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REVIEW ARTICLE

Acetazolamide as a vasodilatory stimulus in cerebrovascular diseases and in conditions affecting the cerebral vasculature

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Pathologic processes affecting the brain vessels may damage cerebral vasodilatory capacity. Early detection of cerebral dysfunction plays an important role in the prevention of cerebrovascular diseases. In recent decades acetazolamide (AZ) has frequently been used for this purpose. In the present work the mechanism of action and the previous studies are reviewed. The authors conclude that AZ tests are useful in cerebrovascular research. Further investigations are recommended to prove how impaired reserve capacity and reactivity influence the stroke risk in patients and whether these tests may indicate therapeutic interventions.

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Cerebrovascular reserve (CVR) can be measured using acetazolamide (AZ), a vasodilatory agent. In the following review we present the mechanisms involved in CVR, and we discuss relevant data on methods to measure CVR with AZ, the mechanisms of action and possible uses under clinical circumstances.

The importance of autoregulation and vasoreactivity testing

Regulation of cerebral arteriolar tone

An adequate function of the cerebral arterioles is essential in regulating cerebral blood flow (CBF). Several factors are known to play a key role in determination of the brain arteriolar tone. The most important ones amongst them are summarized in Fig. 1. These factors exert their action either through increasing the production of nitric oxide, resulting in vasodilation or through an overproduction of the vasoconstrictor endothelin. Cerebral arterioles are involved both in autoregulation and metabolic regulation of the brain; therefore, they can be considered as common actors of these two physiologic mechanisms.

Cerebral autoregulation is the inherent ability of the brain circulation to maintain a constant blood flow over wide ranges of CPP. *Metabolic regulation* tailors local and general circulation of the brain parenchyma to the actual metabolic needs. The most important triggering factors of metabolic regulation are the partial pressures of oxygen and CO_2, the pH and the concentration of ADP and ATP of the brain parenchyma. *Vasomotor reactivity* is defined as the vasodilation capacity of cerebral arterioles to external stimuli, such as increasing extracellular pCO_2 and decreasing extracellular pH. The correlation between cerebral autoregulation, metabolic regulation and vasomotor reactivity seems to be close, most probably all these mechanisms exert their action through cerebral resistance vessels (arterioles). In other words, *autoregulation and metabolic regulation testing* allow information about the complex vasodilatory and vasoconstrictory mechanisms of cerebral arterioles during *physiologic* stimuli (alterations in systemic blood pressure and metabolic factors). In contradiction: assessment of *vasomotor reactivity* measures, how resistance vessels react to *exogenic* vasodilatory stimuli.

Changes of cerebral arteriolar function in pathologic conditions

The dilation of the brain resistance vessels depends on the following factors:

Mean arterial blood pressure
The autoregulation has a lower and an upper limit. Lowering the perfusion pressure below this limit does not result in further vasodilation and the CBF decreases with decreasing CPP. Until a certain limit, increasing of the oxygen extraction fraction maintains normal oxygen supply (Kanno *et al.*, 1988; Powers, 1991). However, further decrease in the CBF leads to hypoxic

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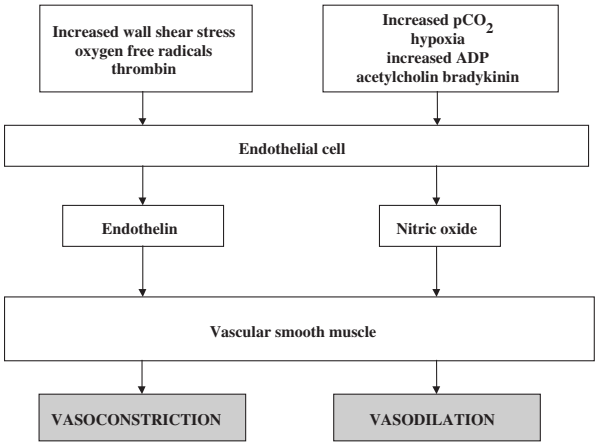

Figure 1

brain damage (pathomechanism of hypoxic brain damage, e.g. after cardiac arrest or in shock situations). Furthermore, increasing the perfusion pressure above the upper limit of autoregulation results in an intraluminal pressure rise in the arterioles and brain edema may develop (pathomechanism of hypertensive encephalopathy).

