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Noninvasive Autoregulation Testing in Normal Volunteers and Patients with Cerebrovascular Disease

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ABSTRACT **Cerebral autoregulation functions to keep blood flow constant over a wide range of mean arterial pressures (MAP) by changing vascular resistance in the microcirculation. This mechanism may be impaired in patients with stenotic or occlusive lesions in the internal carotid and middle cerebral arteries, particularly if collateral circulation is inadequate.**

Purpose: The purpose of this study was to evaluate cerebral autoregulation in patients with unknown or suspected cerebral vascular disease. We tested autoregulation in 29 volunteers (18 males, 11 females) and 55 patients (31 males, 24 females) between January 1994 and May 1997. Of the 55 patients, or 110 hemispheres, 36% (40/110) were omitted due to vessel occlusion, no temporal window for insonation, or a technically inadequate test.

Methods: The bilateral middle cerebral artery (MCA) velocities and the arterial blood pressure were continuously recorded during a rapid, transient drop in blood pressure produced by deflating large bilateral thigh cuffs after 3–5 min suprasystolic inflation. The sudden decrease in pressure induced a drop in MCA velocity, which corresponded to a drop in cerebral blood flow. An autoregulation index (ARI) was calculated using a curve-fitting algorithm comparing the rate of return of velocity in the MCA to the rate of return of the MAP.

Results: In 29 normal volunteers, the ARI was 4.7 ± 1.0. In 35 patients or 68 hemispheres (only one hemisphere was used from each of two patients), 37% (25/68) had a normal ARI and 44% (30/68) were abnormal. An exhausted autoregulatory response was demonstrated in 19% (13/68).

In the group of normal volunteers, no one had an ARI below 2.5; however, in the patient group, 44% (30/68) had an ARI below 2.5, $p \ll 0.001$, which was statistically significant.

Introduction

Cerebral autoregulation functions to maintain a constant level of blood flow to the brain independent of a wide range of blood pressure changes.[1] Through changes in the resistance of the arterioles, cerebral blood flow (CBF) is maintained at a nearly constant level between mean arterial blood pressures (MAP) of 50–150 mm Hg.[2,3] When systemic blood pressure decreases, CBF decreases. The arterioles then vasodilate, which lowers resistance. Thus, flow to the brain is restored to the baseline level. When systemic blood pressure is raised, CBF increases, and the arterioles vasoconstrict, resistance to flow is high, and flow to the brain is decreased. The exact mechanism responsible for this phenomenon remains undetermined, although it is thought to be a multifactorial process that includes mechanical (myogenic), metabolic, and neurogenic factors.[2]

Early observations of this phenomenon were done in 1928 by Fogg when he conducted experiments in cats to investigate how pial arteries would react to a reduction of blood pressure. He visualized the pial arteries through craniotomies using a microscope. The reactions of these arteries were measured while the systemic blood pressure was reduced, and he found that the arteries vasodilated with induced hypotension. These reactions took place even after the carotid sinus, depressor, and cervical sympathetic nerves had been severed. He concluded that the arteriolar responses were directly related to systemic blood pressure changes and not a result of nerve stimulation.[4] By 1959, several authors demonstrated, using quantitative CBF techniques in man, that within a wide range of blood pressure, CBF was independent of the changes in the systemic blood pressure. Moderate reductions of blood pressure did not influence CBF; however, in the presence of significant hypotension or a MAP of less than 50 mm Hg, cerebral vasodilation of the arterioles became inadequate, with resultant

