



# The link between carotid artery disease and ischemic stroke may be partially attributable to autonomic dysfunction and failure of cerebrovascular autoregulation triggered by Darwinian maladaptation of the carotid baroreceptors and chemoreceptors

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**Summary** Carotid artery stenosis is generally thought to induce stroke by either compromising cerebral perfusion or inciting embolic phenomena. Carotid baroreceptors and chemoreceptors are vital adaptations for cerebrovascular autoregulation that can behave maladaptively in the setting of modern diseases such as atherosclerosis. We hypothesize that acute cerebrovascular events may be partially attributable to autonomic dysfunction and cerebrovascular autoregulatory failure secondary to carotid sensor maladaptations. Specifically, we propose that atherosclerotic disease at the carotid bifurcation can interfere with baroreceptor and chemoreceptor function by buffering against accurate detection of physical and chemical parameters. Misperceptions of hypoxia and hypotension can trigger sympathetic bias and autonomic dysfunction which perturb cerebrovascular autoregulation and vasomotor tone, thereby compromising cerebral perfusion. The preferential association of strokes with morning arousal, stress, acute physical activity, winter months, illness, and older age may relate to this phenomenon. Sympathetic bias promotes inflammation and coagulation, a link likely forged during prehistoric evolution when trauma represented a more significant factor in natural selection. In the setting of carotid sensor dysfunction, the resulting inflammation and coagulation can promote acute cardiovascular events. The ensuing cerebral ischemia can induce further derangement of cerebrovascular autoregulation and upregulate adrenergia, inflammation, and coagulation in a feed-forward manner. Inflammation and coagulation can also exacerbate carotid sensor dysfunction by iteratively worsening atherosclerosis. Angioplasty, stenting, and endarterectomy may inadvertently cause acute and chronic carotid sensor dysfunction through manipulation, material interposition, and balloon-induced baroreceptor injury. Acute strokes during these procedures may result from carotid sensor dysfunction rather than embolization. Carotid body and sinus

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electromodulation and non-balloon atherectomy represent new methods to prevent or treat cerebrovascular events. Pharmacologic modulation of autonomic balance, such as adrenergic blockade, long presumed contraindicated due to risk of cerebral hypoperfusion, may counterintuitively offer benefit during acute strokes. Novel diagnostic paradigms may include functional analysis of carotid sensors as well as measurement of the anatomic thickness of calcified and non-calcified plaque near the carotid body. Carotid sensor dysfunction may be a source of systemic sympathetic bias and autonomic dysfunction observed during aging and, by association, many of the ailments associated with senescence. Modulation of carotid sensors may yield pervasive health benefits beyond those found by treating cerebrovascular disease.

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## Hypothesis

Carotid artery stenosis is generally thought to induce stroke by either compromising cerebral perfusion or inciting embolic phenomena. Baroreceptors and chemoreceptors situated in structures at the carotid bifurcation represent vital adaptations for cerebrovascular autoregulation. These sensors can behave maladaptively in the setting of modern diseases such as atherosclerosis, which can create sensor misregistration unanticipated by evolution. We hypothesize that acute cerebrovascular events associated with carotid artery stenosis may be partially attributable to autonomic dysfunction and cerebrovascular autoregulatory failure secondary to carotid sensor maladaptation. Specifically, we propose that atherosclerotic disease at the carotid bifurcation can interfere with baroreceptor and chemoreceptor function by imposing a barrier to accurate detection of physical and chemical parameters.

## Evidence

### Stroke and carotid stenosis

Stroke is the third leading cause of death in the United States [1]. Each year, more than 700,000 strokes lead to 150,000 deaths [2]. Carotid artery disease is a major cause of ischemic stroke [3]. Internal carotid artery stenosis is responsible for approximately 30% of ischemic strokes [4]. The most common site of stenosis is the proximal portion of the internal carotid artery known as the carotid bulb [5].