The condition of the large cerebral arteries and that of the collateral pathways

A hemodynamically significant stenosis or occlusion in the large cerebral arteries may result in a pressure drop distal to the occlusive lesion. In this case, the perfusion pressure ipsilateral to the lesion depends on the capacity of the collateral flow (Ringelstein *et al.*, 1983; Mendelow *et al.*, 1987; Schneider *et al.*, 1988; Schomer *et al.*, 1994). If the collateral supply is insufficient, the resistance vessels dilate locally to keep the CBF constant. However, this vasodilation has a maximal limit, and further decreases in the CPP (e.g. sleep, orthostatic conditions, and hypotensive anesthesia) might be critical for cerebral perfusion (Brierly and Cooper, 1962; Millar-Craig *et al.*, 1978; Ruff *et al.*, 1981). If a strong autoregulatory response is present, in the case of perfusion pressure decrease, no or only minimal further dilatation is possible: the autoregulatory capacity is exhausted. Distal to a cerebral vasospasm after subarachnoidal hemorrhage a similar process may occur. Thus, the resistance arterioles become dilated due to the underlying process, and an external vasodilatory stimulus will not be able to enhance further vasodilation or at least not in the magnitude that is expected under normal conditions.

The condition of the resistance vessels

Pathologic processes, damaging the small resistance vessels (arteriolosclerosis, diabetic microangiopathy, and autoimmune vasculopathies), may diminish the vasodilatory capacity (De Chiara *et al.*, 1993; Csepany *et al.*, 1994). Furthermore, autoregulatory vasoconstriction of the resistance vessels due to increased perfusion pressure in hypertension may cause a slower and smaller vasodilatory response (Ficzere *et al.*, 1997).

In order to maintain a constant blood supply to the brain parenchyma, the vasodilatory response has to fulfill two demands: it should be sufficiently large and it should be fast enough.

Hence, a vasodilatory test must be able to assess both the time course (cerebrovascular reactivity, CR) and the magnitude (CVR capacity, CRC) of the vasodilatory response.

Why acetazolamide?

Various stimuli have been used so far to elicit the reactivity of the cerebral vasculature: e.g. lowering or increasing the blood pressure, cognitive tasks (Droste *et al.*, 1989), CO_2 inhalation (Widder *et al.*, 1994), breath holding and hyperventilation tests (Settakis *et al.*, 2002), and ACZ testing (Sorteberg *et al.*, 1989). The methods most frequently used for the assessment of CVR are CO_2 inhalation and intravenous administration of AZ. During the measurement of CO_2 reactivity, hypercapnia is induced by inhaling a mixture of 2–5% CO_2 in 95–98% oxygen. After stabilization of the end-tidal CO_2 concentration – as determined by capnograph – CBF measurement can be performed (Kleiser and Widder, 1992; Ringelstein *et al.*, 1992). Using positron emission tomography (PET) a good correlation can be detected between CO_2 reactivity values and oxygen extraction fraction (Herold *et al.*, 1988). Comparative investigations show a good correlation when comparing CO_2 inhalation and AZ test results (Ringelstein *et al.*, 1992; Dahl *et al.*, 1994).

The advantages and disadvantages of these two tests are as follows:

Administration and dosage

CO_2 is a more physiologic stimulus compared with AZ. Furthermore, CO_2 inhalation allows CBF measurements on different CO_2 concentrations. Intravenous administration of 1000 mg AZ achieves a supramaximal dilative effect on resistance arteries. However, using AZ, the time course of the vasodilatory answer can also be investigated. A 20-min vasodilatory effect of AZ is ideal for hemodynamic studies.

Patient cooperation

CO_2 inhalation method needs patient cooperation during the investigation (respiratory work). AZ tests can also be performed in non-cooperating patients.

Contraindications

CO_2 inhalation is not performed in patients suffering from obstructive respiratory diseases. Some contraindications of AZ administration are sulphonamid allergy, raised intracranial pressure (Wilkinson, 1989), and severe hepatic or renal diseases.

Side effects

Whilst CO_2 inhalation may cause gasping and fear of death, in case of AZ administration no respiratory discomfort is described (Ringelstein *et al*., 1992). The side effects of AZ are mild (paresthesias of the extremities and of the face – especially around the mouth and tongue – light headedness, and a short lasting, mild diuretic effect), transient and well tolerated by the majority of patients.

