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EDITORIAL COMMENT

# Left Atrial Stiffness in Cryptogenic Stroke

## On Solid Footing or Down the Rabbit Hole?*

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Cryptogenic stroke, or embolic stroke of uncertain source, accounts for ~20% of all ischemic strokes worldwide.[1] Recently, the presence of atrial myopathy has been proposed as a factor potentially associated with cryptogenic stroke.[1,2] The atrial myopathy hypothesis of cryptogenic stroke relies on the assumption that inflammatory and fibrotic changes in the atrium are associated with thrombus formation, followed by cerebral embolization. Indeed, prior research has associated components of atrial myopathy, including increased left atrial (LA) size, LA fibrosis, and premature atrial contractions, with cryptogenic stroke.[3,4]

Speckle-tracking echocardiography, or strain imaging, is a critical component of LA myopathy evaluation. While the macroscopic manifestations of LA myopathy are oftentimes identified late in the disease course, subclinical, or early-stage, LA myopathy may manifest via impairments in LA reservoir, conduit or booster strain.

In this issue of *JACC: Advances*, Sindre et al[5] performed a case-control analysis of the multicenter SECRETO (Searching for Explanations for Cryptogenic Stroke in the Young: Revealing the Etiology, Triggers, and Outcome) cohort to investigate the association between LA stiffness, another marker of LA myopathy, and cryptogenic stroke. The primary results of this study are as follows: 1) presence of LA stiffness, defined as ([mitral E/e']/LA reservoir strain) >0.22 was associated with a >2-fold increase in cryptogenic stroke; 2) higher degrees of LA stiffness were associated with greater likelihood of cryptogenic stroke; 3) factors associated with LA stiffness in cryptogenic stroke patients included obesity, use of antihypertensive medication, greater age, and lower LA contractile strain; and 4) cryptogenic stroke was also associated with lower LA reservoir strain and LA reservoir work. The authors therefore concluded that the presence of LA stiffness is a risk factor for cryptogenic stroke and that management of risk factors including obesity and hypertension may mitigate this increased risk.[5] This study adds to the literature by presenting another subclinical echocardiographic measure associated with cryptogenic stroke. However, the reader should be mindful of important considerations when interpreting the results of this retrospective study.

To date, there are limited data on successful prevention and management strategies for cryptogenic stroke. Among patients with cryptogenic stroke and patent foramen ovale (PFO), meta-analyses demonstrate that closure of the PFO is associated with a lower rate of recurrent stroke.[6] Although the SECRETO protocol required transesophageal echocardiography for participant inclusion, the prevalence of PFO in the SECRETO cohort is not reported in the current study. It is therefore not possible to fully exclude PFO as a cause of cryptogenic stroke in this population.

When stroke is the endpoint of a study, proper adjudication of atrial fibrillation (AF) is of paramount importance. While there are observational studies of patients with cardiac devices capable of continuous rhythm monitoring which suggest that stroke may occur in the absence of a recent, or any, episode of AF,[7,8] these prior analyses did not account for potential confounding variables that also predispose to stroke, differentiate the impact of short-vs long-episodes of AF on rates of stroke, or adjudicate mechanism of stroke.[9] Indeed, more contemporary analyses

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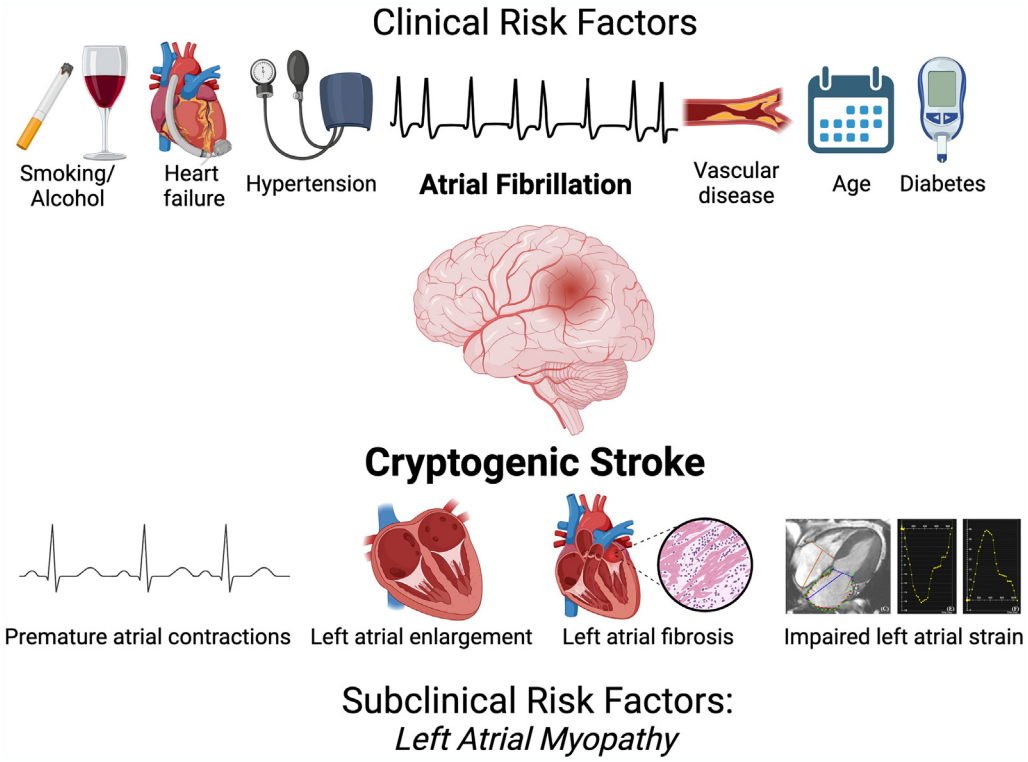
**FIGURE 1** Left Atrial Myopathy and Cryptogenic Stroke




