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Atrial Fibrillation and Mechanisms of Stroke: Time for a New Model

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Introduction

Thirty-three million people have atrial fibrillation (AF), a disorder of heart rhythm.[1] Over the past several decades, we have learned that this dysrhythmia originates in the interplay between genetic predisposition, ectopic electrical activity, and abnormal atrial tissue substrate, and then feeds back to remodel and worsen tissue substrate and thereby propagate itself.[2] Although the importance of AF partly derives from its strong association with ischemic stroke, there have not been as many advances in our understanding of the mechanisms of stroke in AF. Current views rest on a century-old hypothesis that fibrillation of the atrium produces stasis of blood, which causes thrombus to form and embolize to the brain. When other abnormalities are acknowledged to play a role, the dysrhythmia is still considered the primary cause of thromboembolism.[3] While this formulation is intuitively appealing, recent work suggests that the pathogenesis of stroke in AF is more complicated and involves factors in addition to the dysrhythmia.

Possible Stroke Mechanisms in Atrial Fibrillation

AF and stroke have been associated in rigorous studies,[4] indicating a true association rather than a spurious finding. Epidemiological logic suggests three explanations: 1) AF causes stroke, 2) stroke causes AF, and/or 3) AF is associated with other factors that cause stroke.

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Atrial Fibrillation as a Cause of Stroke

To help judge whether one factor *causes* another or whether the two are simply correlated, the epidemiologist Bradford Hill proposed the following widely accepted criteria: 1) strength of association, 2) consistency, 3) specificity, 4) temporality, 5) biological gradient, 6) plausibility, 7) coherence, 8) accordance with experimental results, and 9) analogy.[5] The relationship between AF and stroke fulfills several of these criteria. Patients with AF face a *strongly* elevated risk of stroke—about 3- to 5-fold higher after adjustment for risk factors.[4] AF has been *consistently* associated with stroke in different cohorts.[6] And a causal association is *biologically plausible*. Intuitively, uncoordinated myocyte activity would explain the impaired atrial contraction seen in AF, and by Virchow's triad, the resulting stasis of blood should increase thromboembolic risk.

However, several other Hill criteria do not support a straightforward relationship between AF and stroke. Although many studies have found a *biological gradient* between AF burden and stroke,[7-10] this is not consistent across all studies.[11] Furthermore, a single brief episode of subclinical AF is associated with a 2-fold higher risk of stroke in older patients with vascular risk factors,[12] while young and otherwise healthy patients with clinically apparent AF do not face a significantly increased stroke risk.[13] These conflicting data do not suffice to establish a clear biological gradient between the burden of AF and the risk of stroke.

The relationship between AF and stroke also fails Hill's criterion of *specificity*. If AF causes thromboembolism, it should be specifically associated with embolic strokes. There does appear to be an especially strong association between AF and embolic strokes.[14] However, 10% of patients with lacunar strokes have AF,[14] and large-artery atherosclerosis is twice as common in patients with AF as those without.[15] The link between AF and non-cardioembolic stroke indicates that stroke risk in AF cannot be entirely explained by AF directly causing stroke.

Third, the association between AF and stroke does not fully satisfy Hill's criterion of *temporality*. A recent case-crossover analysis indicated an increased risk of stroke shortly after the onset of AF.[16] On the other hand, two other recent studies found that approximately one-third of patients with both AF and stroke do not manifest any AF until after their stroke, despite undergoing many months of continuous heart-rhythm monitoring before the stroke.[17, 18] These findings suggest that although the dysrhythmia itself can cause thromboembolism, the strong association between AF and stroke also involves other factors.

Fourth, a causal interpretation of the association between AF and stroke does not adequately fit the available *experimental* evidence. If the dysrhythmia is the only cause of thromboembolism, maintaining normal rhythm should eliminate stroke risk. However, in a meta-analysis of eight randomized clinical trials, a rhythm-control strategy had no effect on stroke risk (odds ratio, 0.99; 95% confidence interval, 0.76-1.30).[19] It is unlikely that this simply reflected a failure to reliably maintain sinus rhythm, because rhythm-control strategies showed substantial success in maintaining normal sinus rhythm (odds ratio, 4.39; 95% confidence interval, 2.84-6.78). Furthermore, the structural remodeling seen in experimental models of AF occurs after at least a week of sustained rapid pacing,[20] so any

atrial changes *caused* by AF are unlikely to explain the association between a single 6-minute episode of AF and a heightened risk of stroke in humans.[12] Therefore, robust experimental evidence is lacking to indicate that AF is a *necessary* step in thrombogenesis.

