



# 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

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**Summary** Thromboembolism is considered the inciting cause of many vascular disorders including acute coronary syndrome (ACS), ischemic stroke, pulmonary embolism (PE), deep vein thrombosis (DVT), and mesenteric ischemia. Adrenergia and inflammation are known to accompany these conditions, particularly among arterial thromboembolic disorders, but the teleologic basis of these associations remains poorly understood. We argue that thromboembolism may sometimes be the result, rather than the cause, of acute vascular events, and may be precipitated by underlying adrenergia. Thromboembolic events are most prone to occur during parts of the circadian, seasonal, lifespan, and reproductive cycles with sympathetic dominance, as well as during behavioral, exertional, physiologic, and iatrogenic activation of sympathetic stress. Molecular evidence suggests that adrenergia and inflammation can promote coagulation and lead to co-activation of the pathways. Acute vascular events that occur without angiographic evidence of occlusion suggest that some infarcts may be attributable to adrenergia alone. “Embolitic” disorders may represent asynchronous systemic phenomena rather than clot migration. During acute thromboembolism, downstream tissue hypoxia can activate maladaptive self-propelling cycles of sympathetic bias, inflammation, and coagulation. The counterproductive co-activation of these pathways may reflect a maladaptive interlink forged during the primordial evolution of trauma physiology. Their rapid co-mobilization enables rapid control of hemorrhage, microbial defense, and perfusion maintenance during trauma, but the pathways may behave maladaptively in the setting of modern diseases where endothelial injury may be more often precipitated by smoking, diabetes, dyslipidemia, or hypertension. Sympathetic blockade is already employed in ACS, and  $\beta$ -blockers are used as antihypertensives to prevent stroke. Our hypothesis suggests that the benefits of  $\beta$ -blockers in stroke may be independent of antihypertensive effects, and that adrenergia may represent a target for managing all thromboembolic disorders, independent of anti-coagulative and thrombolytic therapies. Perhaps reducing adrenergia, rather than maintaining high cerebral perfusion pressure, may represent a counterintuitive strategy for treating stroke and for reducing reperfusion injury. Plausible mechanisms by

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which autonomic dysfunction may induce venous thrombosis are discussed, especially in those with baroreceptor dysfunction, immobilization, or dehydration. Unexplained hypercoagulability of cancer may also operate through tumor-induced adrenergia and inflammation.

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## Hypothesis

Thromboembolism is generally viewed as the inciting cause of many diseases including ischemic stroke, pulmonary embolism (PE), deep venous thrombosis (DVT), mesenteric ischemia, and acute coronary syndrome (ACS). Causality is presumed based on the presence of vascular occlusion on angiogram or autopsy after acute events. The conventional wisdom has resulted in anti-coagulants and thrombolytics becoming the mainstay of prevention and treatment of these disorders. It is increasingly becoming apparent that hyperadrenergia and inflammation are also associated with vascular disorders. The evidence is most advanced in ACS and least advanced in venous thromboembolic diseases.

The classic view that thrombosis causes myocardial infarction has been substantially reshaped during the past decade. It is now well accepted that the thrombosis of ACS occurs as part of a broader co-activated cascade that involves inflammation and adrenergia. Sympathetic blockade and anti-inflammatory strategies have been added to anti-thrombotic drugs as part of the therapeutic management of ACS, and  $\beta$ -blockers appear to reduce the risk of acute attacks during periods of perioperative stress [1,2]. It should be noted, however, that the benefits of  $\beta$ -blockers in ACS were originally attributed to the decreased myocardial oxygen demand from heart rate control [3], and the broad role of sympathetic dysfunction was only appreciated later.  $\beta$ -Blockers are also used in the prevention of stroke although the rationale is based on control of hypertension. On the other hand, the role of autonomic dysfunction in other thromboembolic disorders remains poorly studied, and autonomic modulation is currently not a recognized component of prevention or treatment.

