Is the Acetazolamide Test Valid for Quantitative Assessment of Maximal Cerebral Autoregulatory Vasodilation?

An Experimental Study

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Background and Purpose—The cerebral vasodilating effect of acetazolamide (ACZ) injection has been used as an index of the autoregulatory vasodilation (or cerebral perfusion reserve). The question of whether the ACZ test assesses the maximal autoregulatory vasodilating capacity is not definitely resolved. The effects of ACZ injection on this reserve at a dose producing maximal vasodilation have never been evaluated and may help to resolve this problem.

Methods—The effect of ACZ injection on cerebral blood flow (CBF) autoregulation was tested in anesthetized rats. A pilot experiment evaluated the dose-effect relationship of injected ACZ, cumulative doses ($n=4$, group 1), and independent bolus doses ($n=6$, group 2). CBF was estimated by laser-Doppler flowmetry, and cerebrovascular resistance (CVR) was calculated from mean arterial blood pressure (MABP) and from CBF (expressed as a percentage of baseline CBF). A bolus of ACZ of 21 mg/kg produced the maximal cerebral vasodilation that could be obtained by ACZ administration. In the main experiment, MABP was lowered from 110 to 20 mm Hg by stepwise bleeding in 3 groups of 6 animals treated 10 minutes before bleeding by injection of saline (group 3), 7 mg/kg ACZ (group 4), or 21 mg/kg ACZ (group 5).

Results—The CVR-MABP relationship was linear in all groups, indicating that CBF autoregulation was still effective after ACZ administration.

Conclusions—These results indicate that maximal ACZ-induced cerebral vasodilation is not quantitatively equivalent to maximal autoregulatory vasodilating capacity in anesthetized rats. (Stroke. 2000;31:508-515.)

Key Words: acetazolamide • autoregulation • cerebral blood flow • hypotension • rats

Acetazolamide (ACZ) injection is widely used as a cerebral vasodilating stimulus for assessment of the cerebrovascular dilatory reserve in animals,1 in healthy volunteers,2 and in patients.2–4 Intravenous doses of 7 to 30 mg/kg ACZ in rats1–5 and 0.5 to 1 g in humans2–4,6 produce no or little change in blood pressure and an increase in cerebral blood flow (CBF), so that cerebral vascular resistance (CVR) decreases. In clinical investigation, this decrease in CVR in response to ACZ injection is often considered a surrogate of the decrease in CVR elicited by hypotension (ie, autoregulatory vasodilation).5 The fact that these 2 reactivities (to ACZ and to a blood pressure decrease) lead to cerebral vasodilation does not necessarily mean that they are equivalent and that the former can be considered a substitute for the latter. Indeed, these 2 cerebral vasodilations may imply different mechanisms.7 However, this question is still a matter of debate, and a recent report supports the use of the ACZ test to measure the cerebral autoregulatory capacity.8 Nevertheless, it is not certain that the results of an ACZ test provide valuable information on the brain’s capacity to adapt to hypotension or hypoperfusion. This point may be of prime importance in some clinical situations in which the ACZ test is used to check cerebrovascular reactivity, especially in cerebrovascular disease. The aim of the study was to assess the effect of ACZ injection on the cerebral autoregulatory vasodilatory capacity. We investigated the influence of an intravenous ACZ bolus on CBF autoregulation when mean arterial blood pressure (MABP) was decreased in anesthetized rats. The effects of 2 doses of ACZ (7 and 21 mg/kg) were compared with control (saline injection), with the higher dose producing the largest vasodilation that could be obtained with the drug.

Materials and Methods

A first experiment (pilot study) was designed to investigate the dose-effect relationship of injected ACZ on CBF, MABP, and CVR.
to choose a dose that produced a maximal vasodilating effect on the cerebral cortical circulation, and to compare the maximal ACZ-induced vasodilation with that produced by hypercapnia.

The main study investigated the effects of ACZ administration (a low dose of 7 mg/kg and the maximal dose obtained from the pilot study, ie, 21 mg/kg) compared with saline injection on cerebral autoregulatory vasodilation.

