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Review article

ATRIAL CARDIOMYOPATHY AND STROKE PREVENTION - REVIEW

Blagovest Stoimenov, Ralitsa Pancheva
Department of propaedeutics of internal diseases, UMHAT "Alexandrovska"; Medical Faculty, Medical University - Sofia, Bulgaria.

ABSTRACT:

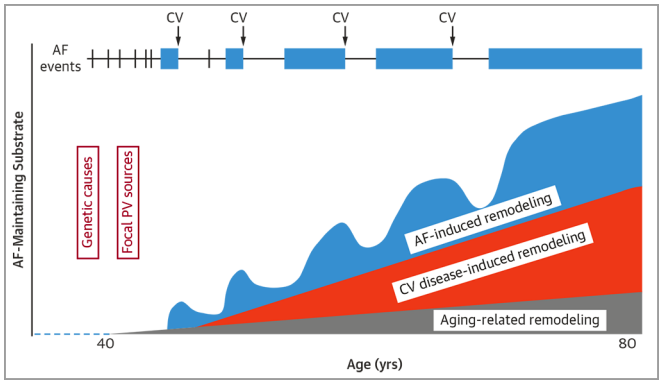
Atrial cardiomyopathy (ACM) represents a novel paradigm in cardiovascular medicine, encompassing structural and functional changes within the atria that contribute to adverse clinical outcomes, notably stroke. This review explores the multifaceted implications of ACM, particularly its relevance independent of atrial fibrillation (AF) and its potential applications in stroke prevention and management. Advancements in imaging modalities, notably speckle-tracking echocardiography, offer valuable insights into atrial remodeling and dysfunction, facilitating early detection of ACM. Markers such as P-wave terminal force, NT-proBNP levels, and left atrial dimensions serve as diagnostic indicators for ACM, aiding in risk stratification in individuals devoid of AF history. Ischemic strokes are one of the most common causes of cardiovascular morbidity and mortality. A significant proportion of patients with ischemic stroke are suspected of embolic stroke without a specific embolic source being found (ESUS). The most recent related clinical trials evaluated tailored anticoagulation strategies in ACM-associated stroke, signaling a shift beyond conventional AF management. In conclusion, ACM emerges as a pivotal concept in stroke prevention, offering opportunities for personalized interventions and refined risk stratification beyond AF.

Keywords: Atrial Cardiomyopathy, Atrial fibrillation, Stroke prevention, Embolic stroke of undetermined source, LA strain,

BACKGROUND

Atrial cardiomyopathy (ACM) is an underdiagnosed and poorly studied condition that was recently defined by the European Heart Rhythm Association as: "Any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically relevant manifestations [1] ACM was sub-classified into four classes: (I) principal cardiomyocyte changes, (II) principally fibrotic changes, (III) combined cardiomyocyte pathology and fibrosis, and (IV) primarily non-collagen infiltration (with or without cardiomyocyte changes) [1] The term cardiomyopathy was introduced by Brigden in 1957 [2] when he proposed it "to indicate isolated non-coronary myocardial disease." Since then, heart-muscle diseases have been termed cardiomyopathies, and the term has been used to refer to any form of disease-producing disorder of cardiac muscle without chamber specification. An enormous amount has been learned about these conditions, and great effort has been made to provide a systematic definition and classification [3]. There is a concept that ACM might contribute to stroke risk independently of atrial fibrillation (AF) [4]. Atrial fibrillation (AF) often begins as short-lasting episodes but becomes more long lasting over time as the AF-maintaining substrate progresses because of cumulative remodeling. Each AF episode that lasts for more than 24 h causes atrial remodeling, which reverses (but not necessarily completely) when AF terminates. In addition to AF-induced remodeling, remodeling due to intercurrent cardiac disease, as well as the normal aging process, contributes to the AF substrate. The remodeling processes cause atrial cardiomyopathic changes [4]

Fig. 1. A schematic representation of the natural history of AF. (Guichard JB, et al. [4])



REVIEW RESULTS

In recent years, there has been an increased emphasis on the characterization of phasic left atrium (LA) function, i.e., reservoir, conduit, and booster function, in disease states and the correlation of these parameters to major adverse cardiovascular events (MACE). [7] LA contractile function has been proposed as a sensitive tool for detecting early stages of LV disease and atrial fibrillation [8], while LA reservoir strain demonstrated prognostic utility in heart failure with preserved ejection fraction [9] and

