

Potential Role of Atrial Myopathy in the Pathogenesis of Stroke in Rheumatoid Arthritis and Psoriasis: A Conceptual Framework and Implications for Prophylaxis

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Patients with chronic systemic inflammatory diseases (including those with rheumatoid arthritis [RA] and psoriasis) are at increased risk of stroke.¹ However, this risk cannot be explained by an increased prevalence of traditional cardiovascular risk factors that lead to accelerated atherosclerosis.² Additionally, inflammatory involvement of the cerebral arteries is not an important contributor to acute ischemic cerebrovascular disease in these patients.³ Instead, the systemic inflammatory process that characterizes both RA and psoriasis may cause adverse structural and functional changes in the walls of the atria, particularly in the left atrium (LA).⁴ The resulting inflammation-related atrial myopathy leads to blood stasis, thrombus formation, and thromboembolic stroke.

RA and Psoriasis Increases the Risk of Stroke

Compared with those without RA, patients with RA have a 60% to 100% increase in the risk of ischemic stroke.^{5,6} The magnitude of the increased risk is particularly striking if afflicted individuals are younger than 65 years; their risk of stroke is increased 3-fold.^{7,8} RA not only increases the risk of an initial stroke, but it increases the risk of recurrent stroke.⁹ Importantly, the increase in stroke risk greatly exceeds that predicted by the presence of traditional cardiovascular risk factors; instead, its magnitude parallels the clinical severity and duration of the arthritic disease and the intensity of systemic inflammation.^{2,10–13}

Similarly, psoriasis is accompanied by a 60% to 100% increase in the risk of ischemic stroke.^{14–16} The increase in

stroke is particularly striking in those who are young or have clinically severe disease, and the intensity of systemic inflammation greatly enhances the risk of stroke.^{15–19} As in the case of RA, the risk of stroke exceeds that expected from traditional cardiovascular risk factors,²⁰ suggesting that the enhanced risk of stroke is not likely to be related to accelerated atherosclerotic disease. Instead, stroke appears to be linked to the occurrence of systemic thromboembolism.^{18,21}

Is Atrial Fibrillation the Cause of Increased Risk of Stroke in Rheumatoid Arthritis and Psoriasis?

Atrial fibrillation (AF) is an important risk factor for the occurrence of stroke in the general community. Is it possible that both RA and psoriasis increase the risk of stroke because the 2 disorders promote the development of AF?

Increased Risk of AF in RA and Psoriasis

Systemic inflammation predicts the occurrence of AF in the community.²² Not surprisingly, RA increases the incidence of AF by 25% to 50%,^{23–25} and this risk is evident even after adjustment for risk factors for AF (eg, hypertension).²⁴ There is a strong parallelism between the incidence of AF and that of stroke in patients with RA in epidemiological studies.²⁶ Analogously, psoriasis increases the incidence of AF by 25% to 50%^{21,27,28}; the risk is particularly apparent in those who are younger and have clinically severe disease and is accompanied by an increased risk of systemic thromboembolism.^{16,29,30} The development of AF may represent an extension of the systemic inflammatory process to the atria.⁴

Is There a Causal Relation Between AF and the Occurrence of Stroke?

Is the increase in stroke in patients with RA and psoriasis related to the increased incidence of AF? Physicians have long believed that the chaotic contraction that is characteristic of AF drives thrombus formation; however, it is the decreased

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flow velocity in the LA attributable to an underlying atrial myopathy that predisposes to thromboembolization,³¹ explaining why mitral regurgitation protects against the stasis of blood in the LA even though it increases the risk of AF by promoting LA dilatation.³² The inflammatory and fibrotic process in the LA is a primary determinant of the impairment of the chamber's conduit functions, even in the absence of AF³³; in addition, inflammation and fibrosis may directly enhance the thrombogenicity of the atrial endocardium.³⁴ Accordingly, atrial fibrosis predisposes to the occurrence of LA thrombus formation and stroke, independently of LA chamber size.³⁵

Doubts about the primacy of AF in causing stroke have been reinforced by the results of longitudinal studies that utilized continuous electrocardiographic monitoring devices to detect AF in patients at risk for or with a history of stroke. In these studies, at-risk patients generally did not exhibit evidence of AF in the month preceding the occurrence of stroke.^{36,37} Patients who suffered a thromboembolic stroke manifested AF only very rarely and transiently,³⁸ and in many patients, AF was observed only after the cerebrovascular event.³⁹ Importantly, in a randomized controlled trial in 2718 patients who had implantable devices that would allow for continuous remote monitoring of their cardiac rhythms, the use of anticoagulants guided by the presence or absence of AF in individual patients at risk did not prevent thromboembolic events.⁴⁰