Equipments

Both cerebrovascular reactivity after CO_2 and AZ can be investigated using transcranial Doppler (Dahl *et al*., 1992), single photon emission computed tomography (SPECT) (Kreisig *et al*., 1987; Chollet *et al*., 1989; Burt *et al*., 1992; Knop *et al*., 1992; Steiger *et al*., 1993) or PET (Herold *et al*., 1988; Dahl *et al*., 1994). Phase-contrast magnetic resonance tomography is also a suitable method for detecting changes in the CBF after vasodilatory stimulus (Patrick *et al*., 1996). For the CO_2 test a further equipment (capnograph) is needed for measuring the end-tidal CO_2 concentration.

Taking all advantages and disadvantages into account, in our opinion AZ has more advantages compared with CO_2 inhalation method for eliciting cerebrovascular responses.

Acetazolamide: mechanism of action

Acetazolamide is a reversible inhibitor of the enzyme carbonic anhydrase. The enzyme catalyzes the following reaction:

$$CO_2 + H_2O = H_2CO_3 = H^+ + HCO_3^-$$

This enzyme was first described by Rougton in the early 1930s in erythrocytes. Since that time it was found to be present in many other tissues: kidney, gastric mucosa, eyes, and the nervous system. AZ increases CBF by the dilatation of the arterioles (Mithoefer *et al*., 1957; Severinghaus and Cotev, 1968). However, the mechanism of vasodilation is still unknown, although it is ascribed to metabolic changes induced by AZ and the direct effect of AZ on cerebral vessels.

Metabolic changes induced by acetazolamide

Most common metabolic changes reported after AZ administration are: increase in extracellular pCO_2, and decrease in extracellular pH and end-tidal pCO_2 (Vorstrup *et al*., 1984; Bickler *et al*., 1988a,b). These phenomena can be explained by the following theory, suggested by Vorstrup (Vorstrup *et al*., 1989): CO_2 and water, produced by glycolysis are transformed into H^+ and HCO_3^- by carbonic anhydrase, located in the erythrocytes. If the dissociation into H^+ and HCO_3^- (and with that the transport in the blood) is blocked by AZ, a carbonic acidosis will result. Carbonic acid crosses the erythrocyte membrane easily, resulting in an increase in the extracellular carbonic acid level. This enzyme has also been found at the external surface of the glial cells (Giacobini, 1962), so it is possible that AZ exerts its effect in the brain not only through erythrocyte carbonic anhydrase, but also by direct inhibition of carbonic anhydrase in the glial cells. For this reason, some investigators looked for, but could not prove (Vorstrup *et al*., 1989) or only a moderate (Kjällquist *et al*., 1969; Heuser *et al*., 1975; Grieb, 1990) intracellular acidosis after AZ. In the lungs carbonic anhydrase transforms H^+ and HCO_3 into CO_2 and water. Using AZ this reaction is also blocked. This could explain the decrease in end-tidal CO_2, extracellular pH, and the increase in extracellular pCO_2 following AZ administration.

Both extracellular pH and pCO_2 play an important role in the dilation of small cerebral vessels. West *et al*. (1992) reported a pH-dependent mechanism regulating Ca-channels in the brain arteries and it is probable that a decrease in extracellular pH could be an important factor in the vasodilation induced by AZ. Although this concept seems to be acceptable for explaining metabolic changes and the mechanism of vasodilatation, some investigators reported about unaltered or decreased extracellular pCO_2 levels, whereas others could not find any decrease in the extracellular pH or changes in the respiration after AZ administration (Hauge *et al*., 1983).

It remains unclear as to whether carbonic anhydrase blockade in the glial cells plays a role in the vasodilatative effect after AZ administration. AZ passes the blood–brain barrier very slowly and the increase in CBF starts after 2 min (Hauge *et al*., 1983). Thus, it seems to be unlikely that this mechanism plays an important role in fast vasodilation.

Direct effect of acetazolamide on cerebral vessels

In recent years carbonic anhydrase has been detected in the wall of small brain arterioles and arteries (Ridderstråle and Hanson, 1985). Theoretically it may be possible that the vasodilatory effect is related to the direct inhibition of the enzyme in the vessels. However, there is no experimental evidence for the existence of such a mechanism.