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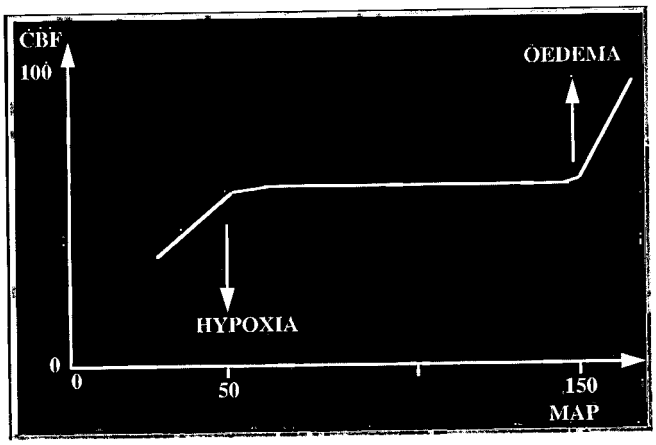

Figure 1

The pressure limits of autoregulation are demonstrated. The mechanism of autoregulation does not function below a MAP of 50 mm Hg with resultant low cerebral blood flow or above a MAP of 150 mm Hg with resultant high cerebral blood flow

reductions in blood flow to the brain. These studies defined the lower limit of autoregulation.[2] It was not until the 1970's that an upper limit of autoregulation was investigated in animal studies.[5,6] Subsequent studies in humans using xenon, laser Doppler, and thermal diffusion methods for measuring CBF have confirmed the pressure limits of cerebral autoregulation to be between MAP's of 50–150 mm Hg (Figure 1).[1]

Most methods of measuring CBF were limited in the frequency of measurement and therefore a static method was used, monitoring changes over minutes. Autoregulation is known to be a fast-acting homeostatic function that occurs within seconds. Aaslid et al. introduced the dynamic method of autoregulation testing in 1989 using transcranial Doppler (TCD). While the middle cerebral artery (MCA) was monitored, a rapid, transient drop in blood pressure was used to induce an autoregulatory response. The blood pressure was dropped by deflating large, thigh blood pressure cuffs that had been inflated suprasystolic for 2 min. TCD allowed continuous, real time, noninvasive analysis of the MCA flow velocities over a period of seconds. Aaslid found that the rate of regulation was strongly dependent on cerebral vascular tone.[7]

To measure relative changes in CBF by measuring MCA flow velocity, the vessel diameter of the MCA cannot significantly change.[7] Newell et al.[8] compared internal carotid artery flow with electromagnetic flowmetry and TCD velocity. During surgical exposure of the internal carotid artery for either carotid endarterectomy or for proximal exposure for control during aneurysm surgery, these investigators simultaneously and continuously measured volume flow from the internal carotid artery (ICA) and velocity from the MCA using TCD and performed dynamic autoregulation tests. They found that the MCA flow velocity and ICA volume flow did not significantly differ with transient decreases in blood pressure and concluded that the MCA vessel diameter does not significantly change during rapid changes of systemic blood pressure.[8] This also supported the concept that autoregulation is primarily a function of the smaller resistance vessels.[1]

Normally, when systemic blood pressure is rapidly dropped, MCA flow velocities will drop. To maintain adequate blood flow in the brain, the arterioles rapidly dilate, causing an increase in cerebral flow and a subsequent increase in the MCA velocity. Conversely, when systemic blood pressure increases, the arterioles constrict to maintain a constant cerebral blood flow.[3] In patients with occlusive lesions that produce decreases in perfusion pressure in the cerebral vessels, autoregulation may be impaired or absent. If impaired, the arterioles dilate only minimally with blood pressure changes to maintain cerebral blood flow. If autoregulation is absent, the arterioles maximally dilate and are unable to dilate further to increase blood flow in the brain. This means that blood flow in the brain is passive to systemic blood pressure and any sustained low systemic blood pressure could cause ischemia.[9]

It has been documented that autoregulation can be impaired in traumatic head injuries and intracranial hemorrhage.[10,11] The purpose of this study was to compare autoregulation in normal volunteers and patients with cerebrovascular disease.