We hypothesize that sympathetic bias can play a causal role in the pathogenesis of arterial and venous thromboembolic disorders. Indeed, sympathetic bias may be the inciting cause of some acute vascular events and thromboembolism may be a secondary *consequence* of the condition rather than its cause. Furthermore, once vascular occlusion occurs, the downstream hypoxia can further promote self-propelling cycles of adrenergia,

inflammation, and coagulation that exacerbate the vasoconstriction and thrombosis. Therefore, we postulate that autonomic modulation may play beneficial roles in the prevention and treatment of all thromboembolic disorders, not just in ACS. The literature is sparse in exploring the teleologic basis of thromboembolic disorders. We propose that the co-activation of adrenergia, inflammation, and coagulation in acute vascular events represents a modern maladaptive response that was shaped during pre-modern evolution when physical trauma was a more dominant driver of natural selection.

## Sympathetic bias in the pathogenesis of acute vascular events

### Epidemiologic evidence

We challenge the conventional wisdom that thromboembolism is the inciting cause behind most acute vascular events such as ACS, stroke, and pulmonary embolism – a view largely based on post hoc presence of vascular occlusion on autopsy or angiography. Even though the actual temporal relationship is often unknown, angiographers or pathologists are generally inclined to attribute the acute vascular event to the thrombosis rather than the other way around. However, one cannot dismiss the possibility that thromboembolism may be a *result* rather than a cause of acute vascular events. Perhaps other triggers such as adrenergia or inflammation initiate the acute vascular syndrome which secondarily induces acute coagulation.

The collective epidemiologic evidence suggests that background sympathetic bias and sudden sympathetic activity are major risk factors for the onset of acute vascular events. The incidence of vascular events has a high temporal correlation with periods of sympathetic bias during circadian, seasonal, lifespan, and reproductive cycles as well as during behavioral, exertional, physiologic, and iatrogenic stress. Numerous epidemiologic studies have shown that acute myocardial infarction [4,5], ischemic and hemorrhagic strokes [6–10], and PE [11–14] are more prevalent during morning arousal, winter months, pregnancy, and

senescence, which are periods of life when background sympathetic bias is high for various adaptive and maladaptive reasons [15,16]. Notably, the phenomenon is attributed to temporal variations in coagulation function by some authors [17–19], but such variations may be driven by oscillations of autonomic balance [20]. Exertion and behavioral stress, both of which can precipitate sympathetic surge, are independently associated with ACS [21,22] as well as ischemic and hemorrhagic strokes [23,24]. While it is generally assumed that embolic events account for the increased rates of strokes [1], PE [25], myocardial infarction [1], and mesenteric ischemia [26] in the peri-operative period, iatrogenic sympathetic bias induced by invasive intervention may be an independent contributing factor. Indeed, there is evidence that invasive procedures induce a shift to sympathetic and Th2 inflammation [27,28].

Co-morbid conditions that induce sympathetic bias or inflammation are also known independent risk factors for acute vascular events. Chronic conditions such as sleep apnea, cystic fibrosis, renal failure, HIV, cancer, asthma, inflammatory diseases, pregnancy, aging, drug abuse, and transplantation can activate sympathetic activity or induce Th2-biased inflammation [29–35], and have been shown to represent independent risk factors for ACS [20,30,34–41]. Strokes and coagulative disorders are associated with conditions such as migraines or eclampsia, which generally manifest increased adrenergic tone and autonomic dysfunction [20,42–45].

Dehydration is a risk factor for various thromboembolic disorders such as DVT [46], PE [47], cerebral sinus thrombosis, and stroke [48–50]. The phenomenon is generally attributed to rheologic factors, but we suggest that dehydration can promote sympathetic activity through activation of autonomic baroreceptors as part of a broader volume preservation response that includes aldosterone and angiotensin [51]. Interestingly, hypertonic rehydration has been shown to decrease systemic inflammation although the phenomenon is currently unexplained [52]. We postulate that hydration may lower inflammation by lowering sympatho-vagal ratio [51].

Immobilization, along with trauma and hypercoagulability, is a risk factor for DVT as part of the Virchow triad. The phenomenon has been generally attributed various rheologic factors [53], but we propose that the pathogenic mechanism of stasis in DVT may operate through autonomic dysfunction. We suggest that immobilization, particularly in patients with underlying baroreceptor dysfunction, may induce systemic autonomic dysfunction

which, as described in the section that follows, contributes to the activation of coagulation. Indeed, immobilization is a component of the tilt test, which is designed to identify autonomic baroreceptor dysfunction [54].