According to Hauge *et al*. (1983), who found no alterations in the arterial pCO_2-level, in respiration and

in the extracellular pH after administration of 500 mg AZ intravenously (the enzyme was not fully inhibited), the increase in CBF is unrelated to carbonic anhydrase inhibition. They presumed a direct effect of the drug on the smooth muscle of the vessel wall.

Dose dependency and kinetics of action

Several investigators have described a dose-dependent vasodilatative effect. Huang *et al.* (1988) found that 250 mg AZ given orally did not alter the flow in the carotid and vertebral arteries of healthy volunteers. Hackett found the same result after intravenous administration of 250 mg AZ. Hauge *et al.* (1983) reported 75% increase in the carotid artery flow velocity after intravenous infusion of 500 mg AZ. However, the same oral dose did not alter CBF (Lassen *et al.*, 1987). A significant increase in the CBF was detected in humans after administering 1000 mg of AZ, both orally and intravenously (Friberg *et al.*, 1990). A dose over 1000 mg does not result in further increase in CBF (Kreisig *et al.*, 1987). When 1 or 2 g of AZ was administered no significant difference was found (Dormehl *et al.*, 1993). On the contrary, Dahl *et al.* (1995) pointed out that at least a dose over 15 mg/kg body weight (corresponding to 1200 mg in a patient weighing 80 kg) is needed for obtaining the maximal vasodilatory effect. They also detected a significant correlation between the serum concentration of AZ and the maximal increase in CBF velocity. The maximal increases in CBF during AZ testing are summarized in Table 1.

An intravenously administered dose of 1000 mg AZ was widely used in a majority of vasoreactivity tests. A significant increase in CBF after AZ administration was found at 2 min using continuous-wave Doppler (Hauge *et al.*, 1983). The vasodilatory effect reaches its maximal level at 10–12 min after injecting the drug. Some investigators observed a plateau between 10 and 30 min (Ringelstein *et al.*, 1992; Dahl *et al.*, 1995), whilst others found the maximal increase in CBF at approxi-

Table 1 Maximal percentage increase in cerebral blood flow and cerebral blood flow velocity after administration of acetazolamide depending on the method used

Reference	Method	Increase in cerebral blood flow/velocity (%)
Posner and Plum (1960)	N_2O method	90
Ehrenreich *et al.* (1961)	N_2O method	65
Hauge *et al.* (1983)	ICA blood flow velocity, Doppler	75
Vorstrup *et al.* (1984)	^{133}Xe inhalation	70
Kreisig *et al.* (1987)	^{133}Xe SPECT	25
Sullivan *et al.* (1987)	^{133}Xe inhalation DSPECT	66
Leinsinger *et al.* (1988)	^{133}Xe DSPECT	25
Bonte *et al.* (1988)	^{133}Xe SPECT	30
Sunada *et al.* (1988)	TCD	24
Sorteberg *et al.* (1989)	TCD	36–42
Piepgras *et al.* (1990)	TCD	40
Sabatini *et al.* (1991)	^{133}Xe DSPECT	1.45
Vorstrup *et al.* (1992)	^{133}Xe SPECT	51
Ringelstein *et al.* (1992)	TCD	50
Sbarigia *et al.* (1993)	TCD	27
Chimowitz *et al.* (1993)	TCD	28–34
Kashimada *et al.* (1994)	Phase contrast magnetic resonance	57
Dahl *et al.* (1994)	^{133}Xe DSPECT	29–30
	TCD	34–35
Hashikawa *et al.* (1994)	^{123}I-AMP SPECT	50
Ulrich *et al.* (1995)	^{133}Xe inhalation	32
	TCD	36
Valikovics *et al.* (1996a)	TCD	30–60, age-dependent
Müller *et al.* (1995)	TCD	64
Karnik *et al.* (1996)	TCD	49 (females) 38 (males)
Patrick *et al.* (1996)	Phase contrast magnetic resonance abnormalities	45
	TCD	39
Gambhir *et al.* (1997)	PET	49
Fülesdi *et al.* (1997)	TCD	64

SPECT, single photon emission computed tomography; DSPECT, Dopper single photon emission computed tomography; TCD, transcranial Doppler; PET, position emission tomography.

mately 15 min, followed by a moderate decrease (Hamann *et al*., 1996). Dahl *et al*. (1995) observed a 68% decrease in velocity to the highest level at 45 min, whereas Hauge *et al*. (1983) reported a 50% decrease of the maximum at 95 min after administering AZ. Two days after administration of AZ, no CBF change could be detected (Friberg *et al*., 1990).