Stroke as a Cause of Atrial Fibrillation

Central nervous system injuries often affect the autonomic nervous system, which plays an important role in the pathogenesis of AF.[21] And necrotic cell death from stroke activates a systemic inflammatory response, which also plays a role in the origin of AF.[22] Clinical observations support the hypothesis that stroke may trigger AF. Strokes affecting cerebral autonomic centers seem particularly associated with new-onset AF that lacks accompaniments of long-standing AF such as left atrial enlargement.[23] However, other clinical findings argue against this hypothesis,[24] and even if stroke can trigger AF, this pathway cannot explain the well-documented association between AF and future stroke.[4, 6]

Atrial Fibrillation-Associated Factors as Causes of Stroke

Besides *causing* stroke, AF may also be associated with *other factors* that cause stroke. Age, male sex, hypertension, diabetes mellitus, valvular heart disease, heart failure, coronary heart disease, chronic kidney disease, inflammatory disorders, sleep apnea, and tobacco use are risk factors for both AF and stroke. Confounding in the AF-stroke association is indicated by its attenuation as more shared risk factors are accounted for.[4, 6] Nevertheless, AF remains independently associated with stroke even after seemingly thorough adjustment for shared risk factors. And AF is associated not just with stroke in general, but most strongly with strokes whose neuroimaging patterns resemble that of cardiac embolism.[25]

Even if the origin of stroke in AF is accepted to be the left atrium, *other atrial factors* in addition to AF may cause thromboembolism. Rather than being the only cause of atrial thromboembolism, could AF sometimes be a marker of other atrial abnormalities that are themselves the actual cause of stroke? AF frequently co-exists with atrial abnormalities such as endothelial dysfunction,[26] fibrosis,[27] impaired myocyte function,[28] chamber dilatation,[29] and mechanical dysfunction in the left atrial appendage.[30] These abnormalities have been documented in both experimental animal models[26] and in humans.[27-30] Such factors have been associated with stroke risk in patients with AF[31]—could these atrial abnormalities also arise independently of AF and cause stroke? If so, they should be associated with stroke even in the absence of AF. Indeed, premature atrial contractions,[32] paroxysmal supraventricular tachycardia,[33] ECG-defined left atrial abnormality,[34-36] and left atrial size[37-39] have been associated with stroke independently of AF (Table 1). Markers of atrial dysfunction are specifically associated with cryptogenic or embolic stroke and not with in-situ cerebral small-vessel occlusion,[34, 36, 38] indicating that these markers signal a specific risk of atrial thromboembolism rather than general vascular risk.

Might these associations be mediated by AF? Left atrial abnormalities may reflect abnormal atrial substrate, which causes paroxysmal and difficult-to-detect AF, which then causes stroke.[37, 39] However, adjustment for clinically apparent AF does not change the association between left atrial abnormalities and stroke[34-36]—an unexpected finding if AF mediates their relationship. Another interpretation of these associations is that subclinical AF causes

abnormal atrial substrate, which then causes stroke. In this interpretation, AF is again *required* for downstream changes to occur and result in thrombogenesis. However, structural remodeling seems to require weeks of AF,[20] not just the 6 minutes that suffice to signify an increased stroke risk.[12] Such inconsistencies undermine the concept of AF as the sole cause of the atrial abnormalities that have been associated with stroke. These associations and their lack of attenuation after adjustment for AF suggest that atrial disease causes thrombogenesis via additional pathways besides AF. Proof of principle is offered by a homozygous mutation of the natriuretic peptide precursor A gene. Even though AF is absent, this disorder leads to atrial dilatation, progressive loss of atrial activity with eventual atrial standstill, and thromboembolism.[45]

Updated Model for the Mechanisms of Stroke in Atrial Fibrillation

Given the findings above, the mechanistic basis of stroke in patients with AF is likely to be more complex than currently appreciated. An up-to-date model must emphasize systemic and atrial *substrate* as well as rhythm (Figure 1). Aging and systemic vascular risk factors cause an abnormal atrial tissue substrate, or atrial cardiopathy, that can result in AF and/or thromboembolism. For atrial cardiopathy to play such a role in thrombogenesis would be analogous to the ventricular cardiopathy seen in myocardial infarction and heart failure, two diseases in which thromboembolism can occur even in the absence of dysrhythmia. Once AF develops, the dysrhythmia causes contractile dysfunction and stasis, which further increases the risk of thromboembolism. In addition, over time the dysrhythmia causes structural remodeling of the atrium, thereby worsening atrial cardiopathy and increasing the risk of thromboembolism even further. In parallel, systemic risk factors increase stroke risk via other mechanisms outside the atrium, such as large-artery atherosclerosis, ventricular systolic dysfunction, and in-situ cerebral small-vessel occlusion. Once stroke occurs, autonomic changes and post-stroke inflammation may transiently increase AF risk.

