Atrial fibrillation (AF), either in its paroxysmal or chronic form, is associated with an increased risk of systemic embolization. Currently, the only effective therapy to reduce this risk is long-term systemic anticoagulation. Such treatment comes at a considerable cost; approximately 3% of patients with nonvalvular AF receiving an oral anticoagulant experience major bleeding events that require hospital admission.1 Considering the often devastating sequelae of cerebral emboli and the potentially life-threatening side effects of chronic anticoagulation, it is alarming how little is known about the mechanisms linking AF to intraatrial thrombus formation. Although several randomized, prospective, nonvalvular AF trials have examined putative hemostatic markers of increased risk for thrombosis,2 knowledge of the etiology and pathophysiology of AF-induced thromboembolic complications has remained sketchy.

A new experimental study by Cai and co-workers3 published in this week’s issue of Circulation sets the stage for a better understanding of the mechanisms underlying thromboembolic events associated with AF. They discovered that 1 week of rapid pacing-induced AF in pigs is associated with a marked decrease in endothelial nitric oxide synthase (eNOS) expression, a reduction in production of nitric oxide (NO), and an increase in expression of plasminogen activator inhibitor 1 (PAI-1) in the left atrial endocardium. Because NO has antithrombotic properties, they concluded that loss of left atrial eNOS activity contributes to the thromboembolic events frequently associated with AF.

As innovative and thought provoking as this study is, and as plausible as this conclusion is in light of the well-established antithrombotic action of NO, some caution in interpreting its results is necessary.

First, we do not know whether the findings apply to other, clinically more relevant experimental models of AF, such as chronic AF caused by mitral valve regurgitation4 or AF associated with chronic heart failure.5 Measurements of NO production should and could be rapidly performed in these animal models of chronic AF to address this important issue. It is noteworthy that Cai and co-workers3 were unable to detect intraatrial thrombi during autopsy in pigs after 1 week of continuous atrial fibrillation. If thrombi were present, they might have embolized before death occurred, although the authors do not report signs or symptoms of emboli. Alternatively, the time period may have simply been too short to result in macroscopically detectable intraatrial thrombi. Interestingly, the authors mention that platelets adherent to the wall were seen only in sections of the endocardium that were deficient in eNOS. It is conceivable that these microthrombi may promote apposition of more platelets, ultimately leading to significant thrombus growth. In any event, the study would have benefited immensely from a thorough documentation of the frequency of both intraatrial thrombi and systemic embolizations. Similar investigations in the future should therefore incorporate these parameters as study endpoints. In addition to measurements of NO production using in vitro techniques, functional imaging of the heart using positron emission tomography or MRI can be used to examine the response of atrial blood flow/metabolism/contractility to interventions that alter atrial NO levels.6 These experiments should enable one to firmly establish a correlation between cardiac NO production and incidence of thromboembolic events in a variety of chronic AF models. Prospects of using genetically engineered mice toward this end, such as those lacking eNOS, are dim. Although short-duration (ie, a few seconds) AF can now be reproducibly induced in mice,7,8 induction of lasting AF remains, at least for now, restricted to larger mammals.

If these initial studies do indeed confirm an inverse relationship between atrial NO production and the incidence of thromboembolic complications, it will be necessary to investigate whether interventions aimed at increasing (or blocking) atrial NO synthesis can prevent (or augment) thromboembolic complications associated with AF. New tools enable researchers to address this important issue in a conclusive manner. Using novel techniques for catheter-based local delivery of adenosine, the effectiveness of transduction of the endocardial endothelium with a constitutively active eNOS9 to at least partially restore protection against AF-induced thrombus formation can be tested. Intrapericardial delivery of the NO donor diazeniumdiolated bovine serum albumin has only recently been demonstrated to significantly reduce flow-restricted coronary lesions after angioplasty in pigs.10 Whether intrapericardial delivery of this slow-release NO donor similarly results in sufficient NO concentration in the left atrial endocardium to exert local antithrombotic action, however, remains to be tested. Local delivery of NO donors should be preferred over systemic administration to avoid systemic effects, which may confound interpretation of the data. Intrapericardial L-arginine can also increase NO production.11

Beside its antithrombotic actions, NO produced by eNOS is involved in cardiomyogenesis,12 regulation of arterial tone,13 and modulation of cardiac electrophysiological prop-

