Autoregulation of Cerebral Blood Flow in Patients Resuscitated From Cardiac Arrest

Claus Sundgreen, MD; Fin Stolze Larsen, MD; Tina Maria Herzog, MD; Gitte Moos Knudsen, MD; Soren Boesgaard, MD; Jan Aldershvile, MD

Background and Purpose—Under normal circumstances, autoregulation maintains cerebral blood flow (CBF) constant within a wide range of mean arterial pressure (MAP). It remains unknown whether patients resuscitated from cardiac arrest have preserved CBF autoregulation. In this study, CBF autoregulation was investigated within the first 24 hours after resuscitation from cardiac arrest.

Methods—Eighteen patients and 6 healthy volunteers had relative changes in CBF determined by transcranial Doppler mean flow velocity (Vmean) in the middle cerebral artery during a stepwise rise in MAP by use of norepinephrine infusion. Vmean was plotted against MAP, and a lower limit of autoregulation was identified by double regression analysis based on the least-squares method.

Results—In patients, Vmean increased from a median of 33 (range 19 to 73) to 37 (22 to 100) cm/s (P < 0.001) during a norepinephrine-induced rise in MAP from 78 (46 to 118) to 106 (60 to 149) mm Hg. Eight of 18 patients had impaired CBF autoregulation, and in 5 of the 10 patients with preserved CBF autoregulation, the lower limit of autoregulation could be identified. The lower limit of CBF autoregulation was 76 mm Hg (41 to 105 mm Hg) in the volunteers and 114 mm Hg (80 to 120 mm Hg) in the 5 patients with preserved autoregulation (P < 0.01).

Conclusions—We conclude that in a majority of patients in the acute phase after cardiac arrest, cerebral autoregulation is either absent or right-shifted. These results indicate that MAP should be kept at a higher level than commonly accepted to secure cerebral perfusion. We recommend, however, that further randomized clinical trials are performed to determine whether sympathomimetic drugs improve neurological outcome. (Stroke. 2001;32:128-132.)

Key Words: arrest ■ arterial pressure ■ brain ■ cerebral blood flow ■ norepinephrine ■ perfusion ■ resuscitation ■ transcranial Doppler

In patients resuscitated from cardiac arrest, neurological outcome depends on prompt restoration of systemic circulation and oxygenation to meet the cerebral oxygen demand. Experimental studies of cerebral blood flow (CBF) after resuscitation indicate that a brief episode of transient and multifocal absence of perfusion is followed by a short period of global cerebral hyperemia associated with a high metabolic rate of oxygen (CMRO2) and glucose. Subsequently, cerebral hypoperfusion with a parallel reduction of CMRO2 develops. Little is known about the regulation of CBF during these phases.

Normally, changes in arterial pressure have only a minor influence on CBF because of reactive dilatation and constriction of cerebral resistance vessels in response to arterial hypotension and hypertension, ie, CBF autoregulation. In experimental studies of global cerebral ischemia, a preserved CBF autoregulation in the delayed hypoperfusion period has been reported. In patients studied 3 days after resuscitation from cardiac arrest, it has been found that the internal jugular vein oxygen saturation increases when mean arterial pressure (MAP) increases during norepinephrine infusion. Whether this reflects impairment of autoregulation, a decrease in the cerebral metabolic rate of oxygen (CMRO2), or an increase in the perfusion of the extracerebral tissue drained into the internal jugular vein remains to be settled.

In this study, we tested the hypothesis that patients resuscitated from cardiac arrest have impaired CBF autoregulation in the secondary delayed hypoperfusion period. Thus, the purpose of this study was to determine whether CBF autoregulation is compromised within the first 24 hours after resuscitation from cardiac arrest.

