Baroreflex: A New Therapeutic Target in Human Stroke?

Marek Sykora, MD; Jennifer Diedler, MD; Peter Turcani, MD; Werner Hacke, MD; Thorsten Steiner, MD

Background and Purpose—Autonomic dysfunction, including increased sympathetic drive and blunted baroreflex, has repeatedly been observed in acute stroke. Of clinical importance is that the stroke-related autonomic imbalance seems to be linked to worse outcome after stroke. Here, we discuss the role of baroreflex impairment in acute stroke and its possible pathophysiological and therapeutic relevance.

Summary of Review—Possible mechanisms linking baroreflex impairment with unfavorable outcome in stroke may include increased cardiovascular morbidity and mortality, promotion of secondary brain injury due to local inflammation, hyperglycemia, or altered cerebral perfusion.

Conclusions—We suggest therefore that the modifying of autonomic functions may have important therapeutic implications in acute ischemic as well as in hemorrhagic stroke. (Stroke. 2009;40:e678-e682.)

Key Words: baroreflex sensitivity ■ acute stroke ■ heart-brain relations ■ outcome ■ therapy

The baroreceptor reflex is the principal neural mechanism involved in blood pressure regulation. Baroreceptors in the carotid arteries, cardiac chambers, and the aortic arch are activated by beat-to-beat fluctuations in systemic blood pressure. The baroreceptors relay information to the nucleus tractus solitarius and the ventrolateral medulla that is further processed in the insula, medial prefrontal cortex, cingulate cortex, amygdala, hypothalamus, thalamus, and cerebellum. The baroreceptors by a rise in blood pressure leads to an increase of cardioinhibitory vagal outflow and a decrease of sympathetic firing, leading to a decrease of peripheral vascular and cardiac tone. This results in a lower heart rate, decreased cardiac contractility, decreased vascular resistance, and venous return.

The impairment of the peripheral baroreceptors, afferent baroreceptive nerves, and central processing can alter baroreflex function. Bilateral atherosclerosis of carotid arteries or autonomic nervous disorders are well-recognized causes of baroreflex impairment. Carotid endarterectomy disturbs the baroreflex function through surgical destruction of the carotid baroreceptors. Brainstem stroke, damaging the baroreflex relay nuclei, is typically associated with baroreflex failure and blood pressure instability. However, hemispheric lesions altering the widespread central autonomic network may impair the baroreflex function as well.

Baroreflex dysfunction seems to play a role in hypertension, coronary artery disease, myocardial infarction, and chronic heart failure. Baroreflex impairment in conjunction with reduced vagal inhibitory outflow results in chronic activation of the sympathetic nervous system. A sustained increase in sympathetic activity contributes to end-organ damage and to disease progression and may predispose to subsequent cardiovascular events. It is clinically important that impaired cardiac baroreceptor reflex sensitivity (BRS) has been shown to independently predict mortality and the incidence of adverse cardiovascular events in hypertension or after myocardial infarction and has been associated with a poor prognosis in chronic heart failure.

Baroreflex Pathophysiology in Acute Stroke

Disease manifestations that may indicate baroreceptor reflex dysfunction, such as hypertensive crises or high blood pressure variability, often accompany the acute phase of ischemic or hemorrhagic stroke. Indeed, baroreflex impairment has been repeatedly shown to be present in acute ischemic and hemorrhagic stroke. Interestingly, the level of baroreflex dysfunction did not differ between ischemic stroke and intracerebral hemorrhage, albeit different mechanisms could be anticipated. Underlying pathophysiologic mechanisms are generally unknown; however, there is increasing evidence that the central autonomic network is involved. The insular cortex seems to play a principal role in modulating BRS. BRS was found to be impaired in stroke patients with left and/or right insular involvement compared with patients without insular involvement or control subjects. This finding suggests that both insulae may participate in the regulation of baroreflex. Both the left and right insulae have been previously suggested to modulate baroreflex sensitivity. Interestingly, baroreflex-related neuronal interconnections have been observed between the right and left...
insulæ, suggesting that the 2 insulæ probably interact in integrating circulatory control information. However, controversy persists on the topic of proposed hemispheric lateralization of the baroreflex and/or autonomic control. In our series, left insular lesions decreased BRS significantly more than right insular lesions did. This is in line with the findings of Hilz et al, who showed a decrease in BRS in conjunction with left-sided hemispheric inactivation in epilepsy patients as well as further studies showing right-sided dominance of sympathetic and left-sided dominance of parasympathetic modulation. On the other hand, some studies in ischemic stroke patients found a reduction in parasympathetic and an increase in sympathetic heart rate modulation in right-sided strokes, leaving the right-left controversy in central autonomic control unsolved.