Age dependency

Comparative investigations in healthy volunteers proved that CVR is an age-dependent parameter. When assessing CVR between 20 and 70 years, the extent of AZ-induced CVR was the greatest in the 31–40-year age group and the smallest in the 61–70-year age group (Valikovics *et al*., 1996b).

Gender differences

Karnik *et al*. (1996) detected an increased vasodilatory response to AZ in women in a series of 36 healthy subjects as did Valikovics *et al*. (1996b) and Oláh *et al*. (2000). Women before menopause responded with higher CVR than age-matched men but this difference was not present when comparing CVRs in females after menopause and men of similar age (Oláh *et al*., 2000).

In what clinical situations may the AZ tests be useful?

Occlusive cerebrovascular diseases

The majority of the AZ studies were performed in patients with severe stenosis or occlusion of the carotid and large cerebral arteries. Although The EC-IC Bypass Study Group (1985) did not prove the beneficial effect of EC-IC bypass surgery, it cannot be excluded that patients with insufficient collateral supply may benefit from bypass surgery (Barnett *et al*., 1987; Hayners *et al*., 1986; Ishikawa *et al*., 1992; Yamashita *et al*., 1992). AZ tests might be of significant value in diagnosing this patient group. It may also be helpful in the decision making by surgical intervention of an asymptomatic carotid stenosis (North American Symptomatic Carotid Endarterectomy Trial Collaboration, 1991).

Correlation between impaired CRC and stroke incidence
Patients with internal carotid artery occlusion have a yearly incidence of stroke between 2 and 8% (Dyken *et al*., 1974; Furlan *et al*., 1980; Norrving *et al*., 1981; Cote *et al*., 1983; The EC-IC Bypass Study Group, 1985). Several authors reported higher stroke risk in patients with an impaired CRC in occlusive cerebrovascular diseases. Kleiser and Widder (1992) investigated 85 patients with CO_2 inhalation and found a 55% risk for cerebral ischemic events during a follow-up of 38 ± 15 months in the group with an exhausted CRC. Powers *et al*. (1989b) found a 29% stroke rate in a 1-year follow-up in patients with internal carotid artery occlusion by PET study. AZ tests assessing CRC provided similar results: 27% of the patients with impaired, and 3% with normal CRC suffered from stroke during an 18-month follow-up (Durham *et al*., 1991), whilst Yonas *et al*. (1993) found a 36% stroke risk in the impaired group. Gur *et al*. (1996) confirmed that cerebral ischemic events occurred more frequently in patients with asymptomatic, significant internal carotid artery stenosis and impaired cerebrovascular reactivity than in those with normal reactivity. Hasegawa and Yamaguchi (1993), in a prospective long-term follow-up AZ study in 76 patients with significant stenosis or occlusion of the large cerebropetal arteries, did not detect a poor prognosis in case of impaired CRC. The majority of the ischemic events occured in the first months after ICA occlusion (Kleiser and Widder, 1992; Yonas *et al*., 1993). Kuroda *et al*. (2001) performed a prospective, longitudinal ^{133}Xe-SPECT AZ stress test study in medically treated patients suffering from internal carotid artery and middle cerebral artery occlusions with a follow-up of 42.7 months. They concluded that the risk of ipsilateral strokes was higher in patients with decreased CVR, indicating that subgroups of patients with higher risk of ischemic stroke may be identified if they are medically, but not surgically, treated.

