Cerebral Autoregulation in Stroke
A Review of Transcranial Doppler Studies

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Background and Purpose—Cerebral autoregulation may become impaired after stroke. To provide a review of the nature and extent of any autoregulation impairment after stroke and its course over time, a technique allowing repeated bedside measurements with good temporal resolution is required. Transcranial Doppler (TCD) in combination with continuous blood pressure measurements allows noninvasive continuous bedside investigation with high temporal resolution of the dynamic and the steady-state components of cerebral autoregulation. Therefore, this review focuses on all TCD studies on cerebral autoregulation in the setting of documented ischemic stroke.

Methods—PubMed and EMBASE were searched for studies of stroke, autoregulation, and TCD. Studies were either acute insults (like hypertension). Cessation of blood flow then initiates a related series of processes that effects endothelial cell and receptor dysfunction and smooth muscle activation, all leading to impaired vasoregulator function. The primary focus of this review is on the nature and extent of cerebral autoregulation impairment and its course over time. For this, a definition of autoregulation and a description of various evaluation methods are required.

Cerebral autoregulation is the inherent ability of blood vessels to keep cerebral blood flow (CBF) relatively constant over a wide range of systemic BP levels by means of complex myogenic, neurogenic, and metabolic mechanisms. The CBF depends on vascular conductance and arterial blood pressure. Cerebral vascular tone is sensitive to arterial CO2. In response to a variation in perfusion pressure, an adaptation in cerebrovascular resistance will cause CBF to return to its baseline.

Key Words: chemical vasomotor autoregulation ■ dynamic cerebral autoregulation ■ ischemic stroke ■ static cerebral autoregulation ■ transcranial Doppler ultrasonography

It is generally accepted that cerebral autoregulation may become impaired after stroke. Autoregulation impairment in the presence of moderate to severe ischemia may render penumbral tissue particularly vulnerable to alterations in cerebral perfusion. It may be crucial in the survival of ischemic penumbra, especially during interventions in the stroke unit such as blood pressure (BP) manipulation or mobilization, and, as such, may confound trials of interventions in the stroke unit. Important research questions concern the reasons for cerebral autoregulation impairment, the nature of and the extent to which autoregulation becomes impaired, and how impairment progresses over time. Autoregulation is hypothesized to become impaired by damage to cerebral arterioles and capillaries during ischemia or other chronic insults (like hypertension). Cessation of blood flow then rapidly initiates a related series of processes that effects endothelial cell and receptor dysfunction and smooth muscle activation, all leading to impaired vasoregulator function. The primary focus of this review is on the nature and extent of cerebral autoregulation impairment and its course over time. For this, a definition of autoregulation and a description of various evaluation methods are required.

Cerebral autoregulation is the inherent ability of blood vessels to keep cerebral blood flow (CBF) relatively constant over a wide range of systemic BP levels by means of complex myogenic, neurogenic, and metabolic mechanisms. The CBF depends on vascular conductance and arterial blood pressure. Cerebral vascular tone is sensitive to arterial CO2. In response to a variation in perfusion pressure, an adaptation in cerebrovascular resistance will cause CBF to return to its baseline.
Evaluations of cerebral autoregulation have traditionally been performed under steady-state conditions: a measurement of CBF was obtained at a constant baseline BP and constant CBF, followed by another steady-state measurement after manipulation of BP. This “static” autoregulation was supposed to be intact if CBF was maintained at or near the baseline level despite BP changes.\(^5,10\) The group of Stirling used such “classic” steady-state methods to demonstrate different dysautoregulation responses to various anatomic ischemic locations, various risk factors, and duration after stroke.\(^11\) Drawbacks of single steady-state evaluations are the vulnerability to confounding by spontaneous non-BP-related variability, such as CO\(_2\) changes,\(^12\) the time-consuming nature of procedures, the need for invasive pharmacological interventions, and the lack of information on any period of hypoperfusion possibly preceding the eventual return to stable perfusion.\(^6,7\)