The investigation of baroreflex changes in acute stroke patients may represent a methodologic challenge. Because stroke is frequently associated with carotid atherosclerosis, heart failure, coronary artery disease, a history of hypertension, and previous antihypertensive treatment, all conditions known to alter the baroreflex function, revealing the true etiology of stroke-related baroreflex changes is complex. In our recently published study, baroreflex impairment in acute stroke was seen independently of carotid atherosclerosis. We observed decreased baroreflex function in stroke patients compared with controls matched for atherosclerosis and other possible confounding factors, which we thus attribute to lesions affecting central autonomic regions. Factors like age, heart failure, coronary artery disease, diabetes mellitus, history of hypertension, and previous antihypertensive treatment represent confounders for the assessment of BRS in acute stroke. Hence, most studies examining BRS in acute stroke exclude patients with heart failure, coronary artery disease, and a history of myocardial infarction or diabetes to prevent bias. Confounders like age and concomitant medication are often inevitable and should definitely be included in the analysis. Nevertheless, the effects of previous antihypertensive therapy on BRS may not be ruled out completely. However, in our series, we found no statistical significant influence when we tested for this. Effects of age and hypertension on BRS, albeit not significant, were seen in the control group. We hypothesize that these effects were also present in the stroke group but were presumably outweighed by stroke-related changes in baroreflex sensitivity.

How Does Impaired Baroreflex Influence Outcome After Stroke?
In analogy to cardiac patients, baroreflex impairment has been independently related to less favorable long- and short-term outcomes after acute ischemic stroke or after intracerebral hemorrhage. In previous studies, conditions such as hypertensive crises or increased blood pressure variability were associated with negative outcome in stroke. Dawson et al reported that a poor outcome at 30 days after ischemic stroke was dependent on blood pressure variability obtained within the first 72 hours of the ictus. Similarly, Stead et al showed wide fluctuations in blood pressure in the first 3 hours of acute ischemic stroke to be associated with an increased risk of death at 90 days in a cohort of 71 patients. In a recent study, hypertensive crisis on admission was independently linked to a worse outcome and deterioration after ischemic stroke. However, none of these studies addressed the possible underlying mechanism, and thus the relation to baroreflex impairment remains speculative.

Altered Cerebral Perfusion
Recently, we demonstrated a significant and independent association between impaired BRS, blood pressure variability, and short-term outcome in patients with intracerebral hemorrhage. Because cerebrovascular autoregulation seems to be impaired in both acute ischemic and hemorrhagic stroke, fluctuations in blood pressure may significantly alter cerebral perfusion. In another study, baroreflex dysfunction and blood pressure fluctuations seemed to boost perihematomal edema, resulting in neurologic deterioration.

Increased Cardiovascular Complications
Patients presenting with a shift in autonomic balance seem to be at increased risk for developing cardiac complications and demonstrate a significantly higher cardiovascular morbidity and mortality. Suggested pathophysiologic mechanisms include raised arrhythmogenic potential, increased platelet aggregability, coronary vasoconstriction, and impaired ventricular remodeling, which are all thought to be associated with increased sympathetic activity. Interestingly, in line with the aforementioned findings regarding the left insula being involved in human BRS regulation, Laowattana et al found left insular stroke to be associated with a significantly adverse long-term cardiac outcome, particularly in patients without coronary artery disease. The mechanism proposed by the authors includes involvement of the baroreflex arch with decreased parasympathetic tone and increased sympathetic drive. Further manifestations of autonomic dysfunction after insular stroke include disturbed circadian blood pressure patterns, higher norepinephrine levels, cardiac arrhythmias or QT prolongation, outlining mechanisms possibly contributing to the adverse outcome.

