Chronically Impaired Autoregulation of Cerebral Blood Flow in Long-Term Diabetics

BY NIELS BENTSEN, M.D., BO LARSEN, M.D., AND NIELS A. LASSEN, M.D.

Abstract:
Chronically Impaired Autoregulation of Cerebral Blood Flow in Long-Term Diabetics

Using the arteriovenous oxygen difference method autoregulation of cerebral blood flow (CBF) was tested in 16 long-term diabetics and eight control patients. Blood pressure was raised by angiotensin infusion and lowered by trimethaphan camysylate infusion, in some cases combined with head-up tilting of the patient. Regression analysis was carried out on the results in order to quantify autoregulatory capacity.

In the control patients CBF did not vary with moderate blood pressure variations, indicating normal autoregulation. In four of the 16 diabetic patients CBF showed significant pressure dependency, indicating impaired autoregulation. The cause of impaired autoregulation in some long-term diabetics is believed to be diffuse or multifocal dysfunction of cerebral arterioles due to diabetic vascular disease. Other conditions with impaired autoregulation are discussed and compared with that seen in long-term diabetics.

Additional Key Words: arteriovenous oxygen difference method, diabetic angiopathy, arterial hypertension

Introduction

Autoregulation of the cerebral circulation is a mechanism that ensures a constant cerebral blood flow (CBF), and thereby a sufficient oxygen supply, despite variations in arterial blood pressure. This mechanism is believed to be dependent on normally functioning cerebral arterioles (resistance vessels), capable of dilating when blood pressure is lowered, and of constricting when blood pressure is raised. Autoregulation is only operating in a certain blood pressure interval around the resting mean arterial blood pressure (MABP), breaking down at a lower and upper limit. At the lower limit, which is 60 to 70 mm Hg MABP for a normotensive person with a resting MABP of about 90 mm Hg,1-3 CBF begins to decrease, but sufficient oxygen supply is still ensured by an increase in the arteriovenous (AV) oxygen extraction. At still lower blood pressures (for a normotensive person about 35 to 40 mm Hg) also this mechanism fails, and cerebral hypoxia develops.4 At the upper limit the capacity of the arterioles to resist the increased intraluminal pressure is overcome resulting in a sudden rise in blood flow, the so-called "breakthrough" phenomenon.5, 4

Long-term diabetes mellitus and arterial hypertension are known to be associated with arteriolar disease and therefore could very well be conditions in which cerebral autoregulation was not functioning properly. The present study was undertaken in order to investigate the autoregulatory capacity in long-term diabetics.

Patients and Methods

Sixteen long-term diabetics were examined (table 1), of whom two (Cases 1 and 6) were examined on two separate occasions. Long-term diabetes in this study signifies either a duration of diabetes of 15 years or more, or unequivocal signs of diabetic retinopathy, regardless of known duration of diabetes. Ages ranged from 35 to 77 years, average 57 years. Known duration of diabetes ranged from 4 to 34 years, average 17 years.

All were outpatients in such physical and mental condition that they could live a normal or nearly normal life at home. Cases 3, 4, 7, and 11 were temporarily hospitalized at the time of study.

Thirteen of the patients had diabetic retinopathy to a varying degree and three patients (Cases 12, 15, and 16) had arterial hypertension. One patient (Case 8) had previously had myocardial infarction, but at the time of study none of the patients had any cardiorespiratory complaints. No specific investigations were undertaken to determine blood flow in the lower extremities, renal function or the presence or degree of diabetic neuropathy. Eight patients had or had previously had intermittent claudication or gangrene in the lower extremities. Albuminuria was present in eight patients, of whom three also had increased serum creatinine. This was attributed to diabetic nephropathy.

Case 10 had complaints of vertigo prior to the study. Case 13 had organic dementia, probably related to chronic alcoholism, and two weeks prior to the study had had an apoplectic attack from which a slight hemiparesis remained. Except for these two patients none of the patients studied had any complaints of vertigo, headache, and syncope or any other symptoms or signs that could be attributed to diffuse or focal intracranial disease.

In addition eight non-diabetic control patients were examined (table 2). Their ages ranged from 41 to 71 years, average 52 years.