Preparation of Animals
The experiments were performed on 28 male Sprague-Dawley rats (weight, 270 to 460 g). Principles of laboratory animal care (EEC Guideline 86/609/EEC) were followed as well as specific French laws (décret of October 19, 1987, and arrêté of October 29, 1990). Furthermore, this study was performed under license No. 92007 delivered by the French Ministry of Defense.

Rats were anesthetized with halothane in an O2/N2 mixture (4% on induction, progressively reduced to 1% for the surgery) and α-chloralose (40 mg/kg SC). Rectal temperature was maintained at 37°C to 38°C throughout the experiment with a thermostatically controlled blanket. All skin incisions were infiltrated with 2% lidocaine hydrochloride. First, a polyethylene catheter (ID, 0.58 mm; OD, 0.96 mm) was advanced into the abdominal aorta from the site of cannulation in the femoral artery. This catheter was used to induce a decrease in MABP by bleeding. Second, a femoral vein was cannulated (ID, 0.58 mm; OD, 0.96 mm) to perform intravenous injections. Third, a polyethylene catheter (ID, 0.38 mm; OD, 0.76 mm) was introduced into a brachial artery for MABP recordings. Heparin was given intravenously to ensure patency of the catheters (6 IU/h). The rats were then tracheotomized and artificially ventilated to keep PaO2 and PaCO2 within physiological ranges.

The rats were positioned in a Kopf stereotaxic frame, and the skull surface was drilled to translucency unilaterally over the frontoparietal cortex so that the pial vessels were visible. The probe (tip diameter of 0.8 mm with 3 optical fibers, 1 light emitter, and 2 collectors, interaxis distance of 0.5 mm) of the laser-Doppler flowmeter (LDF monitor, Moor Instruments England) was carefully positioned to avoid major cerebral vessels. Halothane was reduced to 0.5% to 0.2%, and α-chloralose was given hourly (20 mg/kg SC) until the end of the experiment.

After stabilization of CBF and MABP, an arterial blood gas analysis was performed. The reactivity of cerebral arterioles investigated by the laser-Doppler flowmeter was then tested by making the animals breathe an O2/N2 mixture (45%/45%) enriched with 10% CO2. Reactivity to CO2 was expressed as the percentage of increase in CBF induced by a 1-mm Hg increase in PaCO2.

Experimental Protocol
The experiments started approximately 2 hours after the beginning of anesthesia and 5 minutes after the end of the hypcapnic test.

Pilot Study
In the first part of the pilot study, the animals (group 1, n=4) received increasing bolus doses of ACZ at 10-minute intervals: 7 mg/kg ACZ, 14 mg/kg ACZ, and 21 mg/kg ACZ. Since the effects of injected ACZ on CBF are sustained (at least 60 minutes in rats),1 we considered that the doses administered were cumulative, and thus the rats successively received 7 mg/kg ACZ, 21 (ie, 14 + 7) mg/kg ACZ, and 42 (ie, 21 + 21) mg/kg ACZ. The choice of a 10-minute interval was based on the fact that continuous monitoring revealed in our model that the CBF response to ACZ is maximal and stable after 7 to 8 minutes (Figure 1).

In the second part of the pilot study, the rats (group 2, n=6) received a bolus injection of 42 mg/kg ACZ, and hemotocrit was measured before and 10 minutes after ACZ injection. Finally, the animals inhaled an O2/N2 mixture (46.5%/46.5%) enriched with 7% CO2, and CBF was again determined. In this experiment the proportion of CO2 was limited to 7% to avoid any risk of excessive vasodilation and consecutive lethal increase in intracranial pressure due to the summation of the vasodilating effects of ACZ and CO2.

At the end of this pilot study, and on the basis of the results obtained (Table 1, Results), the 21 mg/kg ACZ bolus was considered to produce the maximal cerebral vasodilatation that could be obtained by ACZ injection in this model.