Inflammation, Hyperglycemia, and Blood–Brain Barrier Breakdown
Autonomic impairment also potentially plays an important role in nonhemodynamically mediated secondary brain injury after stroke. A shift to sympathetic predominance has previously been shown to be associated with proinflammatory cytokine production, hyperglycemia, and increased blood–brain barrier permeability. In turn, these mechanisms have been proposed to be involved in secondary brain injury after stroke. In line with that, arterial baroreflex function has been shown to be an important determinant of acute cerebral ischemia in rats with middle cerebral artery occlusion. Baroreflex dysfunction significantly increased the levels of the proinflammatory factors interleukin-1 and interleukin-6, as well as infarct volume.
Cross-Linked Mechanisms
Possible links between autonomic dysfunction and cerebrovascular reactivity have been described. In traumatic brain injury patients, Lavinio et al.\(^5^2\) observed a correlation between the pressure-reactivity index, a validated index of cerebrovascular reactivity, and a low spectral power of heart rate variability, a measure of autonomic function. This important finding may imply that cerebrovascular autoregulation and autonomic drive are a part of 1 underlying regulatory continuum. Cross-linked impairment of cerebrovascular autoregulation and altered autonomic drive and/or cardiovascular regulation may be responsible for several of the aforementioned effects, ranging from impaired cerebral perfusion to metabolic and inflammatory reactions.

In summary, we hypothesize that autonomic dysfunction in acute stroke as expressed by decreased BRS sensitivity may have effects on outcome via (1) inadequate cerebral perfusion due to the increased blood pressure variability and impaired cerebral autoregulation, (2) increased cardiovascular complications, and (3) secondary brain injury due to inflammation, hyperglycemia, and blood–brain barrier disruption.

Baroreflex Modulation: A New Therapeutic Target in Stroke?
Existing knowledge about baroreflex dysfunction in acute stroke raises questions regarding the therapeutic implications of this finding. Baroreflex sensitivity can be positively influenced by certain drugs, especially \(\beta\)-blockers.\(^53\),\(^54\) Interestingly, a recent study by Loawattana et al.\(^55\) including 111 ischemic stroke patients showed that use of \(\beta\)-blockers was independently associated with less severe stroke on presentation and that sympatholytic effects may have cerebroprotective properties. In an animal model, \(\beta\)-blockers given before the induction of experimental ischemia led to a reduction in infarct volume by 40%.\(^56\) Analogously, \(\beta\)-blockers were able to reduce brain edema in a histologic model of traumatic brain injury.\(^57\) Positive effects of \(\beta\)-blockade on outcome have also been reported in patients with traumatic brain injury.\(^58\),\(^59\)

The use of \(\beta\)-blockers in acute human stroke may appear controversial. Atenolol and propranolol tested in a randomized, controlled study of 302 acute stroke patients showed a trend toward increased death and disability in the treatment group.\(^60\) Through negative inotrope activity, \(\beta\)-blockers may potentially reduce global cerebral blood flow. However, other studies did not demonstrate any harmful effect of \(\beta\)-blockers in acute stroke; on the contrary, possible neuroprotective properties have been advocated.\(^61\)–\(^63\)

Several other drugs have been proposed to enhance baroreflex sensitivity. In the study by Liu et al.\(^64\) ketanserin at doses of 3.0 mg/kg per day decreased blood pressure and enhanced BRS, whereas 0.3 mg/kg per day only enhanced BRS. Importantly, both dosages markedly reduced the incidence of fatal strokes (\(P<0.0001\) vs control group). Clonidine, moxonidine, and mecobalamin may also improve baroreflex sensitivity. A central mechanism of action is supposed in the effects of clonidine and moxonidine, whereas a peripheral mechanism is suggested for mecobalamin.\(^65\),\(^66\) Most recently, clonidine was shown to increase the activity of baroreceptor neurons in the ventrolateral medulla, enhance the slope of the cardiac baroreflex, and reduce pressure lability.\(^67\) New devices stimulating baroreceptors are emerging in the treatment of chronic refractory hypertension. Mediated through the central sympatohinditory effect by stimulating the carotid baroreceptors electrically, these devices ameliorate baroreflex sensitivity and reduce hypertension. Ongoing trials on these devices are finding significant and sustained reductions in blood pressure, a good safety profile, and tolerable side effects.\(^68\) However, the evidence is insufficient to draw further conclusions, in particular regarding acute stroke therapy.

Conclusions
Previous studies uniformly confirm an association between baroreflex impairment and worse short- and/or long-term outcomes after ischemic or hemorrhagic stroke. The mechanisms by which autonomic derangement affects outcome may include increased cardiovascular complications, secondary brain injury due to inflammation, and inadequate cerebral perfusion due to increased blood pressure variability and impaired cerebral autoregulation. However, the proposed underlying mechanisms are so far mostly speculative. Whether baroreflex modulation can change the course of acute stroke remains to be elucidated. Nevertheless, it seems that baroreflex should definitely become a therapeutic target in future acute stroke research.

Disclosures
None.

References


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