Generally, CBF is decreased in the occluded side in patients with carotid artery occlusion even at rest (Schneider *et al*., 1988; Holzschuh *et al*., 1991; Dahl *et al*., 1992; Chimowitz *et al*., 1993). There is not always a CBF difference between affected and non-affected hemispheres at rest in patients with carotid stenosis (Sullivan *et al*., 1987; Russell *et al*., 1990; Burt *et al*., 1992; Chimowitz *et al*., 1993). AZ administration both in patients with significant carotid stenosis and occlusion causes a focal rCBF decrease in the majority of patients (Vorstrup *et al*., 1986; Hojer-Pedersen, 1987; Sullivan *et al*., 1987; Batjer *et al*., 1988; Lord *et al*., 1988; Gratzl *et al*., 1990; Piepgras *et al*., 1990; Cikrit *et al*., 1992; Hasegawa *et al*., 1992; Lord *et al*., 1992; Rosenkranz *et al*., 1992; Yamashita *et al*., 1992; Demarin *et al*., 1993; Nighoghossian *et al*., 1994) and reduced vasomotor reactivity is also present in the ophthalmic artery ipsilateral to the significant stenosis (Bornstein *et al*., 2000). Orosz *et al*. (2002) compared CVR asymmetry in symptomatic and asymptomatic carotid stenoses and occlusions. They found that asymmetry index of CVR was near to 1 only in cases of

asymptomatic, hemodynamically significant carotid stenoses, indicating that vascular reserve to AZ was of similar magnitude in the affected and non-affected hemispheres. In contrast to this, significant side asymmetries of CVR were detected amongst patients with asymptomatic occlusions and symptomatic stenoses and occlusions. Several studies proved that revascularization procedure leads to an increase in CBF and CRC in patients with significant stenoses and occlusions (Leblanc *et al*., 1987; Schroeder *et al*., 1987; Vorstrup *et al*., 1987; Batjer *et al*., 1988; Russell *et al*., 1990; Ramsay *et al*., 1991; Yamashita *et al*., 1991; Cikrit *et al*., 1992; Demarin *et al*., 1993; Hartl *et al*., 1994; Barzó *et al*., 1996; Karnik *et al*., 1996; Wiart *et al*., 2000).

Clinical significance: contradictory opinions

Only few studies have used hemodynamic criteria in the selection of patients for revascularization procedures. Using PET, Powers *et al*. (1989b) investigated 30 patients with abnormal hemodynamics caused by a more than 75% stenosis or occlusion of the carotid arteries. They found no differences in a 1-year stroke incidence in the operated and conservatively treated group. Hayners *et al*. (1986) investigated the efficacy of EC-IC bypass in patients with ophthalmic collaterals, but could not detect any benefit in the operated group. Using AZ, Kuroda *et al*. (1993) reported on a lower stroke risk after EC-IC bypass in a patient group with preoperatively impaired CRC or impaired CRC and decreased rCBF as measured with AZ-SPECT. However their group was small (32 patients), no randomization was performed and no sufficient number of controls was available. A similar result was published by Ishikawa *et al*. (1992) using PET. Because of the same insufficiencies (no randomization and small number of investigations) the clinical validity of these results are questionable.

Thus, it generally seems to be true that CRC is impaired distally to significant occlusive lesions of the large cerebral arteries and surgical revascularization improves cerebral vasodilatory responses. However, it should be noted that there are also some contradictory data.

Criteria for patient selection. These vary widely between different studies. Two sets of criteria may be recognized: anatomic criteria (severity of occlusive lesion) and functional criteria (reaction to hemodynamic provocations).

Anatomic criteria. One group of investigators examined only patients with internal carotid artery occlusions, others studied a heterogenous group (ICA occlusion, ICA stenosis, MCA stenosis, and occlusion). According to Powers *et al*. (1987, 1989a), the CRC in hemodynamically significant stenosis or occlusion of the internal carotid artery depends only on sufficient collaterals and is independent of the severity of the occlusive lesion. Others found that impairment of CRC is most severe in patients with carotid artery obstruction, moderately severe in case of hemodynamically significant carotid stenosis, and non-significant carotid stenosis leads to no or only mild decrease in the CRC (Chimowitz *et al*., 1993).

Functional criteria. Powers *et al*. (1987, 1989a) and Powers (1991) were the first to indicate that protective mechanisms of cerebral autoregulation are organized in a stepwise fashion: mild decrease in CPP causes vasodilation of the small vessels, maintaining a normal CBF (stage 1). In this stage hemodynamic tests will show a normal CBF at rest, and a focally decreased CRC after AZ stimulation. If the CPP decreases further, the autoregulatory vasodilatation becomes insufficient to maintain even the normal CBF at rest, and after AZ there is no or only a borderline CRC detectable (stage 2). In some cases a focal decrease in the CBF after vasodilatory stimulus may occur (steal phenomenon) (Vorstrup *et al*., 1986, 1992).