Cryptogenic stroke is a heterogeneous disease with multiple clinical risk factors. Growing evidence suggests left atrial electrical and mechanical dysfunction (ie, LA myopathy) are associated with cryptogenic stroke. Whether LA myopathy, independent of atrial fibrillation, is causally related to cryptogenic stroke remains unclear. LA = left atrial.

of stroke and AF tell a different story. Specifically, a recent study of stroke patients with a cardiac implantable electronic device, in which each patient served as their own control, demonstrated a significantly higher odds ratio of stroke in the 30 days following AF onset, with the highest risk of stroke occurring within 5 days of AF initiation, thus establishing that risk of stroke is strongest shortly after AF onset.[10] Furthermore, a separate analysis of >20,000 CIED (cardiac implantable electronic device) patients demonstrated a threshold of AF duration, measured in hours, that confers an increased risk of stroke.[11] In light of these contemporary data, it is therefore important to comprehensively evaluate for the presence of occult AF in any study evaluating ischemic stroke.

The likelihood of diagnosing AF when present is directly proportional to the time of monitoring.[12] In the present study, preexisting AF was determined with a single 24-hour ambulatory rhythm monitor, which carries only ~20% or ~40% sensitivity for detection of low- and high-burden AF, respectively.[13] Importantly, patients who suffered a cryptogenic stroke did not undergo prolonged ambulatory rhythm monitoring poststroke in the SECRETO cohort. As >10% of patients may have AF on continuous rhythm monitoring within 12 months after cryptogenic stroke, it is therefore possible that patients with occult AF were included in the analytic cohort. This bias is compounded by the fact that patients with a history of AF, even at low burden, have lower LA reservoir strain in sinus rhythm than those without AF.[14] For these reasons, it cannot be fully ruled out that the association between LA stiffness and cryptogenic stroke is confounded by a history of AF.

The importance of excluding AF in cryptogenic stroke is further highlighted due to differences in management strategies based upon AF status. Although patients with known AF who suffer a stroke benefit from oral anticoagulation, broader populations of cryptogenic stroke patients without AF who receive anticoagulation do not appear to have reduced risk of recurrent stroke.[15] Furthermore, results of the ARCADIA (Atrial Cardiopathy and

Antithrombotic Drugs in Prevention After Cryptogenic Stroke) trial, which randomized patients with signs of LA myopathy (defined as: abnormal p wave amplitude, elevated serum NT-proBNP (N-terminal pro-B-type natriuretic peptide), or enlarged LA diameter index) and no clinical history of AF to apixaban or aspirin, similarly demonstrated no benefit of anticoagulation for secondary prevention of stroke. The authors should be congratulated on bringing attention to the potential utility of LA stiffness as an echocardiographic measure of LA myopathy. Specific analyses to determine whether anticoagulation benefits those with cryptogenic stroke and abnormal LA strain or stiffness would be informative.

The data in this retrospective analysis demonstrate an association between obesity, use of antihypertensive medication, and LA stiffness. Based on these associations, along with the primary outcome of LA stiffness predicting cryptogenic stroke, the authors conclude that treatment of obesity and hypertension may reduce the risk of stroke. Prevention of obesity and hypertension are key pillars of preventive cardiology, and the current findings further highlight potential importance of preventing these cardiometabolic comorbidities even in young and middle-aged adults. Whether treatment of obesity and hypertension can fully mitigate risk of recurrent stroke and whether the benefits of weight loss and blood pressure control toward reducing stroke risk are fully mediated by improved LA stiffness are both unknown.

Despite searching for a unifying cause, current data suggest that the etiology of cryptogenic stroke is multifactorial. LA myopathy has become an increasingly recognized entity to be associated with cryptogenic stroke (**Figure 1**). The authors should therefore be applauded for investigating this subclinical marker and furthering our understanding of the complex relationship of LA function and stroke. Nonetheless, it remains unclear if LA myopathy truly causes stroke, independent of AF. Further investigations, potentially leveraging human genetic instruments of LA dysfunction or animal models of atrial myopathy,[16] are required to comprehensively understand if the relationship between LA myopathy and stroke is causal, and therefore worthy of direct therapeutic targeting.

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**KEY WORDS** cryptogenic, left atrium, myopathy, stroke