In patients with carotid artery disease, the risk of stroke is directly related to the severity of stenosis and the presence of symptoms [6]. With asymptomatic stenosis, the annual risk of ipsilateral stroke appears to range from 1% to 3%, depending on the degree of stenosis [7–9]. Although most studies have been unable to identify baseline clinical

characteristics that predict the risk of stroke in patients with asymptomatic disease, increasing degrees of stenosis appear to correlate with increasing stroke risk in patients with symptomatic disease. Severe carotid obstruction has been found to impair dynamic cerebral autoregulation, and is remedied by carotid recanalization [10].

The most common cause of carotid artery stenosis is atherosclerosis [11]. Atherosclerosis of the brachiocephalic trunk, including the carotid arteries, causes more than half of all strokes [12]. Traditional views on the significance of atherosclerotic changes in carotid arteries typically center on either reduced cerebral perfusion secondary to decreased flow [13] or the atherosclerotic plaque as either the source or nidus of thromboembolic phenomena [14].

### The significance of baroreceptor and chemoreceptor function

In 1923, Hering was the first to discover the carotid sinus reflex, whereby compression of the common carotid bifurcation produces hypotension and deceleration of heart function, and showed that the responsible nerve fibers are in the carotid sinus and at the bifurcation. The carotid sinus consists of an enlargement of the internal carotid artery at the site of its origin from the common carotid artery. The reflex is mediated through sensory efferent structures termed baroreceptors. Baroreceptors detect pressure changes through the mechanical distortion and dilation of the vessel wall in which they reside. An acute increase in sensed pressure leads to reflex inhibition of sympathetic activity and activation of the parasympathetic system. Impaired baroreceptor sensitivity has been shown to associate with increased mortality in both myocardial infarction and heart failure [15]. Aging, arterial hypertension, obesity, myocardial infarction, and heart failure all have been shown to reduce baroreceptor sensitivity [15].

Chemoreceptors are situated in the carotid body, a structure located adjacent to the carotid

sinus. The carotid body is organized into functional sensor units called glomeruli, comprising both specialized dopamine-laden cells called glomus cells, and sustentacular cells, which appear to provide metabolic support. Hypoxia causes the inhibition of potassium channels in glomus cells [16–18], triggering secretion of dopamine and stimulation of afferent sensory fibers to the medullary vasomotor centers. Sympathetic activity increases upon stimulation of these sensors in response to decreased oxygen concentration, a response first identified by Heymans in 1930. Because of their mutual pathway of action, baroreceptor and chemoreceptor reflexes interact; decreased blood pressure increases the sympathetic response to chemoreceptor stimulation, and conversely hypertension results in inhibition of this response [19].

Normal baroreceptor function is particularly required for appropriate cerebrovascular function. Impaired cardiac baroreceptor reflex sensitivity is associated with increased long-term mortality after acute ischemic stroke, irrespective of age, sex, stroke type, and blood pressure [20]. Stroke patients with impaired baroreceptor function have a significantly worse prognosis than those with normal function [20]. Numerous studies have shown that baroreceptor function is critical. Hierarchical multiple regression analyses have shown that reduced baroreceptor sensitivity is associated with greater intimal-medial thickness, a marker for subclinical atherosclerosis in the carotid sinus [21]. The presence of rigid atheroma at the carotid sinus region is associated with decreased baroreceptor sensitivity involving an impairment of afferent baroreceptor activity [22]. Autonomic balance and baroreceptor sensitivity has been shown to be greater in patients with well-preserved carotid artery distensibility than in those with impaired carotid artery distensibility, another proxy for the extent of atherosclerotic disease [23].

The role of chemoreceptors in cerebral ischemia and stroke has been notably less well studied. Low ventilatory hypoxic sensitivity has been found prior to carotid endarterectomy with occasional increase following removal of the plaque [24]. Impaired cerebrovascular reactivity to carbon dioxide inhalation consistently improves after endarterectomy [10], suggesting a link between chemoreceptors at this site and cerebrovascular regulation. However, unilateral surgical removal of the carotid body in a rat stroke model does not lead to exacerbation of behavioral compromise or infarct volume [25].