Main Study
Three groups of rats were studied in the main experiment. In group 3 (n=6), saline (0.5 mL IV) was given to the rats. In group 4 (n=6), a low dose of ACZ was administered (7 mg/kg IV). The animals of group 5 (n=6) were injected with ACZ 21 mg/kg IV.

PaO2, PaCO2, and pHa were measured 10 minutes after the injection of saline or ACZ. MABP was then decreased stepwise by blood withdrawal from the arterial femoral catheter. A stable blood pressure was maintained for 1 minute after each 10-mm Hg reduction. CBF was measured during the last 30 seconds to allow autoregulatory mechanisms to be effective at each MABP level.8 MABP was reduced to 20 mm Hg, which is below the lower limit of CBF autoregulation (40 to 60 mm Hg), to ensure that the maximum of autoregulatory vasodilatation was reached. Blood was then reinfused, and the rats were killed by barbiturate injection.

Measurements and Statistical Analysis
Because CBF estimated with laser-Doppler flowmetry correlates better with relative changes in CBF rather than with absolute values,9 changes were calculated as percentages of baseline CBF (CBF0). The mean flow obtained during the minute before the injection of either saline or ACZ. Each animal was characterized by its CBF/MABP relationship. CVR was calculated as the ratio of MABP to concomitant CBF, and the CVR/MABP relationship was taken as an index of autoregulatory capacity. It should be kept in mind that laser-Doppler flowmetry does not measure actual volumetric blood flows and thus does not allow the calculation of absolute CVR. Nevertheless, we have used throughout this report the classic terms of CBF and CVR to mean relative changes in CBF and CVR, respectively.

Results are expressed as mean±SD. P<0.05 was considered statistically significant.

In the pilot experiment, intragroup and intergroup comparisons resulted from distribution-free rank sign tests, paired and unpaired, respectively. In the main experiment, intergroup comparisons were performed by an ANOVA followed by a 2-sided protected least significant difference test.

Results
Pilot Study
Table 1 shows the effects of different ACZ doses on MABP, CBF, and CVR. It appears that the cumulative 42-mg/kg injection (group 1) did not further decrease CVR compared with the decrease elicited by the 21-mg/kg dose.

To take into account the initial difference in MABP between groups 1 and 2, the intergroup comparison of changes in MABP and CVR was performed on the relative variations. It revealed that a single bolus injection of ACZ of 42 mg/kg (group 2) induced a relative decrease in CVR (−44.7±3.0%) similar to those produced by the cumulative doses of 21 and 42 mg/kg, ie, −43.0±3.9% and −43.8±5.5%, respectively. Subsequently, inhaled CO2 induced a further and significant decrease in CVR (−55.7±6.4%; P<0.01 versus pre-CO2 value). Finally, hematocrit was not modified by ACZ at 42 mg/kg (40.0±5.6% before versus 40.1±5.8% after injection, ie, a mean change of −0.07±1.77%) (P=NS).

Main Study: Control Data
The mean values of the physiological variables during the minute preceding the injection are given in Table 2 for the 3
groups. There was no statistically significant difference between the groups.

Effects of ACZ Injection on CBF, MABP, CVR, and Blood Gas Analysis

ACZ injection elicited an increase in CBF in groups 4 and 5 (Figure 1). In these 2 groups, the elevation in CBF was significant by 1 minute after the injection and reached a plateau 10 minutes after the injection. The rise in CBF increased with increasing doses of ACZ. ACZ injection induced a minor decrease in MABP, and this effect occurred 5 minutes after injection. The concomitant changes in CBF and MABP resulted in a decrease in CVR that was significant 1 minute after injection and that plateaued 10 minutes after injection. The reduction in CVR was greater in group 5 than in group 4. The injection of 21 mg/kg ACZ also induced an increase in PaCO₂ (Table 2) and a decrease in pHa. The lowest dose of ACZ had a significant effect only on pHa (Table 2). The injection of saline (group 3) had no statistically significant effect on any of the variables studied.