A reduced CRC may be normalized in some patients without any surgical intervention during follow-up (Kleiser and Widder, 1992; Hasegawa and Yamaguchi, 1993; Widder *et al*., 1994).

The initially increased CBF decreases during long term follow-up after EC-IC bypass surgery (Holzschuh *et al*., 1991).

PET studies have shown that revascularization increases the CBF/CBV ratio, but does not alter cerebral oxygen metabolism of the brain tissue (Leblanc *et al*., 1987).

Perspectives in the future: trials are necessary

To date, whether hemodynamic parameters can be used to indicate surgical revascularization (EC-IC bypass or endarterectomy) is a matter of debate. There is convincing evidence suggesting that severely impaired cerebrovascular reactivity predicts the risk of ipsilateral stroke and transient ischemic attacks (TIAs) in carotid artery occlusion and asymptomatic stenosis (Silvestrini *et al*., 2000; Markus and Cullinane, 2001). Prospective, randomized trials using strict selection criteria and based on long-term follow-up with relevant outcome parameters can answer the question whether revascularization will reduce the stroke risk in patients with exhausted cerebrovascular reactivity. Essential features of such a study should be: precise description of the severity of the occlusive lesion and collateral pathways, the use of well-described and standardized hemodynamic criteria, and the use of valid outcome measures in terms of mortality and functional recovery.

Hypertensive intracerebral hemorrhage

Cerebrovascular reserve capacity decreases in acute stages of hypertensive putaminal hemorrhages. Kitahara *et al.* (1996) showed that CVR increases after surgical evacuation of the hematoma, with a recovery to the normal level in the subacute and chronic phase. Whether decreased CVR in the acute stage is indicative of surgical intervention remains unknown.

Vasospasm after aneurysmal subarachnoid hemorrhage

The diagnosis of vasospasm after subarachnoid hemorrhage is important because it is believed that it may help in decision making, whether an intervention is necessary, and may be useful in post-operative management. AZ test is an indicator of vasospasm. Low perfusion areas on the SPECT after AZ correlate well with the severity of ischemia: 77% of the patients with Hunt and Hess grades I and II, and every patient with grades III–V showed low perfusion areas. Therefore, AZ tests may help in timing surgery and in the follow-up of patients after the operation (Mourier *et al.*, 1991; Shinoda *et al.*, 1991; George *et al.*, 1992). Many years after vasospasm due to aneurysmal subarachnoid hemorrhage, CVR is similar to that measured in age-matched controls, indicating that after resolution of the vasospasm vasoreactivity also returns to its normal level (Kitahara *et al.*, 1996; Szabó *et al.* 1997).

Hypertension

Chronic hypertension results in a damage of the small vessel wall. It is supposed that decreased vasodilatory ability of the cerebral arterioles is caused by hypertensive vasculopathy; therefore, vasodilatory testing may detect early damages in the small vessel wall structure and may be helpful in selecting the optimal antihypertensive treatment. Previous cerebrovascular reactivity test using CO_2 as vasodilatory stimulus (Maeda *et al.*, 1994) suggested a negative correlation between cerebrovascular reactivity and severity of hypertension, referring to an arteriolar dysfunction. Ficzere *et al.* (1997) investigated the CRC in 25 hypertensive patients without any neurologic deficit and found a significantly slower reaction to AZ in this patient group when compared with normal controls. The maximal percentual velocity increase after AZ (CVR) was also significantly lower in the hypertensive group than in normotensive subjects.