chronic kidney disease [10]. Left atrial cardiomyopathy is both a clinical and histological diagnosis [9]. The relationship between ACM and AF on the one hand and ACM and embolic stroke of undetermined source (ESUS) on the other suggests that correct diagnosis of ACM is of clinical benefit. As mentioned above, there is no uniform definition of ACM to date. [1] Several studies have characterized the disease differently and used various methods. Recently, Eichenlaub et al. evaluated the LA emptying fraction in patients with AF for the diagnosis of ACM and prediction of arrhythmia recurrence after pulmonary vein isolation [11]. A left ACM was defined as an LA low-voltage area ≥2 cm^2 at 0.5 mV threshold on endocardial contact mapping. Patients with left ACM had lower LA emptying fractions than patients without ACM (27 vs. 41%, $p < 0.0001$) [12]. Furthermore, LA emptying fraction < 34% was a significant predictor of both left ACM, with an area under the curve of 0.846, and recurrence of arrhythmia after PVI [11]. Moreover, LA longitudinal strain rate < 23.5% predicted left ACM, defined as LA low-voltage area ≥2 cm^2 at 0.5 mV threshold on endocardial mapping, with an area under the curve of 0.878, a sensitivity of 92.3% and specificity of 82.4%. In patients with left ACM, the LA strain rate during the reservoir phase was significantly lower (15.2 vs. 29.4%, $p < 0.0001$) and showed a linear correlation with left ACM amount [11] [12]. Speckle-tracking echocardiography can be used to specify the functional remodeling in different regions of the atrium. For example, a declined LA lateral wall longitudinal strain was found to be a predictor of arrhythmia recurrence after AF ablation [13].

In the ASSERT (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial) study, investigators assessed the temporal relationship between subclinical AF events and strokes in patients under continuous rhythm monitoring via implanted devices [5]

They noted that AF events were detected within the 30 days before stroke in only 8% of individuals and that 16% of stroke victims had their first AF event after their strokes. [5] Additional support for a direct association between atrial cardiomyopathy and stroke comes from a couple of conditions that disproportionately affect the atria. Cardiac amyloidosis is associated with an increased risk of thromboembolic events, including stroke [6]

Table 1. EHRAS Classification of Atrial Cardiomyopathy

I	Primarily cardiomyocyte dependent
II	Primarily fibroblast dependent
III	Mixed cardiomyocyte-fibroblast dependent
IV	Primarily noncollagen deposits
EHRAS = European Heart Rhythm Association Sore	

Table 2. EHRAS Classification of Atrial Cardiomyopathy

I	Morphological or molecular changes affect "primarly "the cardiomyocytes in terms of cell hypertrophy and myocytolisis; no significant pathological tissue fibrosis or other interstitial changes.
II	Predominantly fibrotic changes. Cardiomyocytes show a normal appearance.
III	Combination of cardiomyocyte changes (e.g. cell hypertrophy, myocytolysis) and fibrotic changes
IVa	Accumulation of amyloid
IVf	Fatty infiltration
IVi	Inflammatory cells
IVo	Other interstitial alternations

What are the potential applications of the atrial cardiomyopathy concept?

The first set of issues relates to stroke prevention. If atrial cardiomyopathy is a significant stroke risk factor independent of AF, can individuals without an AF history who are at increased risk of atrial thromboembolic events be identified and protected by OAC? The CHA2DS2-VASc score is predictive of thromboembolic risk in the absence of any AF history in patients with heart failure [14]. Similarly, the CHA2DS2-VASc score correlates with the presence of LA spontaneous echo contrast in patients with rheumatic mitral stenosis and no AF history, who are at risk of LA thrombus formation and thromboembolism despite sinus rhythm [15]. The possibility that atrial cardiomyopathic risk factors can be used to identify patients with sinus rhythm who might have strokes that could be prevented by OAC would need to be tested in a prospective randomized trial. Presently, a variety of scoring systems are used to select patients with AF who require anticoagulation [16]. Until now, the randomized clinical trial data have shown that cessation of anticoagulation given maintenance of sinus rhythm may be harmful and that the benefit of AF suppression can be achieved only when anticoagulation is maintained. [17] One potential explanation is that the AF is an epiphenomenon, serving as a marker of an underlying atrial myopathy or atrial cardiopathy, and not necessarily causal. [18] If true, this would suggest that the optimal selection of patients for anticoagulation might not rely solely on evidence of AF but rather on other biomarkers of atria prone to forming thrombi. [19] The patients who need the most such biomarkers are those with cryptogenic stroke [20]. Several studies have examined the role of anticoagulation vs antiplatelet treatment in patients with ESUS. In randomized trials comparing either rivaroxaban [21] or dabigatran [22] with aspirin, no advantage of anticoagulation over aspirin in unselected cohorts of patients with

ESUS was demonstrated. ARCADIA trial tested the hypothesis that anticoagulation with apixaban is superior to antiplatelet therapy for preventing recurrent stroke in patients with a recent cryptogenic stroke and evidence of atrial cardiopathy. The atrial cardiomyopathy can be diagnosed via P-wave terminal force in electrocardiogram lead V1 greater than 5000 ìV ×ms, serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) level greater than 250pg/mL, or left atrial diameter index of 3cm/m2 or greater determined by echocardiography. [23]