Effects of ACZ on Autoregulatory Capacity

Figure 2 illustrates data obtained from each animal and pooled in each group. Interindividual variability of the lower limit of CBF autoregulation makes this limit less obvious on such a graph. The CBF values for MABP < 40 mm Hg are,
However, significantly lower (P<0.05) than values corresponding to higher values of MABP. Nevertheless, after ACZ injection, CBF and CVR at low MABPs were always significantly higher and lower, respectively, than CBF and CVR measured in the control group, except when MABP was maintained at its lowest level, ie, under the lower limit of CBF autoregulation. The CVR/MABP was fitted to a linear model (P<0.001) in each animal. Thus, the slope of the CVR/MABP relationship was found because the correlation coefficient was always >0.8. Conversely, the mean slope of the CVR/MABP curve was lowered after administration of 21 mg/kg ACZ, compared with the control group.

Interestingly, the mean CVR measured 10 minutes after an injection of 21 mg/kg ACZ (0.64±0.07 mm Hg/% CBF0) was greater than the minimal CVR obtained by bleeding below the lower limit of CBF autoregulation in the control group (ie, at a MABP of 21±1 mm Hg, CVR=0.31±0.06 mm Hg/% CBF0).

**Discussion**

The main finding of the present study is that cortical autoregulatory dilatory mechanisms are still effective after both doses of ACZ. In animals, assessments of the autoregulatory capacity are ideally based on (1) imposed acute blood pressure variations and (2) online simultaneous CBF measurements. Classically, decreases in MABP are obtained by

### TABLE 1. Effects of Increasing Total Doses of ACZ (Group 1, n=4) and of a Bolus Dose of 42 mg/kg (Group 2)

<table>
<thead>
<tr>
<th>Group 1 (cumulative doses)</th>
<th>CBF, % CBF0</th>
<th>MABP, mm Hg</th>
<th>CVR, mm Hg/% CBF0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before ACZ injection</td>
<td>100</td>
<td>121±7</td>
<td>1.21±0.08</td>
</tr>
<tr>
<td>10 min after 7 mg/kg ACZ bolus</td>
<td>142±22†</td>
<td>117±6*</td>
<td>0.83±0.09†</td>
</tr>
<tr>
<td>10 min after cumulative dose of 21 mg/kg</td>
<td>186±32‡</td>
<td>124±5§</td>
<td>0.69±0.12‡</td>
</tr>
<tr>
<td>10 min after cumulative dose of 42 mg/kg</td>
<td>192±49‡</td>
<td>124±10§</td>
<td>0.68±0.15‡</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 2 (bolus dose)</th>
<th>CBF, % CBF0</th>
<th>MABP, mm Hg</th>
<th>CVR, mm Hg/% CBF0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before ACZ injection</td>
<td>100</td>
<td>100±5</td>
<td>1.00±0.05</td>
</tr>
<tr>
<td>10 min after 42 mg/kg ACZ bolus</td>
<td>172±23†</td>
<td>93±10*</td>
<td>0.55±0.10†</td>
</tr>
<tr>
<td>42 mg/kg ACZ bolus +7% CO2 inhalation</td>
<td>213±40#</td>
<td>92±16</td>
<td>0.44±0.10#</td>
</tr>
</tbody>
</table>

*P<0.05, †P<0.01, ‡P<0.001, significantly different from values determined before injection in the same group.

§P<0.05, ||P<0.01, significantly different from values determined after 7 mg/kg ACZ injection.

#P<0.01, significantly different from values determined after bolus ACZ injection.

