



# Is atherosclerosis a neurogenic phenomenon?

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**Summary** Identified risk factors for atherosclerosis include diet, age, gender, family history, stress, lifestyle, smoking, diabetes, dyslipidemias, hypertension, and HIV. The mechanistic rationale to explain these associations remains poorly understood. We believe that these seemingly unrelated entities may promote atherosclerosis through a common pathway by inducing adventitial autonomic dysfunction, specifically as an adventitial stress dysfunction of neurogenic origin. Atherosclerosis may represent a local vascular manifestation of the global autonomic dysfunction induced by age, smoking, hypertension, HIV, and diabetes. Atherosclerosis may also participate in a feed-forward cycle as aging, diabetes, dyslipidemia, and hypertension may also represent independent downstream consequences of global sympathetic bias. Chronic physiologic stress and behavioral stress can shift the autonomic balance towards a state of sympathetic predominance. The highly communicable nature of behavioral stress may partially implicate the familial association of atherosclerosis as an epigenetic phenomenon, independent of putative genetic mechanisms. Host stress, global autonomic dysfunction, and sympathetic bias may also arise from chronic maladaptive consumption of stressed foods, as organisms detect and assimilate the stress phenotypes of their dietary constituents through a process called xenohormesis. The benefits of exercise may operate through reduction of chronic physiologic stress associated with global sympathetic bias. The neurogenic adventitial stress response may explain the local tissue remodeling seen in atherosclerosis, including adventitial adipose dysfunction, inflammation, adventitial angiogenesis, thrombosis, and endothelial dysfunction. We believe that the locations of atherosclerotic lesions correspond to regions of neurogenic adventitial autonomic dysfunction, in similar fashion to the segmental patterns of involvement found in inflammatory bowel disease. The diffuse atherosclerosis exhibited in transplanted hearts may reflect a diffuse sympathetic bias of the donor heart, since tissues and organs exhibit an intrinsic sympathetic bias in the absence of an extrinsic source of autonomic hegemony. Once we regard atherosclerosis as a neurogenic phenomenon manifested in adventitial autonomic dysfunction, novel diagnostic and therapeutic paradigms become evident.

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## Hypothesis

Risk factors for atherosclerosis include diet, age, gender, family history, stress, lifestyle, smoking,

diabetes, dyslipidemias, hypertension, HIV, and other comorbid conditions, but the mechanistic explanation behind the association is not well understood [1–4]. We believe that these disparate risk factors encourage the development of atherosclerosis by promoting adventitial autonomic dysfunction and sympathetic bias [5]. We accordingly propose that atherosclerosis is caused by stress

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dysfunction, particularly that of neurogenic origin. Such an explanation not only ties together the seemingly disparate risk actors for atherosclerosis, but also has future implications for biopharmaceutical and mechanical treatment.

## Evidence

Many risk factors for atherosclerosis induce global autonomic dysfunction and sympathetic bias. They do so either directly through autonomic neuropathy or indirectly through tissue stress. One such factor is diabetes where the resultant autonomic neuropathy causes sympathetic nerve hyperactivity [6]. Furthermore, patients with early diabetic autonomic neuropathy exhibit parasympathetic impairment, thus further tipping the scales of sympathovagal balance towards that of a sympathetic state [6]. Hypertension is twice as common in diabetics versus the general population; Perin et al. describes the central role sympathetic hyperactivity plays in the pathogenesis of hypertension in diabetes [6]. Baroreceptor dysfunction may be an independent mechanism of hypertension associated with autonomic dysregulation [7]. Sympathetic bias has been directly implicated in the pathogenesis of hypertension independent of diabetes [8,9].

Age, smoking, and HIV also induce autonomic dysfunction and sympathetic bias. Although various downstream factors activating the renin–angiotensin–aldosterone system can be seen as causative, ultimately neurogenic sympathetic bias may represent the common etiologic pathway invoked by these risk factors. A study of military personnel showed that smoking induced autonomic changes, namely an increase in sympathetic activity [10]. Another study demonstrated that patients with HIV lipodystrophy had altered cardiovagal modulation with increased sympathetic modulation and lower heart rate variability [11]. Aging has been shown to tilt the autonomic balance to sympathetic bias, as measured by decreased heart rate variability (HRV) [12]. While the mechanism for this age-related bias is likely pleiotropic in nature, degeneration of central control centers of autonomic balance such as the suprachiasmatic nucleus may play a pivotal role [13].

Indeed, we assert that aging, diabetes, dyslipidemia, and hypertension represent independent downstream consequences of global sympathetic bias, thereby creating a vicious feed-forward cycle with atherosclerosis. Seals and Esler describe a whole body increase in sympathetic state with increasing age [14]. A study of diabetic patients demonstrated vagal downregulation and sympa-

thetic ventricular control [15], whereas another study of one hundred and sixty three hypertensive patients demonstrated sympathetic predominance [16]. We believe that any chronic stress state can foster atherogenesis through this mechanism. For example, patients suffering from phobic anxiety, a behavioral stress state, exhibit low heart variability and have higher rates of sudden cardiac death and coronary artery disease than control populations [17–20]. Low HRV is associated with decreased parasympathetic input and a consequent increased sympathetic state. Of note, behavioral stress is highly communicable and may partially explain the familial association of atherosclerosis as an epigenetic phenomenon, independent of putative genetic mechanisms [3,21].