Furthermore, pharmacological control or procedural abolition of AF does not reduce the risk of stroke in large-scale randomized controlled clinical trials. Randomized controlled trials that have compared rate-control and rhythm-control strategies in patients with established AF have demonstrated no reduction in the risk of systemic thromboembolism or stroke in patients assigned to rhythm control, even though these patients had a reduced burden of AF.⁴¹ Paradoxically, the rhythm-control group experienced an increased risk of thromboembolic events,⁴² possibly because oral anticoagulation was discontinued in some patients, based on the mistaken belief that AF (rather than the atrial myopathy) was the primary driver of stroke. Finally, abolition of AF by catheter ablation did not reduce the risk of stroke in a large-scale randomized controlled trial; in this study, oral anticoagulation therapy was maintained, although it was not likely to be in the therapeutic range in many patients.⁴³

Importantly, the severity of LA disease drives the risk of stroke and vascular brain injury in patients, with or without AF.^{44,45} Accordingly, in patients who do not have risk factors that reflect the existence of an atrial myopathy, the risk of stroke in patients with AF is similar to that in patients without AF.^{34,46} Furthermore, current risk scores that are to guide the use of oral anticoagulants (which identify patients with an atrial myopathy) predict the occurrence of stroke, even in

patients without AF,⁴⁷ and in patients with high risk scores, the risk of thromboembolic events that is determined by the atrial myopathy is not increased further by the presence of AF.⁴⁸ Accordingly, AF may simply be a biomarker for the severity of the underlying inflammation-related atrial myopathy.^{44–46,49}

It is noteworthy that among individuals with known AF, the rate of stroke in patients with RA and psoriasis is greater than can be explained by the conventional CHA₂DS₂-VASc score that is used to guide the use of oral anticoagulants,¹⁸ presumably because it does not incorporate measures of systemic inflammation or assessments of the severity of the atrial myopathy.

Importance of Atrial Myopathy in Rheumatoid Arthritis and Psoriasis

The concept that many patients with RA and psoriasis have an undiagnosed atrial myopathy is strongly supported by the available evidence. These patients frequently show abnormalities of electrical activation in the atria, and derangements in atrial geometry and filling, particularly affecting the LA.^{50–54} Changes in LA structure progress more rapidly in patients with RA than in the general population.⁵⁵ The magnitude of these abnormalities closely parallels the severity of clinical inflammation (Figure).

Pathogenesis of Atrial Disease in Systemic Inflammatory Disorders

The systemic inflammation in both RA and psoriasis is accompanied by coronary microvascular dysfunction as well as fibrosis; these abnormalities are related to the disease severity and duration, but are not explained by traditional

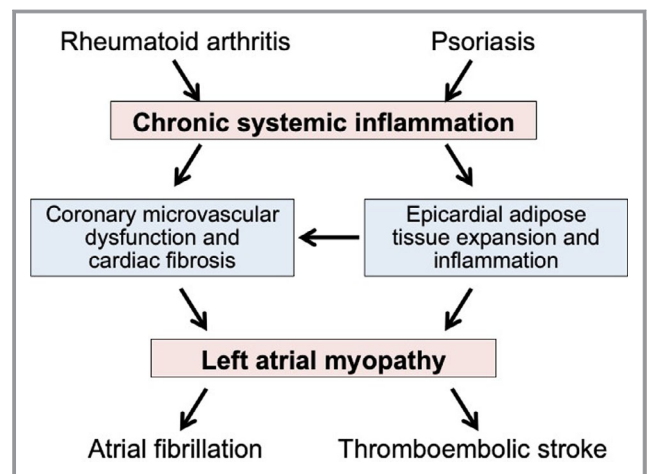


Figure. Proposed pathways by which rheumatoid arthritis and psoriasis can lead to an increased risk of ischemic stroke.

cardiovascular risk factors.^{56–60} Changes in LA geometry are directly linked to the intensity of systemic inflammation.⁶¹ In addition, the systemic inflammatory process in both RA and psoriasis can be transmitted to the adipose tissue residing in the epicardium, thereby expanding its mass and transforming its biology into a proinflammatory state. The secretion of proinflammatory adipocytokines from this epicardial fat depot can cause microcirculatory injury and fibrosis in the underlying tissues, particularly the atrial myocardium.^{62,63}

These observations explain several important findings. First, both RA and psoriasis are associated with an expansion of epicardial adipose tissue mass that is proportional to the clinical severity of the disease but independent of body mass.^{64–66} Second, in patients with AF, there is a close association between the thickness and inflammatory state of epicardial fat and the severity of electrical abnormalities in the adjacent myocardium.⁶⁷ Accordingly, epicardial fat volume predicts the incidence of AF in the community even in the absence of cardiovascular disease.⁶⁸ Epicardial adipose tissue mass increases as AF evolves from a paroxysmal to a persistent arrhythmia.⁶⁹ Third, there is a strong association between epicardial adipose tissue mass and derangements in LA geometry and function,^{70,71} potentially explaining why an expansion of epicardial adipose tissue presages an exaggerated risk of thromboembolic events.⁷²

Conventional and Novel Approaches to Stroke Prevention in Patients With RA and Psoriasis

The current approach to stroke prevention in RA and psoriasis resembles that in other disorders, that is, control of traditional cardiovascular risk factors (particularly hypertension) and the judicious use of oral anticoagulation in patients who have elevated CHA₂DS₂-VASc risk scores. However, as noted above, the CHA₂DS₂-VASc risk score does not incorporate information about systemic inflammation, and thus, it underestimates the risk of thromboembolic events in patients with RA and psoriasis.¹⁸ Some have proposed that the CHA₂DS₂-VASc risk score be multiplied in patients with a systemic inflammatory disorder.⁷³ Conceivably, oral anticoagulants might prevent stroke in patients with systemic inflammatory disorders who demonstrate an atrial myopathy, even without AF; however, randomized controlled trials supporting such an approach are lacking.