Cancer-associated hypercoagulability is a well-known risk factor for thromboembolic diseases, but an adequate explanation for the association has been elusive [55]. We previously hypothesized that tumors may shift host autonomic balance to sympathetic bias and induce Th2 inflammation to promote their own fitness [56]. The hypercoagulability of cancer may represent an epiphenomenon related to tumoral activation of the sympathetic and inflammatory cascades. That chemotherapy increases the risk of venous thrombosis [55] may also be attributable to the hyperadrenergic state of chemotherapy recipients [30].

The collective evidence suggests that acute vascular events are frequently preceded by periods of sympathetic bias. The consistent pattern offers indirect support for the notion that sympathetic bias may play a *causal* role in the pathogenesis of thromboembolism and acute vascular events.

## Molecular pathway evidence

While the epidemiologic data offer indirect support for causality, the molecular evidence provides direct support for the idea that adrenergia and inflammation can play inciting roles in thromboembolism and acute vascular events. Sympathetic activity may promote coagulation by upregulating platelet activation, von Willebrand factor (vWF), and clotting factor VIII while downregulating the fibrinolytic cascade [57–60]. The associated activation of the renin-angiotensin system also promotes coagulation [61]. Catecholamines promote inflammation by upregulating T helper (Th)2 cytokines such as IL-10 and TGF- $\beta$  while inhibiting Th1 cytokines such as IL-12, TNF- $\alpha$ , and interferon- $\gamma$  [62–67]. Inflammatory cytokines such as IL-1, IL-6, and TNF- $\alpha$  promote coagulation, possibly through chemokines such as CCL17 and CCL22 [68–70]. Exposure of endothelium to pathogens can initiate coagulation, and inflammation can promote human coagulation factor  $\beta$ -FXIIa, which has sympathomimetic effects [71–74]. Thrombin and other components of the coagulation cascade such as factor Xa and tissue factor–factor VIIa complex can promote inflammation or exaggerate sympathetic drive [75–80]. These studies elucidate molecular pathways by which adrenergia or inflammation can induce, and be further activated by, thromboembolism.

## Acute vascular events without thrombosis

The enigma of angiographically negative acute vascular events provides additional support for the notion that antecedent sympathetic bias and inflammation, separate from thromboembolism, may play a significant causal role in acute vascular events. It is well known that some patients with infarcts demonstrate no evidence of vascular occlusion on angiography. Various theories for the phenomenon have been proposed, but we believe that transient acute sympathetic bias may be the common underlying variable in each case.

Numerous authors have noted that myocardial infarcts, particularly among young patients, can occur without angiographic evidence of thrombosis [81–83]. The phenomenon has been attributed to various theories such as vasospasm, dissection, minimal atherosclerotic disease, and vasculitis, but the exact mechanism remains unknown [81–83]. It is plausible that self-propelling cycles of adrenergia or inflammation may cause sufficient vasoconstriction to compromise perfusion without manifesting thrombosis. Indeed, signatures of inflammation (infection and fever) and signatures of autonomic dysfunction (migraines and vasospasm) are often associated with angiographically normal myocardial infarctions [84,85], and impaired vasodilatory function has been observed in these patients [86].

Potential causal roles of adrenergia and inflammation in the pathogenesis of stroke are evident in cases where patients present with stroke symptoms but no evidence of vascular occlusion is found on angiography. When beading of vessels without occlusion is seen on angiography in patients with stroke symptoms, the presumptive diagnosis of vasculitis is often made [87,88]. However, this conclusion is problematic since the sensitivity of angiographic findings for biopsy-proven vasculitis is 40% [88]. Furthermore, the specificity of the angiographic appearance for vasculitis is only 22% [89], suggesting that angiograms without thrombosis in patients with cerebral ischemic events are vastly over-attributed to vasculitis. Perhaps some of these cases reflect the capacity of adrenergia and inflammation to induce ischemic stroke independent of thrombosis.