Subjects

Twenty-nine normal volunteers (18 male and 11 female) between 18 and 72 years of age were screened for cerebrovascular disease using an 8-MHz continuous wave Doppler ultrasound transducer and TCD. Volunteers with known cerebrovascular disease or peripheral vascular disease were excluded. Fifty-five patients, 31 male and 24 female, between the ages of 28 and 69 with known cerebrovascular disease underwent baseline TCD, CO_2 challenge (vasomotor reserve), carotid duplex, Magnetic Resonance Imaging/Magnetic Resonance Angiography (MRI/MRA), and or cerebral angiography. Of the 55 patients, 36% (40/110 hemispheres) were omitted due to hyperostosis or lack of a temporal window, revascularization of the lower extremity, MCA occlusion, or a technically inadequate test.

All patients had 50% or greater lesions either extracranially or intracranially, uni- or bilaterally. Sixty-six percent (23/35) of the patients had atherosclerotic lesions, 11% (4/35) had fibromuscular dysplasia, another 11% (4/35) had Moya Moya disease, 6% (2/35) had ICA dissections, 3% (1/35) had a surgical occlusion of the ICA for entrapment of an aneurysm, and 3% (1/35) had a traumatic occlusion of the ICA from a gun shot wound to the neck.

Autoregulation index (ARI) testing in volunteers was approved by the University of Washington Human Subject Review Committee with written informed consent signed by each participant. ARI

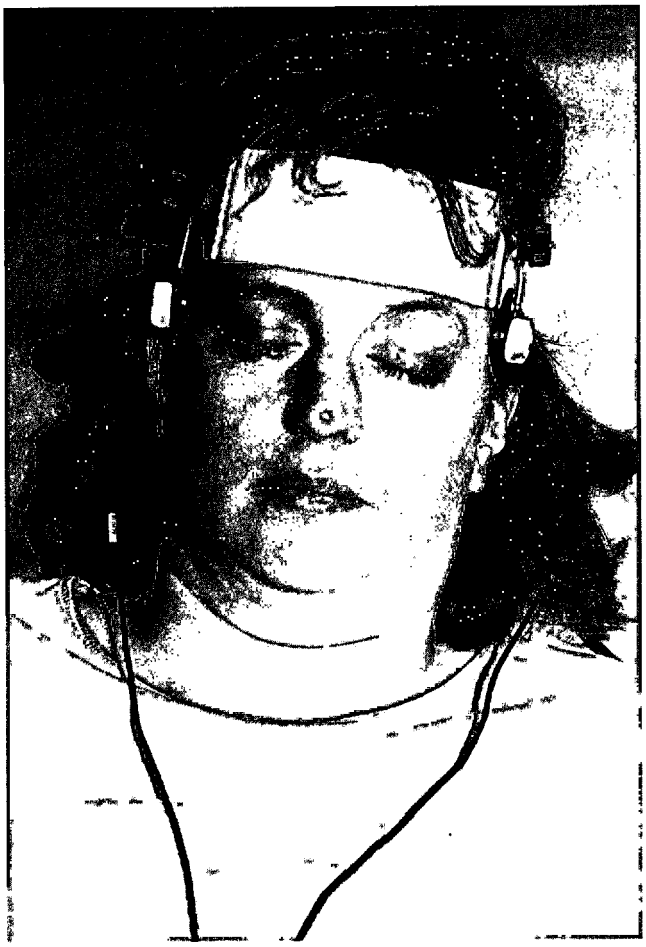

Figure 2

The MCA's were monitored using a headband providing continuous, bilateral flow velocites.

testing of patients is part of a clinical noninvasive work-up.

Materials and Methods

All subjects were tested in a supine position. The bilateral MCA's were identified by previously described methods[12] with TCD (Multidop X; DWL Corporation, Sipplingen, Germany). A headband was used to secure the transducers to the temporal windows for continuous monitoring (Figure 2). A tonometric sensor (N-CAT 500, Nellcor Corporation, Hayward, CA) was placed over the radial artery to continuously, noninvasively monitor the systemic blood pressure and MAP (Figure 3). A pneumatic calibration cuff was placed on the upper arm. Clinical accuracy testing of the tonometric sensor exceeded the requirements of the Association for the Advancement of Medical Instrumentation with systolic and diastolic standard deviations of less than 0.9 mm Hg.[13] Large blood pressure cuffs were placed on both thighs and attached to a rapid inflation/deflation device (Hokanson, Bellevue, WA) (Figure 4).