This updated model largely resolves the inconsistencies between the Hill criteria and recent data on the association between AF and stroke. If AF and thromboembolism occur as parallel but separate downstream effects of atrial cardiopathy, then AF can increase thromboembolic risk but is *not necessary* for thromboembolism to occur, so the timing and burden of dysrhythmia need not be coupled with the timing and burden of stroke. Under this construct, it would not be surprising that a brief period of AF is associated with stroke months later[12] or that one-third of patients with AF and stroke do not manifest AF until after their stroke.[17] An atrial substrate model also explains the lack of *specificity* between AF and embolic stroke. AF patients often have non-embolic strokes because AF serves as a marker of upstream systemic vascular risk factors. Lastly, a substrate model accords with *experimental* evidence and explains the otherwise puzzling observation that rhythm-control treatments do not eliminate stroke risk.[19] If AF is only a *secondary* contributor to abnormal atrial tissue substrate, successful elimination of the dysrhythmia will not eliminate the thrombogenic potential of the underlying atrial cardiopathy.

Implications of an Updated Model of Stroke

By placing atrial cardiopathy alongside AF as a cause of thromboembolic stroke, an updated model may help explain why one-third of strokes have no known cause.[46] Many cryptogenic strokes are suspected to arise from cardiac embolism, but only one-third of these patients manifest AF even after 3 years of continuous heart-rhythm monitoring.[47] Since we currently conceive of AF as the *sine qua non* of atrial thromboembolism, we may be failing to recognize cases that occur in the absence of AF and incorrectly labeling these strokes cryptogenic.

An updated model of stroke and AF may lead to better strategies for identifying thromboembolic risk in patients with established AF. Assessing markers of abnormal atrial tissue substrate in addition to the burden of upstream vascular risk factors may better identify the few patients with truly *lone* AF who do not face a substantial risk of stroke.[13] An updated model may also allow better screening for thromboembolic risk in the general population without known AF. AF screening is important but has been hampered by the difficulty of prolonged heart-rhythm monitoring. Assessment of atrial substrate by a standard ECG or echocardiogram can be done at a single point in time, and may help augment AF screening efforts.

A substrate model has several implications for therapeutic strategies to prevent stroke. The perception that the dysrhythmia is the only cause of thromboembolism often makes providers and patients reluctant to continue anticoagulant therapy during stretches of normal sinus rhythm.[3] A greater emphasis on the atrial cardiopathy that led to AF in the first place, and which persists even if sinus rhythm returns, may reinforce the importance of continuing proven anticoagulant treatments. Similarly, recognition of atrial cardiopathy highlights the findings from randomized clinical trials that rhythm-control therapies, such as catheter ablation of AF, should not be viewed as a stand-alone form of thromboprophylaxis.[19]

An updated model implies that treatments to reverse abnormal atrial substrate, not just to restore normal rhythm, may be beneficial in reducing thromboembolic risk. Underlying risk factors such as obesity and the metabolic syndrome promote AF and atrial cardiopathy through numerous mechanisms.[48] Local epicardial fat is increasingly recognized as a contributor to local inflammation in the atrium, while obesity-induced obstructive sleep apnea raises intra-atrial pressures.[49] Intensive vascular risk factor management after AF ablation appears to improve the underlying atrial substrate.[50] Therefore, future trials may be warranted to assess whether treatment of atrial substrate reduces stroke risk. In addition, if AF is a downstream marker of vascular risk factors that separately produce non-atrial stroke mechanisms such as carotid atherosclerosis or cerebral small-vessel disease, a comprehensive approach to stroke prevention should explore and emphasize intensive management of all risk factors, rather than just focusing on recommendations regarding anticoagulant therapy. Current guidelines on AF do not emphasize global risk factor management.[51]

A substrate model also has implications for stroke prevention in patients *without* AF. If AF serves as a marker of thrombogenic atrial substrate, the benefit seen with anticoagulant

drugs in AF may extend to patients with atrial cardiopathy but no AF. Randomized trials comparing anticoagulant versus antiplatelet therapies may be warranted in patients with markers of atrial cardiopathy and no evidence of AF.

