamide, which was, as they speculated, probably not enough to fully inhibit carbonic anhydrase.

Assessment of CVRC by means of TCD and acetazolamide injection in 21 symptomatic patients correlated with D-SPECT results in either hemisphere. Sensitivity of the TCD test was satisfying; four of six false-negative tests had borderline results, and there was only one false-positive result.

In accordance with other studies,\textsuperscript{23} CVRC in the contralateral, asymptomatic hemisphere does not necessarily have to be lower than that in the symptomatic hemisphere. Acetazolamide had no significant influence on systemic arterial blood pressure, PaCO$_2$, or PaO$_2$, in agreement with other authors.\textsuperscript{24} Theoretically, the induction of peripheral vasodilation in subjects with impaired cerebral perfusion might lead to symptoms of cerebral ischemia. For this situation, volume substitution is imperative. In >1,000 examinations, we have never experienced this complication.

There is no final proof for the efficacy of any treatment for cerebral ischemia. Recent studies\textsuperscript{25,26} suggest that CVRC can indicate a subgroup of patients with hemodynamic augmentation who might benefit from revascularizing or recanalizing procedures. To determine available therapy in this subgroup, our TCD-based test can be used as a simple screening method in institutions in which CBF measurements are not available. Our TCD-based test might further be helpful in clinical studies to clarify the frequency of ischemic stroke of hemodynamic origin.

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References

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KEY WORDS • acetazolamide • cerebral blood flow • tomography, emission computed • ultrasonics

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