Baseline MCA flow velocities and MAP were recorded in a color-coded trend (red for MAP, orange for the right MCA, and green for the left MCA) (Figure 5). After 3.5–4 min of 30–40 mm Hg suprasystolic inflation, the cuffs were rapidly deflated, causing a transient drop in systemic blood pressure and stimulating an autoregulatory response. The computer calculated an index from the changes of the systemic blood pressure and MCA flow velocities just prior to and after the release of the thigh cuffs. It also compared the rate of return of the MCA flow velocity with the rate of return of the MAP and assigned a curve fitting algorithm to the trend (Figure 6). The mathematical equation describing the curve-fitting algorithm has been published elsewhere.[14] The calculated index is between 0.0, which would be exhausted, and 9.0, which would indicate an accentuated autoregulatory response. The longer the time for the MCA flow velocity to return to baseline, the lower the ARI. Conversely, the quicker the time for the MCA flow velocity to return to baseline, the higher the ARI. When the MCA flow velocity did not return to base-

Figure 3

The blood pressure and MAP was noninvasively and continuously monitored by a tonometric sensor placed over the radial artery secured by velcro straps.

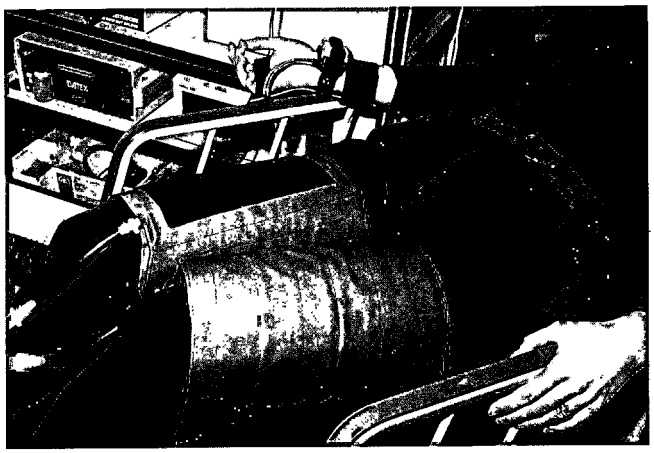

Figure 4

To induce a transient drop in systemic blood pressure, large cuffs were placed on both thighs and inflated suprasystolic for 3.5–4 min and then rapidly deflated.