All patients gave their informed consent to participate in the study. This also applies to Case 13 with organic...
**TABLE 1**

**Diabetic Patients**

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Known duration of diabetes (years)</th>
<th>Retinopathy*</th>
<th>MAP (rest)</th>
<th>Intermittent claudication or gangrene of lower extremities</th>
<th>Previous MI</th>
<th>Albuminuria</th>
<th>Increased serum creatinine</th>
<th>Vertigo, headache, syncope</th>
<th>b†</th>
<th>r‡</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>56</td>
<td>19</td>
<td>(+)</td>
<td>83</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0.4778</td>
<td>0.9375</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>77</td>
<td>14</td>
<td>+ +</td>
<td>116</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.2713</td>
<td>0.6892</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>68</td>
<td>15</td>
<td>0</td>
<td>86</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0.2690</td>
<td>0.9434</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>56</td>
<td>19</td>
<td>(+)</td>
<td>90</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0.2073</td>
<td>0.7175</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>69</td>
<td>23</td>
<td>+++</td>
<td>109</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.1339</td>
<td>0.5954</td>
<td>NS</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>38</td>
<td>19</td>
<td>+++</td>
<td>115</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0.1315</td>
<td>0.7319</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>47</td>
<td>16</td>
<td>+</td>
<td>86</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.1301</td>
<td>0.3781</td>
<td>NS</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>47</td>
<td>16</td>
<td>+</td>
<td>82</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.1255</td>
<td>0.4362</td>
<td>NS</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>46</td>
<td>4</td>
<td>++</td>
<td>98</td>
<td>+</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0.1070</td>
<td>0.4451</td>
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<tr>
<td>10</td>
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<td>+</td>
<td>104</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0.0917</td>
<td>0.4045</td>
<td>NS</td>
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<tr>
<td>11</td>
<td>F</td>
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<td>(+)</td>
<td>87</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.0906</td>
<td>0.3118</td>
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</tr>
<tr>
<td>12</td>
<td>M</td>
<td>67</td>
<td>16</td>
<td>+++</td>
<td>113</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Vertigo</td>
<td>0.0603</td>
<td>0.4222</td>
<td>NS</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>51</td>
<td>30</td>
<td>++</td>
<td>113</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0.0545</td>
<td>0.1672</td>
<td>NS</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
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<td>11</td>
<td>++</td>
<td>138</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0.0452</td>
<td>0.1314</td>
<td>NS</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
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<td>+++</td>
<td>113</td>
<td>+</td>
<td>0</td>
<td>0</td>
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<td>0.0223</td>
<td>0.0794</td>
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<td>16</td>
<td>F</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0.0208</td>
<td>0.0573</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Degree of diabetic retinopathy: (+) = slight but manifest, + = moderate, ++ = severe, +++ = proliferative retinopathy.
†Slope of regression line.
‡Coefficient of correlation.
CEREBRAL AUTOREGULATION IN DIABETES

dementia, whose mental condition was not seriously deteriorated. The control patients were examined as part of their clinical investigation.

No cerebral, cardiovascular or other complications occurred in the patients during or after the study.

CBF was measured by the arteriovenous oxygen difference method. If the cerebral metabolic rate of oxygen (CMRO2) is assumed to be constant, CBF can be calculated from the arteriovenous oxygen difference (AV O2) by means of the Fick principle:

\[
\text{CBF} = \frac{\text{CMRO}_2}{\text{AV O}_2}
\]

where \( \frac{1}{\text{AV O}_2} \) gives a relative measure of CBF, which is expressed as a percentage of the resting \( \frac{1}{\text{AV O}_2} \) value (CBF%). CMRO2 has repeatedly been shown to be constant in conscious man in the resting condition and during variations in MABP, including hypotension with signs of hypoxia.

In each individual study the various CBF% values were corrected for small variations in Paco. A difference in Paco, of 1 mm Hg was assumed to correspond to a change in CBF% of 4%. Corrections were carried out only when no signs of hypoxia were present.

The study was started at 8 A.M. The patients were not fasting, and the diabetics had had their usual morning insulin doses. A catheter was placed with the tip in the right jugular bulb under fluoroscopic control either from a superficial right arm vein or via one femoral vein by the Seldinger technique. Another catheter was placed in either a brachial or femoral artery. A regular intravenous infusion set was placed in a superficial arm vein connected to an infusion pump. Arterial and jugular venous pressures were continuously measured with transducers (EMT-34, Elema-Schönander). Regardless of the position of the arterial catheter and the patient, the transducers for blood pressure monitoring were constantly kept level with the patient's external acoustic meatus to avoid hydrostatic error.

The arterial blood pressure was raised by intravenous infusion of angiotensin amide (Hypertensin, CIBA) and lowered by infusion of trimethaphan camsylate (Arfonad) via the infusion pump, in some cases combined with head-up tilting of the patient. In this way observations in a wide MABP interval above and below the resting MABP were obtained in each case.

Neither of these drugs has any direct effect on cerebral circulation; consequently, changes in CBF during their administration must be due to changes in systemic blood pressure.

