Cerebral Autoregulation Under Moderate Hypothermia in Patients With Acute Stroke

D. Georgiadis, MD; S. Schwarz, MD; D.H. Evans, PhD; S. Schwab, MD; R.W. Baumgartner, MD

Background and Purpose—We undertook this study to examine the integrity of cerebral autoregulation in patients with acute ischemic stroke treated with moderate hypothermia (33°C).

Methods—Fourteen patients, aged 58±11 years, with an acute anterior circulation infarction and National Institutes of Health Stroke Scale score >15 were evaluated. Patients received catecholamines (norepinephrine) via continuous intravenous infusion and were mechanically ventilated. Alpha-stat was used for pH maintenance. Arterial pressure (AP) and intracranial pressure (ICP) were invasively monitored. Flow velocity in the middle cerebral artery (MCA) supplying the unaffected hemisphere was continuously monitored. Instantaneous maximum flow velocity (Vmax MCA), ICP, and AP were simultaneously recorded in real time. Mean values of Vmax MCA (Vmean MCA) and AP (MAP) were calculated over 1 minute. Static cerebral autoregulation (sCA) was calculated as sCA=(%ΔCVR/%ΔMAP)×100% (where %ΔCVR is an estimate of percent change in cerebrovascular resistance). An sCA value of 0% indicates absent autoregulation, and a value of 100% indicates perfect autoregulation. Autoregulation is considered impaired when sCA values are <40%. MAP changes were produced by increasing the rate of the norepinephrine infusion. Six patients were examined under both normothermic and hypothermic conditions, while 8 were examined only under hypothermia.

Results—The induced MAP increase was 22±7 mm Hg (minimum 13, maximum 40 mm Hg). Mean sCA was 64±16% (minimum 40%, maximum 100%). No effect of moderate hypothermia on sCA or Vmean MCA was evident in any of the 6 serially examined patients. Normocapnia was observed in all cases.

Conclusions—sCA appears intact under moderate hypothermia with the use of alpha-stat for pH maintenance. (Stroke. 2002;33:3026-3029.)

Key Words: autoregulation ■ stroke, acute ■ stroke, ischemic ■ stroke management

Moderate hypothermia is emerging as an alternative approach for treatment of intracranial hypertension in patients with acute ischemic stroke. To date, the effect of moderate hypothermia on cerebral autoregulation has been evaluated in only 1 animal study and 1 clinical study of healthy volunteers, in which the induced temperature variations were minimal (0.3°C). This issue is particularly important to estimate the effect of blood pressure variations on cerebral perfusion in patients treated with moderate hypothermia and to decide on optimal blood pressure management.

We undertook this study to examine the effect of moderate hypothermia on cerebral autoregulation in patients with acute ischemic stroke.

Subjects and Methods

A total of 17 consecutive patients treated with moderate hypothermia were prospectively examined. Fourteen patients (9 men and 5 women aged 58±11 [range, 37 to 72] years) were enrolled in the study, and 3 were excluded because of insufficient temporal bone windows that prevented insonation of the middle cerebral artery (MCA) with transcranial Doppler ultrasonography (TCD). Severe stenosis or occlusion of the contralateral MCA or internal carotid artery also served as an exclusion criterion but was not diagnosed in any of the 14 patients. This study was performed according to local ethical committee standards. Informed consent was obtained from the patients’ relatives. Data were analyzed without patient identification.