More recent developments, such as transcranial Doppler ultrasonography (TCD) and servo-controlled finger photoplethysmography, have offered the advantage of investigating beat-to-beat dynamics of the pressure–flow relationship of the cerebral circulation and of differentiating between fast and slow response mechanisms.\(^5,6\) This “dynamic” approach uses the induced or spontaneous rapid changes in BP as an autoregulatory stimulus and compares BP and CBF velocity (CBFV) during the whole autoregulatory process (dynamic pressure autoregulation).\(^5,6,13\) Obviously, TCD can be used to quantify pressure autoregulation using TCD. TCD studies are indicated for observational studies (www.equator-network.org) was used.\(^20\)

Contrasting with the classical static autoregulation, no uniform method exists to provoke, measure, analyze, and report dynamic or chemical vasomotor autoregulation. Recently, some excellent articles\(^6–8,13,18,19\) provided an overview of the different methods to provoke hemodynamics and quantify pressure autoregulation using TCD. TCD studies are highlighted in this review because TCD studies allow evaluation of the steady-state and dynamic components of cerebral autoregulation, and because TCD together with finger photoplethysmography stands out as a technique with excellent temporal resolution, allowing noninvasive continuous bedside monitoring of CBFV and BP and, thus, autoregulation.

The central question of this review is what the nature and extent of autoregulation impairment after stroke as measured by TCD is. All 3 study approaches to cerebral autoregulation are considered: static pressure, dynamic pressure, and chemical vasomotor or combination autoregulation studies.

Materials and Methods

Study Identification

Cochrane Collaboration methodology for meta-analysis reviews modified for observational studies (www.equator-network.org) was used.\(^20\)

Search Strategy

Studies were identified with a search strategy across 2 English language databases (Medline and Embase) between 1966 and October 2009 accommodating different MeSH terms or subcategories available in each database (Table 1 and Supplemental material available online at http://stroke.ahajournals.org). Bibliographies of selected articles were screened for additional relevant articles.

Inclusion and Exclusion Criteria

Included were published TCD studies of human cerebral autoregulation after ischemic stroke. Eligibility was assessed by reading abstracts and, if necessary, whole articles. The effects of impaired cerebral autoregulation on neurological outcome were assessed. Excluded were case reports, non-English language articles, posterior territory stroke studies, and studies with ultrasound contrast agent injection. Carotid stenosis or known intracranial artery stenosis confounds the effect of stroke on cerebral autoregulation and was an additional reason for exclusion of studies.

Data Extraction

The following data were extracted: (1) stroke population; (2) stroke severity; (3) number of patients and controls; (4) acute (<96 hours after index stroke) vs chronic phase assessment (>96 hours after index stroke); (5) cerebral autoregulation challenges (input); (6) method of data analysis; (7) autoregulation evaluation method (steady-state vs dynamic autoregulation); (8) neurological outcome (Barthel score, NIHSS change, or necessity of craniectomy); (9) main conclusions of the authors; (10) presence, timing, and conclusion of follow-up studies; and (11) status of cerebral autoregulation in both hemispheres. Furthermore, important technical aspects of TCD observational studies such as bilateral probe recordings, reporting of CO\(_2\) values, and use of continuous BP recording during the measurements were extracted.

Study quality was assessed using a checklist proposed previously for authors, editors, and reviewers of meta-analyses of observational studies.\(^30\) This checklist was adapted to include 13 items relevant to TCD autoregulation observational studies (Table 2 and Supplemental material).\(^6–8,13,18,19\)