Subjects and Methods

Patients

Eighteen patients (3 women, median age 69 years, range 42 to 81 years) resuscitated from cardiac arrest were included. Six healthy men (median age 30 years, range 21 to 61 years) served as control subjects, as previously reported. Six patients were resuscitated from...
TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Sex</th>
<th>History</th>
<th>Location</th>
<th>Time to ROSC, min</th>
<th>Initial Rhythm</th>
<th>Cause</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>M</td>
<td>Mitral regurgitation, recent surgery</td>
<td>In</td>
<td>3</td>
<td>Asystole</td>
<td>Asphyxia</td>
<td>Recovery</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>F</td>
<td>Breast cancer</td>
<td>In</td>
<td>8</td>
<td>VF</td>
<td>Acute MI</td>
<td>Recovery</td>
</tr>
<tr>
<td>3</td>
<td>71</td>
<td>F</td>
<td>MI, CHF</td>
<td>Out</td>
<td>15</td>
<td>Asystole</td>
<td>IHD</td>
<td>Died</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>M</td>
<td>CHF, hypertension, AP</td>
<td>Out</td>
<td>10</td>
<td>Bradycardia</td>
<td>Pulmonary edema</td>
<td>Died</td>
</tr>
<tr>
<td>5</td>
<td>81</td>
<td>M</td>
<td>Recent MI</td>
<td>In</td>
<td>10</td>
<td>VF</td>
<td>IHD</td>
<td>Died</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>M</td>
<td>AP, NIDDM, claudication, AAA, recent surgery</td>
<td>In</td>
<td>8</td>
<td>Asystole</td>
<td>IHD</td>
<td>Died</td>
</tr>
<tr>
<td>7</td>
<td>68</td>
<td>M</td>
<td>Hypertension, stroke, COPD</td>
<td>Out</td>
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<td>Bradycardia</td>
<td>IHD</td>
<td>Died</td>
</tr>
<tr>
<td>8</td>
<td>52</td>
<td>M</td>
<td>None</td>
<td>Out</td>
<td>8</td>
<td>VF</td>
<td>IHD</td>
<td>Recovery</td>
</tr>
<tr>
<td>9</td>
<td>70</td>
<td>M</td>
<td>ASD</td>
<td>Out</td>
<td>8</td>
<td>VF</td>
<td>IHD</td>
<td>Died</td>
</tr>
<tr>
<td>10</td>
<td>72</td>
<td>M</td>
<td>MI, AP, CHF</td>
<td>Out</td>
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<td>Asystole</td>
<td>IHD</td>
<td>Died</td>
</tr>
<tr>
<td>11</td>
<td>62</td>
<td>M</td>
<td>Hypertension, MI, AP</td>
<td>Out</td>
<td>5</td>
<td>VF</td>
<td>IHD</td>
<td>Partial recovery</td>
</tr>
<tr>
<td>12</td>
<td>78</td>
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<td>COPD, CHF</td>
<td>Out</td>
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<td>Bradycardia</td>
<td>Asphyxia</td>
<td>Recovery</td>
</tr>
<tr>
<td>13</td>
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<td>Mitral valve stenosis, recent surgery</td>
<td>In</td>
<td>7</td>
<td>Asystole</td>
<td>Unknown</td>
<td>Died</td>
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<tr>
<td>14</td>
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<td>None</td>
<td>Out</td>
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<td>Asystole</td>
<td>Asphyxia</td>
<td>Recovery</td>
</tr>
<tr>
<td>15</td>
<td>60</td>
<td>M</td>
<td>Hypertension, AP</td>
<td>Out</td>
<td>20</td>
<td>VF</td>
<td>Acute MI</td>
<td>Partial recovery</td>
</tr>
<tr>
<td>16</td>
<td>51</td>
<td>M</td>
<td>MI, AP</td>
<td>Out</td>
<td>21</td>
<td>VF</td>
<td>Acute MI</td>
<td>Died</td>
</tr>
<tr>
<td>17</td>
<td>78</td>
<td>M</td>
<td>AP, rectal cancer</td>
<td>In</td>
<td>12</td>
<td>VF</td>
<td>Acute MI</td>
<td>Recovery</td>
</tr>
<tr>
<td>18</td>
<td>73</td>
<td>M</td>
<td>MI, prior cardiac arrest, prostate cancer</td>
<td>Out</td>
<td>15</td>
<td>VF</td>
<td>IHD</td>
<td>Died</td>
</tr>
</tbody>
</table>

Median 69  
Range 42–81

ROS indicates return of spontaneous circulation; MI, myocardial infarction; CHF, congestive heart failure; AP, angina pectoris; NIDDM, non–insulin-dependent diabetes mellitus; AAA, abdominal aortic aneurysm; COPD, chronic obstructive pulmonary disease; ASD, atrial septal defect; VF, ventricular fibrillation; and IHD, ischemic heart disease.