Role of Rhythm Control in Preventing Stroke in RA and Psoriasis

The available evidence suggests that the presence and severity of an atrial myopathy—and not AF—is the primary

driver of the risk of stroke. Accordingly, a role of rhythm control in preventing stroke in patients with RA and psoriasis who have AF has not been demonstrated. As noted earlier, randomized controlled trials that have compared rate-control and rhythm-control strategies in patients with established AF have shown no reduction in the risk of systemic thromboembolism or stroke in patients assigned to rhythm control, even though these patients had a reduced burden of AF.⁴¹ Most strikingly, catheter ablation can abolish AF for meaningful periods of time in many patients, but those with an atrial myopathy are at increased risk of AF recurrence,⁷⁴ and ablation adds to the preexisting fibrotic burden of the left atrium, further compromising chamber capacitance and its transport function.⁷⁵ The atrial injury produced by ablation has important thrombogenic effects, explaining why the procedure itself carries a high immediate risk of systemic thromboembolism.⁷⁶ Importantly, there was no reduction in stroke risk in the CABANA (Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation) trial, even though AF was controlled more effectively in the patients who had ablation than those receiving antiarrhythmic drugs.⁴³

Role of Anti-Inflammatory Agents in Preventing Stroke in RA and Psoriasis

If systemic and epicardial adipose tissue inflammation leading to the development of an atrial myopathy is responsible for an increased risk of stroke, then other opportunities emerge for stroke prevention in RA and psoriasis. Although some work has identified potential proinflammatory mediators,^{62,63,77,78} the systemic inflammatory process (regardless of cause) can be targeted by disease-modifying biological anti-inflammatory agents; their use has been accompanied by a reduced risk of stroke in both RA^{79,80} and psoriasis.^{81,82} In contrast, the risk of stroke may be increased by the use of glucocorticoids,^{83,84} possibly because they have additional effects to promote adverse cardiac remodeling and thus exacerbate the atrial myopathy. Glucocorticoids can alter calcium kinetics in cardiomyocytes and can signal through mineralocorticoid receptors to promote myocardial inflammation and fibrosis.^{85–87} The adipogenic effects of glucocorticoids may also enhance epicardial adipose tissue mass and its deleterious biological effects.⁸⁸

Can the epicardial adipose tissue inflammation be targeted directly to reduce the risk of stroke? Interestingly, statins exert anti-inflammatory effects independent of their actions to lower serum cholesterol, and these actions may be sufficient to treat the arthritic and dermatological manifestations of RA and psoriasis, respectively.^{89–92} Statins can also reduce the mass and inflammatory state of epicardial adipose tissue,^{93,94} which may explain their actions to alleviate inflammation and the development of atrial myopathy.^{95–97} The use of statins is

accompanied by a decrease in the risk of AF in randomized controlled trials^{98,99} and with a reduced likelihood of thromboembolic stroke in observational studies.^{100,101} The utility of statins in preventing systemic thromboembolism in patients with RA and psoriasis has yet to be fully evaluated.

Conclusions

Both RA and psoriasis are accompanied by an increased risk of stroke, which cannot be explained by an increased prevalence of traditional cardiovascular risk factors that are focused on atherosclerosis. Instead, the risk of stroke is likely to be related to an effect of systemic inflammation to promote the development of an atrial myopathy, resulting in blood stasis within the LA, thrombus formation, and systemic thromboembolism. The systemic inflammatory process in RA and psoriasis can directly impair the integrity of the endothelium of the coronary microcirculation of the atrial myocardium. In addition, systemic inflammation can cause expansion of the epicardial adipose tissue adjacent to the LA; the secretion of proinflammatory adipocytokines from the epicardial fat depot can exaggerate the adverse structural and functional changes in the LA, leading to the atrial myopathy that provides the substrate for thromboembolic stroke. Interventions that are directed toward alleviation of the atrial myopathy and the resulting risk of thrombus formation are worthy of further evaluation in reducing the burden of cerebrovascular disease in patients with RA and psoriasis.

Disclosures

Dr Packer has recently consulted for Abbvie, Actavis, Akcea, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiorentis, Daiichi Sankyo, Gilead, Johnson & Johnson, NovoNordisk, Pfizer, Relypsa, Sanofi, Synthetic Biologics, and Theravance. None of these relationships are relevant to the topic of this manuscript.

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