Results

Literature

Two-hundred thirty-eight publications met the search criteria and were evaluated. Inclusion criteria were met by 14 controlled studies and 13 observational studies. Three studies were excluded because of unclear timing of measurements after stroke onset.\(^21–23\) and 1 was excluded because TIA and minor stroke patients were grouped together.\(^24\) Hence, 23 publications were eligible for review. Study details are summarized in Tables 1 and 2. Patient number ranged from 6 to 100. Sixteen studies included patients in the acute (range, 20–96 hours) and 7 included patients in the chronic (range, 7–458 days) phase of stroke. Six studies had follow-up measurements between 3 days and 3 months after stroke. In 9 studies, the initial stroke severity was not reported,\(^25–33\) and 8 studies failed to provide information about other clinical conditions (such as arrhythmias, diabetes mellitus, and carotid pathology) associated with impaired cerebral autoregulation.\(^25,30,32–37\) All studies allowed hypertensive patients to be included. In 2 studies, only information about the nonaffected hemisphere was presented because of permanent occlusion of contralateral middle cerebral artery.\(^32,38\) One study only provided information about the residual CBFV in the affected hemisphere.\(^34\) Eleven studies reported the end-tidal CO\(_2\) levels during the measurements.\(^25,31,36,38–45\) Six studies...
did not use continuous BP monitoring.25,27,29,34,37,45 One study included patients who received tissue plasminogen activator treatment.41 Information about clinical course and outcome after acute stroke in relation to autoregulation was provided in 5 studies.32,33,35,41,45 One study reported the correlation between baseline severity, disability scores, and cerebrovascular reactivity.37 Cerebrovascular reactivity is impaired in both hemispheres; poor correlations between CBFV asymmetry during pTTT (80°) and hypertensive (20°) groups were not possible by using ARI method and rate of autoregulation regression model.37

Three studies used different tests to calculate cerebrovascular reactivity in the acute phase of stroke. Cupini et al31 used the breath-holding index in different infarct types to show, particularly in 14 patients who already had multiple subcortical infarcts, impaired cerebrovascular reactivity in both hemispheres during the acute phase of a new stroke. Gur et al,37 using slow infusion of acetazolamide in patients with moderate stroke, found impaired autoregulation in cortical strokes only. Bilateral nonsignificant impairment was detected in the subgroup of 24 patients with subcortical stroke, although no corrections were made for asymptomatic lacunar infarct status. Additionally, they failed to find a correlation between baseline severity, disability scores, and cerebrovascular reactivity.37 Cerebrovascular reactivity measurement using 5% CO₂ inhalation in 100 minor stroke patients showed that impaired reserve capacity in the affected hemisphere was independently associated with early neurological deterioration within 72 hours.45

Acute Stroke and Dynamic Autoregulation
All studies are unanimous in their conclusion that dynamic pressure cerebral autoregulation is impaired in acute

<table>
<thead>
<tr>
<th>Study</th>
<th>Stroke Type</th>
<th>Stroke Severity</th>
<th>Age, y (SD)</th>
<th>Input Method</th>
<th>Analysis Method</th>
<th>N of Patients</th>
<th>Timing (Mean)</th>
<th>Follow-up (mo)</th>
<th>Hemispheric Affected?</th>
<th>Main Results and Conclusions (N of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molina 1999</td>
<td>LAS</td>
<td>Unknown</td>
<td>57 (13)</td>
<td>ACZ</td>
<td>Cvr</td>
<td>46</td>
<td>3 mo</td>
<td>NP</td>
<td>Unclear (mean of both used)</td>
<td>Chemical vasomotor CA is impaired in lacunar stroke; there is an association between infarct load and decreased CBFV asymmetry in both hemispheres.</td>
</tr>
<tr>
<td>De Leeuw 2003</td>
<td>LAS</td>
<td>Unknown</td>
<td>52 (12)</td>
<td>CO₂</td>
<td>Cvr</td>
<td>12</td>
<td>Day 7</td>
<td>NP</td>
<td>Both</td>
<td>Chemical vasomotor CA is impaired in both hemispheres.</td>
</tr>
<tr>
<td>Novak 2003</td>
<td>ATS</td>
<td>Minor</td>
<td>52 (2)</td>
<td>CO₂ pTTT</td>
<td>Cvr</td>
<td>20</td>
<td>2 mo</td>
<td>NP</td>
<td>One (affected)</td>
<td>Chemical vasomotor CA is impaired during orthostatic stress; significant CBFV asymmetry during pTTT (80°) differentiated stroke patients from control (20°) and hypertensive (90°) groups.</td>
</tr>
<tr>
<td>Kwan 2004</td>
<td>ATS</td>
<td>Unknown</td>
<td>73 (11)</td>
<td>HGM</td>
<td>TFA (without coherence)</td>
<td>6</td>
<td>&lt;7 d</td>
<td>At 1.5 and 3 mo</td>
<td>Both</td>
<td>Dynamic pressure CA (phase) improves globally up to 3 mo after stroke.</td>
</tr>
<tr>
<td>Novak 2004</td>
<td>ATS</td>
<td>Minor</td>
<td>53 (2)</td>
<td>VM</td>
<td>Nonlinear frequency analysis</td>
<td>15</td>
<td>18 mo</td>
<td>NP</td>
<td>Both</td>
<td>Dynamic pressure CA is altered globally in hypertension (20°) and stroke patients as compared to healthy controls (15°); differentiation was not possible by using ARI method and rate of autoregulation regression model.</td>
</tr>
<tr>
<td>Treger 2006</td>
<td>ATS</td>
<td>Unknown</td>
<td>58 (12)</td>
<td>pTTT</td>
<td>CBFV</td>
<td>13</td>
<td>Day 16</td>
<td>NP</td>
<td>Both</td>
<td>Orthostatic hypotension with pTTT (static pressure CA) is associated with low CBFV in both hemispheres.</td>
</tr>
<tr>
<td>Gommer 2009</td>
<td>LAS</td>
<td>Unknown</td>
<td>67</td>
<td>SBPF ACZ</td>
<td>TFA Cvr</td>
<td>24</td>
<td>3 mo</td>
<td>NP</td>
<td>None</td>
<td>Dynamic pressure and chemical vasomotor CA is not impaired in both hemispheres; poor correlations between CBFV and dynamic CA phase angles.</td>
</tr>
</tbody>
</table>