Cerebral Autoregulation

Relative changes in cerebral perfusion were determined by transcranial Doppler ultrasonography (Multi Dop X, DWL). With a 2-MHz pulsed Doppler probe, 1 of the middle cerebral arteries was insonated to a depth of 45 to 55 mm, and mean flow velocity (Vmean) was recorded. The transducer was kept fixed in place by a headband. Cerebral autoregulation was assessed by raising MAP ~30 mm Hg by intravenous infusion of norepinephrine (5 to 30 μg·kg⁻¹·min⁻¹) with simultaneous recording of Vmean for each 5 to 10 mm Hg increase in MAP. Six healthy men served as control subjects. In the healthy control subjects (median age 30 years, range 21 to 60 years), MAP was recorded by a catheter in the left radial artery. After norepinephrine infusion, MAP was also lowered by use of lower-body negative pressure and infusion of trimethapam, as reported earlier.³

To assess CBF autoregulation, MAP was plotted against the Vmean and a possible lower limit of autoregulation was identified by a computer program.¹⁰ This program fits a linear regression line for MAP below the lower limit of autoregulation and a horizontal line above the lower limit by least-squares measurements, comparing the result with that of fitting a single linear regression line to the data. Autoregulation was considered to be preserved if the following criteria were fulfilled: (1) the standard error of the identified value of the lower limit should constitute <25% of the value itself; (2) ≥3 simultaneous recordings of MAP and Vmean exceeded the MAP value of the lower limit; and (3) the sum of squares for fitting with 2 lines was less than the sum of squares for 1 single regression line. The autoregulation was also considered to be preserved if (4) the slope of the single regression line was ≤0.33%/mm Hg.¹⁰ If these criteria were not fulfilled, autoregulation was considered impaired. According to these criteria, the patients were divided into those with intact autoregulation and those with impaired autoregulation.

Statistical Analysis

Continuous variables are expressed as median and range. The Wilcoxon test was used for paired data and the Mann-Whitney test was used for unpaired data. Nonparametric tests were used when the data was not normally distributed. The Fisher exact test was used when the data was categorical. The time to return of spontaneous circulation (ROSC) was compared across groups by using the Wilcoxon test. The Kruskal-Wallis test was used to compare ROSC with the causes of cardiac arrest. The Mann-Whitney test was used to compare ROSC time with the clinical characteristics of the patients. All statistical analyses were performed using STATA software (Version 11.2; StataCorp, College Station, Texas).
for comparison of unpaired data. Fischer’s exact test was used for comparison of groups; a value of $P < 0.05$ was considered significant.

**Results**

In the 18 resuscitated patients, $V_{\text{mean}}$ increased from 33 (16 to 73) to 37 (22 to 100) cm/s ($P = 0.001$) during a norepinephrine-induced rise in MAP from 78 (46 to 118) to 106 (60 to 149) mm Hg. The rise in $V_{\text{mean}}$ was dependent on an increase in both $V_{\text{systole}}$ (11% [−13% to 48%]) and $V_{\text{diastole}}$ (3% [−29% to 35%]). According to the preselected criteria, 10 of the 18 patients had preserved CBF autoregulation (group 1). In these patients, $V_{\text{mean}}$ increased from 30 (19 to 49) to 39 (22 to 64) cm/s ($P < 0.05$), whereas MAP was raised from 76 (46 to 104) to 111 (60 to 137) mm Hg by norepinephrine infusion. In 5 of these 10 patients, a lower limit of autoregulation could be identified at a MAP higher than baseline MAP. The lower limit was identified when MAP reached a value of 114 (80 to 120) mm Hg, where the corresponding value of $V_{\text{mean}}$ reached a plateau at 47 (27 to 64) cm/s. In the remaining 5 patients in group 1, $V_{\text{mean}}$ remained constant at 23 (16 to 48) cm/s despite a rise in MAP. Thus, in these patients, the lower limit of autoregulation was located below the value of MAP at baseline, 70 (46 to 82) mm Hg.

Eight patients did not fulfill the criteria of intact cerebral autoregulation (group 2). $V_{\text{mean}}$ increased from 34 (21 to 73) to 45 (26 to 100) cm/s ($P < 0.05$) when MAP was raised from 78 (64 to 118) to 103 (90 to 149) mm Hg, and a lower limit of autoregulation could not be identified. Although the maximum value of MAP obtained in this group was lower than in the 5 patients with an identifiable lower limit of CBF autoregulation (125 [91 to 137] mm Hg), there was no statistical difference.