Mesenteric ischemia can also occur in the absence of thromboembolism [90]. The predisposing circumstances, which include sepsis, vasoconstriction, renal failure, and stress, suggest that sympathetic bias or inflammation may be entry-points for pathogenesis of mesenteric ischemia even in the absence of thromboembolism [90]. As with stroke

and ACS, even when vascular occlusion is seen it would be difficult to determine if it was the primary source of the acute event or a secondary consequence of sympathetic and inflammatory activity. Cocaine toxicity, a trigger of hyperadrenergia [91], can cause vasoconstriction-induced mesenteric ischemia [92], cerebral vascular disease [93], and myocardial infarction [91,94] without manifesting thrombosis.

Certain pulmonary vascular events such as amniotic fluid embolism and fat embolism can mimic PE in their clinical presentation without manifesting thrombosis. The release of pro-inflammatory and adrenergic moieties may account for the systemic autonomic and inflammatory dysfunctions evident in amniotic and fat embolisms. The conditions are often preceded by hip fracture or labor, both of which are essentially forms of trauma, and activate the sympathetic and inflammatory systems [95–98]. Lipids, which can be introduced into circulation from the marrow of fractured bone, have intrinsically pro-inflammatory properties [99]. While the immunomodulatory properties of amniotic fluid have not been elucidated, the adaptive immune tolerance requirements for gestation would predict that amniotic fluid has Th2 pro-inflammatory properties [100]. Indeed, inflammation and symptoms of adrenergia such as tachycardia, hypertension, and cardiovascular dysfunction generally accompany fat and fluid embolisms [101–104].

That adrenergia and inflammation can directly induce acute vascular events supports the notion that thromboembolism may sometimes be a secondary process during acute vascular syndromes rather than its inciting cause.

## Rethinking the concept of embolism

Our hypothesis has potential implications for understanding “embolic” disorders. If coagulation can be improperly initiated by systemic adrenergia and inflammation, is it possible that “embolic” disorders are not truly migratory phenomenon of dislodged clots, but instead represent asynchronous multi-location manifestations of coagulation due to systemic dysfunctions? For instance, pulmonary embolism (PE) is currently viewed as a coagulation disorder of the pulmonary arteries that results from mechanical propagation of deep venous thrombosis (DVT). However, the “embolism” of PE is a presumptive description based on the occasional concomitant identification of DVT. The classical theory that all pulmonary embolisms represent clots dislodged from the deep venous

system, however, is not fully supported by data. A recent study shows that 31% of patients with pulmonary embolisms do not have evidence of DVT [105]. Superficial venous thrombosis, which is not presumed to propagate into the pulmonary arteries, is also associated with a significantly higher rate of pulmonary embolisms [106]. Placement of vena cava filters in patients with DVT does not appear to improve outcome and may increase the occurrence of more venous clots [107], an effect possibly attributable to the chronic traumatic vascular injury caused by presence of instrumentation in the vessel. Perhaps release of inflammatory cytokines may induce downstream thrombosis and vasoconstriction [108], independent of any “embolic” phenomenon. It is well known that appendicitis, diverticulitis, and pancreatitis are among many gastrointestinal inflammatory conditions that predispose to downstream portal, splenic, and mesenteric venous thrombosis [109]. Similarly, cerebral infections, pneumonia, and endocarditis can induce downstream vascular occlusions [95,110,111], possibly as a host adaptation to quarantine the infection. Migratory thrombophlebitis, currently a condition of unknown etiology, may fit within the same spectrum. Nonetheless, all obstructing pulmonary arterial clots visualized on imaging studies and on autopsies are uniformly considered “embolic” whether or not a source is identified. There remains a possibility that some cases of DVTs and PEs may represent asynchronous de novo local coagulation events attributable to systemic physiologic dysfunctions rather than a migratory embolic phenomenon.

### Sympathetic bias in the propagation of acute vascular events

In the context of acute thromboembolism, the host physiologic response to vascular occlusion can behave maladaptively. Tissue hypoxia downstream of the vascular occlusion activates autonomic chemoreceptors and promotes adrenergia, setting up a self-propelling, nefarious cycle. The counterproductive adrenergic response to coronary ischemia has been previously reviewed [95].