ACZ indicates acetazolamide; ARI, autoregulatory index; ATS, anterior territory stroke; CA, cerebral autoregulation; CBFV, cerebral blood flow velocity; CBFV, cerebrovascular reactivity; HGM, handgrip method; LAS, lacunar stroke; NP, not performed; Pts, posterior territory stroke; pTTT, passive tilt table test; SBPF, spontaneous blood pressure fluctuations; TFA, transfer function analysis; VM, Valsalva maneuver.
Table 2. Overview of Transcranial Doppler Studies With Measurements <96 Hours After Index Stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>Stroke Type</th>
<th>Severity</th>
<th>Age, y (SD)</th>
<th>Input Method</th>
<th>Analytical Method</th>
<th>N of Patients</th>
<th>Timing (Mean)</th>
<th>Follow-Up (d)</th>
<th>Hemispheres Affected</th>
<th>Main Results and Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dawson 2000 ATs</td>
<td>Moderate</td>
<td>69 (12)</td>
<td>TCM HGM</td>
<td>ARI CBFV</td>
<td>54</td>
<td>&lt;96 hr</td>
<td>NP</td>
<td>Both</td>
<td>Dynamic pressure but not static pressure CA appears to be globally impaired in comparison to healthy controls (61)</td>
<td></td>
</tr>
<tr>
<td>Cupini 2001 ATs</td>
<td>Unknown</td>
<td>60 (10)</td>
<td>BHI CO₂</td>
<td>CVR</td>
<td>41</td>
<td>Between 1 and 3 mo</td>
<td>NP</td>
<td>Both</td>
<td>Static pressure and chemical vasomotor CA appears to be globally impaired in (multiple) subcortical infarctions in comparison with healthy controls (15)</td>
<td></td>
</tr>
<tr>
<td>Georgiadis 2001 ATs</td>
<td>Severe</td>
<td>49 (12)</td>
<td>PEEP</td>
<td>CBFV</td>
<td>14</td>
<td>&lt;96 hr</td>
<td>NP</td>
<td>None (healthy side tested)</td>
<td>No significant difference in CBFV and ICP on the various PEEP levels with increasing MAP; however, in 3 hemi- craniectomy patients a decrease in MAP resulted in CBFV decrease (static pressure CA)</td>
<td></td>
</tr>
<tr>
<td>Schwarz 2002 ATs</td>
<td>Severe</td>
<td>59 (2)</td>
<td>Norepinephrine infusion</td>
<td>CBFV</td>
<td>19</td>
<td>58 hr</td>
<td>NP</td>
<td>Both</td>
<td>Induced hypertension enhances CPP (30%) and augments the CBFV (static pressure CA); this was more pronounced on the affected side and in patients who underwent decompressive craniectomy (8)</td>
<td></td>
</tr>
<tr>
<td>Georgiadis 2002 ATs</td>
<td>Severe</td>
<td>58 (11)</td>
<td>Norepinephrine infusion</td>
<td>CBFV</td>
<td>16</td>
<td>&lt;96 hr</td>
<td>NP</td>
<td>None (healthy side tested)</td>
<td>Induced hypertension (22% increase) under moderate hypothermia does not affect static pressure CA</td>
<td></td>
</tr>
<tr>
<td>Eames 2002 ATs</td>
<td>Moderate</td>
<td>70 (9)</td>
<td>SBPF</td>
<td>ARI</td>
<td>56</td>
<td>&lt;72 hr</td>
<td>NP</td>
<td>Both</td>
<td>Dynamic pressure CA is globally impaired in comparison to healthy controls (56)</td>
<td></td>
</tr>
<tr>
<td>Schwarz 2002 ATs</td>
<td>Severe</td>
<td>61 (2)</td>
<td>HOBT</td>
<td>CBFV</td>
<td>18</td>
<td>&lt;96 hr</td>
<td>NP</td>
<td>Both</td>
<td>Moving from horizontal to 30° HOB position decreased CBFV by 25% in affected hemisphere (static pressure CA), and in more patients who underwent decompressive craniectomy (7)</td>