$P_{\text{CO}_2}$ was similar in the 2 groups both at baseline and at the maximum value of MAP. There were no differences between MAPs at baseline between groups 1 and 2 or in the induced increase in MAP, just as there were no differences between the 2 subgroups in group 1 fulfilling criteria 1 to 3 and criterion 4, respectively. Nor did the relative changes in $V_{\text{diastole}}$ (15% [−29% to 30%] versus 13% [−7% to 35%]) or in $V_{\text{systole}}$ (9% [−14% to 29%] versus 14% [0% to 48%]) in the 2 groups differ.

In a multiple logistic regression model, there was no correlation between, on the one hand, autoregulation profile and on the other hand, baseline MAP, baseline $V_{\text{mean}}$, age, time to return of spontaneous circulation, time between cardiac arrest and inclusion in the study, treatment with pressor agents, sedation, known hypertension, or history of cardiac disease.

In the 6 control subjects, MAP was lowered to 39 (34 to 50) mm Hg and subsequently raised to 112 (110 to 124) mm Hg. The corresponding values of $V_{\text{mean}}$ were 38 (31 to 46) and 65 (53 to 90) cm/s, respectively ($P < 0.05$). Baseline $V_{\text{mean}}$ was significantly higher, 67 (53 to 85) cm/s ($P < 0.01$), in the healthy control subjects than in the patients. In all healthy volunteers, a lower limit of CBF autoregulation was identified at a median value of 76 (41 to 105) mm Hg.

The lower limit of cerebral autoregulation was significantly higher in the 5 patients in group 1 in whom a lower limit of CBF autoregulation could be identified than in the control subjects ($P < 0.01$) (Table 2).

The autoregulation curves resulting from plotting MAP against $V_{\text{mean}}$ are shown for selected patients in Figure 1.

### Table 2. Lower Limit of Cerebral Autoregulation in the 5 Patients in Whom a Lower Limit of Cerebral Autoregulation Could Be Identified and in 6 Control Subjects

<table>
<thead>
<tr>
<th>Patient</th>
<th>Lower Limit, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>114</td>
</tr>
<tr>
<td>11</td>
<td>109</td>
</tr>
<tr>
<td>15</td>
<td>118</td>
</tr>
<tr>
<td>16</td>
<td>120</td>
</tr>
<tr>
<td>Median</td>
<td>114*</td>
</tr>
<tr>
<td>Range</td>
<td>80–120</td>
</tr>
<tr>
<td>Control subjects</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>76</td>
</tr>
<tr>
<td>B</td>
<td>78</td>
</tr>
<tr>
<td>C</td>
<td>79</td>
</tr>
<tr>
<td>D</td>
<td>41</td>
</tr>
<tr>
<td>E</td>
<td>64</td>
</tr>
<tr>
<td>F</td>
<td>105</td>
</tr>
<tr>
<td>Median</td>
<td>76*</td>
</tr>
<tr>
<td>Range</td>
<td>41–105</td>
</tr>
</tbody>
</table>

Lower limit indicates calculated value of lower limit of autoregulation. See text for details.

* $P < 0.01$.

Discussion

The absolute baseline values of $V_{\text{mean}}$ were significantly lower in the patients than in the control subjects. Although only changes in $V_{\text{mean}}$ are validated as a measure of changes in $V_{\text{mean}}$. See text for details.

* $P < 0.01$.

**Figure 1.** The relationship between MAP and $V_{\text{mean}}$ in the middle cerebral artery in 1 patient (patient 15) with right-shifted lower limit (solid circles), in 1 patient (patient 13) with impaired CBF autoregulation (solid triangles), and in 1 healthy control subject (open squares). The lines represent the calculated lower limit of CBF autoregulation (patient 15 and control subject C) and the single regression line ($r^2 = 0.98$) (patient 13).
Hossmann et al\textsuperscript{7} showed that CBF remained constant when MAP was altered in the range of 80 to 200 mm Hg in the cat after 1 hour of global cerebral ischemia. In a study of 8 dogs after 15 minutes of global cerebral ischemia, Nemoto et al\textsuperscript{6} using external detection of $^{133}$Xe clearance, failed to find any significant increase in regional CBF during an increase in cerebral perfusion pressure (CPP) from 40 to 200 mm Hg. Christopherson et al\textsuperscript{8} found a $>20\%$ decrease in CBF in 2 of 6 dogs studied when CPP was lowered from 111 to 64 mm Hg after 12 minutes of global ischemia and in 1 of 3 dogs after 18 minutes of global ischemia. When CPP was increased to 135 mm Hg, there was no significant increase in CBF. This latter observation could be explained by a right shift of the lower limit of autoregulation to values of CPP greater than the lowest CPP studied.

