



# Peripheral arterial disease: A manifestation of evolutionary dislocation and feed-forward dysfunction

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Received 19 March 2006; accepted 21 March 2006

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**Summary** Peripheral arterial disease in the legs represents a subset of atherosclerosis that manifests a particularly sinister profile. A predominance of sympathetic activity in the periphery favors the development of neurogenic atherosclerosis. Atherosclerosis may then produce flow derangements and decreased physical activity that serves to escalate sympathetic bias in a vicious cycle. Restoration of normal flow in peripheral arterial disease may not only produce local benefit due to improved perfusion, but also represent a gateway to correcting many systemic conditions that may at first glance appear unrelated but share a common etiology of autonomic dysfunction, such as gout, acute coronary syndromes, stroke, sleep apnea, arrhythmias, depression, erectile dysfunction, inflammation, hypercoagulability, sleep disorders, bowel dysfunction, renal failure, and aging.

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## Introduction

Atherosclerosis may represent a modern maladaptation of the prehistoric trauma response that links sympathetic activity, inflammation, and coagulation [1]. Peripheral arterial disease refers to a particular manifestation of atherosclerosis in the legs. As humans typically assume an upright posture, in order to minimize pooling of blood in the legs, the autonomic disposition of the legs favors that of increased sympathetic activity, thereby ensuring

an adequate return of blood to the heart. Natural thermal, oxygenation, and pressure gradients also favor increased sympathetic tone in the extremities. We believe that this tendency predisposes to peripheral arterial disease. The worsening of this condition with age, another source of progressive sympathetic bias, supports this assertion [2]. Intermittent claudication, a symptom of peripheral arterial disease, has also been noted as a paraneoplastic entity distinct from the oft-cited phenomenon of cancer-associated venous thrombosis [3,4]. Since sympathetic bias favors the development of cancer, the witnessed association may be one not of causality, but of correlation with upstream factors.

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## The significance of flow

In the intravascular setting, as with any biologic flow phenomenon, physical insult to the fluid container occurs. The formation of either thrombus or atherosclerotic plaque on the inner aspect of an arterial wall, or intravascular injury with consequent fibrosis, may produce a transient or permanent contour irregularity so as to distort the surface topography of the interior of the vessel. Flow through that segment would then assume turbulent rather than laminar features, yielding several important consequences.

Turbulent flow may lead to degradation of physical information manifest as flow within the artery. The parameter of pulse wave velocity becomes degraded from that of a triphasic pattern with three audible components by Doppler to that of a biphasic or even nonexistent pattern [5]. This loss of signal may carry significance with respect to overall systems monitoring. Components of the system which fail to sense normal or adequate signal may then undergo compensatory changes that could prove maladaptive.

Disruption of the contour of the vessel wall may also produce shear stress on the endothelium. Evidence has shown that shear stress can alter the behavior of the vascular endothelium [6] and serve as a stimulus for arteriogenesis [7]. As shearing forces buffet the internal lining of the vessel wall, they may activate cellular responses to trauma and stress. Such changes may then ripple through the cellular constituents of a particular milieu and fractally yield a more perverse effect.

Ultimately, a disturbance in flow may generate a decrease in dynamic pressure distal to the affected portion of the vessel. During prehistoric evolution, a decrease in intravascular dynamic pressure may have signaled hemorrhage through trauma [8]. This message may carry particular significance in the extremities. A significant disparity in intravascular dynamic pressure between the distal and proximal portions of a vessel may indicate the presence of distal injury. The central residence of more critical organs within the torso enables their preservation should distal elements require sacrifice due to functional compromise.

Consequently, induction of vasoconstriction through an increase in adrenergic activity would produce an adaptive response with an increase in the systemic pressure. However, this sympathetic escalation would also promote inflammation and coagulation. The compromised site of occlusion or injury would logically serve as a nidus to predispose to further events, contributing to a feed-for-

ward cycle that would ultimately lead to complete occlusion of the affected vessel. The iterative sequence would then comprise the following series of events: trauma producing a compromise in flow with a lowering of distal pressure, followed by compensatory sympathetic upregulation so as to generate hypercoagulability and inflammation, leading to exacerbation and amplification of the initial insult. The typical clinical picture of peripheral arterial disease thus emerges – that of inadequate distal perfusion giving rise to chronic pain and inflammation, and ultimately resulting in loss of the affected limb.