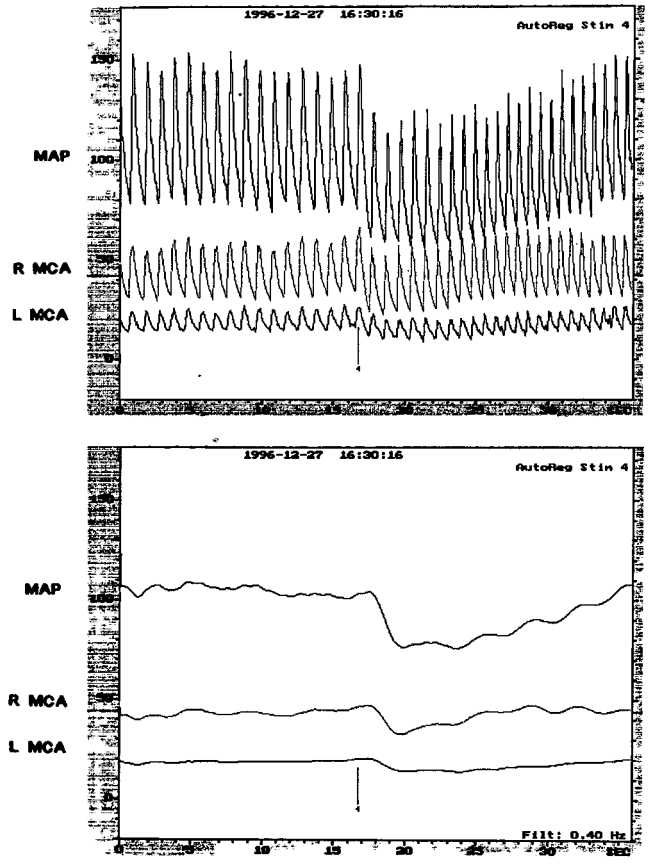

Figure 5

(A) An example of the trend of the MAP, LMCA, and RMCA. (B) Demonstration of the same trend only filtered for measuring data.

line within 30 sec, the ARI was 0.0. The test was repeated several times until 2–3 technically adequate results were reproduced, which were then averaged for an autoregulation index.

Statistical Analysis

Results were analyzed using the Student's *t*-test (unpaired) and the chi-square test. Differences were considered significant at the $p < 0.05$ level. Values are expressed as means ± standard deviation for inclusion of a larger normal range.

Results

All data were reanalyzed off-line. The normal values from the volunteers for ARI were 4.7 ± 1. Values below 2.7 (2 SD below the normal value) were then abnormal and an ARI of 0.0 was exhausted or blood flow was passive to blood pressure. Of the 35 patients, or 68 hemispheres (one hemisphere was used from each of two patients), 48% (33/68) of the patients had a normal ARI, 31% (21/68) had an abnormal ARI, and 21% (14/68) were exhausted. Within the exhausted group, 13% (9/68) had normal MCA flow (55 ± 12 time-averaged mean flow velocity)[12]

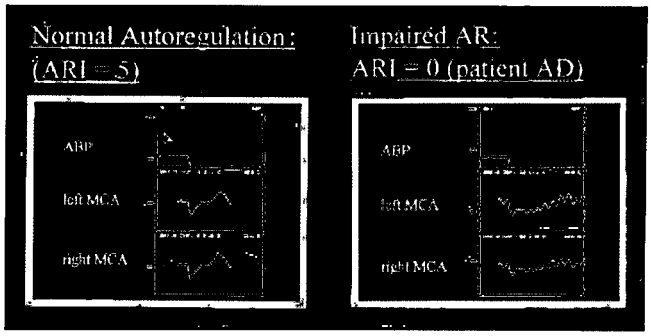

Figure 6

An example of a normal and abnormal autoregulation study. Note the longer period of time for the MCA flow velocities to return to baseline in the abnormal test.

and 7% (5/68) had abnormal MCA flow velocities. Four patients were abnormally low flow and one patient was abnormally high flow secondary to a hyperdynamic state.

The left MCA (LMCA) velocities of the patients were not statistically different than the volunteers and the right MCA (RMCA) velocities were not highly statistically different. The ARI of the patients were lower and statistically significant when compared to the volunteers (Table I). Within the normal volunteers, no one had an ARI below 2.7; however, of the total patients, 52% (35/68) had an ARI below 2.7, which was also statistically significant ($p < 0.001$). As a group, the volunteers' ARI values formed a nearly perfect distribution when plotted as a histogram; however, the patients demonstrated a scattering (Figure 7). The normal volunteer ARI's were averaged together as well as the patient ARI's because there were no statistically significant differences between the hemispheres.

Only one patient was asymptomatic and referred for a preoperative work-up for known cerebrovascular disease. Treatment to improve cerebral perfusion was done on 15% (10/68) of the hemispheres with ARI's < 2.7 and 7% (5/68) with an ARI > 2.7. Extracranial to intracranial by-pass procedures were done on 15% (10/68) of the hemispheres; 6% (4/68) were carotid endarterectomies and 2% (1/68) were stent placements in the common carotid artery.