<td></td>
</tr>
<tr>
<td>Dawson 2003 ATs</td>
<td>Moderate</td>
<td>69 (11)</td>
<td>TCM</td>
<td>ARI CBFV</td>
<td>30</td>
<td>&lt;96 hr</td>
<td>14 d</td>
<td>Both</td>
<td>Dynamic, but not static, pressure CA is globally impaired and remains abnormal for at least 2 wk in comparison to healthy controls (51)</td>
<td></td>
</tr>
<tr>
<td>Alvarez 2004 ATs</td>
<td>Minor</td>
<td>70 (10)</td>
<td>CO₂</td>
<td>CVR</td>
<td>100</td>
<td>&lt;24 hr</td>
<td>NP</td>
<td>Both</td>
<td>Chemical vasomotor CA impairment is associated with higher risk of early neurologic deterioration</td>
<td></td>
</tr>
<tr>
<td>Wojner 2004 ATs</td>
<td>Large</td>
<td>60 (15)</td>
<td>HOBT</td>
<td>CBFV</td>
<td>22</td>
<td>&lt;24 hr</td>
<td>NP</td>
<td>One (only affected side tested)</td>
<td>Moving from horizontal to 30° HOB position, residual CBFV decreased by 17%, indicating impaired static pressure CA, neurologic improvement in 3 patients was noticed</td>
<td></td>
</tr>
<tr>
<td>Immink 2005 ATs</td>
<td>Severe/</td>
<td>60 (4)</td>
<td>SBPF</td>
<td>TFA</td>
<td>20</td>
<td>&lt;72 hr</td>
<td>NP</td>
<td>Both (LAS)</td>
<td>Compared to healthy controls (10), dynamic pressure CA is impaired in affected hemisphere in large ATS stroke and bilaterally in moderately severe LAS</td>
<td></td>
</tr>
<tr>
<td>Renhard 2005 ATs</td>
<td>Minor</td>
<td>61 (12)</td>
<td>SBPF</td>
<td>Mx TFA</td>
<td>33</td>
<td>&lt;22 hr</td>
<td>6 d</td>
<td>Both</td>
<td>Dynamic pressure CA did not seem to be relevantly disturbed at the subacute stage, slight global autoregulatory disturbance may be present</td>
<td></td>
</tr>
<tr>
<td>Gur 2007 ATs</td>
<td>Moderate/</td>
<td>76 (13)</td>
<td>ACZ</td>
<td>CVR</td>
<td>47</td>
<td>&lt;24 hr</td>
<td>NP</td>
<td>Both</td>
<td>Chemical vasomotor CA disturbance in cortical &gt; subcortical stroke; CA impairment not associated with baseline stroke severity and disability</td>
<td></td>
</tr>
<tr>
<td>Renhard 2008 ATs</td>
<td>Severe</td>
<td>67 (12)</td>
<td>SBPF</td>
<td>Mx TFA</td>
<td>16</td>
<td>&lt;20 hr</td>
<td>3–5 d</td>
<td>One (affected)</td>
<td>Dynamic pressure CA is increasingly impaired, mainly on the affected side, over the first 5 days of stroke after unsuccessful tissue plasminogen activator thrombolysis</td>
<td></td>
</tr>
<tr>
<td>Brodie 2009 ATs</td>
<td>Minor</td>
<td>69</td>
<td>SBPF</td>
<td>ARI</td>
<td>39</td>
<td>&lt;42 hr</td>
<td>14 d</td>
<td>One (affected)</td>
<td>Dynamic pressure CA was reduced in the affected hemisphere, but after 14 days it was no longer significantly different from healthy controls (22)</td>
<td></td>
</tr>
<tr>
<td>Atkins 2010 ATs</td>
<td>Minor</td>
<td>67 (11)</td>
<td>SBPF</td>
<td>ARI</td>
<td>19</td>
<td>&lt;36 hr</td>
<td>4 d</td>
<td>Both</td>
<td>As compared with TIA (17) and healthy controls (22), dynamic CA is only impaired in the affected hemisphere at baseline (even after correction for ipsilateral significant carotid stenosis)</td>
<td></td>
</tr>
</tbody>
</table>