We believe that baroreceptor and chemoreceptor function is not only essential in recovery from

stroke, but also in preventing the development of stroke, and that the association of carotid stenosis and atherosclerosis with stroke stems not from decreased perfusion or propensity for embolic phenomena, but rather from compromise of baroreceptor and chemoreceptor function.

### Atherosclerosis alters autonomic balance

The location of baroreceptors at the bifurcation of the common carotid does not occur by accident. Since the total pressure measured at the bifurcation of a parent vessel corresponds to the static pressure found in an upstream daughter vessel, positioning of sensors at bifurcations enables the rapid determination of dynamic pressures using Bernoulli's principle [26] and the accurate mobilization of appropriate responses.

Two scenarios involving carotid atherosclerosis could produce deterioration of cerebral perfusion and subsequent ischemia. First, the formation of an atherosclerotic plaque at the carotid bifurcation itself, as such lesions tend to favor [27], would lead to reduced baroreceptor sensitivity due to imposition of a physical barrier to detection. The loss of dynamic range would create a dampened response to any change in pressure. Decreased pressure may lead to inadequate reflex compensation, leading to reduced perfusion and resultant ischemia.

In addition, plaque formation would lead to perceived intravascular oxygen deficit through imposition of a physical and chemical barrier to chemoreceptor function at the carotid bifurcation. Impairment of diffusion of oxygen through the plaque and increased metabolic activity within the atheroma would lead to an impression of hypoxia with consequent upregulation of sympathetic activity, further worsening any problems already extant due to dysfunctional baroreceptor activity. Loss of dynamic range in oxygen sensing may also lead to downstream attenuation of response to acute changes in true oxygen content, further increasing the risk of an ischemic event.

Alternatively, the narrowing of the internal carotid artery by atherosclerosis could produce broad downstream derangement. Since the narrowed carotid segment is located upstream from the cerebral arteries, baroreceptors would fail to recognize any decrease in dynamic pressure in the cerebral arteries, since total pressures are equally affected in both the carotid and the cerebral arteries. So the difference remains preserved between the two measurements, corresponding to the calculated dynamic pressure in the cerebral artery, and the system fails to perceive a change. Consequently,

a dampened response to decreased pressure could again lead to inadequate reflex compensation, leading to reduced perfusion and resultant ischemia.

### Darwinian perspective

Reduced baroreceptor and chemoreceptor sensitivity would tend to shift autonomic balance towards sympathetic dominance. Cardiovascular autonomic neuropathy has been associated with carotid atherosclerosis in type 2 diabetic patients [28]. Adrenergia has been shown to promote inflammation and coagulation in addition to vasoconstriction, a likely byproduct of a persistent prehistoric response to the hypovolemia induced by trauma, now maladaptive [29]. These processes would lead to both extension of atherosclerosis and further occlusive phenomena within the lumen of the vessel so as to further iterate these derangements.

Moreover, as the level of adrenergia increases, chemoreceptor behavior may hasten its escalation. Inflammation and thrombus formation would cause local chemoreceptors, such as those in the carotid body, to sense a hypoxic state generated by increased metabolic activity. The resultant increase in chemoreceptor activity would result in further promotion of sympathetic bias. Although local autoregulatory mechanisms may serve to counteract some aspects of this cascade, the net overall effect is likely one of progressive vasoconstriction and reduced blood flow so as to encourage ischemia.

### Implications

Autonomic dysfunction constitutes a recognized response to decreased brain perfusion [30]. By interpreting existing clinical evidence within a new paradigm of baroreceptor and chemoreceptor function, we have reason to believe that it can also be invoked as a cause of ischemic events.

Numerous therapeutic implications for stroke are apparent from this model. The use of adrenergic antagonists in the setting of cerebral ischemia is currently minimal due to the fear of inducing a decrease in cerebral perfusion pressure [31]. Pharmacologic modulation of autonomic balance, such as adrenergic blockade, may counterintuitively offer benefit during acute strokes. Electromodulation of the carotid sinus or normalization of sensor function by non-balloon atherectomy may represent new methods to prevent or treat cerebrovascular events.