## The importance of exercise

Recent data has shown that exercise has benefits for patients with peripheral arterial disease [9], yet ironically, exercise becomes limited due to pain and fatigue associated with the disease. During exercise, the sympathetic nervous system mediates vasoconstriction in both unutilized muscle and viscera to redistribute blood flow to exercising muscles [10]. However, sympathetic vasoconstriction also occurs in active skeletal muscle, so as to balance active muscle vasodilatation with the rise in cardiac output in order to maintain systemic arterial pressure. Although vessels in exercising muscle have a decreased sensitivity to  $\alpha$ -adrenergic stimuli, a phenomenon referred to as “functional sympatholysis”, sympathetic restraint of active muscle blood flow still contributes to the maintenance of systemic blood pressure [11].

Under resting conditions, sympathetic vasoconstrictor outflow to skeletal muscle increases progressively with advancing age in humans, as evidenced by elevated basal systemic noradrenaline spillover rates and muscle sympathetic nerve activity [12]. The increasingly tonic nature of ongoing stimulation may lead to the decline of vasoconstrictor responsiveness seen with resting skeletal muscle with advancing age. However, vasoconstrictor responsiveness to exercise does not decrease with age, but instead undergoes augmentation [13].

Consequently, exercise may contribute to reduced progression of peripheral arterial disease in two ways. First, as we have previously articulated [14], the intermittent sympathetic stimulation produced by periodic exercise may paradoxically lead to decreased chronic sympathetic tone, thereby reducing overall susceptibility to inflammation and coagulation predisposing to further injury. Sec-

ond, global vasoconstriction with exercise may minimize the tendency of areas of injury and inflammation to induce sympathetic bias by reducing pressure gradients between segments proximal and distal to these sites.

## Implications

### Local significance

Since the legs already exhibit a sympathetic bias with an associated immunologic shift towards Th2 helper cell subsets, many of the diseases that localize to the feet may arise as a downstream manifestation of peripheral arterial disease due to amplification of the neurologic and immunologic imbalances already present. Accordingly, reflex sympathetic dystrophy most commonly occurs in the feet. It remains unknown whether entities such as diabetic neuropathy or Morton's neuroma in the lower extremities emerge as a consequence of the sympathetic bias with which they are often associated. Fungal infections such as onychomycosis may elude immune surveillance and flourish due to the predominance of Th2 over Th1 helper cell subsets. Sympathetic bias may contribute to venous dysfunction both directly in a fashion similar to that found in the arteries, and through heightened levels of downstream inflammation and coagulation. Accordingly, restoration of blood flow to the legs may potentially improve these conditions not simply by rejuvenating circulation, but also by eliminating autonomic and immunologic changes that may have favored their development.

Gout is a rheumatologic condition typically seen in distal limb joints, particularly among the elderly when systemic sympathetic bias is the highest. Cyclosporine, a drug known to induce systemic stress and Th2 shift, causes worsening of gout [15]. Cyclosporine use is also associated with small vessel vasoconstriction and vasculopathy in the brain [16]. Autonomic dysfunction may also influence the development of gout in distal joints; gout often emerges under conditions of sympathetic bias such as syndrome X and hypertension [17], and worsens with acute sympathetic events such as trauma and hemorrhage. Gout is thought to be exacerbated by renal failure, but perhaps gout and renal failure also represent independent consequences of sympathetic bias.

### Systemic significance

The autonomic nervous system acts to constantly monitor our body, recalibrating its functional set-

tings to compensate for any stresses that arise. For example, it receives and integrates feedback information regarding blood pressure in all parts of the body. Changes in posture and ambient temperature both change blood pressure and cause the body to respond in kind. In prehistoric times, this central means of control may have ensured a coordinated response to physical trauma through mechanisms such as vasoconstriction, coagulation, and inflammation.

However, modern society has reduced the frequency of such events such that the system has become maladaptive – the nature of the trauma to which it responds is that of attrition rather than that of catastrophe. Central recalibration now serves to amplify seemingly inconsequential injury in an iteratively escalating fashion, insidiously transforming a clinically imperceptible molehill into a mountain of wholesale systemic stress. Conditions such as peripheral arterial disease may represent a response to one type of initiating event – in this case, atherosclerotic plaque – that define an intermediate stage of progression with respect to autonomic escalation before ultimately culminating with phenoptosis. Removal of the initiating source of stress, be it atheroma or clot, may serve to reset those parameters which served to trigger this escalation. Doing so may not only treat the symptoms of the disease, but also correct manifestations in other systems that resulted from ongoing sympathetic bias. Such a change may reduce the risk of many conditions associated with sympathetic excess including acute coronary syndromes, stroke, sleep apnea, arrhythmias, depression, erectile dysfunction, inflammation, hypercoagulability, sleep disorders, bowel dysfunction, renal failure, and aging [8,18–21].

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