ACZ indicates acetazolamide; ARI, autoregulatory index; ATS, anterior territory stroke; BHI, breath-holding index; CA, cerebral autoregulation; CBFV, cerebral blood flow velocity; CPP, cerebral perfusion pressure; CVR, cerebrovascular resistance; HGM, handgrip method; HOB, head of bed test; ICP, intracranial pressure; LAS, lacunar stroke; Mx, correlation index; NP, not performed; PEEP, positive end-expiratory pressure; PTS, posterior territory stroke; SBPF, spontaneous blood pressure fluctuations; TCM, thigh-cuff method; TFA, transfer function analysis.
stroke, particularly when stroke is moderate to severe, or after follow-up. In 5 studies, impaired autoregulation also could be demonstrated in the nonaffected hemisphere, which was particularly the case for first-ever lacunar stroke. Eames et al showed that these bilateral changes are unrelated to previous antihypertensive treatment, baseline BP levels, or BP changes after stroke, age, and stroke subtype or stroke severity. In 3 studies, dynamic cerebral autoregulation was recorded from spontaneous fluctuations of BP using the approaches of frequency domain (transfer function analysis [TFA]) and time domain analysis. In sum, TFA is a complex linear analysis to estimate the magnitude and the phase relationship between spontaneous or induced changes in BP and CBFV. In the time domain analysis, either the delay of CBFV counter-regulation during changes in BP or the degree of correlation between averaged CBFV and BP over time is used. Five studies calculated the autoregulatory index. In sum, this is a linear curve-fitting procedure, which compares the CBFV response (measured directly or predicted) after a rapid step-like decrease in BP with a family of 10 theoretical flow-velocity curves to calculate dynamic cerebral autoregulation. Two studies used rapid thigh-cuff method deflation as input challenges. Three studies used spontaneous BP changes to reconstruct (by inverse fast-Fourier transformation using TFA functions) the (predicted) CBFV step response. Comparable low-frequency ranges (0.06–0.12 Hz) were used for TFA analyses.