Current procedures such as carotid angioplasty, stenting, and endarterectomy may actually exacerbate carotid sinus dysfunction through injury, material interposition that dampens pressure signal, and balloon-induced baroreceptor trauma. Carotid angioplasty has been shown to stimulate baroreceptors so as to markedly reduce heart rate and blood pressure during the procedure [32]. Acute hypotension in the setting of already extant ischemia could prove catastrophic, and may explain the incidence of acute strokes that occur during carotid angioplasty or stent placement, as opposed to the oft-invoked rationale of mechanical embolization. The physical presence of a stent may itself interfere with baroreceptor function and lead to altered regulation over time. In similar fashion, disturbance of baroreceptors often occurs during plaque removal with endarterectomy, as determined by attempts at intraoperative stimulation [33]. This disruption can lead to loss of function that is not recovered [22], which produces not only an increased risk of perioperative complications, but an increased risk of subsequent stroke for several years [22]. The development of interventional or pharmacologic techniques that strive to remove impeding atherosclerotic lesions in a controlled, physically unobtrusive fashion, may lead to better control of these intraoperative and postprocedural sequelae.

Finally, if baroreceptor and chemoreceptor sensitivity and sympathetic dominance both play significant roles in determining both susceptibility and prognosis, testing to determine susceptibility to insult and tendency towards sympathetic bias may prove valuable in identifying those patients at highest risk for both onset of disease and complications from treatment. Novel diagnostic paradigms may include functional analysis of carotid sinus and body activity as well as measurement of anatomic thickness of calcified and non-calcified plaque at the carotid bifurcation by both physical and imaging techniques. Furthermore, those patients identified at risk may benefit from prophylactic measures to improve baroreceptor and chemoreceptor function and compensate for any deficiencies in autonomic regulation. It may be possible to restore baroreceptor function and autonomic balance long before more entrenched changes in structure or function develop [34].

The key role played by autonomic dysfunction would explain why stroke typically occurs more often during periods of increased adrenergic activity, such as morning arousal, stress, acute physical activity, winter months, illness, and older age [35]. Moreover, dysfunction of sensors at the carotid bifurcation may potentially constitute the

source of systemic sympathetic bias observed during aging. Atherosclerosis may represent a particularly exaggerated form of dampening, but all individuals develop thickening and rigidity of the intima, or inner layer, of vessel walls over time. Since baroreceptors and chemoreceptors are both located in the adventitia, or the outer layer, of vessel walls, accurate conveyance of luminal information to sensors would consequently undergo progressive derangement over time. This gradual decay of signal would favor the development of progressive sympathetic bias from the perspective of both the baroreceptor reflex, in the form of decreased sensed pressures, and the chemoreceptor reflex, in the form of decreased sensed blood oxygen content. We have previously noted that progressive sympathetic bias is an emergent property of aging that contributes to a myriad of systemic dysfunctions associated with senescence [36]. The mechanism of the progressive age-related sympathetic bias is likely to involve numerous factors, and the theory presented in this paper, the iterative dysfunction of carotid sensors due to atherosclerosis, may constitute one of these factors. Hypertension may represent but one example of a disease of aging that occurs via this mechanism, whereby systemic blood pressure gradually and inexorably increases via a progressive induction of autonomic dysfunction. Therefore interventions to reduce the risk of cerebral ischemia and stroke that take this intellectual framework into account may ultimately yield more pervasive benefits in the treatment of a wide variety of systemic diseases related to autonomic dysfunction.