Many of the studies that found associations between atrial cardiopathy and stroke used consensus definitions of biomarker thresholds, but more work is required to determine whether additional markers, such as cardiac magnetic resonance imaging of tissue fibrosis and computed tomographic assessment of left atrial appendage morphology, may better identify the risk of atrial thromboembolism. Combined with further research on the benefits of anticoagulation for varying degrees of atrial cardiopathy, such work would allow for a consensus definition of atrial cardiopathy to aid clinical decision making.

Conclusion

The prevailing model of AF and thromboembolism is likely incomplete. A straightforward association between AF and stroke does not convincingly demonstrate temporality, specificity, or a biological gradient, and it is not concordant with the totality of the available experimental evidence. A model in which thromboembolism is caused by both AF *and* abnormal systemic and atrial tissue substrate better fits the available data. Such a model has several important implications for stroke prevention strategies. By emphasizing systemic and atrial *substrate* in addition to *rhythm*, it points to new strategies for identifying and treating patients at risk of thromboembolism. Further research to test this model and the various strategies it suggests may result in improvements in stroke care and a reduction in the burden of this disabling disease, which accounts for 10% of deaths worldwide.

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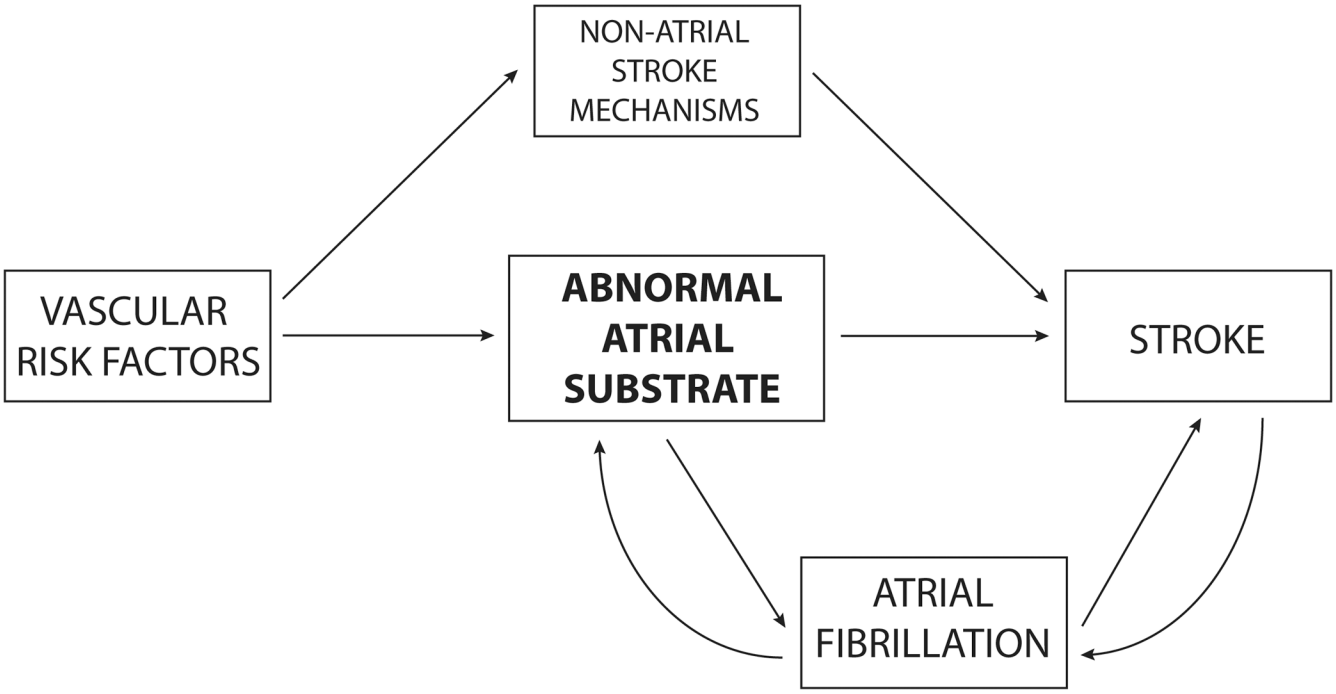

Figure 1.

