

## EDITORIAL COMMENT

# Atrial Fibrillation and Myopathy Predisposing to Stroke and Dementia



## What Came First, Chicken or Egg?\*

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**A**trial fibrillation (AF) is the most frequent sustained cardiac arrhythmia, with a prevalence of 0.4% to 1% in the general population and 9% in the elderly, carrying high morbidity and mortality.<sup>1</sup>

Importantly, the presence of AF is associated with a fivefold increased risk of stroke, which represents the first manifestation of AF in 2% to 5% of patients.<sup>2</sup> Its genesis has been attributed to left atrial (LA) appendage thrombi formation as a result of blood stasis, with subsequent dislodgement and embolization to the brain. AF has also shown to be correlated with various forms of dementia, independent of history of stroke. The pathophysiology is likely multifactorial and has not been fully explained.<sup>3</sup> One plausible mechanism may be repetitive microclots/macroclots embolization, chronically leading to brain dysfunction. In fact, previous studies showed a reduction in the incidence of dementia in AF patients properly treated with anticoagulation<sup>4</sup> or undergoing effective and early ablation of AF.<sup>5</sup> This would suggest a shared pathophysiology for dementia and stroke as connected to atrial disease.

For years, the atrial blood stasis due to AF has been acknowledged as the mechanism of AF-related thromboembolism<sup>6</sup>; however, recent evidence has suggested the presence of atrial myopathy (AM) as an alternative hypothesis. AM is defined as “any

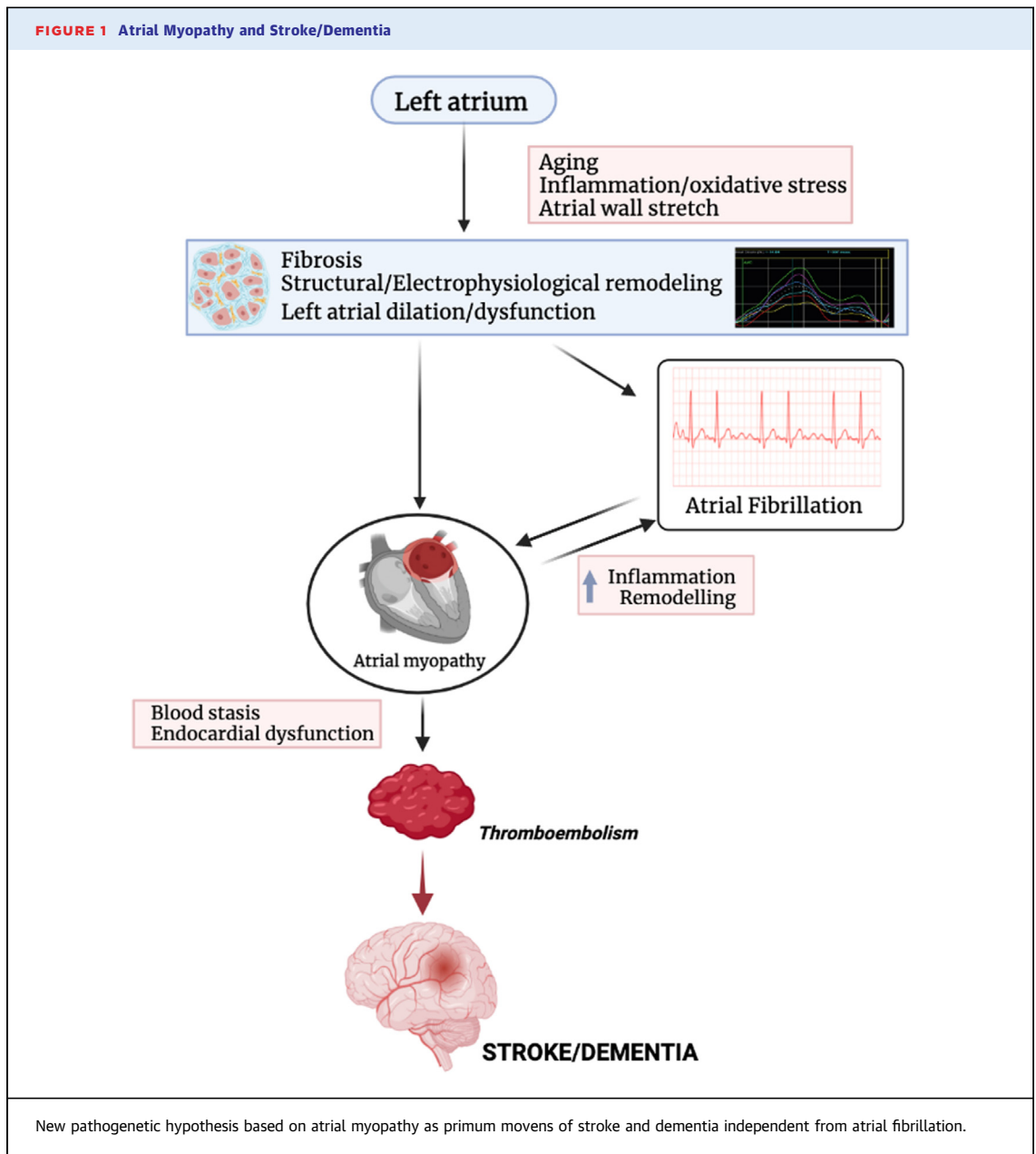
complex of structural, architectural, contractile, or electrophysiological changes affecting the atria with the potential to produce clinically relevant manifestations” and appears with LA dysfunction and dilation.<sup>7</sup> Emerging evidence suggests that thromboembolism can occur in AM even without AF.<sup>8</sup> However, AM and AF are strictly correlated with a cause-consequence relationship. In fact, LA fibrosis, characterizing AM, affects LA compliance and function and often leads to AF.<sup>9</sup> Furthermore, AF and the subsequent hemodynamic overload may elicit atrial remodeling, stiffness, and fibrosis, leading to AM.<sup>10</sup>