According to our institutional protocol, all patients had suffered an acute anterior circulation infarction involving at least two thirds of the left MCA territory, and the presenting National Institutes of Health Stroke Scale score was >15. Patients were nursed in the 30° upright position. Midazolam was used for sedation, fentanyl for analgesia, and atracurium for neuromuscular blockade. Patients received catecholamines (norepinephrine) via continuous intravenous infusion at the time of examination. No other vasoactive drugs that may affect cerebral autoregulation were administered during the study period. The patients were ventilated with a volume-controlled, pressure-regulated mode and an inspiratory/expiratory ratio of 1:2 (Servo Ventilator 300, Siemens). Alpha-stat was used for pH maintenance. Moderate hypothermia was induced and maintained by either external cooling with blankets and air fans or endovascular cooling (CoolGard, Alsius Corporation). Target temperature was 33°C. Hypothermia induction was initiated 26 (range, 18 to 28)
hours after onset of symptoms; target temperature was reached after an additional 4±1 hours. Arterial pressure (AP) was invasively monitored via a catheter inserted in the radial artery. Intracranial pressure (ICP) was monitored with a parenchymal catheter inserted ipsilateral to the affected hemisphere in all cases. Both the AP and the ICP transducers were kept at the level of the foramen of Monro.

The MCA supplying the unaffected hemisphere was identified at an insonation depth of 52 to 58 mm and continuously monitored with the 2-MHz transducer of a pulsed-wave TCD machine (Multi-Dop X-4, DWL). The transducer was fixed on the skull with an appropriate mounting device to minimize movement artifacts. The TCD machine extracted the instantaneous maximum flow velocity (Vmax MCA) from the Doppler signal and exported this in ASCII format at a rate of 50 samples per second together with the corresponding values of ICP and AP acquired through its analog inputs. Thus, instantaneous values of Vmax MCA (Vmean MCA) and AP (MAP) were calculated over periods of 1 minute (3000 data values).

Static cerebral autoregulation (sCA) was assessed as the percent change in estimated cerebrovascular resistance (ΔCVR) in relation to the change in MAP, according to the method described by Tiecks et al6: sCA=ΔCVR/MAP×100%.

An sCA value of 0% indicates absent autoregulation, and an sCA value of 100% indicates perfect autoregulation. Autoregulation is considered impaired when sCA values are <40%. A proxy for cerebrovascular resistance CVR(p) was calculated as MAP/Vmax MCA, and the percent changes were calculated as ΔCVR=|CVR(p)−CVR(p)|/CVR(p), and ΔMAP=MAP−MAPMAP.

CVR(p) was initially calculated under resting conditions to acquire baseline values (value 1: 1-minute recording immediately before an increase of the epinephrine infusion rate); subsequently the rate of the norepinephrine infusion was increased by 10% of the initial value, and CVR(p) was recalculated after the MAP stabilized at a higher level (value 2) (MAP was considered stable when observed variations were <5% of the actual value for at least 5 minutes). We used a set increase of the rate of the epinephrine infusion instead of targeting a predefined increase in MAP. A CVR(p) 1 and CVR(p) 2 measurements.

The induced MAP increase was 22±7 mm Hg (mean±SD; minimum 13, maximum 40 mm Hg) (Table). Mean sCA was 64±16% (minimum 40%, maximum 100%). Detailed data from each single examination together with corresponding temperature and ICP values are provided in the Table. No systemic effect of moderate hypothermia on sCA was evident in any of the 6 serially examined patients.

Normocapnia was observed in all cases (PCO2 between 3.97 and 5.01). ICP values are listed in the Table. ICP values >15 mm Hg were observed only during 3 monitoring sessions; therefore, the potential influence of increased ICP on cerebral autoregulation cannot be evaluated from our results.

Discussion
The major finding of the present study was that sCA does not appear impaired in the unaffected hemisphere in patients with acute ischemic stroke treated with moderate hypothermia. Early studies in which the 133Xe method was used demonstrated that cerebral autoregulation is globally impaired, ie, impaired not only in the affected hemisphere but also in the healthy hemisphere.1,7 Recently, similar results were obtained when dynamic cerebral autoregulation was evaluated with TCD with the use of thigh cuff release8 or beat-to-beat blood pressure variability.10 sCA was additionally evaluated in 1 of these studies and reported as intact.9 The authors postulated that this finding could be due to preferential influence of the dynamic pathway by either central damage to the modulation of the central nervous system or the efferent arms of the baroreceptor reflex. Interestingly, Tiecks et al6 also suggested that dynamic cerebral autoregulation may be more vulnerable than sCA because of the different control mechanisms involved. These observations imply that a potential impairment of cerebral autoregulation cannot be excluded solely on the basis of sCA testing and suggest that our results should be treated with caution. Doering et al4 observed a significant reduction of the autoregulation index in healthy volunteers whose core temperature decreased by 0.3°C through cold baths, using TCD and dynamic autoregulation testing. Obviously, the temperature changes induced in that study were mild and not comparable to our application. The discrepant findings could be due to the fact that (1) Doering et al monitored differences over a shorter time period and thus potentially with a higher sensitivity or (2) dynamic cerebral autoregulation instead of sCA was evaluated.