### TABLE 2. Physiological Data Before and 10 Minutes After Injection of Saline (Group 3), 7 mg/kg ACZ (Group 4), and 21 mg/kg ACZ (Group 5)

<table>
<thead>
<tr>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO2 reactivity, % CBF0/mm Hg Before injection</td>
<td>2.2±0.9</td>
<td>1.9±0.8</td>
</tr>
<tr>
<td>CBF, % CBF0 After injection</td>
<td>94±12</td>
<td>141±32§</td>
</tr>
<tr>
<td>MABP, mm Hg Before injection</td>
<td>116±14</td>
<td>117±14</td>
</tr>
<tr>
<td>After injection</td>
<td>121±11</td>
<td>107±13§</td>
</tr>
<tr>
<td>CVR, mm Hg/% CBF0 Before injection</td>
<td>1.16±0.14</td>
<td>1.14±0.15</td>
</tr>
<tr>
<td>After injection</td>
<td>1.31±0.17</td>
<td>0.80±0.15§</td>
</tr>
<tr>
<td>PacO2, mm Hg Before injection</td>
<td>38±2</td>
<td>41±4</td>
</tr>
<tr>
<td>After injection</td>
<td>35±3</td>
<td>49±9</td>
</tr>
<tr>
<td>PacO2, mm Hg Before injection</td>
<td>133±19</td>
<td>129±10</td>
</tr>
<tr>
<td>After injection</td>
<td>142±12</td>
<td>140±7</td>
</tr>
<tr>
<td>pHa Before injection</td>
<td>7.44±0.08</td>
<td>7.42±0.08</td>
</tr>
<tr>
<td>After injection</td>
<td>7.41±0.05</td>
<td>7.37±0.07*</td>
</tr>
<tr>
<td>Rectal temperature, °C Before injection</td>
<td>37.9±0.3</td>
<td>37.6±0.2</td>
</tr>
<tr>
<td>After injection</td>
<td>37.5±0.2</td>
<td>37.6±0.2</td>
</tr>
</tbody>
</table>

There was no statistically significant difference between the groups before injection.

*P<0.05, †P<0.01, ‡P<0.001, significantly different from values determined before injection in the same group.

§P<0.05, ||P<0.01, significantly different from values determined after injection in group 3.

#P<0.001, significantly different from values determined after injection in group 4.
administration of vasodilating drugs, although these may interfere with the autoregulatory process, or by bleeding with the use of vascular surgery. In experimental studies, one advantage of the ACZ test is that it only necessitates an intravenous injection. In humans, the ACZ test is safe, inasmuch as it does not induce large blood pressure variations. It is well tolerated, with few contraindications. In addition, the effects of an ACZ injection are long lasting, so that a high temporal resolution of the measurement is superfluous. It is thus sufficient to measure CBF twice, ie, before and after ACZ. Reactivity to ACZ varies in parallel with the mean stump pressure during carotid balloon occlusion in patients. It is thus tempting to consider that the simple ACZ test can be a substitute for more sophisticated procedures of CBF autoregulation assessment, especially in patients.

ACZ is a competitive inhibitor of carbonic anhydrase, and its effects on CBF are probably explained by variations in the pH of the perivascular tissues. This putative mechanism appears to be similar to that of the cerebrovascular reactivity to CO2. Changes in Paco2 affect CVR since an increase in Paco2 results in an increase in CBF. This parallelism between ACZ and CO2 effects is con-

| TABLE 3. Effects of Injection of Saline (Group 3), 7 mg/kg ACZ (Group 4), and 21 mg/kg ACZ (Group 5) on Linear CVR/MABP Relationship |
|-----------------|-----------------|-----------------|
| Range of Correlation Coefficient | Slope (% CBFo) |
| Group 3 | 0.95–0.98 | $8.40 \times 10^{-3} \pm 1.89 \times 10^{-3}$ |
| Group 4 | 0.82–0.99 | $5.82 \times 10^{-3} \pm 1.28 \times 10^{-3}$ |
| Group 5 | 0.89–0.99 | $4.64 \times 10^{-3} \pm 0.62 \times 10^{-3}$ |

*P<0.001, significantly different from group 1.
firmed by a recent report\textsuperscript{13} that suggests a link between ACZ and CO\textsubscript{2} reactivities in humans.