Diabetes mellitus

Diabetes leads to vascular complications. Both small and large vessel disease may occur. Earlier studies with CO_2 inhalation showed a diminished cerebrovascular reactivity in diabetic patients (Bentsen *et al.*, 1975). Similar results were found after AZ stimulation in insulin-dependent diabetes mellitus patients. In type 1 diabetic patients a significantly decreased CVR was observed when compared with healthy controls (De Chiara *et al.*, 1993; Fülesdi *et al.*, 1997). In this diabetes subtype CVR decreased parallel with disease duration and showed a positive relationship with other vascular complications such as microalbuminuria and retinopathy (Fülesdi *et al.*, 1997). Similarly, Rodriguez *et al.* (1993) also detected a negative correlation between basal global CBF and disease duration in patients with type 1 diabetes. Further studies proved that CVR is independent of the actual glucose and insulin levels, and the severity of diabetic neuropathy (Fülesdi *et al.*, 1999; Hidasi *et al.*, 2002). CVR is also decreased in type 2 diabetes mellitus with longer disease duration (Fülesdi *et al.*, 1999).

Systemic lupus erythematosous

Small vessel complications in systemic lupus erythematosous (SLE) are well-known phenomena. Csépány *et al.* (1995) and Settakis *et al.* (2002) detected a significant decrease in CRC in patients suffering from long-lasting SLE. Patients with serious neurologic symptoms and magnetic resonance imaging (MRI) abnormalities showed a significantly lower response to AZ in the affected side than in the non-affected hemisphere. A case of a patient suffering from SLE was also decribed by Grunwald *et al.* (1995). In this report PET showed no major abnormalities, but AZ-SPECT revelaed a marked reduction in the cortical CVR.

Leukoaraiosis

Isaka *et al.* (1994) investigated a group of patients with cerebrovascular risk factors and asymptomatic periventricular hyperintensities on MRI. They detected a decreased CRC in the cerebral cortex, and suggested that this might be due to atherosclerotic damage of the cortical arterioles. Turc *et al.* (1994) performed SPECT-AZ tests in a patient group suffering from leukoaraiosis as diagnosed by MRI and could not detect any differences in the vasodilatory answer between the control and the leukoaraiosis group. AZ reactivity was normal in patients with leucoaraiosis alone and a decreased vasomotor reactivity could only be detected if leucoa-

raiosis was accompanied by lacunar infarctions (Mochizuki *et al*., 1997; Oishi *et al*., 1998; Ioshi and Mochizuki, 1999).

Migraine

The results of vasoreactivity of migraineurs have so far been contradictory. Some authors, using CO_2 inhalation, reported increased reactivity (Thie *et al*., 1990; Thomas *et al*., 1990), whereas others, using AZ (Schlake *et al*., 1992; Valikovics *et al*., 1996a), did not. Schlake *et al*. (1992) performed SPECT before and after intravenous administration of AZ in 20 patients suffering from migraine with aura. They found some hypoperfused areas in the baseline SPECT, which did not show perfusion increase after administration of AZ. They conluded that this test could be useful in the differential diagnosis of TIAs and migraine attacks. Valikovics *et al*. (1996a) were also not able to detect any difference between CRC of migraineurs and that of healthy subjects. Due to these conflicting results AZ tests in migraine may only help in better understanding the pathophysiologic alterations during the attacks.

Familiar hypercholesterinemia

Hypercholesterinemia is a minor risk factor for cerebrovascular diseases. Rodriguez *et al*. (1994) investigated a group of 15 patients with SPECT-AZ tests. CRC was normal in this patient group. Others, using transcranial Doppler, could not detect any differences between the CVR capacity of hypercholesterolemic patients and that of the normal subjects (Kerenyi *et al*., 2000).

AZ tests: present and future

Testing of the CRC using AZ has been used for more than 15 years. The data from various AZ studies have provided information mainly about the pathophysiologic background of different vascular diseases, but no clear evidence exists as to whether a decreased or impaired reactivity is an independent risk factor for ischemic cerebrovascular events or therapeutic decisions. Testing with AZ is an useful tool for detecting the altered cerebrovascular reactivity in different diseases. It is able to detect small vessel diseases in the brain in early preclinical phase and it also allows the measurement of hemodynamic consequences in large cerebral artery obstructions. Changes in cerebral vasomotor reactivity can be sensitively followed by non-invasive transcranial Doppler-AZ tests.

Before CRC testing using AZ can be accepted as routine diagnostic method, the following issues should be settled: Is the impaired CVR an independent risk factor for ischemic cerebrovascular events? Can we select high-risk patients using this test, who might benefit from carotid surgery? Prospective studies of sufficient size and with sufficiently long follow-up should establish the first point and randomized controlled studies may prove the second one.

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