Blood samples from the jugular bulb and the femoral artery were drawn simultaneously in the resting condition and at various blood pressure levels above and below this value. Steady state was secured by not drawing the blood samples until two to five minutes had elapsed after the blood pressure had stabilized at a particular value. Oxygen content in arterial and jugular venous blood was determined by measuring the hemoglobin oxygen saturation spectrophotometrically and Paco, was measured with a Severinghaus electrode.

Results

Based on AV O2 the relative CBF was calculated as percent of rest (CBF%) and corrected for differences in Paco as described above. In each individual study these values were plotted against MABP and a graph was obtained by simple visual interpolation of the points (fig. 1). In order to further quantify the results a linear regression analysis was carried out according to the following principles: Only corresponding values of CBF% and MABP that seemed to naturally fit a straight line within the normal range of autoregulation have been used in the regression analysis (fig. 2). Thus care was taken not to include observations that seemed to lie beyond the upper and lower limit of the MABP interval, in which autoregulation is expected to function properly in normal and hypertensive man. In each case the coefficient of correlation (r) was calculated (tables 1 and 2).

Among the diabetics five out of 18 studies (four patients [Cases 1, 2, 3, and 5] of whom Case 1 was reexamined) showed an r-value significantly different from 0, corresponding to 25% of the diabetic patients (table 1), whereas among the control patients no r-value was significantly different from 0 (table 2).

Average resting CBF in diabetics and control patients...
patients was 105 mm Hg and 97 mm Hg, respectively. The maximum increase in CBF with increasing MABP amounted to about 20% (Cases 1 and 3).

**Discussion**

The crucial point in the AV O₂ method is the constancy of CMRO₂. In the literature it seems well established that CMRO₂ remains constant in conscious normal man, when MABP is varied. This applies even when MABP values are so low that hypoxia is manifest and syncope imminent.\(^3\)\(^4\)

When evaluating cerebral autoregulation it is essential not to include observations in the regression analysis from outside of the MABP interval, in which autoregulation is operating. It is impossible to predict with certainty the MABP values of the upper and lower limits from the resting MABP value. In most cases the interval from the resting MABP to the upper limit is greater than from the resting MABP to the lower limit, but this is not always so (fig. 3). Furthermore, as seen in figure 1, CBF very often begins to decrease at MABP values just below the resting MABP. Thus, in order to obtain a correct picture of the patient’s autoregulatory function and its range, it is necessary to measure CBF over a wide range of MABP values above and below the measured resting MABP. This, in order to obtain a correct picture of the patient’s autoregulatory function and its range, it is necessary to measure CBF over a wide range of MABP values above and below the measured resting MABP value. Only in this way is it possible to avoid including observations from outside of the particular patient's autoregulatory range in the regression analysis.

If only two observations are made, for instance one at the resting level and one at a blood pressure below this level, the risk of including observations from outside of the particular patient's autoregulatory range must be faced, thus perhaps resulting in a false impression of impaired autoregulation. By exploiting the advantage of the AV O₂ method enabling us to make multiple measurements of CBF over a wide range of MABP values below and above the resting MABP, we have endeavored to avoid such mistakes.

Autoregulation of the cerebral circulation has repeatedly been shown to be a very precisely operating mechanism, i.e., within the autoregulatory range changes in MABP will elicit practically no change in CBF.\(^1\)\(^2\)

When testing the autoregulatory function in 16 long-term diabetics, we found four patients with statistically non-horizontal curves (Cases 1, 2, 3, and 5). One of these patients (Case 1) was reexamined five months later, again resulting in a non-horizontal curve. None of these four patients had any signs or symptoms that could be attributed to diffuse or focal intracranial disease. No cerebral symptoms developed during the test in these patients, and, in particular, no signs of hypoglycemia were noted. By visual examination of the regression lines (fig. 4) there appears to be a continuous spectrum from practically horizontal to more and more oblique lines, indicating a smooth transition from normal to definitely impaired autoregulation.

Our interpretation of these findings is that among

**TABLE 2**

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>MABP (rest)</th>
<th>b*</th>
<th>r f</th>
<th>r ≠ 0</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>57</td>
<td>93</td>
<td>0.0928</td>
<td>0.3717</td>
<td>NS</td>
<td>Cerebral atrophy, vertigo</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>45</td>
<td>100</td>
<td>0.0878</td>
<td>0.5272</td>
<td>NS</td>
<td>L ICA occlusion</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>41</td>
<td>100</td>
<td>0.0439</td>
<td>0.2633</td>
<td>NS</td>
<td>Lipothymia</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>71</td>
<td>100</td>
<td>0.0323</td>
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<td>NS</td>
<td>Lipothymia</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>61</td>
<td>88</td>
<td>-0.0367</td>
<td>-0.2991</td>
<td>NS</td>
<td>Lipothymia</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>45</td>
<td>92</td>
<td>-0.0538</td>
<td>-0.2117</td>
<td>NS</td>
<td>Chronic alcoholism, vertigo</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>49</td>
<td>84</td>
<td>-0.0737</td>
<td>-0.3305</td>
<td>NS</td>
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</tr>
<tr>
<td>8</td>
<td>F</td>
<td>45</td>
<td>118</td>
<td>-0.1075</td>
<td>-0.3760</td>
<td>NS</td>
<td>Epilepsy, vertigo</td>
</tr>
</tbody>
</table>

* Slope of regression line.
† Coefficient of correlation.
L = left, ICA = internal carotid artery.
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long-term diabetics without clinical signs of diffuse or focal intracranial disease some have a chronic impairment of cerebral autoregulation.

