

Atrial fibrillation progression: How sick is the atrium?

Lluís Mont, MD, PhD and Eduard Guasch, MD, PhD

Hospital Clinic, Universitat de Barcelona; IDIBAPS, Catalonia, Barcelona, Spain

Word count: 1450 words

*To whom correspondence should be sent:

Lluís Mont

lmont@clinic.ub.es

Cardiology Department, Hospital Clinic

C/Villarroel, 170. 08036 Barcelona

Tel: (+34)932275551

Fax: (+34)934513045

After many years of lack of interest in the atrium by clinical cardiologists, the evidence of increased morbidity and mortality in patients with atrial fibrillation (AF) relocated the atrium to a central position in cardiology more than 2 decades ago.¹ First came the studies showing improved outcome with the use of anticoagulants; later, the ever-lasting controversy on rate vs rhythm control; and at present, new imaging techniques and new therapeutic tools to better define atrial remodeling and improve therapy.

Despite recent advances, the clinical classification of AF based on the traditional 3 categories proposed by Gallagher and Camm in 1997² (paroxysmal, persistent and permanent) has remained the cornerstone for the management of AF with few modifications, such as the addition of “long-standing AF” to define patients with continuous AF for more than one year as still susceptible for interventional therapies.³ The classification retains its utility by guiding therapy in combination with other considerations such as symptoms and management of underlying risk factors.⁴ However, data on progression from paroxysmal to persistent forms are scarce, and little is known about the mechanisms and time frame of the evolution of the disease. Persistent forms are associated with a more advanced atrial remodeling (e.g., larger size, increased sphericity⁵ and fibrosis⁶).

The long-term follow-up of the AF-CARAF study⁷ analyzed the probability of progression from paroxysmal to persistent AF at 10 years, and the factors associated with this evolution. At 10 years after an initial diagnosis of paroxysmal AF in a population with a mean age of about 60 years, the probability of progression to persistent forms despite therapeutic efforts is about 35%, and about 30% of patients do not survive. Main factors leading to AF progression were age, mitral regurgitation, left atrial dilation, aortic stenosis and LV hypertrophy. Interestingly, after taking into account the competing mortality risk, LV hypertrophy and aortic stenosis were no longer associated with progression. Of the three remaining independent factors, aging is not modifiable and mitral regurgitation, present in a minority of patients (24%), may be correctable. Finally, in the AF-CARAF study, the antero-posterior left atrium (LA) diameter seems to be the most robust and useful information to stratify the risk of progression in clinical practice. LA diameter also has been reported as a simple and useful measurement to predict ablation success.⁸ It is becoming apparent that how “sick” or remodeled the atrium is will determine the progression from paroxysmal to persistent AF. And yet today, we are still using basic and indirect measurements, such as M-mode antero-posterior diameter of LA, to infer the extent of atrial disease. Moreover, in clinical practice the analysis of atrial remodeling is often overlooked, and only begins to gain

attention after AF is diagnosed. AF should probably be considered a symptom of an underlying atrial cardiomyopathy. A recent consensus has proposed a definition of atrial cardiomyopathy as follows: “Any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically relevant manifestations”.⁹ This definition certainly reinforces the concept that AF is frequently a manifestation of an atrial cardiomyopathy that has been developing silently for years, long before AF appears. Camm et al¹⁰ proposed that a new classification of AF should consider a “pre-AF” category of patients with a sick atrium who have not yet developed AF. To summarize, what we see as a progression from paroxysmal to persistent AF is probably a surrogate for the progression of the underlying atrial cardiomyopathy. The analysis of this progression has been plagued by the very limited tools available to successfully explore the atrium; therefore, the possibility to deal with the underlying atrial cardiomyopathy more efficiently will be strongly related to the available tools to explore the atrium.

