JACC: ADVANCES VOL. 2, NO. 5, 2023

EDITORIAL COMMENT

Atrial Fibrillation and Myopathy Predisposing to Stroke and Dementia

What Came First, Chicken or Egg?*

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Atrial 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.[1]

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.[2] 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.[3] 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[4] or undergoing effective and early ablation of AF.[5] 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[6]; 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.[7] Emerging evidence suggests that thromboembolism can occur in AM even without AF.[8] 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.[9] Furthermore, AF and the subsequent hemodynamic overload may elicit atrial remodeling, stiffness, and fibrosis, leading to AM.[10]

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.[11] LA strain has shown high sensitivity in identifying wall fibrosis and increased atrial stiffness as compared to cardiac magnetic resonance[12] and biopsy assessment.[13] Patients with paroxysmal AF showed increased LA stiffness measured by STE indices compared to controls.[14] Also, LA strain provided additional information on acute embolisms over CHA_2DS_2-VASc score in patients with paroxysmal/permanent AF.[15] 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[16] 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

*Editorials published in *JACC: Advances* reflect the views of the authors and do not necessarily represent the views of *JACC: Advances* or the American College of Cardiology.

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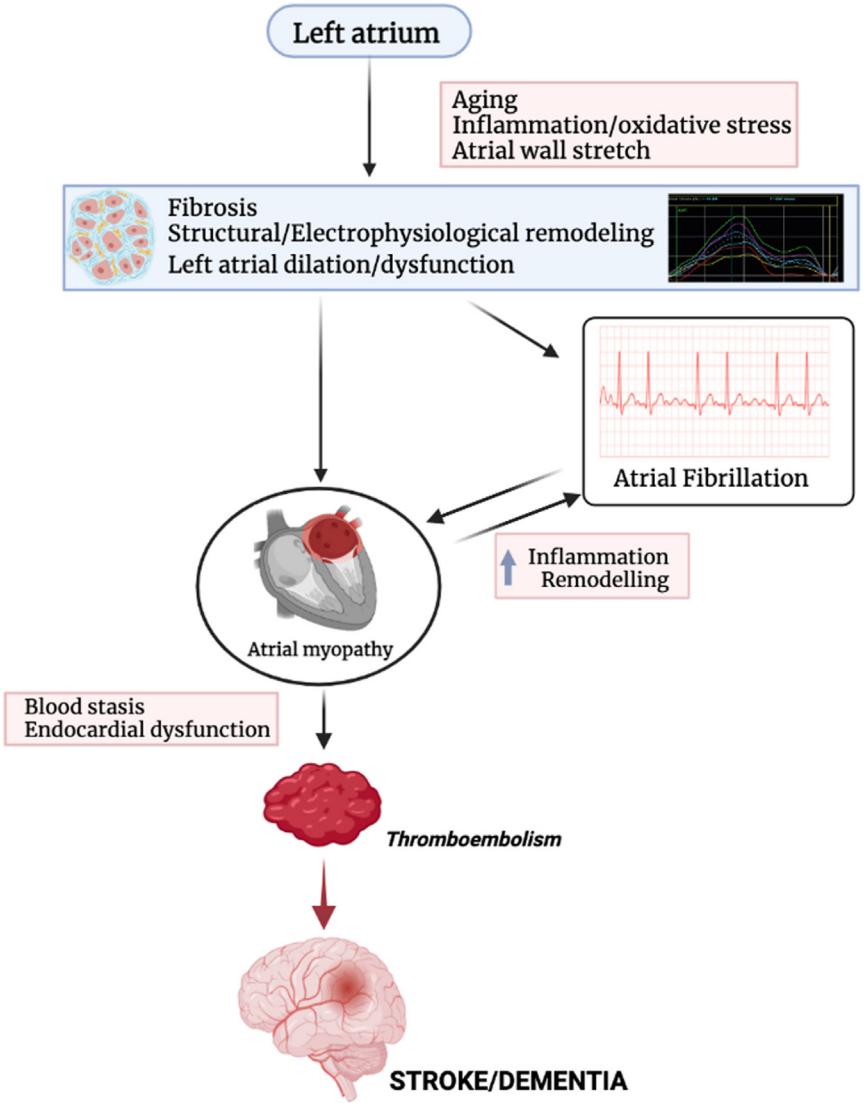
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2023.100427

FIGURE 1 **Atrial Myopathy and Stroke/Dementia**



New pathogenetic hypothesis based on atrial myopathy as primum movens of stroke and dementia independent from atrial fibrillation.