Autoregulation seemed increasingly impaired in the first few days after a large stroke (mainly affected side) with unsuccessful thrombolysis and did not improve in moderate stroke over the course of 2 weeks. In minor stroke patients (after adjustment for covariates), cerebral autoregulation was similar to that in healthy controls after 2 weeks.

Chronic Phase of Stroke and Steady-State and Dynamic Autoregulation

Five of 7 studies found bilaterally impaired autoregulation between week 1 and 18 months after minor and moderate strokes. Novak et al only detected changes in the affected hemisphere of minor stroke patients, although the same group detected impaired dynamic autoregulation in both hemispheres during the Valsalva maneuver in 15 minor stroke patients using a nonlinear frequency shift method. Gommer et al, studying first-ever lacunar infarct, found TFA values and cerebrovascular reserve capacities in the normal range when examining their patients after 3 months. Information about stroke severity was not documented in this study. One research group repeated their initial measurements in the chronic phase and found some improvement after 3 months. Three studies included both steady-state and dynamic cerebral autoregulation measurements in the same patients and found disturbed dynamic autoregulation only.

Discussion

There seems to be general agreement that stroke is associated with impaired cerebral autoregulation, even in minor stroke. Cerebral autoregulation may become impaired in both hemispheres, although in some large stroke studies only measure-
ments in the nonoccluded middle cerebral artery vessel (nonaffected hemisphere) were possible. Interestingly, this bilateral effect seems to be more pronounced in lacunar stroke. Two studies showed (some degree of) progressive impairment of cerebral autoregulation in the first days after stroke, which may affect the penumbral salvage. Cerebral autoregulation has been shown to recover over the next 3 months. Impaired cerebral autoregulation in stroke is related to acute neurological deterioration, necessity of decompressive surgery, and poor outcome. How the process of cerebral autoregulation progresses from impairment to improvement and which factors determine this process are unclear. Three studies investigated both dynamic and steady-state autoregulation and found dynamic impairment only. This may be explained by differences in underlying mechanisms studied by dynamic vs steady-state investigation techniques, or simply by a greater sensitivity of dynamic investigation techniques for detection of stroke related autoregulation changes. The clinical relevance of such changes is unclear. In only 1 study with healthy subjects, dynamic measurement of cerebral autoregulation (with rapid cuff deflation) yielded results similar to classical static testing (phenylephrine infusion) under conditions of intact autoregulation and after pharmacologically induced impairment. However, the evaluation of the “classical” lower limits of the cerebral pressure autoregulatory plateau requires considerable manipulations of BP, making the method invasive and potentially harmful for stroke patients. Therefore, attention has been increasingly directed toward dynamic autoregulation. However, Zhang et al found that dynamic autoregulation may interact with changes in steady-state cerebrovascular resistance or vascular compliance or both leading to changes in dynamic autoregulation by TFA function. In this regard, a more comprehensive model to include both the autoregulatory mechanisms and steady-state vascular parameters should be explored to improve the precision of the model prediction.

The interpretation of the TCD autoregulation studies is hampered by several methodological issues. First, studies using TCD rely on the assumption that changes in CBFV are continuously. Also, relatively small numbers of patients were studied, with even smaller numbers of control subjects recruited. All these emphasize the importance of more complex models with a multivariate approach to take into account the contribution of other variables that can influence CBF regulation. Finally, severe extracranial or intracranial artery stenosis and clinical conditions (eg, chronic hypertension, diabetes mellitus, and silent infarcts) may confound the assessment of cerebral autoregulation. In addition, 6 studies (all steady-state) did not measure BP continuously. To determine autoregulation, BP ideally should be measured continuously. Also, relatively small numbers of patients were studied, with even smaller numbers of control subjects recruited. All these emphasize the importance of more complex models with a multivariate approach to take into account the contribution of other variables that can influence CBF regulation.

The effects of presence of collateral or cross-flow need to be established in future studies. As an illustration, the finding of generally impaired autoregulation in lacunar stroke may be related to generalized small vessel disease attributable to chronic hypertension or diabetes. Longitudinal studies are required for lacunar stroke to show whether impaired cerebral autoregulation is a consequence of acute lacunar stroke or a correlate of widespread small vessel disease.