Table I

Comparison Between the Normal Volunteer and Patients, MCA Flow Velocities and ARI's; p-Values Were Calculated by Students t-Test (Unpaired)

	Volunteers	*Patients*	*p-Value*
LMCA velocities	61 ± 14	53 ± 20	0.085
RMCA velocities	60 ± 13	50 ± 17	0.013
LMCA ARI	4.6 ± 1.0	2.3 ± 2.17	>0.001
RMCA ARI	4.8 ± 1.0	2.9 ± 1.90	>0.001

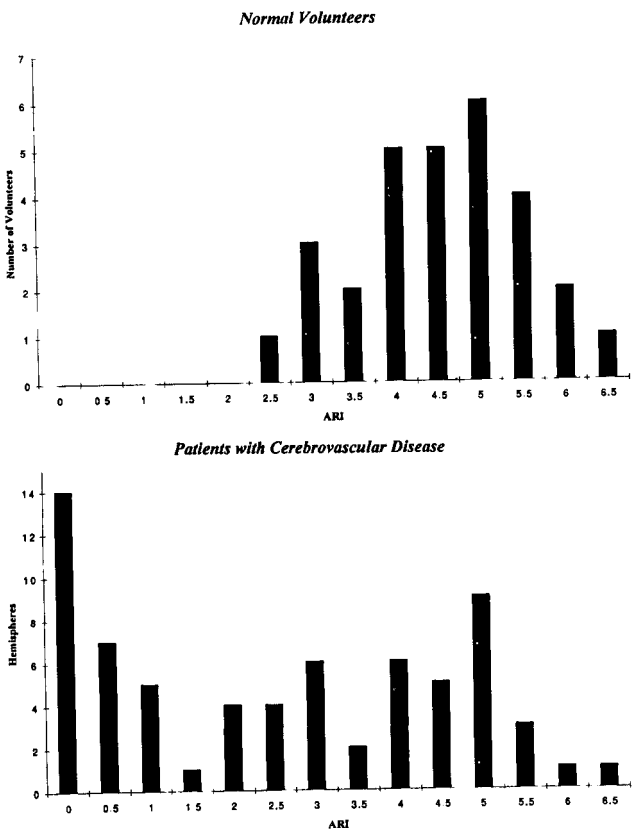

Figure 7

(A) Histogram of the normal volunteers ARI 4.7 ± 1, demonstrating a nearly perfect distribution. (B) Histogram of the patients' ARI's, which demonstrates a scattering.

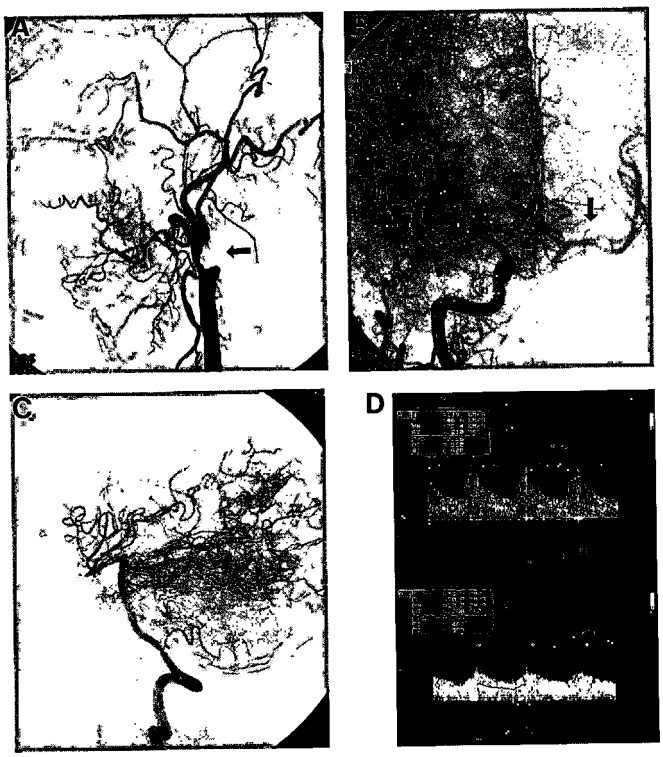

Figure 8

Angiographic finding demonstrating an (A) occluded left ICA, (B) right to left collateral cross-over via a patent AcoA, and (C) posterior to anterior collateral via the left PcoA. (D) Comparison of the right and left MCA flow velocities. Note the lower flow of the left MCA and slowed systolic upstroke.