Updated Model of Thromboembolic Stroke. This model emphasizes the importance of systemic and atrial *substrate* as well as rhythm in explaining the relationship between atrial fibrillation (AF) and stroke. In this model, aging and systemic vascular risk factors cause an abnormal atrial tissue substrate, or atrial cardiopathy, that can result in AF and/or thromboembolism. Once AF develops, the dysrhythmia causes contractile dysfunction and stasis, which further increases the risk of thromboembolism. In addition, over time the dysrhythmia causes structural remodeling of the atrium, thereby worsening atrial cardiopathy and increasing the risk of thromboembolism even further. In parallel, systemic risk factors increase stroke risk via other mechanisms outside the atrium, such as large-artery atherosclerosis, ventricular systolic dysfunction, and in-situ cerebral small-vessel occlusion. Once stroke occurs, autonomic changes and post-stroke inflammation may transiently increase AF risk.

Table 1

Studies Demonstrating an Association between Markers of Abnormal Atrial Substrate and Incident Stroke Independently of Atrial Fibrillation

Marker	Authors	Year	Outcome	Association	
				Not Adjusted for AF	Adjusted for AF
ECG markers					
Frequent PACs	Binici et al[40]	2010	Stroke	1.79 (1.14-2.81)*	1.73 (1.09-2.75)*
PSVT	Kamel et al[33]	2013	Stroke	N/A	2.10 (1.69-2.62)†
$PTFV_1$	Kamel et al[35]	2014	Stroke	1.22 (1.03-1.45)‡	1.21 (1.02-1.44)‡
$PTFV_1$	Kamel et al[41]	2014	Infarct§	1.09 (1.04-1.16)‡	1.09 (1.04-1.15)‡
Frequent PACs	Larsen et al[32]	2015	Stroke		2.00 (1.16-3.45)//
$PTFV_1$	Kamel et al[34]	2015	Non-lacunar stroke	1.44 (1.04-1.99)#	1.49 (1.07-2.07)#
$PTFV_1$	Kamel et al[36]	2015	Cryptogenic or cardioembolic stroke	1.28 (1.07-1.53)‡	1.31 (1.08-1.58)‡
Echocardiographic markers					
Left atrial size	Benjamin et al[37]	1995	Stroke	N/A	2.4 (1.6-3.7)**
Left atrial size	Di Tullio et al[39]	1999	Stroke	N/A	1.47 (1.03-2.11)††
Left atrial size	Karas et al[42]	2012	Stroke	N/A	1.35 (1.12-1.62)‡‡
Left atrial size	Yaghi et al[38]	2015	Cryptogenic or cardioembolic stroke	N/A	1.55 (1.01-2.37)‡‡
Left atrial volume	Barnes et al[43]	2004	Stroke	N/A	1.63 (1.08-2.46)§§
Left atrial volume	Russo et al[44]	2013	Infarct	N/A	1.37 (1.04-1.80)////
Left atrial function	Russo et al[44]	2013	Infarct	N/A	0.67 (0.50-0.90)##

Abbreviations: AF, atrial fibrillation; ECG, electrocardiographic; PACs, premature atrial contractions; PSVT, paroxysmal supraventricular tachycardia; $PTFV_1$, P-wave terminal force in lead V_1

*Hazard ratio (HR) and 95% confidence interval (CI) for the primary outcome of death or stroke.

†HR (95% CI) associated with a diagnosis of PSVT.

‡HR (95% CI) per 1-standard deviation (SD) increase in $PTFV_1$.

§Infarct refers to silent brain infarcts detected on magnetic resonance imaging.

//HR (95% CI) associated with excessive PACs, defined as ≥30 PACs per hour.

#HR (95% CI) associated with ECG-defined left atrial abnormality ($PTFV_1$ ≥4,000 ms*μV).

** HR (95% CI) per 10-mm increase in left atrial size in men. The association was not significant in women (HR, 1.4; 95% CI, 0.9-2.1).

†† Odds ratio (OR) and 95% CI per 10 mm/1.7 m^2 increase in the left atrial diameter divided by body surface area (left atrial index).

‡‡ HR (95% CI) per 1-SD increase in left atrial size.

§§ HR (95% CI) for left atrial volume ≥32 ml/m^2.

//// HR (95% CI) per 1-SD increase in left atrial minimum volume.

OR (95% CI) for each 1-SD increase in the left atrial ejection fraction.