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EDITORIAL COMMENT

Left Atrial Strain to Address the Cryptogenic Puzzle*

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The quantification of left atrial structure and function from speckle tracking echocardiography or with cardiac magnetic resonance identifies the presence of subclinical atrial disease and predicts incident heart failure, atrial fibrillation (AF), stroke, and other thromboembolic events among asymptomatic individuals, among patients with a history of atrial fibrillation, and in the general population. Individuals at increased risk of AF, in particular, are more likely to benefit from targeted anticoagulation therapy (1,2). It would seem logical, therefore, that the use of left atrial strain could help in the improved stratification of patients at increased risk of future AF and who may benefit from targeted therapy or increased monitoring. In this issue of *iJACC*, the likelihood of identifying such a subgroup of patients among patients with cryptogenic stroke is the subject of a study by Pathan et al. (3).

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Cryptogenic stroke usually refers to strokes with no clearly defined etiology, is seen in as many as 30% to 40% of ischemic strokes, and commonly is either embolic or nonembolic in etiology among other rarer pathophysiologic mechanisms (4). Therefore, in a large proportion of patients with strokes, there is no identifiable cause, and their treatment is complicated. The lack of an identifiable cause could result from inexact timing or incomplete diagnostic strategies, but could also be due to the fact that the cause is undiscovered as of yet. Although identification of the exact cause can be difficult, the identification of impaired left atrial function could have implications beyond identification of those at risk of AF, as left atrial strain has shown prognostic value for thromboembolic events, heart failure, and other cardiovascular events (5).

In the study by Pathan et al. (3), the authors evaluated 658 patients who had an echocardiogram (transthoracic echocardiogram [TTE]) following presentation with cryptogenic cerebrovascular events. The TTEs were evaluated for reservoir, contractile, and conduit atrial strains using speckle tracking of 2- and 4-chamber long-axis images, in addition to left atrial volume and other standard echocardiographic parameters. In the follow-up to identify participants who developed atrial fibrillation over 5 years, the authors find that left atrial strain adds independent and incremental predictive value to risk scores—CHARGE-AF (Framingham Heart Study and Cohorts for Heart and Aging Research in Genomic Epidemiology Atrial Fibrillation) and CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65 to 74 years, sex category). The reservoir and contractile function were found to have independent and incremental value over the 2 clinical risk scores used for the prediction of the 61 participants who went on to develop AF. The authors additionally used a Classification and Regression Tree algorithm to identify cutoff values of strain and the risk scores that best stratified the participants into different groups of AF risk. They identify a high-risk group with low reservoir strain and high conduit strain, while also recognizing a low-risk group with high reservoir function and low CHARGE-AF risk score.

In retrospective analysis of prospectively collected data (prospective nonconcomitant studies), there are a few design weaknesses including: 1) the use of multiple vendors for TTE, which is known to result in variations across participants; 2) not all participants had atrial-specific images; and 3) the ascertainment of AF

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was not uniform and is directly linked to the cardiac investigations performed. Yet, the authors should be commended for a well-performed study, that furthers the study of atrial myopathy in those with cerebrovascular disease, adding to the growing body of evidence showing that subclinical atrial disease, not yet manifest as AF, could already be present in a significant proportion of those with cryptogenic stroke. However, extension of the current work to future prospective concomitant studies is key to validating the cutoffs used for the Classification and Regression Tree algorithm (6) (external validation), and to understanding if the CHARGE-AF and CHA_2DS_2-VASc risk scores (developed in populations different from the current study) are indeed optimal.

This study also highlights the usefulness and elegance of left atrial strain, yet again, in the prediction of AF. Left atrial maximum volume has long been used as a marker of both left atrial structure and function (1). With the advent of speckle tracking echocardiography and feature-tracking magnetic resonance imaging, quantification of left atrial strain and left atrial emptying fractions was made easy. Both strain and emptying fractions are seen to be more closely associated with electrical abnormalities (7), left ventricular fibrosis and dysfunction (8), left atrial myopathy (9,10), and filling pressures (11). In addition, they are also superior as prognostic indicators of incident AF (12-14), heart failure (15), cardiovascular events and stroke (16), and mortality (17) in the general population, stroke after catheter ablation in patients with AF (18), recurrence of AF (19), and post-stroke mortality (20).

Left atrial strain has been used in those with ischemic stroke and specifically, in cryptogenic stroke patients, including the prediction of AF (20). The authors here extend the study of left atrial mechanics to also study conduit and contractile function in addition to reservoir function. Particularly interesting is the identification of a high-risk group characterized by low reservoir function and high conduit function (perhaps also reflective of low booster pump function). It is important to recognize that left atrial strain measures could reflect left atrial myopathy and left ventricular performance. For the sake of simplicity, left atrial function can be roughly broken down to 3 time periods: 1) reservoir function corresponds to atrial filling during ventricular systole and is largely governed by atrial compliance; 2) conduit function when the left atrium acts as a conduit for pulmonary venous return for ventricular filling during early diastole is governed by atrioventricular pressure gradients, ventricular compliance, and atrial compliance; and 3) atrial booster pump function which largely corresponds to atrial contractility. The 3 phases, however, are strongly interlinked with total left atrial emptying fraction (reservoir) representing the summation of the passive (conduit) and active (booster pump, contractile) functions (1).

This study supports the contention that left atrial strain is essential for efficient characterization of left atrial performance, and is a promising tool for guiding therapies in cryptogenic stroke, where a lack of understanding of the underlying cause hampers efficient therapy. Further prospective studies are required to verify this discovery, before incorporation into risk stratification and decision-making strategies. Considerable data also support the use of left atrial strain and function for predicting cardiovascular events and AF in several disease states and in the general populations. However, an understanding of the longitudinal evolution of strain in large populations and prospective outcome trials are needed to understand the complex evolution of left atrial functional components and confirm the incremental predictive ability of left atrial strain. Some of the challenges and needed advances include standardization across different imaging modalities, understanding vendor differences in data acquisition and analyses techniques, a consensus on reference values for left atrial strain across age, sex, and race categories, and a greater understanding of the evolution of left atrial myopathy and how therapies can restore left atrial function.

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