There are several ways by which improving the knowledge of the progression of atrial disease could help to control it more efficiently in the near future. Nevertheless, these should be preceded by a conceptual change, beginning to explore the atrium in the “pre-AF” state, whenever a condition that is known to affect the atrium is present but before AF has occurred. In that way, an upstream therapy to prevent progression could be started before an irreversible remodeling becomes established. A number of new tools are available, or will be in the near future, and will eventually help in exploring the atrium. New fibrosis biomarkers such as BNP¹¹ and micro-RNA¹² could possibly give information about the “atrial status”. On the other hand, more sophisticated imaging techniques such as MRI will allow us to measure fibrosis^{6,13} and sphericity⁵ more efficiently, aimed at detecting atrial cardiomyopathy in its early stages. The extent of atrial fibrosis measured with late gadolinium enhancement has been shown to predict success after AF ablation,⁶ and could possibly be used to screen for a “pre-AF” status in populations at risk, such as patients with hypertension. Another proposed imaging method is the assessment of shape deformation. Recent studies have shown that sphericity of the LA has independent predictive value for post-ablation success,⁵ and is a better predictor for stroke than atrial volume.¹⁴ New echocardiographic measurements such as strain rate are also able to detect atrial disease.¹⁵

In summary, atrial fibrillation is probably the tip of the iceberg. More efficient exploration and earlier detection of the presence of silent atrial cardiomyopathy may lead to more efficacious prevention of disease progression using upstream therapies and controlling causal risk factors more efficiently.

Funding

The authors have received funding from the European Union's Horizon 2020 Research and Innovation Programme under grant agreement 633196 (CATCH ME), CIBER 16/11/00354, and Instituto de Salud Carlos III — Fondo de Investigaciones Sanitarias (PI16/00435).

1. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D: Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998; 98:946–952.
2. Gallagher MM, Camm J: Classification of atrial fibrillation. *Am J Cardiol* 1998; 82:18N–28N.
3. Calkins H, Kuck KH, Cappato R, et al.: 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-up, Definitions, Endpoints, and Research Trial Design A rep. *Hear Rhythm* 2012; 9:632–+.
4. Kirchhof P, Breithardt G, Bax J, et al.: A roadmap to improve the quality of atrial fibrillation management: proceedings from the fifth Atrial Fibrillation Network/European Heart Rhythm Association consensus conference. *Europace* 2016; 18:37–50.
5. Bisbal F, Guiu E, Calvo N, et al.: Left atrial sphericity: A new method to assess atrial remodeling. impact on the outcome of atrial fibrillation ablation. *J Cardiovasc Electrophysiol* 2013; 24:752–759.
6. Marrouche NF, Wilber D, Hindricks G, et al.: Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. *JAMA* 2014; 311:498–506.
7. Padfield GJ, Steinberg C, Swampillai J, Connolly SJ, Dorian P, Green MS, Humphries KH, Klein GJ, Sheldon R, Talajic M, Kerr CR: Progression of paroxysmal to persistent atrial fibrillation: Canadian Registry of atrial fibrillation 10-year follow up. *Heart Rhythm* 2017; .
8. Berruezo A, Tamborero D, Mont L, Benito B, Tolosana JM, Sitges M, Vidal B, Arriagada G, Méndez F, Matiello M, Molina I, Brugada J: Pre-procedural predictors of atrial fibrillation recurrence after circumferential pulmonary vein ablation. *Eur Heart J* 2007; 28:836–841.
9. Goette A, Kalman JM, Aguinaga L, et al.: EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: Definition, characterization, and clinical implication. *Hear Rhythm* 2017; 14:e3–e40.
10. Camm AJ, Al-Khatib SM, Calkins H, et al.: A proposal for new clinical concepts in the management of atrial fibrillation. *Am Heart J Mosby, Inc.,* 2012; 164:292–302.e1.
11. Lind L, Sundström J, Stenemo M, Hagström E, Ärnlöv J: Discovery of new biomarkers for atrial fibrillation using a custom-made proteomics chip. *Heart* 2016; :heartjnl-2016-309764.

12. Weckbach LT, Grabmaier U, Clauss S, Wakili R: MicroRNAs as a diagnostic tool for heart failure and atrial fibrillation. *Curr Opin Pharmacol Elsevier Ltd*, 2016; 27:24–30.
13. Benito EM, Carlosena-remirez A, Guasch E, et al.: Left atrial fibrosis quantification by late gadolinium-enhanced magnetic resonance : a new method to standardize the thresholds for reproducibility. 2016; :1–8.
14. Bisbal F, Gómez-pulido F, Cabanas-Grandío P, et al.: Left Atrial Geometry Improves Risk Prediction of Thromboembolic Events in Patients With Atrial Fibrillation. *J Cardiovasc Electrophysiol* 2016; 27:804–810.
15. Ma XX, Boldt LH, Zhang YL, et al.: Clinical Relevance of Left Atrial Strain to Predict Recurrence of Atrial Fibrillation after Catheter Ablation: A Meta-Analysis. *Echocardiography* 2016; 33:724–733.