The degree of impairment in our studies is relatively small and cannot be expected under normal conditions to have any clinical significance for the patient. Thus none of our four patients with statistically non-horizontal curves had complaints that could be ascribed to dysfunction of cerebral circulation. In some patients, however, this autoregulatory impairment might be severe to a degree, where clinical significance could be expected under special circumstances, e.g., development of cerebral ischemia during arterial hypotension in connection with general anesthesia.

Our method does not allow us to draw conclusions as to the exact nature of the abnormality that causes impaired autoregulation in some long-term diabetics. Neither does it distinguish between multifocal and focal pathology, since what is measured is the overall cerebral perfusion.

That our findings should be due to impaired function of the sympathetic nervous system as a result of diabetic neuropathy seems unlikely. No report in the literature until now has convincingly demonstrated that an intact sympathetic nervous system is necessary for proper functioning of the autoregulatory mechanism. On the contrary, evidence is accumulating that neither surgical nor pharmacological sympathectomy diminishes autoregulatory capacity. Eklöf et al. (1971) showed that surgical sympathectomy two weeks prior to the study had no influence on the autoregulatory function in monkeys. Fitch et al. have recently shown that in baboons acute surgical sympathectomy causes only a paired autoregulation due exclusively to sympathetic denervation is, however, for the reasons given above, difficult to accept. Furthermore, reports of this phenomenon are few and somewhat conflicting. Among these different disease states only chronic idiopathic autonomic insufficiency can be said, in a strict sense, to represent a condition with chronically impaired autoregulation due to arteriolopathy due to sympathetic denervation is, however, for the reasons given above, difficult to accept. Furthermore, reports of this phenomenon are few and somewhat conflicting. Among these different disease states only chronic idiopathic autonomic insufficiency can be said, in a strict sense, to represent a condition with chronically impaired autoregulation due to arteriolopathy.

In autopsy studies of the brains of long-term diabetics, Reske-Nielsen et al. found abnormalities of the arteriolar walls in all cases. No clear-cut correlation between degree of angiopathy and symptoms and signs of cerebral disease could be established. Neither did degree of retinopathy seem to correlate with degree of cerebral angiopathy. In our studies no correlation between slope of curve and degree of retinopathy, known duration of diabetes, age or resting MABP could be deduced.

The most probable explanation to our findings thus seems to be a diffuse or multifocal dysfunction of cerebral arterioles due to diabetic vascular disease.

The autoregulatory response to variations in cerebral perfusion pressure seems to be quite vulnerable, and abnormalities of autoregulation are described in association with a variety of different conditions, e.g., intracranial tumor, subarachnoid hemorrhage, cerebral infarction, cerebral hypoxia, meningitis, encephalitis and brain trauma. Impaired autoregulation associated with the syndromes of normal pressure hydrocephalus and chronic idiopathic autonomic insufficiency also has been reported.

Among these different disease states only chronic idiopathic autonomic insufficiency can be said, in a strict sense, to represent a condition with chronically impaired autoregulation in patients with no signs of intracranial disease, that could be ascribed exclusively to arteriolar dysfunction. In this respect chronic idiopathic autonomic insufficiency and chronic arterial hypertension are comparable with long-term diabetes.

The existence of a condition of chronically impaired autoregulation due exclusively to sympathetic denervation is, however, for the reasons given above, difficult to accept. Furthermore, reports of this phenomenon are few and somewhat conflicting. Among these different disease states only chronic idiopathic autonomic insufficiency can be said, in a strict sense, to represent a condition with chronically impaired autoregulation due to arteriolopathy.

When comparing these two conditions, we seem to be dealing with two different types of chronic autoregulatory abnormality. Whereas the arteriolaropathy in hypertension causes a shift to the right of the autoregulation curve with preservation of the autoregulatory plateau, this plateau is absent in patients with impaired autoregulation due to diabetic arteriolaropathy, where CBF seems to vary continuously with MABP.

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Stroke. 1975;6:497-502
doi: 10.1161/01.STR.6.5.497
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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