Additional knowledge is needed about the physiological and pathological determinants of cerebral autoregulation in stroke so that determinants of autoregulation can be better controlled for in future studies or taken into account with the help of multivariate (time and frequency domain) models. Until proven otherwise, it is possible that some clinical conditions disrupt myogenic mechanisms whereas others impair autoregulation by blocking metabolic or neurogenic pathways. Dohmen et al demonstrated impaired autoregulation in the peri-infarct tissue of large middle cerebral artery such as hypercapnia or hypocapnia and extreme hypoxia.
infarct patients who had malignant brain edema by studying the relation between perfusion pressure and local oxygen pressure (invasive monitoring), together with metabolic makers of brain damage (microdialysis). They stress the important issue of combining continuous monitoring of surrogate markers of CBF (like CBFV) with local brain information. In that view, the use of (multichannel) near-infrared spectroscopy in stroke seems promising. Near-infrared spectroscopy is a noninvasive technique that allows continuous monitoring of cerebral hemoglobin oxygen desaturation, with a significant positive relationship between CBFV and near-infrared spectroscopy changes during clamping with carotid artery surgery. Also, MRI with blood oxygen level-dependent signal is used to monitor dynamic autoregulation changes, with the benefit of allowing good spatial resolution.

**Conclusion**

In summary, TCD appears to offer a practical bedside method with a high temporal resolution for cerebral autoregulation evaluation in stroke patients. TCD studies have shown impairment of cerebral autoregulation in various subtypes of ischemic stroke. In some patients, this impaired autoregulation is probably temporary and caused by the stroke; in others, it is preexisting and might have contributed to the stroke (eg, in chronic hypertension). In view of intervention studies in the stroke unit, such as the ongoing BP-lowering trials in acute stroke, correct identification of patients with impaired or adapted autoregulation may lead to the establishment of important subgroups in such trials. Although some general conclusions can be drawn on the course of autoregulation over time, this topic requires further study. Variances in TCD study techniques, parameters, and interpretations limit further conclusions (Figure). To improve the synthesis of data from various research groups (including stroke), there is great need for a uniform assessment of cerebral autoregulation in the whole field of autoregulation studies.

Future study goals are: (1) the determinants of cerebral autoregulation after stroke; (2) the development of multivariate models; (3) the status of both steady-state and dynamic autoregulation; (4) the course of cerebral autoregulation over time; and (5) the impact of cerebral autoregulation impairment on outcome with clinically relevant cut-off points.

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**Disclosures**

None.

**References**


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**Table 1. Search Strategy used in Medline**

A similar strategy using the closest available terms was used in Embase.

The following key terms were used: (stroke (MESH) OR stroke (all fields)) AND (dynamic cerebral autoregulation (all fields) OR cerebrovascular autoregulation (all fields) OR cerebral autoregulation (all fields) OR cerebral vasomotor reactivity (all fields) OR cerebral perfusion (all fields) OR cerebral vasoregulation (all fields) OR cerebrovascular reactivity (all fields) OR chemical vasomotor autoregulation (all fields)) AND ((Doppler ultrasonography, transcranial (MESH) OR Doppler ultrasonography, transcranial (all fields) OR Doppler ultrasonography (all fields)).
Table 2. A proposed checklist of observational TCD autoregulation studies

<table>
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<tr>
<th>Hypothesis statement in introduction or method section</th>
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<tbody>
<tr>
<td>Threshold values of study outcome parameters described in introduction and/or methods</td>
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</tr>
<tr>
<td>Sample size calculation before start of experiment</td>
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</tr>
<tr>
<td>Publication in peer reviewed journal</td>
<td>1</td>
</tr>
<tr>
<td>Medical ethics review with informed consent</td>
<td>1</td>
</tr>
<tr>
<td>Conflict of interest authors described</td>
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<tr>
<td>Patient spectrum/population described sufficiently</td>
<td>1</td>
</tr>
<tr>
<td>Confounding factors sufficiently mentioned in introduction, methods or limitations</td>
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</tr>
<tr>
<td>Analysis described sufficiently (mathematical and statistics)</td>
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<tr>
<td>Proven reproducibility of data</td>
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<tr>
<td>Consecutive patient recruitment</td>
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<tr>
<td>Type of intervention/exposure described sufficiently (or with literature reference)</td>
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<tr>
<td>Considerations of alternative explanation for observed results in discussion</td>
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<td>Total points</td>
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