Atrial Fibrillation and Thrombogenesis
Innocent Bystander or Guilty Accomplice?*

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Atrial fibrillation (AF) is the most common sustained clinical arrhythmia and its incidence is increasing with projections exceeding 10 million by 2050 (1). It is associated with increased mortality and morbidity, the most devastating outcome being thromboembolic stroke. AF is detectable in 25% to 30% of patients with cryptogenic stroke (2–4), and the concept of AF as a direct cause of stroke has been a long-standing tenant in the practice of medicine. However, AF is also highly associated with increasing age and comorbidities that are independent causes of stroke (e.g., hypertension). As such, AF may simply be a marker of severity of underlying conditions that cause stroke as opposed to an active participant in stroke pathogenesis. This concept, although unpopular at first, is gaining significant momentum with recent data from large randomized controlled trials demonstrating no temporal correlation whatsoever between AF episodes and stroke events (5–7).

Rudolph Virchow’s 1856 initial description of factors associated with pulmonary embolism includes interrupted blood flow, vessel damage, and abnormal coagulation. The modern interpretation of this “triad” has been extended to thrombosis and consists of blood stasis, endothelial damage, and hypercoagulability; all of which are present in AF. Blood stasis, evidenced by reduced left atrial appendage flow velocities, is present in AF and is associated with spontaneous echo contrast and thrombus formation (8). AF leads to loss of laminar blood flow and reductions in velocity and shear stress that are known to cause down-regulation of nitric oxide synthase and endothelial dysfunction (9,10). In addition to decreased left atrial nitric oxide bioavailability, AF may predispose to thrombosis by increasing plasminogen activator inhibitor-1 expression (11). Further evidence for hypercoagulability in AF is provided in early studies demonstrating increased levels of platelet aggregation, release products, and surface antigens in patients with AF compared with those with sinus rhythm (12). More recently, examination of a defined duration of AF in patients who served as their own control subjects revealed that short episodes of AF increase cardiac platelet activation, thrombin generation, and endothelial dysfunction (13). This protocol was subsequently reproduced to extend the findings to the left atrium (14). Thus, AF provides plausible biological mechanisms for thrombogenesis, and it is associated with both comorbidities that equally offer such plausible mechanisms. The extent to which AF independently contributes to stroke risk, over and beyond the traditional risk factors, is unclear.

In this issue of JACC: Clinical Electrophysiology, Lim et al. (15) attempted to further assess the relative contribution of the arrhythmia itself versus comorbidities to the thrombogenic process. They compared control patients with no history of AF to those with lone AF and others with AF and comorbidity. AF burden was adjusted for by using continuous monitoring to exclude more than 30 s of AF in the 48 h prior to the study. The CHA2DS2-VASc score is not indicated, but hypertension appears to be the main risk factor that differentiated the 2 AF groups. The investigators demonstrate an increase in markers of platelet activation, thrombosis, and endothelial dysfunction in the AF groups, but these findings are difficult to interpret in the clinical context. Although there was a gradient of platelet activation and thrombin generation between the atria and

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The peripheral circulation of AF patients, there was no difference in the degree of atrial platelet activation and thrombin generation between the AF and control groups. Furthermore, it is well known that the risk of stroke is highly and independently associated with age. There was a significant difference in age among the study groups that was not adjusted for and which may explain the prothrombotic findings independent of rhythm or any other comorbidity. It is also unclear from a pathophysiological standpoint why the AF patients would have selective and persistent left atrial platelet activation and thrombin generation, given that they were completely free of any recent AF. The findings of endothelial dysfunction also require a mechanistic explanation. A stepwise increase in asymmetric dimethylarginine levels was observed among control, lone AF, and AF with comorbidity groups, which is consistent with an incremental effect of rhythm and comorbidity to endothelial dysfunction. However, in each group, asymmetric dimethylarginine levels were similar in the atria and periphery, indicating a state of persistent global endothelial dysfunction despite the lack of recent AF. In patients with comorbidities, this may be due to the underlying disease processes. But how can it be explained in arrhythmia-free “lone AF” patients?

One potential explanation lies in the possibility that the lone AF group may have subclinical comorbidity that is unmeasured and unadjusted, but that is the cause of biomarker elevation. Thus the underlying inflammatory and prothrombotic processes that lead to “lone AF” may, in fact, independently lead to a prothrombotic state in the absence of AF itself. Therefore, at least to some extent, AF may simply be a marker of an underlying inflammatory, fibrotic, and prothrombotic condition, as opposed to being the direct cause. This raises the question of whether much of the classification of “lone AF” is in reality related to a subclinical or unmeasured comorbidity (16). It would explain the lack of clinical correlation between AF episodes and stroke (5–7) and would also explain the prothrombotic state found in “lone AF” patients in the current study despite the documented lack of recent arrhythmia.

The association among AF, comorbidities, and stroke is unequivocal and has been recognized for decades, but the relative contribution of each remains unknown. Determining the underlying cause(s) of this inflammatory, profibrotic, and prothrombotic state in patients with “lone AF” and no other “comorbidity” is critical for our understanding. In the meantime, the old question remains whether AF is an innocent bystander that is a marker of comorbidity severity or a guilty accomplice that contributes to thrombogenesis.

REFERENCES


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