Case Study

DH is a 50-year-old male who presented with a history of progressive recurrent transient ischemic attacks (TIA's) with right-sided weakness, left amaurosis fugax, and dysphasia. His risk factors are significant for hypertension and tobacco abuse. In October 1996, he experienced a sudden onset of right-sided weakness and expressive aphasia. His weakness resolved within 24 hr, but he continued to stutter and use the wrong words. An angiogram documented a total occlusion of the left ICA, 50–70% stenosis of the right ICA, and a 75–85% left vertebral origin stenosis. He was placed on Coumadin and continued to have almost daily left hemisphere TIA's.

The patient was referred to our institution because of failed medical management and was seen in our laboratory for a TCD, CO_2 challenge, and autoregulation studies in June 1997. The TCD was remarkable for low flow velocities in the LMCA with right to left collateral flow via a patent anterior communicating artery (ACoA), posterior to anterior collateral via a patent left posterior communicating artery (PcoA), and poststenotic low flow in the left vertebral artery. These findings were consistent with the angiogram done in May 1997 (Figure 8). The CO_2 or vasomotor reactivity (VMR) of the LMCA was −5%, which was severely reduced, and the RMCA was 108%, which was a normal response. The ARI of the LMCA was 1.0 or impaired and the ARI of the RMCA was 5.0 or normal (Figure 9). A CT scan done on September 3, 1997, showed focal volume loss and a hypodensity consistent with infarction within the left frontal opercular region (Figure 10).

Despite the presence of collaterals, flow velocities in the LMCA were low, with a severely reduced VMR and an impaired ARI. The patient underwent a left external carotid endarterectomy to enhance blood flow to the left hemisphere in September 1997. Nine days postoperative, he returned with continuing TIA's referable to the left hemisphere. A left superficial temporal artery to the left MCA by-pass was then performed October 1997. DH continues to have some persistent speech problems; however, his TIA's have significantly improved, with only an occasional tingling in his right hand.

Conclusion

Cerebrovascular occlusive disease may produce arterial occlusions or stenoses that can reduce cerebral perfusion pressure (CPP) and cause impairment or absence of autoregulation. Because autoregulation is a pressure-dependent phenomenon, when the CPP falls beyond the lower limit of autoregulation (Figure