In contrast, there is no strong evidence allowing the assimilation of decreases in CVR induced by ACZ or CO\textsubscript{2} to autoregulatory vasodilation. Furthermore, some studies have demonstrated that, under specific conditions, CO\textsubscript{2} reactivity and autoregulatory vasodilation do not vary in parallel. Nemoto et al\textsuperscript{14} demonstrated that during postischemic cerebrohypoperfusion in dogs, CO\textsubscript{2} reactivity was abolished and autoregulation was present. Lundaar et al\textsuperscript{7} established that, during cardiopulmonary bypass in 5 patients, CO\textsubscript{2} reactivity was preserved, whereas there was no evidence of cerebral autoregulation. Florence et al\textsuperscript{15} demonstrated in anesthetized rabbits that spreading depression reversibly impairs cerebral autoregulatory vasodilation but, in contrast, induces a long-lasting decrease in the cerebrovascular reactivity to CO\textsubscript{2}. In contrast, other reports suggest that CO\textsubscript{2} interacts with autoregulation, which can even be exhausted during hypercapnia.\textsuperscript{16} Okudaira et al\textsuperscript{a} established a correlation between ACZ reactivity and autoregulatory vasodilation in patients during a carotid balloon occlusion test. The parallelism between these 2 vasodilatory responses may only reflect the fact that they both result in a cerebral vasodilation. Certainly, it does not definitively demonstrate that they are similar.

The question as to whether or not the vasodilatory effect of ACZ injection is quantitatively similar to autoregulatory vasodilation can only be solved by comparing the maximal decrease in CVR obtained after ACZ injection with the maximal decrease in CVR obtained by bleeding and by the study of the effects of ACZ on autoregulatory vasodilation capacity. These objectives can be met by using simultaneous direct assessments of CVR variations. If the largest cerebral vasodilating effect of ACZ does not exhaust the autoregulatory vasodilation, this necessarily means that the 2 maximal vasodilations are not quantitatively equivalent.

Laser-Doppler flowmetry allows rapid, instantaneous measurements of blood flow variations by measuring red cell flux. Since results can vary with hematocrit changes, in the pilot study we monitored the absence of any significant short-term effect of ACZ on hematocrit. Intergroup comparisons of CBF variations are thus valid with respect to this parameter.

In our study, blood pressure was modified by bleeding. Arterial bleeding induces hypovolemia, hypocapnia, and alkalois,\textsuperscript{8} but it produces rapid and controlled hypotension. Anesthesia obtained by \textalpha;-chloralose plus halothane allows studies of the cerebrovascular reactivity inasmuch as its effects on this reactivity are only transient.\textsuperscript{17}

When compared with saline (group 3), both doses of ACZ produced a slight hypotension and the classically described decrease in CVR.\textsuperscript{5} It appeared from continuous monitoring that, in our model, ACZ effects on CBF or CVR plateaued 7 to 8 minutes after the injection (Figure 1). We thus chose to start measurements 10 minutes after ACZ injection. This time is similar to that observed by Kawata et al in rats,\textsuperscript{8} slightly shorter than that of 10 to 15 minutes measured by Bickler et al in rabbits,\textsuperscript{12} and slightly shorter than that of 10 to 20 minutes measured by Postiglione et al in rats.\textsuperscript{1} The effects of ACZ on Paco\textsubscript{2} and pH are well known\textsuperscript{11} and probably explain in part the mechanism by which ACZ affects CVR.

One major finding of our study is that a dose of 7 mg/kg of ACZ does not produce a maximal decrease in CVR. A dose of 21 mg/kg results in a greater (1.5-fold) effect on CBF and CVR and does not further decrease blood pressure. The results of our pilot study also established that injection of 42 mg/kg ACZ (cumulative or bolus doses) did not produce significantly larger effects than 21 mg/kg.