## References

- [1] Thorvaldsen P, Kuulsamaa K, Rajakangas AM, Rastenyte D, Sarti C, Wilhemsen L. Stroke trends in the WHO MONICA project. *Stroke* 1997;28:500–6.
- [2] American Heart Association. 1998 Heart and stroke statistical update. Dallas, TX: American Heart Association; 1997.
- [3] Barnett HJM, Gunton RW, Eliasziw M, Fleming L, Sharpe B, Gates P, et al. Causes and severity of ischemic stroke in patients with internal carotid artery stenosis. *JAMA* 2000;283:1429–36.
- [4] Timsit SG, Sacco RL, Mohr JP, Foulkes MA, Tatemichi TK, Wolf PA, et al. Early clinical differentiation of cerebral infarction from severe atherosclerotic stenosis and cardioembolism. *Stroke* 1992;23(4):486–91.
- [5] Sacco RL, Ellenberg JH, Mohr JP, Tatemichi TK, Hier DB, Price TR, et al. Infarcts of undetermined cause: the NINCDS Stroke Data Bank. *Ann Neurol* 1989;25(4):382–90.
- [6] Inzitari D, Eliasziw M, Gates P, Sharpe BL, Chan RK, Meldrum HE, et al. The causes and risk of stroke in patients with asymptomatic internal-carotid-artery stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med* 2000;342(23):1693–700.
- [7] European Carotid Surgery Trialists Collaborative Group. Risk of stroke in the distribution of an asymptomatic carotid artery. *Lancet* 1995;345:209–12.
- [8] Norris JW, Zhu CZ, Bornstein NM, Chambers BR. Vascular risks of asymptomatic carotid stenosis. *Stroke* 1991;22:1485–90.
- [9] Mackey AE, Abrahamowicz M, Langlois Y, Battista R, Simard D, Bourque F, et al. Outcome of asymptomatic patients with carotid disease. Asymptomatic cervical bruit study group. *Neurology* 1997;48(4):896–903.
- [10] Reinhard M, Roth M, Müller T, Guschlbauer B, Timmer J, Czosnyka M, et al. Effect of carotid endarterectomy or stenting on impairment of dynamic cerebral autoregulation. *Stroke* 2004;35:1381–7.
- [11] Fisher CM, Gore I, Okabe N, White PD. Atherosclerosis of the carotid and vertebral arteries: extracranial and intracranial. *J Neuropathol Exp Neurol* 1965;24:455–76.
- [12] Ailawadi G, Stanley JC, Rajagopalan S, Upchurch GR. Carotid stenosis: medical and surgical aspects. *Cardiol Clin* 2002;20(2):599–609.
- [13] Derdeyn CP, Grubb Jr RL, Powers WJ. Cerebral hemodynamic impairment: methods of measurement and association with stroke risk. *Neurology* 1999;53(2):251–9.
- [14] De Reuck JL. Pathophysiology of carotid artery disease and related clinical syndromes. *Acta Chir Belg* 2004;104(1):30–4.
- [15] Piccirillo G, Di Giuseppe V, Nocco M, Lionetti M, Moise A, Naso C, et al. Influence of aging and other cardiovascular risk factors on baroreflex sensitivity. *J Am Geriatr Soc* 2001;49(8):1059–65.
- [16] Duchon MR, Caddy KW, Kirby GC, Patterson DL, Ponte J, Biscoe TJ. Biophysical studies of the cellular elements of the rabbit carotid body. *Neuroscience* 1988;26(1):291–311.
- [17] Lopez-Barneo J, Lopez-Lopez JR, Urena J, Gonzalez C. Chemotransduction in the carotid body: K<sup>+</sup> current modulated by PO<sub>2</sub> in type I chemoreceptor cells. *Science* 1988;241(4865):580–2.
- [18] Obeso A, Gonzalez C, Dinger B, Fidone S. Metabolic activation of carotid body glomus cells by hypoxia. *J Appl Physiol* 1989;67(1):484–7.
- [19] Heistad DD, Abboud FM, Mark AL, Schmid PG. Interaction of baroreceptor and chemoreceptor reflexes. Modulation of the chemoreceptor reflex by changes in baroreceptor activity. *J Clin Invest* 1974;53(5):1226–36.
- [20] Robinson TG, Dawson SL, Eames PJ, Panerai RB, Potter JF. Cardiac baroreceptor sensitivity predicts long-term outcome after acute ischemic stroke. *Stroke* 2003;34(3):705–12.
- [21] Gianaros PJ, Jennings JR, Olafsson GB, Steptoe A, Sutton-Tyrrell K, Muldoon MF, et al. Greater intima-media thickness in the carotid bulb is associated with reduced baroreflex sensitivity. *Am J Hypertens* 2002;15(6):486–91.
- [22] Sigaud-Roussel D, Evans DH, Naylor AR, Panerai RB, London NL, Bell P, et al. Deterioration in carotid baroreflex during carotid endarterectomy. *J Vasc Surg* 2002;36(4):793–8.
- [23] Tomiyama H, Nishikawa E, Abe M, Nakagawa K, Fujiwara M, Yamamoto A, et al. Carotid arterial distensibility is an important determinant of improvement in autonomic balance after successful coronary angioplasty. *J Hypertens* 2000;18(11):1621–8.
- [24] Vanmaele RG, De Backer WA, Willems MJ, Van Schil PE, De Maeseneer MG, Van Look RF, et al. Hypoxic ventilatory response and carotid endarterectomy. *Eur J Vasc Surg* 1992;6(3):241–4.