One must take into account that alpha-stat was used for pH maintenance in this study. During alpha-stat management, arterial PCO2 tension is maintained at 40 mm Hg when measured at 37°C. Because of the increased gas solubility under hypothermia, alpha-stat management is associated with controlled hyperventilation. Paulson et al9 demonstrated that hyperventilation-associated hypocapnia can, at least partially, restore cerebral autoregulation in the healthy hemisphere of patients with supratentorial brain tumors as well as in patients with apoplexy. Thus, our study cannot provide any clear-cut evidence on the influence of moderate hypothermia on sCA because we cannot differentiate between a primarily unaffected sCA and an affected sCA that was restored through hypocapnia. This statement is further supported by the study of Verhaegen et al,3 who evaluated cerebral autoregulation in normothermic and hypothermic (30.5°C) rats. Cortical blood
The flow was measured with a laser-Doppler flowmeter, and hemorrhagic hypotension was used as stimulus. Hypothermic animals were further divided into 2 groups, depending on whether alpha- or pH-stat was used for acid-base management. Cerebral autoregulation was completely abolished in hypothermic animals in which pH-stat was used for acid-base maintenance but was found to be intact (albeit reduced) under alpha-stat acid-base management, which is in accordance with our results.

Thus, we can safely conclude that sCA is not compromised under moderate hypothermia when alpha-stat is used for pH maintenance. This is derived not only by the observation that all sCA values but 1 were above the limit of 40% but also by the fact that no changes in sCA were observed in the patients.

### Influence of Moderate Hypothermia on sCA

<table>
<thead>
<tr>
<th>Pt No./Age/Sex</th>
<th>Temperature, °C</th>
<th>ICP, mm Hg</th>
<th>MAP1, mm Hg</th>
<th>MAP2, mm Hg</th>
<th>%ΔMAP</th>
<th>CVR(p)1</th>
<th>CVR(p)2</th>
<th>%ΔCVR</th>
<th>sCA</th>
</tr>
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<tbody>
<tr>
<td>1/54/M</td>
<td>33.0</td>
<td>12</td>
<td>74</td>
<td>111</td>
<td>50</td>
<td>2.0</td>
<td>2.6</td>
<td>36</td>
<td>71</td>
</tr>
<tr>
<td>2/44/F</td>
<td>33.0</td>
<td>22</td>
<td>72</td>
<td>93</td>
<td>29</td>
<td>1.2</td>
<td>1.4</td>
<td>12</td>
<td>41</td>
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<tr>
<td>3/37/M</td>
<td>33.0</td>
<td>15</td>
<td>81</td>
<td>96</td>
<td>19</td>
<td>1.9</td>
<td>2.1</td>
<td>13</td>
<td>72</td>
</tr>
<tr>
<td>4/40/F</td>
<td>33.0</td>
<td>4</td>
<td>68</td>
<td>96</td>
<td>41</td>
<td>3.0</td>
<td>3.6</td>
<td>20</td>
<td>49</td>
</tr>
<tr>
<td>5/65/M</td>
<td>33.0</td>
<td>7</td>
<td>60</td>
<td>83</td>
<td>38</td>
<td>1.8</td>
<td>2.5</td>
<td>43</td>
<td>100</td>
</tr>
<tr>
<td>6/66/F</td>
<td>33.0</td>
<td>5</td>
<td>84</td>
<td>112</td>
<td>33</td>
<td>3.4</td>
<td>4.0</td>
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<tr>
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<td>75</td>
<td>98</td>
<td>31</td>
<td>1.3</td>
<td>1.6</td>
<td>26</td>
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<tr>
<td>8/56/M</td>
<td>33.0</td>
<td>8</td>
<td>86</td>
<td>99</td>
<td>15</td>
<td>2.3</td>
<td>2.5</td>
<td>6</td>
<td>43</td>
</tr>
<tr>
<td>9/65/F</td>
<td>32.8</td>
<td>10</td>
<td>89</td>
<td>109</td>
<td>22</td>
<td>2.7</td>
<td>3.0</td>
<td>9</td>
<td>41</td>
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<tr>
<td>10/53/M</td>
<td>32.7</td>
<td>10</td>
<td>96</td>
<td>115</td>
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<td>2.7</td>
<td>2.9</td>
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<tr>
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<td>83</td>
<td>98</td>
<td>18</td>
<td>2.4</td>
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<tr>
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<td>88</td>
<td>108</td>
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<td>3.0</td>
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<tr>
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<td>85</td>
<td>115</td>
<td>18</td>
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<tr>
<td>15/61/F</td>
<td>33.7</td>
<td>7</td>
<td>95</td>
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<td>35</td>
<td>2.7</td>
<td>3.1</td>
<td>15</td>
<td>43</td>
</tr>
</tbody>
</table>