The trial was stopped early for futility on the recommendation of the data and safety monitoring board after its review of an interim analysis prespecified to take place after 75 primary outcome events. There was no indication of safety concerns. The primary efficacy outcome of recurrent stroke occurred in 40 patients in the apixaban group and in 40 patients in the aspirin group, each resulting in an annualized rate of 4.4% and a statistically significant hazard ratio of 1.00 (95% CI,0.64-1.55). No differences in the secondary efficacy outcomes of recurrent ischemic stroke or systemic embolism or recurrent stroke or death were observed between the groups. Intracranial hemmorage occurred in zero patients in apixaban arm and in 7 patients in aspirin arm. [23] In this first major randomized trial to tackle stroke prevention in left atrial cardiopathy absent evidence of AF, apixaban failed to exhibit superior efficacy compared with low-dose aspirin. However, a subgroup analysis of the NAVIGATE-ESUS trial demonstrated that patients with moderate and severe LA dilatation had a significant benefit from therapy with rivaroxaban [24]. The results suggest that a proportion of patients with ESUS have LACM, which increases cardioembolic risk. The presumed mechanism of stroke due to atrial cardiopathy arises from embolism of a left atrial appendage thrombus, a process promoted by poor left atrial appendage function that has been observed even in the absence of AF. [25]

CONCLUSION:

Ischemic strokes are one of the most common causes of cardiovascular morbidity and mortality. A significant proportion of patients with ischemic stroke are suspected of embolic stroke without a specific embolic source being found (ESUS) (26). The clinical significance of ESUS results from the frequency of the disease and the fact that the recurrence risk for a new stroke is 4–5% per year despite antiplatelet agents (27). Studies specifically addressing LACM are extremely limited, and randomized controlled trials are lacking so far. Further investigation is urgently needed to improve the diagnostic capabilities and management of patients with LACM. By expanding our understanding of atrial dysfunction and thromboembolic risk, ACM heralds a new era in clinical practice aimed at mitigating stroke burden and improving outcomes in high-risk populations.

REFERENCES:

1. Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, et al. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Europace.* 2016 Oct; 18(10):1455-1490. [PubMed]

2. Brigden W. Uncommon myocardial diseases: the non-coronary cardiomyopathies. *Lancet.* 1957 Dec 21;273(7008):1243-9. [PubMed]

3. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation.* 2006 Apr 11;113(14): 1807-16. [PubMed]

4. Guichard JB, Nattel S. Atrial Cardiomyopathy: A Useful Notion in Cardiac Disease Management or a Passing Fad? *J Am Coll Cardiol.* 2017 Aug 8;70(6):756-765. [PubMed]

5. Brambatti M, Connolly SJ, Gold MR, Morillo CA, Capucci A, Muto C, et al. Temporal relationship between subclinical atrial fibrillation and embolic events. *Circulation.* 2014 May 27;129(21):2094-9. [PubMed]

6. Hausfater P, Costedoat-Chalumeau N, Amoura Z, Cacoub P, Papo T, Grateau G, et al. AL cardiac amyloidosis and arterial thromboembolic events. *Scand J Rheumatol.* 2005 Jul-Aug;34(4):315-9. [PubMed]

7. Kessler Iglesias C, Pouliopoulos J, Thomas L, Hayward CS, Jabbour A, Fatkin D. Atrial cardiomyopathy: Current and future imaging methods for assessment of atrial structure and function. *Front Cardiovasc Med.* 2023 Mar 31;10:1099625. [PubMed]

8. Blume GG, Mcleod CJ, Barnes ME, Seward JB, Pellikka PA, Bastiansen PM, et al. Left atrial function: physiology, assessment, and clinical implications. *Eur J Echocardiogr.* 2011 Jun;12(6):421-30. [PubMed]

9. Shah AM, Shah SJ, Anand IS, Sweitzer NK, O'Meara E, Heitner JF, et al. Cardiac structure and function in heart failure with preserved ejection fraction: baseline findings from the echocardiographic study of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial. *Circ Heart Fail.* 2014 Jan;7(1):104-15. [PubMed]

10. Gan GCH, Kadappu KK, Bhat A, Fernandez F, Gu KH, Cai L, et al. Left Atrial Strain Is the Best Predictor of Adverse Cardiovascular Outcomes in Patients with Chronic Kidney Disease. *J Am Soc Echocardiogr.* 2021 Feb;34(2):166-175. [PubMed]