In ischemic stroke, cerebral hypoxia triggers dysfunctions of perfusion autoregulation [29,112,113]. The resulting elevated systemic blood pressure has been attributed to various causes [114–118], but is generally consistent with sympathetic excess. Numerous authors have advocated not treating the elevated pressure based on the theoretical argument that high pressure can

enhance perfusion to hypoxic cerebral tissues [119,120], but the practice is not supported by randomized data [114,121]. We argue that permitting sympathetic excess to persist during acute ischemic stroke may predispose to undesirable activation of the inflammatory and coagulation pathways. Indeed, results from the recent Glycine Antagonist in Neuroprotection (GAIN) International trial suggest that elevated pulse pressure and mean arterial pressure during acute stroke are associated with poorer outcomes [122]. We postulate that reduction of sympatho-vagal ratio may avert maladaptive co-activation of adrenergia, inflammation, and coagulation during acute ischemic stroke and improve outcomes. Modulation of autonomic balance must be performed judiciously as severe hypotension can lead to poorer outcomes [114].  $\beta$ -Blockers are currently used in the prevention of stroke in the context of reducing hypertension, one of the risk factors for stroke [123]. We postulate that the reduction of sympatho-vagal ratio may offer preventive benefits, independent of the reduction in blood pressure.

The autonomic response in hemorrhagic stroke also has maladaptive features. Endothelial breach at the site of bleeding and ischemic consequences from the mass effect of a hematoma can independently activate adrenergia and inflammation. The activation of coagulation is generally beneficial in hemorrhagic stroke, but the adrenergia-mediated hypertension can be counterproductive. Delayed infarction is common in subarachnoid hemorrhage (SAH) and is thought to be caused by vasospasm presumably related to autonomic dysfunction [124]. During embolization therapy for intracranial hemorrhage or vascular malformations, we propose that it may be prudent to initiate concurrent pharmacologic or device-oriented blockade of the sympathetic and inflammatory systems. Interestingly, recent evidence suggests that cervical sympathetic blockade after SAH reduces the risk of secondary infarction [125]. Such methods may play beneficial roles in mitigating reperfusion injury and provide neuroprotection during stroke since inflammation and sympathetic bias are increasingly being implicated in reperfusion injury [126–128]. An in vitro study showed that  $\beta$ -blockers can reduce cytotoxic damage from hypoxia and reperfusion [129].

The symptoms associated with PE such as pulmonary hypertension, cardiovascular instability, and tachycardia also suggest a maladaptive sympathetic response to the initial insult [130,131]. The hyperadrenergic response to pulmonary arterial occlusion is counterproductive since it worsens vasoconstriction, inflammation, and coagulation

in a self-propelling cycle [95,130–132]. Indeed, early animal evidence suggests that sympathetic blockade may mitigate the severity of the clinical course associated with PE [133]. Mesenteric ischemia may represent another example of a maladaptive response. End-organ gastrointestinal hypoxia from vascular occlusion can initiate local mesenteric vasoconstriction through activation of local sympathetic, renin-angiotensin, and inflammatory responses, which can exacerbate the underlying hypoxia [95,134,135].

The consistent pattern of counterproductive sympathetic response to various acute vascular events suggests that a fundamental maladaptation may be operating in modern humans.

### Darwinian considerations

The fundamental reason why the adrenergic, inflammatory, and coagulative systems respond maladaptively during acute vascular events is currently poorly understood. We postulate that the co-activation of adrenergia, inflammation, and thrombosis was shaped during prehistoric evolution when physical trauma was the primary intended target of this coordinated response. Serious trauma is an uncommon determinant of fitness among modern humans, but it is intuitively appealing to speculate that it served a far larger role in the natural selection of our primordial predecessors. Indeed, there is some empiric support for the view [136–140]. The rapid co-mobilization of adrenergia, inflammation, and coagulation enables rapid control of hemorrhage, microbial defense, and perfusion maintenance during trauma, but the pathways may behave maladaptively in the setting of modern diseases where endothelial injury may be more often precipitated by smoking, diabetes, dyslipidemia, hypertension, and syndrome X. If vascular compromise ensues, the downstream tissue hypoxia further activates sympathetic bias in a maladaptive fashion. However, among our predecessors, hypoxia may have been typically caused by traumatic injury to the limb or torso in which case the co-activation of adrenergia, inflammation, and coagulation could have been life-saving. As is sometimes the case in evolution, the environmental factors of natural selection may have changed, and insufficient time may have passed for human physiology to adapt appropriately. Alternatively, the negative selection pressure may be insufficient to override the fitness benefits of the current response.