A chronic condition with a high sympathetic tone causes constriction of the larger cerebral resistance vessels and a right shift of the lower limit of CBF autoregulation toward higher pressure.\textsuperscript{4} It could be speculated that the impairment and right shift of the lower limit of autoregulation in this study was due to administration of sympathomimetic drugs in the hours before this study. The autoregulation profile, however, did not differ between the patients who received sympathomimetic drugs before the study and those who did not.

For autoregulation studies in humans, transcranial Doppler sonography provides a noninvasive means of monitoring relative changes in CBF by determining flow velocity in the major basal cerebral arteries.\textsuperscript{13,14} Measurement of $V_{\text{mean}}$ has previously been shown to be valid for determination of the lower limits of autoregulation in humans.\textsuperscript{13,14} The use of transcranial Doppler ultrasonography as a relative measure of CBF, however, is based on the assumption that the diameter of the insonated artery is constant during infusion of norepinephrine. This has been demonstrated in numerous studies including healthy volunteers\textsuperscript{13} and in patients with acute liver failure.\textsuperscript{15} Norepinephrine increases the peripheral resistance but normally has no influence on the resistance vessels in the cerebral circulation,\textsuperscript{16} and it does not alter the cerebral metabolism.\textsuperscript{16,17} In the case of blood-brain barrier (BBB) disruption, however, norepinephrine may increase metabolism and blood flow.\textsuperscript{16} The permeability of the BBB after cardiac arrest has not been investigated in adult patients. Experimental studies after resuscitation in the adult dog have shown intact BBB,\textsuperscript{18} whereas in immature swine\textsuperscript{19} and neonatal piglets,\textsuperscript{20} some degree of BBB malfunction takes place.

Hypoxia-induced cerebral swelling may in severe cases increase intracranial pressure. Accordingly, the perfusion pressure (MAP minus intracranial pressure) may be significantly lower than MAP. Because intracranial pressure was not measured in this study, the lower limit of autoregulation determined may have been overestimated in the patients. This would imply that the baseline arterial pressure was maintained well below safe limits with regard to brain oxygenation. In indirect support of this assumption is the fact that the lower limit could be identified at a higher arterial pressure in 5 of the 13 patients. Conversely, there is no evidence of generally increased intracranial pressure shortly after resus-

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**Figure 2.** Relative changes in $V_{\text{mean}}$ in the middle cerebral artery during a norepinephrine-induced increase in MAP. Open symbols represent baseline and maximum values in 8 patients with impaired autoregulation. Solid symbols represent baseline values and the values just below the calculated lower limit of CBF autoregulation in 5 patients with preserved but right-shifted lower limit of CBF autoregulation. Values above the lower limit are not shown.

CBF, this finding may be an indicator of the reduction of CBF seen in the secondary delayed hypoperfusion phase.

In this study, we found that in 8 patients, CBF autoregulation was absent and in 5 patients, the lower limit of autoregulation was significantly right-shifted. This left only 5 patients with a normal autoregulation profile in the delayed hypoperfusion phase after resuscitation from cardiac arrest. The possibility cannot be ruled out that some of the patients with absent CBF autoregulation might have had extreme right-shifted autoregulation curves and that the lower limit of autoregulation would have been reached if a further increase in MAP had been obtained. In only 2 of these patients was the maximum value of MAP above the median value of the lower limit of CBF autoregulation found in the 5 patients with a right-shifted autoregulation curve. Conversely, we did not find any significant difference in the maximum value of MAP obtained. In practice, this means that CBF changes considerably when MAP is manipulated, both in patients with absent CBF autoregulation and in the subgroup of patients with a right-shifted lower limit of CBF autoregulation (Figure 2).

Nishizawa et al\textsuperscript{8} reported that all of the 8 patients investigated after resuscitation from cardiac arrest had impaired autoregulation, with MAP in the range from 64 to 118 mm Hg, as evaluated by the cerebral arterial-to-venous oxygen difference method. This conclusion presumes, however, that the CMRO$_2$ is constant during the induced changes in arterial pressure. In contrast to our study, their patients were studied on the third day after resuscitation, when the secondary delayed hypoperfusion phase probably had resolved. Furthermore, at that time all their patients were comatose, and none survived. Thus, it is possible not only that differences in the methodology used may account for the discrepancies between their and our results but also that the patients in their study were more severely affected than our patients.


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Stroke. 2001;32:128-132
doi: 10.1161/01.STR.32.1.128

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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