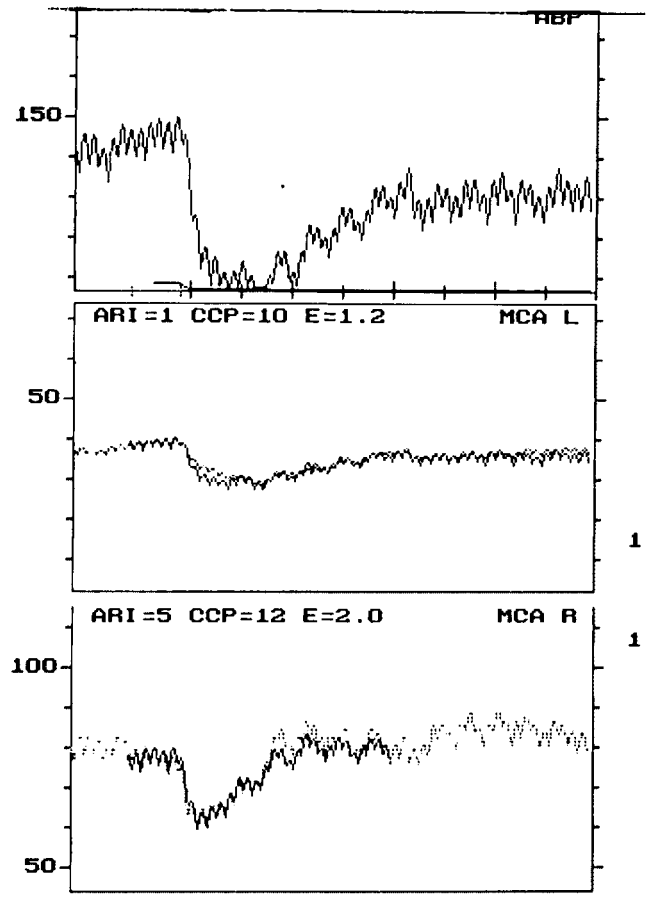

Figure 9

An example of one autoregulation test demonstrating the left MCA ARI to be 1.0 or impaired and the right MCA ARI to be 5.0 or normal.

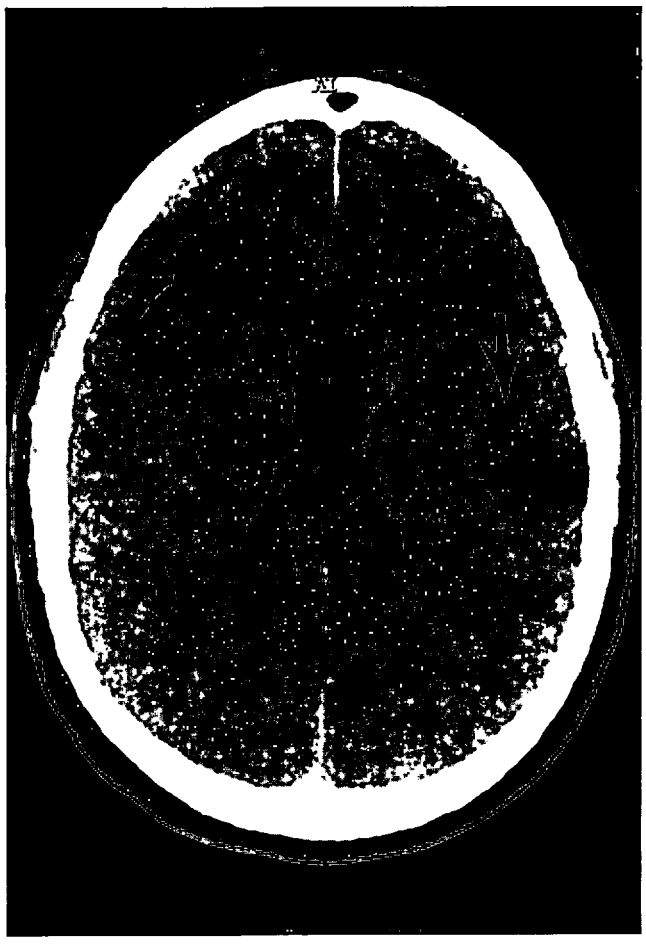

Figure 10

Illustration of the CT scan. The arrow shows the hypodensity consistent with infarction.

1), patients may be at risk for primary ischemia and or secondary ischemia associated with embolization. Embolization may occur due to stasis of blood distal to the hemodynamic lesion. All patients with abnormal or absent ARI's had >80% stenosis or occlusion angiographically within the ipsilateral hemisphere; however, clinical symptoms varied. In our total patient population, 52% (35/68) had an abnormal ARI of <2.7. In patients with normal MCA velocities, 40% (27/68) had an ARI below 2.7, with 13% (9/68) being exhausted. This suggests that patients with pressure-reducing lesions may have impaired or absent autoregulation, even though the TCD exam has what may be considered adequate collaterals based on normal MCA flow velocities. We conclude that normal MCA flow velocities are not a reliable predictor for a normal ARI. Autoregulation studies can contribute valuable information regarding cerebral blood flow control by identifying or confirming patients at high risk for cerebral ishemia due to impaired perfusion. Cerebrovascular reactivity testing may identify candidates who would benefit from procedures to augment cerebral blood flow. Further clinical studies are required to determine the significance of impaired perfusion and impaired autoregulation in patients with cerebrovascular disease.

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