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The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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and enzymes involved in glycolysis. Lack of NO would seem to be able to directly inhibit mitochondrial respiration overload during tachycardia/fibrillation. Additionally, NO deficiency may then accentuate cellular calcium from rapid atrial pacing-induced AF can be mimicked by acute atrial ischemia, lending some credibility to the possibility that reduced NO production may promote cardiomyocyte loss and fibrosis via induction of relative atrial ischemia. Furthermore, structural changes associated with chronic rapid atrial pacing could arise from relative atrial ischemia. Because NO from eNOS relaxes smooth muscle in small resistance arteries, it is expected that the atrial coronary vasculature deficient in NO cannot adequately respond to an increased energy demand, such as that occurring during atrial fibrillation. Jayachandran et al have previously demonstrated that the shortening of atrial refractoriness resulting from rapid atrial pacing-induced AF can be mimicked by acute atrial ischemia, lending some credibility to the possibility that reduced NO production may promote cardiomyocyte loss and fibrosis via induction of relative atrial ischemia. In further support of the potentially deleterious effects of chronic NO deficiency is the observation that eNOS-derived NO strongly regulates myocardial contractility and energetics. NO-induced inhibition of L-type calcium current (I_{Ca,L}) by cGMP-dependent and -independent mechanisms leads to less activation of the calcium-induced calcium release process, thereby reducing atrial contractility, and, consequently, energy consumption. NO-induced reduction of I_{Ca,L} may also act to protect cardiomyocytes from atrial tachycardia/fibrillation-induced calcium overload, which is emerging as a key player in the electrical remodeling process. Conversely, NO deficiency may then accentuate cellular calcium overload during tachycardia/fibrillation. Additionally, NO seems to be able to directly inhibit mitochondrial respiration and enzymes involved in glycolysis. Lack of NO would then increase oxygen consumption at any given workload, apparently reducing the efficiency of O_{2} utilization. It is tempting to speculate that reduced NO production compromises atrial energy balance, further promoting the progression of functional and structural changes that perpetuate AF. NO also attenuates sympathetic effects on cardiac atrioventricular nodal conduction and sinus node automaticity while enhancing parasympathetic effects. Whether increased sympathetic input to the atria resulting from atrial NO deficiency plays a role in the pathophysiology of chronic AF remains to be seen. Because the data by Cai and co-workers suggest a heterogeneous loss of NO production in the left atria, it is tempting to speculate that the spatial non-uniformity of NO levels leads to a corresponding pattern of sympathetic input. Heterogeneous sympathetic denervation promotes chronic atrial fibrillation in dogs, and rapid pacing-induced AF leads to an upregulation of atrial sympathetic innervation.

We know from clinical studies that the incidence of thromboembolic complications increases shortly after cardioversion of AF. Assuming that endocardial NO production resumes after successful cardioversion, it is conceivable that the increase in NO may then actually favor detachment of existing thrombi from the atrial wall, causing a paradoxical situation where restoration of sinus rhythm and the associated increase in NO levels may potentially be harmful to the patient.

Both reduced expression of eNOS and alterations in its function may have contributed to the decline in NO production in the left atrial endocardium. Because eNOS is known to be expressed within the heart in the endothelium of both the endocardium and the coronary vasculature (including capillary and venular endothelium), in atrial cardiomyocytes, and in specialized conduction tissue, NO production could have been reduced in one or several cell types simultaneously. Whereas little is known about transcriptional regulation of eNOS, it is well established that eNOS activity in endothelial cells and cardiomyocytes is tightly regulated by the concentration of free intracellular calcium ions (and calmodulin); increases and decreases in intracellular free calcium ([Ca^{2+}]_{i}) over the physiological range augment and reduce eNOS activity, respectively. As 1 week of incessant tachycardia can significantly decrease action potential-evoked intracellular calcium transients in canine atrial myocytes, it is possible that the reduction of atrial NO production in the study by Cai et al reflects a decrease in the average [Ca^{2+}]_{i} in cardiomyocytes of the fibrillating atria. Whether AF is associated with a chronic decrease in endothelial cell intracellular calcium concentration is currently unknown. Because atrial fibrillation in humans is associated with reduced potassium channel expression in atrial cardiomyocytes, it is conceivable that similar alterations can occur in endothelial cells. Changes in expression of functional potassium channels will influence [Ca^{2+}]_{i} by means of altering the electrical driving force for Ca^{2+} entry, which in turn will regulate NO production from eNOS in endothelial cells.

Integrative research into the regulation of cardiomyocyte and endothelial cell NO production from eNOS and its alteration in the diseased heart will undoubtedly contribute to a more in-depth understanding of the molecular events underlying atrial pathophysiology and help find new therapeutic modalities to prevent thromboembolic complications without imposing new risks to the patient. The study by Cai and co-workers will hopefully motivate basic researchers and clinicians to work toward these goals.
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References

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