11. Eichenlaub M, Mueller-Edenborn B, Minners J, Allgeier M, Lehrmann H, Allgeier J, et al. Echocardiographic diagnosis of atrial cardiomyopathy allows outcome prediction following pulmonary vein

isolation. *Clin Res Cardiol.* 2021 Nov;110(11):1770-1780. [PubMed]

12. Eichenlaub M, Muller-Edenborn B, Minners J, Jander N, Allgeier M, Lehrmann H, et al. Left Atrial Hypertension, Electrical Conduction Slowing, and Mechanical Dysfunction - The Pathophysiological Triad in Atrial Fibrillation-Associated Atrial Cardiomyopathy. *Front Physiol.* 2021 Aug 5;12:670527. [PubMed]

13. Mirza M, Caracciolo G, Khan U, Mori N, Saha SK, Srivathsan K, et al. Left atrial reservoir function predicts atrial fibrillation recurrence after catheter ablation: a two-dimensional speckle strain study. *J Interv Card Electrophysiol.* 2011 Sep;31(3): 197-206. [PubMed]

14. Wolsk E, Lamberts M, Hansen ML, Blanche P, Køber L, Torp-Pedersen C, et al. Thromboembolic risk stratification of patients hospitalized with heart failure in sinus rhythm: a nationwide cohort study. *Eur J Heart Fail.* 2015 Aug; 17(8): 828-36. [PubMed]

15. Belen E, Ozal E, Pusuroglu H. Association of the CHA2DS2-VASc score with left atrial spontaneous echo contrast: a cross-sectional study of patients with rheumatic mitral stenosis in sinus rhythm. *Heart Vessels.* 2016 Sep;31(9):1537-43. [PubMed]

16. Calenda BW, Fuster V, Halperin JL, Granger CB. Stroke risk assessment in atrial fibrillation: risk factors and markers of atrial myopathy. *Nat Rev Cardiol.* 2016 Sep; 13(9):549-59. [PubMed]

17. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, et al. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. *N Engl J Med.* 2020 Oct 1;383(14): 1305-1316. [PubMed]

18. Kamel H, Bartz TM ,Elkind MSV, Okin P, Thacker E, Patton K, et al. Atrial cardiopathy and the risk of ischemic stroke in the CHS (Cardiovascular Health Study). *Stroke.* 2018 Apr;49(4):980-986. [PubMed]

19. Marcus GM, Ovbiagele B. Anticoagulation for Atrial Cardiopathy in Cryptogenic Stroke. *JAMA.* 2024 Feb 20;331(7):564-566. [PubMed]

20. Yaghi S, Bernstein RA, Passman R, Okin PM, Furie KL. Cryptogenic stroke: research and practice. *Circ Res.* 2017 Feb 3;120(3):527-540. [PubMed]

21. Hart RG, Sharma M, Mundl H, Kasner S, Bangdiwala S, Berkowitz S, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med.* 2018 Jun 7;378(23):2191-2201. [PubMed]

22. Diener H C, Sacco RL, Easton JD, Granger C, Bernstein R, Uchiyama S, et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source *N Engl J Med.* 2019 May 16;380(20):1906-1917. [PubMed]

23.Kamel H, Longstreth WT Jr, Tirschwell DL, Kronmal RA, Marshall RS, Broderick JP, et al. Apixaban to Prevent Recurrence After Cryptogenic Stroke in Patients With Atrial Cardiopathy: The ARCADIA Randomized Clinical Trial. *JAMA.* 2024 Feb 20; 331(7):573-581. [PubMed]

24.Healey JS, Gladstone DJ, Swaminathan B, Eckstein J, Mundl H, Epstein AE, et al. Recurrent stroke with rivaroxaban compared with aspirin according to predictors of atrial fibrillation: secondary Analysis of the NAVIGATE ESUS randomized clinical trial. *JAMA Neurol.* 2019 Jul 1;76(7): 764-73. [PubMed]

25. Nguyen HT, Nguyen HVB ,Nguyen HQ, Le HQ. Prevalence of left atrial appendage thrombus in patients with acute ischaemic stroke and sinus rhythm: across-sectional study. *BMJ Open.* 2021 Dec 17;11(12): e051563. [PubMed]

26. Hart RG, Diener H-C, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, et al. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol.* 2014 Apr;13(4):429-38. [PubMed]

27. Ntaios G. Embolic stroke of undetermined source: JACC review topic of the week. *J Am Coll Cardiol.* 2020 Jan 28;75(3):333-340. [PubMed]

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Addressforcorrespondence:
Blagovest Stoimenov
Departmentof Propaedeutics of internal diseases, UMHAT "Alexandrovska"; Medical Faculty, Medical University-Sofia,
1, Georgi Sofiiski Str., Sofia, Bulgaria.
E-mail:stoimenov90@gmail.com,