Mechanisms of Stroke in Atrial Fibrillation

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KEYWORDS

• Atrial fibrillation • Stroke • Thromboembolism • Cardiac arrhythmia

KEY POINTS

- Atrial fibrillation (AF) is the most common form of arrhythmia and its prevalence is projected to increase. The risk of stroke in patients with AF is increased by 5-fold, and strokes in association with AF are more often fatal, disabling, and associated with greater morbidity and recurrence than other causes of stroke.
- The causes of thrombus formation in the context of AF are multifactorial and include changes in flow, atrial anatomy, prothrombotic alterations in blood constituents, and inflammation.
- Improved risk stratification is critical to distinguish which patients may be safely treated without anticoagulation.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder, affecting 1% to 2% of the general population.[1] Its incidence increases dramatically with age, from less than 0.5% at 40 to 50 years, to 10% in octogenarians.[2] The prevalence of AF is likely to increase even further over the next 50 years, mainly due to the increasing mean age of the general population, the obesity epidemic, and improvements in the management of cardiovascular disease, such that by 2050, sixteen million Americans are predicted to have AF.[1]

The yearly incidence of stroke in patients with nonvalvular AF is about 5%, which is 5 times higher than that in matched populations without any form of arrhythmia.[3] Strokes associated with AF are often fatal, and patients who survive are left more disabled, suffer greater morbidity, have longer hospital stays, are less likely to be discharged to their own homes, and are more likely to suffer a recurrence than patients with other causes of stroke. As a result, the risk of death from AF-related stroke is 2-fold that of stroke in patients without AF, and the cost of care is increased 1.5-fold.[4] Moreover, the risk of AF-related stroke mortality increases from 1.5% in those aged 50 to 59 years to 24% in those aged 80 to 89 years.

AF is a major public health problem because of the associated mortality, disability, and health care costs. The problem is amplified by the substantial nationwide undertreatment of patients who would benefit from anticoagulation for stroke prevention. According to one economic model, approximately 1.265 million patients with AF not receiving antithrombotic prophylaxis suffer 58,382 strokes annually with an associated total direct cost to Medicare of $4.8 billion.[5] Furthermore, early recognition and appropriate prophylaxis are hindered by the frequently

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asymptomatic nature of AF, occurring in at least one-third of patients. Consequently, earlier detection and more widespread recognition of patients likely to benefit from anticoagulation have the potential to reduce the rising burden of cardioembolic stroke in patients with AF.

PATHOPHYSIOLOGY OF THROMBUS FORMATION

Despite gaps in our knowledge, it is now clear that the pathogenesis of thrombus formation in AF is a multifactorial process that includes not only stasis in a poorly contractile left atrium, but also the presence of a prothrombotic or hypercoagulable state.[6] As reflected in Virchow triad, thrombogenesis in patients with AF occurs as a result of endocardial damage, blood stasis, and abnormal regulation of blood constituents responsible for clot formation and fibrinolysis (Fig. 1).

Prothrombotic Atrial Anatomy

The left atrial appendage (LAA) is by far the most common site of intra-atrial thrombus formation, both in patients with AF and in the presence of sinus rhythm. Among patients with AF presenting with stroke, LAA thrombus can be seen in approximately 23%.[7] The morphology of the LAA, a frequently long, narrow, and hooked extension of the left atrium, creates an anatomic substrate for blood stasis and thrombus formation. Interestingly, the shape of the LAA is highly variable between patients, and more complex lobular structures have been associated with a higher likelihood of thromboembolism in patients with AF, independent of other established stroke risk factors.[8]

Changes in the structure of the LAA can also be a consequence of AF. A wrinkled appearance attributable to edema and fibrinous transformation, as well as small areas of endothelial denudation and thrombotic aggregation, has been reported in patients with AF and stroke.[9] Further work has demonstrated the presence of myocytic hypertrophy and/or necrosis, as well as a mononuclear cell infiltrate, within the LAA in patients with AF. There is also mounting evidence that AF predisposes to alterations in collagen degradation products and impaired extracellular matrix degradation, which is also affected as a consequence of various AF-related comorbidities (most notably hypertension).[10] Such alteration of the extracellular matrix has been shown to induce fibrosis and infiltration of the endocardium and may be an additional factor associated intra-atrial thrombus formation. These structural changes could account, at least in part, for the delay in return of atrial systole after successful cardioversion or ablation. Such changes highlight the residual risk for thrombus formation and the importance of anticoagulation even after restoration of sinus rhythm.[11]

Abnormal Blood Stasis

Stasis in the setting of AF occurs not only because of loss of atrial systole but also in relation to left atrial dilatation. Atrial dilatation is a crucial risk factor for thrombogenesis, as indicated by the finding that atrial size corrected for body surface area is an independent risk factor for stroke.[12] Abnormal stasis in the left atrium and LAA can be visualized on transesophageal echocardiogram with spontaneous echo contrast (SEC), which is thought to reflect an increased interaction between fibrinogen and erythrocytes, and its presence is related to the relative concentrations of each, with more fibrinogen needed to induce the same SEC effect at lower hematocrit levels. SEC highly depends on flow rate and therefore is more likely to occur in patients in AF. Importantly, SEC can also be seen after restoration of sinus rhythm, occurring in up to 37% of such patients at 3 months.[13] Thus, the presence of an increased LA size and SEC demonstrable on echocardiography further illustrates the imperative to consider the residual risk of thrombus formation after sinus rhythm restoration.

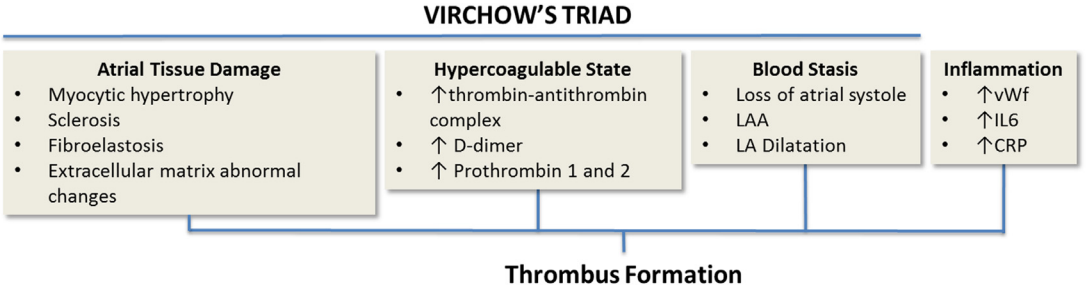

Fig. 1. Pathophysiological mechanisms underlying thrombus formation in AF.