The CVR/MABP relationship during blood withdrawal describes the autoregulatory capacity. In the case of a nonautoregulated cerebral circulation, blood pressure variations induce proportional changes in CBF, with CVR remaining unchanged. Under these conditions, the CVR/MABP relationship would appear as a straight horizontal line. In contrast, perfect autoregulation will ideally result in a straight linear CVR/MABP relationship with a slope that significantly differs from zero and that reflects the autoregulatory capacity. In our animals, CBF is expressed as a percentage of baseline flow. If it remains unchanged, its value is thus by definition 100%. In the case of a perfectly efficient autoregulation, the CVR/MABP relationship is described by a line with a slope of 1/100, ie, 0.01. The slope of the CVR/blood pressure obtained from the autoregulation testing in the control group (Table 3) is 0.0084±0.0019 and does not significantly differ from the “theoretical” slope of 0.01.

Another important point is that the minimal values of CVR obtained after the injection of both doses of ACZ and before bleeding (0.80±0.15 and 0.64±0.07 mm Hg/% CBF\textsubscript{0}, groups 4 and 5, respectively) are not as low as the CVR measured after lowering blood pressure under the limit of CBF autoregulation in controls (0.31±0.06 mm Hg/% CBF\textsubscript{0} at an MABP of 21±1 mm Hg). This comparison is limited by the fact that it does not take into account the variations of intracranial pressure. This pressure may increase after ACZ-induced cerebral vasodilation, leading to an overestimation of CVR, especially before bleeding. At the lowest MABP values, maximal autoregulatory vasodilation probably makes this intergroup difference negligible.

Carbonic anhydrase inhibition produced by ACZ is reversible and thus surmountable. ACZ-induced accumulation of CO\textsubscript{2} is probably limited compared with that obtained by CO\textsubscript{2} inhalation, as is the resulting increase in CBF. This hypothesis was confirmed by the results of our pilot study showing that a 7% CO\textsubscript{2} inhalation resulted in a further cerebral vasodilation in rats that were given a maximal vasodilating dose of ACZ.

ACZ injection thus appears to limit the efficiency of the autoregulatory process inasmuch as, after both doses, CBF slightly decreased during blood withdrawal. Nevertheless, even after the maximal dose of 21 mg/kg, ACZ administration did not exhaust the cortical autoregulation. The main effect of ACZ, a dose-dependent decrease in the CVR/MABP slope, is probably nonspecific and due to the cerebral vasodilating properties of ACZ that impair the ability of the cerebral arterioles to further dilate. This may explain the correlation found between autoregulatory capacity and ACZ effects in humans.\textsuperscript{8}
The response of cerebral blood flow (CBF) to acetazolamide, an inhibitor of carbonic anhydrase, is frequently used in clinical settings to evaluate cerebrovascular reserve capacity (CVRC). Inhibition of carbonic anhydrase is thought to induce vasodilation by a mechanism similar to that of CO$_2$-induced dilation. Reduced CVRC has been used to identify patients with compromised hemodynamics who may be at increased risk of cerebral ischemia. In patients with carotid artery occlusion, impaired CVRC has been associated with increased stroke risk. It is not clear, however, whether the acetazolamide test is a good indicator of cerebrovascular autoregulatory capacity, the ability of the cerebral circulation to further dilate in response to hemorrhage-induced hypotension. Autoregulation was attenuated, but otherwise remained intact, after administration of acetazolamide, which led the authors to conclude that the mechanism of acetazolamide-induced dilation is different and independent form that of autoregulatory dilation in response to hypotension, and thus is not a valid measure of autoregulatory reserve capacity.

The study addresses a clinically relevant question of how accurate the acetazolamide test is in identifying patients with impaired autoregulation. The finding of the study that CBF response to acetazolamide is not a good indicator of autoregulatory capacity is in contrast to the finding of Nishimura et al. who observed with positron-emission tomography (PET) in patients with occlusive cerebral artery disease that impaired autoregulation was associated with diminished CO$_2$ reactivity. A dissociation between hypercapnic and acetazolamide vasoreactivities has been reported in subpopulations of patients with
occlusive cerebral artery disease. These contradicting reports indicate that further studies are necessary to address this issue and assess the ability of cerebrovascular reactivities to CO₂ and acetazolamide to predict autoregulatory impairment and risks of cerebral ischemia in patients with hemodynamically compromised cerebral circulation.

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References
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