Alhakak et al.[17] 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[18] 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.[19] Furthermore, considering that the mechanism hypothesized by Zhang et al[18] 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.[20] 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.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2019;74(1):104–132.

2. Lubitz SA, Yin X, McManus DD, et al. Stroke as the initial manifestation of atrial fibrillation: the Framingham Heart study. *Stroke*. 2017;48(2):490–492.

3. Bunch TJ. Atrial fibrillation and dementia. *Circulation*. 2020;142(7):618–620.

4. Friberg L, Rosenqvist M. Less dementia with oral anticoagulation in atrial fibrillation. *Eur Heart J*. 2018;39(6):453–460.

5. Jin MN, Kim TH, Kang KW, et al. Atrial fibrillation catheter ablation improves 1-year follow-up cognitive function, especially in patients with impaired cognitive function. *Circ Arrhythm Electrophysiol*. 2019;12(7):e007197.

6. Watson T, Shantsila E, Lip GY. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet*. 2009;373(9658):155–166.

7. Goette A, Kalman JM, Aguinaga L, et al. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Heart Rhythm*. 2017;14(1):e3–e40.

8. Brambatti M, Connolly SJ, Gold MR, et al. Temporal relationship between subclinical atrial fibrillation and embolic events. *Circulation*. 2014;129(21):2094–2099.

9. Triposkiadis F, Pieske B, Butler J, et al. Global left atrial failure in heart failure. *Eur J Heart Fail*. 2016;18(11):1307–1320.

10. Miller JD, Aronis KN, Chrispin J, et al. Obesity, exercise, obstructive sleep apnea, and modifiable atherosclerotic cardiovascular disease risk factors in atrial fibrillation. *J Am Coll Cardiol*. 2015;66(25):2899–2906.

11. Cameli M, Mandoli GE, Loiacono F, Sparla S, Iardino E, Mondillo S. Left atrial strain: a useful index in atrial fibrillation. *Int J Cardiol*. 2016;220:208–213.

12. Kuppahally SS, Akoum N, Burgon NS, et al. Left atrial strain and strain rate in patients with paroxysmal and persistent atrial fibrillation: relationship to left atrial structural remodeling detected by delayed-enhancement MRI. *Circ Cardiovasc Imaging*. 2010;3(3):231–239.

13. Lisi M, Mandoli GE, Cameli M, et al. Left atrial strain by speckle tracking predicts atrial fibrosis in patients undergoing heart transplantation. *Eur Heart J Cardiovasc Imaging*. 2022;23(6):829–835.

14. Yoon YE, Kim HJ, Kim SA, et al. Left atrial mechanical function and stiffness in patients with paroxysmal atrial fibrillation. *J Cardiovasc Ultrasound*. 2012;20(3):140–145.

15. Obokata M, Negishi K, Kurosawa K, et al. Left atrial strain provides incremental value for embolism risk stratification over CHA_2DS_2-VASc score and indicates prognostic impact in patients with atrial fibrillation. *J Am Soc Echocardiogr*. 2014;27(7):709–716.e4.

16. Sade LE, Keskin S, Can U, et al. Left atrial mechanics for secondary prevention from embolic stroke of undetermined source. *Eur Heart J Cardiovasc Imaging*. 2022;23(3):381–391.

17. Alhakak AS, Biering-Sørensen SR, Møgelvang R, et al. Usefulness of left atrial strain for predicting incident atrial fibrillation and ischaemic stroke in the general population. *Eur Heart J Cardiovasc Imaging*. 2022;23(3):363–371.

18. Zhang MJ, Ji Y, Wang W, et al. Association of atrial fibrillation with stroke and dementia accounting for left atrial function and size. *JACC Adv*. 2023;2:100408.

19. Smiseth OA, Morris DA, Cardim N, et al. Multimodality imaging in patients with heart failure and preserved ejection fraction: an expert consensus document of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2022;23(2):e34–e61.

20. Kittleson MM, Panjrath GS, Amancherla K, et al. 2023 ACC expert consensus decision pathway on management of heart failure with preserved ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2023;81(18):1835–1878.

KEY WORDS atrial fibrillation, atrial myopathy, dementia, left atrium, stroke