Patients 1 to 8 were examined only under moderate hypothermia; patients 9 to 14 were examined under both moderate hypothermia and after rewarming. MAP1 and CVR(p)1 were acquired under baseline conditions; MAP2 and CVR(p)2 were acquired after the rate of epinephrine infusion was increased.
seriously examined under both hypothermic and normothermic conditions. Obviously, the main concern in patients with acute stroke is the perfusion of the affected hemisphere and specifically of the penumbra. However, hypothermia was induced a median of 26 hours after symptom onset as a means to control intracranial hypertension and not for neuroprotection. It can therefore be assumed that no potentially salvageable penumbral tissue was present during our examination. The clinical interest of cerebral autoregulation in this context is rather associated with the potential to tolerate arterial hypotension, which represents a major complication of moderate hypothermia. Our study provided initial evidence that sCA is preserved under hypothermia, even at low cerebral perfusion pressure, suggesting that such values could be compensated by the healthy hemisphere.

A main limitation of TCD is the fact that it measures velocity rather than blood flow. Nevertheless, 2 studies demonstrated the validity of dynamic autoregulation testing with TCD: (1) Newell et al11 found that relative changes in maximal peak mean MCA flow velocity accurately reflect relative changes in internal carotid artery flow (measured with an electromagnetic flowmeter) during dynamic autoregulation testing with TCD, and (2) Larsen et al12 reported that the lower limit of cerebral autoregulation is not significantly different when evaluated with TCD or with the $^{133}$Xe method.

This study had a number of limitations. First, the number of patients examined was small, particularly in regard to serial examinations. Still, it must be taken into account that induction of moderate hypothermia is not common; the reported cases represent the total number of patients treated with moderate hypothermia over a 2-year period. Because our results were unequivocal, we do not believe that the study would greatly profit from a greater number of patients. Second, only the MCA supplying the healthy hemisphere was insonated. This was due to the fact that approximately 50% of MCAs supplying the affected hemisphere were permanently occluded and therefore could not be examined. Additionally, it is well known that vessels supplying the infarcted area are maximally dilated during the acute stage of infarction and therefore show no autoregulatory response.13

In conclusion, this study provides initial data on the integrity of sCA under moderate hypothermia in patients with acute ischemic stroke. The potential influence of acid-base management on sCA and patency of dynamic cerebral autoregulation under moderate hypothermia remain to be evaluated.

References

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