- [25] Yu G, Xu L, Hadman M, Hess DC, Borlongan CV. Intracerebral transplantation of carotid body in rats with transient middle artery occlusion. *Brain Res* 2004;1015:50–6.
- [26] Conley BR, Doux JD, Lee PY, Bazar KA, Daniel SM, Yun AJ. Integrating the theories of Darwin and Bernoulli: maladaptive baroreceptor network dysfunction may explain the pathogenesis of aortic aneurysms. *Med Hypotheses* 2005;65(2):266–72.
- [27] VanderLaan PA, Reardon CA, Getz GS. Site specificity of atherosclerosis: site-selective responses to atherosclerotic modulators. *Arterioscler Thromb Vasc Biol* 2004;24:12–22.
- [28] Gottsater A, Ryden-Ahlgren A, Szelag B, Hedblad B, Persson J, Berglund G, et al. Cardiovascular autonomic neuropathy associated with carotid atherosclerosis in Type 2 diabetic patients. *Diabet Med* 2003;20(6):495–9.
- [29] Yun AJ, Lee PY, Bazar KA. Can thromboembolism be the result, rather than the inciting cause, of acute vascular events such as stroke, pulmonary embolism, mesenteric ischemia, and venous thrombosis? A maladaptation of the prehistoric trauma response. *Med Hypotheses* 2005;64(4):706–16.
- [30] Sundt Jr TM. The cerebral autonomic nervous system. A proposed physiologic function and pathophysiologic response in subarachnoid hemorrhage and in focal cerebral ischemia. *Mayo Clin Proc* 1973;48(2):127–37.
- [31] Raicevic R, Jovicic A, Krgovic M, Tavcioski D, Ratkovic N, Djordjevic D, et al. Beta blockers and ischemic cerebral disease. *Vojnosanit Pregl* 1998;55(4):417–27.
- [32] Mangin L, Medigue C, Merle JC, Macquin-Mavier I, Duvaldestin P, Monti A, et al. Cardiac autonomic control during balloon carotid angioplasty and stenting. *Can J Physiol Pharmacol* 2003;81(10):944–51.
- [33] Gaunt ME, Sigauco-Roussel D, Panerai R, Evans DH, London NL, Naylor AR, et al. Intraoperative change in baroreceptor function during carotid endarterectomy. *Brit J Surg* 2000;87(4):494–5.
- [34] Chappleau MW, Cunningham JT, Sullivan MJ, Wachtel RE, Abboud FM. Structural versus functional modulation of the arterial baroreflex. *Hypertension* 1995;26(2):341–7.
- [35] Yun AJ, Lee PY, Bazar KA. Temporal variation of autonomic balance and diseases during circadian, seasonal, reproductive, and lifespan cycles. *Med Hypotheses* 2004;63(1):155–62.
- [36] Yun AJ, Lee PY, Bazar KA. Many diseases may reflect dysfunctions of autonomic balance attributable to evolutionary displacement. *Med Hypotheses* 2004;62(6):847–51.

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