Although cardiac magnetic resonance is the gold standard method to assess the extent of fibrosis, speckle tracking echocardiography (STE) has emerged as a noninvasive, quicker, and more available alternative technique. The study of LA deformation, called “strain”, offers important information on early modification of LA structure and function and predicts the occurrence and persistence of AF.<sup>11</sup> LA strain has shown high sensitivity in identifying wall fibrosis and increased atrial stiffness as compared to cardiac magnetic resonance<sup>12</sup> and biopsy assessment.<sup>13</sup> Patients with paroxysmal AF showed increased LA stiffness measured by STE indices compared to controls.<sup>14</sup> Also, LA strain provided additional information on acute embolisms over CHA<sub>2</sub>DS<sub>2</sub>-VASc score in patients with paroxysmal/permanent AF.<sup>15</sup> Given these promising results, some researchers used STE to focus on AM as lone disease and not just as a “collateral” or consequent finding of AF, likely being the primary cause of unfavorable events traditionally attributed to AF. In fact, Sade et al<sup>16</sup> demonstrated that a reduction in LA strain could stratify AF risk in patients with cryptogenic stroke. Moreover, in low-risk general population, a reduction in LA reservoir strain was an independent predictor of long-term risk of AF and ischemic stroke, as demonstrated by

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Alhakak et al.<sup>17</sup> These studies suggest that LA strain may be used to study LA fibrosis and stiffness characterizing AM, which may drive the risk of stroke independent of AF. Therefore, one should consider that AM itself may lead to AF, but it could also be a consequence of AF, providing higher severity to the disease (Figure 1). Nevertheless, no author has considered the possible influence of underlying AM in increasing the risk of ischemic stroke and dementia in patients with AF.

In this issue of *JACC: Advances*, we find an interesting study addressing this question. Zhang et al<sup>18</sup> investigated the association between AF, stroke, and

dementia, adjusted for echocardiographic parameters of AM. After adjusting for LA reservoir strain, they found that the apparent association between AF and incident stroke and dementia lost its strength and statistical significance. The large number of patients and accurate methods for the analysis represent main strength of this study. Limitations of the study include the older age of the cohort and heterogeneity in the methods used to detect stroke, dementia, and AM. One other limitation is the definition of AM, as there is no consensus or standardization for the echocardiographic definition of AM. In this study, the authors used STE parameters that, despite having

been shown to have high sensitivity for atrial structural rearrangements and fibrosis, are not currently regarded as the gold standard for detecting AM. However, LA strain was recommended as an additional parameter to detect diastolic dysfunction in heart failure with preserved ejection fraction in the latest recommendations of the European Association of Cardiovascular Imaging.<sup>19</sup> Furthermore, considering that the mechanism hypothesized by Zhang et al<sup>18</sup> for the association between AM and stroke is based on the presumption that impaired LA compliance predisposes to the formation of LA thrombi, LA strain is likely the right parameter to evaluate AM as a sensitive index of LA deformation. However, the latest American College of Cardiology consensus on heart failure with preserved ejection fraction does not mention LA strain in the diagnostic evaluation.<sup>20</sup> This may be due to the more general and clinical overview provided by this document, unlike the European Association of Cardiovascular Imaging paper, which is focused on multimodality imaging, or to the need for more evidence on LA strains as marker of diastolic function to standardize its use.

Considering its feasibility and increasing availability, LA strain may improve risk stratification for stroke and dementia in clinical practice. This may lead to alternative indications for anticoagulation treatment for primary prevention of stroke, not only extending the indication to patients without AF at high risk of stroke but also addressing whether to prescribe anticoagulants in patients with AF in “grey-zone” risk categories for stroke according to current indices. However, the current study is based on observational data, and randomized controlled trials with safety/efficacy data on AM as lone indication to anticoagulation are eagerly awaited in the future.

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