### Therapeutic implications

Anti-coagulants and thrombolytics play dominant roles in the current management of many thromboembolic conditions including ischemic stroke, ACS, PE, DVT, mesenteric ischemia, and limb ischemia. While adrenergia and inflammation have been observed in many thromboembolic disorders – far more commonly among arterial than venous disorders – insufficient understanding of the nature of this relationship may account for why anti-adrenergic and anti-inflammatory strategies are not part of the current treatment paradigms for acute vascular events except in ACS. Given our hypothesis, we envision a beneficial role of reducing sympathovagal ratio and inflammation in all thromboembolic conditions, independent of anti-coagulative and thrombolytic therapies. In ACS,  $\beta$ -blockers are already well known to reduce the risk of acute events during the peri-operative period [1] as well as during the sympathetic surge of morning arousal [4,5]. Although  $\beta$ -blockers are widely used in the prevention and treatment of ACS, it should be noted that the practice began serendipitously as part of the management of hypertension as a risk factor of ACS rather than intrinsic insights into direct role of sympathetic dysfunction in the pathogenesis of ACS.

As with ACS, anti-coagulants and thrombolytics remain the preferred methods of preventing and treating PE and ischemic stroke [123]. However, empiric data regarding the use of thrombolytics during acute PE remain controversial [141]. Similarly, the practice of using thrombolytics during acute ischemic stroke is not well supported by randomized data. Of the five randomized trials evaluating thrombolytic therapy in acute ischemic stroke, only a single study showed benefit [142–146], suggesting that ample room remains for improvements in therapy. Attention has increasingly turned to inflammation and other potential targets for the prevention of stroke [147].  $\beta$ -Blockers are used to control hypertension, a risk factor for stroke, but we believe that the anti-adrenergic effects may offer preventive benefits that are independent of blood pressure. Whereas sympathetic blockade is generally not pursued during acute ischemic stroke, we believe that judicious downregulation of adrenergia may improve the acute course during ischemic and hemorrhagic strokes and also reduce the effects of reperfusion injury.

The current management of mesenteric ischemia includes administration of analgesics, thrombolytics, oxygen, fluid resuscitation, and antibiotics. It is perhaps not a coincidence that analgesics,

oxygen, and fluid resuscitation are treatments which can lower sympathetic tone. Oxygenation reduces hypoxia-induced chemoreceptor activation of sympathetic tone, which can precipitate counterproductive arteriolar vasoconstriction [29]. Morphine can also reduce undesirable sympathetic activation by dampening the pain pathway [148,149]. Intravenous fluid resuscitation can reduce sympathetic tone by baroreceptor modulation [51]. Increased recognition of the role of maladaptive sympathetic bias in the pathogenesis of mesenteric ischemia may portend more active strategies to reduce sympatho-vagal ratio. Early evidence indicates that  $\beta$ -blockers may play a beneficial role in mesenteric ischemia [150].

Finally, we note that part of the benefit of thrombolytic and anti-coagulation therapies may be derived from anti-inflammatory and anti-adrenergic properties of the drugs. Teleologically driven functional overlap between inflammation and coagulation suggests that anti-coagulants and thrombolytics may have immunomodulatory properties [151,152]. Heparin has been found to promote T cell immunity [153], which can lower Th2 inflammation, and also lowers plasma aldosterone levels [154], a component of the broad sympathetic response. Aspirin has been shown to have both anti-thrombotic and anti-inflammatory properties [155]. Discoveries of anti-adrenergic and anti-inflammatory functions of other thrombolytics and anti-coagulants may be forthcoming. We anticipate continued broad usage of such drugs in the management of thromboembolic disorders.

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