In addition, chronic stress from altered signals in the food chain may also influence atherogenesis. Through a process termed xenohormesis, organisms use diet to detect and assimilate stress phenotypes of their prey through a process called xenohormesis. Chronic maladaptive consumption of stressed foods may induce host stress, global autonomic dysfunction, and sympathetic bias, once again encouraging the development of atherosclerosis [22,23].

The lack of exercise and a sedentary lifestyle is well known to contribute to atherosclerosis [3]. The benefits of exercise in atherosclerosis may operate through reduction of chronic physiologic stress associated with global sympathetic bias. Enhanced efferent vagal activity increases HRV, whereas sympathetic stimulation decreases HRV [24]. Low HRV is associated with increased cardiac events and mortality [25,26]. Studies show that exercise strengthens vagal input and increases HRV [27–29], suggesting that repetitive sympathetic challenges may cause vagal rehabilitation and reduce the sympathovagal ratio. Even a single episode of submaximal exercise appears to increase HRV and promote parasympathetic function [28]. The lack of exposure to intermittent acute stress in the form of exercise may engender chronic physiologic stress, sympathetic bias, and atherosclerosis.

The neurogenic adventitial stress response explains the local tissue remodeling seen in atherosclerosis including adventitial adipose dysfunction, inflammation, adventitial angiogenesis, thrombosis, and endothelial dysfunction. Adventitial adipose tissue has been difficult to study, but it clearly differs histologically from that of visceral adipose tissue. Diseased vessels also show increased angiogenesis in the adventitia, which in turn may arise from increased nerve activity in accordance with the stress response. Many vascular phenomenon, such as anti-angiogenesis, may operate

through adventitial neuromodulation. We believe that locations of atherosclerotic lesions correspond to regions of neurogenic adventitial autonomic dysfunction, much like the segmental patterns of found in inflammatory bowel disease [5,14,30]. The diffuse atherosclerosis seen in transplanted hearts represents an extreme example of this physiology. That such hearts exhibit this pattern of atherosclerosis may reflect a pervasive sympathetic bias of the donor heart. In the absence of an extrinsic source of autonomic hegemony, tissues and organs exhibit an intrinsic sympathetic bias [31,32].

The treatment benefits for vascular disease afforded by sympatholytics provide indirect evidence to support this thesis. Monkeys undergoing sympathectomy show decreased progression of atherosclerosis. Monkeys given propranolol also showed a decrease in atherosclerotic progression, although less dramatically [33]. With an imbalance in the autonomic system changing hemodynamic and lipid parameters in addition to direct adrenergic effects, the vasculature inevitably becomes affected [34]. Atherosclerosis represents the local vascular manifestation of this neurologic dysfunction.

## Implications

Novel diagnostic and therapeutic paradigms are evident when viewing atherosclerosis as a neurogenic phenomenon manifested by adventitial autonomic dysfunction. The current paradigm of diagnosis relies on symptomatic classification, with the diagnosis rendered following recognition of a particular set of cardinal features, such as those which occur in conjunction with stroke, acute coronary syndrome, or lower extremity claudication. A more complete and unified understanding of the pathogenesis of atherosclerosis as a neurogenic phenomenon rather than an amalgamation of apparently disparate factors may shift this paradigm towards earlier recognition of risk. It may also encourage the development of preemptive measures to curtail atherogenesis and its potential sequelae.

The same rationale applies to treatment. The existing model for therapy focuses on lifestyle modification, pharmacological management, and surgical intervention. Lifestyle modifications such as diet and exercise, which represent risk factor reductions, may exert their benefit by decreasing sympathetic bias [35]. Current pharmacological treatment focuses on cholesterol lowering medications to reduce endoluminal fat deposits, anti-platelet medications to prevent platelet aggregation, anticoagulation to prevent thrombus formation, anti-hypertensives to de-

crease progression, and other risk factor specific medications such as hypoglycemic agents. These treatments may acutely decrease atherosclerosis. However, if the underlying sympathetic bias remains unaddressed, then the inciting etiology remains, and may reconstitute the disease burden in short order. Current surgical interventions include endoluminal approaches such as angioplasty, endarterectomy, stents, thrombolytics, and bypass. Again, although they may provide temporary satisfaction by permitting the observation of direct physical clearance, these surgical interventions may activate the body's trauma response through vessel damage and sympathetic bias, thus paradoxically reinitiating and even exacerbating atherogenesis [5]. Autonomic neuromodulation may be an avenue to treat vascular disease without triggering the body's own trauma response. Understanding atherosclerosis as a neurogenic phenomenon may shift the standard for treatment towards the reduction of chronic stress and restoration of sympathovagal balance through medical device, biopharmaceutical, and behavioral approaches.

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