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REVIEW

Role of imaging in assessment of atrial fibrosis in patients with atrial fibrillation: state-of-the-art review

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Atrial fibrillation (AF) is the most common arrhythmia in the world. Despite the large number of studies focused on the causes and mechanisms of AF, it remains a clinical challenge. Atrial electrical and structural remodelling caused by AF is responsible for the perpetuation of the arrhythmia. However, a validated noninvasive method for assessment of atrial fibrosis in clinical practice is lacking. In this review, we aim to present an update about the origins and mechanisms of atrial remodelling, particularly focusing on atrial fibrosis, and compare imaging techniques that can detect atrial changes and greatly contribute to the clinical management of patients with AF.

Keywords Atrial fibrosis • Atrial fibrillation • Atrial function • Strain

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the world.[1] Although often considered a benign disease, AF is the leading cause of cardioembolic stroke.[2,3] Atrial structural, electrical, and functional changes caused by AF are the substrates responsible for the arrhythmia's perpetuation and tendency to recur, resulting in poor quality of life. In the last 20 years new imaging techniques to calculate atrial function and predict risk of AF recurrence after treatment, echocardiography and magnetic resonance imaging in particular, were developed with the goal of tailoring management of patients with AF. In this review, we aim to present an update about the origins and mechanisms of atrial remodelling, particularly focusing on atrial fibrosis, and compare imaging techniques that can detect atrial changes and greatly contribute to the clinical management of patients with AF.

'A glance' at atrial function

The left atrium's (LA) role in cardiovascular system function has always been considered ancillary. In recent years, the LA has garnered more attention with noninvasive assessment of its function by means of new technologies.

In each cardiac cycle, the LA acts as a reservoir, receiving pulmonary venous return during left ventricular (LV) systole; as a conduit, passively transferring blood to the LV during early diastole; and as a pump, actively pushing blood to the LV in late diastole.[4] In normal subjects, the reservoir, passive conduit, and pumping phases account for 40, 35, and 25% of atrial contribution to stroke volume, respectively.

Tissue Doppler imaging (TDI) and two-dimensional (2D) speckle tracking are two echocardiographic techniques to assess atrial strain. TDI-derived strain was the first used and revolutionized atrial assessment. The technique is highly feasible for studying the contractility of myocardial tissue, allowing the quantification of low-velocity, high-amplitude, and long-axis intrinsic myocardial velocities in both systole and diastole. However, TDI-derived strain is limited by suboptimal reproducibility, angle dependency, and signal artefacts. The technique also only allows for the measurement of regional strain and does not obtain information about the curved portion of the atrial roof.[5,6]

Largely independent of translational effects due to tethering by neighbouring myocardial segments, 2D speckle-tracking-derived strain and strain rate imaging may overcome the major limitation of TDI.[4,7–9] Moreover, the feasibility and reliability of this new method was evaluated by several studies[10,11] that demonstrated adequate tracking quality in 97% of patients with AF, with inter- and intraobserver variability ranging between 2.9 and 5.4%.

With normal atrial function, 2D strain analysis enables identification of a positive peak that corresponds to LA reservoir function during ventricular systole, whose positive deflection is closely related with LA compliance (*Figure 1A*). Additionally, in a normal subject, atrial strain rate deformation analysis during ventricular

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diastole enables identification of two negative peaks, the first corresponding to passive early LV filling and the second to atrial booster pump function (*Figure 1B*). During AF, electrical activation pathway is disrupted and atrial mechanical performance becomes abnormal. As a consequence, complete loss of atrial pump function occurs, demonstrated by the absence of one of the two negative strain rate curves during diastole, which is the most characteristic pattern during AF (*Figure 1E*). Moreover, due to atrial fibrosis and reduced atrial compliance, an impairment of reservoir function can be detected even before atrial dilatation has occurred (*Figure 1D*).

Local strain heterogeneity also is a reflection of atrial wall fibrosis, as it can be assumed from the greater temporal and spatial dispersion of local strain and strain rate curves in patients with AF compared with controls (*Figure 1*). This electrical dispersion, due to the disruption of the electrical pathway, may play a key role in the onset and maintenance of the arrhythmia. Moreover, it has been demonstrated that longer atrial electromechanical coupling, inter- and intra-atrial electromechanical delay measured with TDI, and greater *P*-wave dispersion are well-known electrophysiological characteristics of the atria prone to fibrillation.[4]

Atrial remodelling and fibrosis

Whether the presence of atrial fibrosis in patients with AF is a problem is still debated. The first studies[12–14] that focused on structural remodelling of the atria emphasized increased vulnerability to AF in animal models with dilated atria and increased amounts of connective tissue between the myocytes. The susceptibility to AF in the models was explained by increased interstitial fibrosis and a higher likelihood of local intra-atrial conduction block leading to smaller and more numerous reentrant circuits. The mechanisms underlying fibrosis are still unclear. Collagens are major extracellular matrix proteins in the heart and, out of five different collagen isoforms found in the heart, fibrillar collagen type I and III comprise ~85% of the cardiac interstitium.[15] Fibrosis, not only in the atria, usually results from an accumulation of fibrillar collagen deposits, occurring most commonly as a reparative process to replace degenerating myocardial tissue with concomitant reactive fibrosis, which causes interstitial expansion.[16,17] Atrial fibrosis, however, involves multifactorial processes that result from complex interactions among neurohormonal and cellular mediators.[18–23] It was shown in humans that reparative fibrosis replaces degenerating myocardial cells, but the coexisting reactive fibrosis causes interstitial expansion between bundles of myocytes, which physically separates remaining myocytes and creates a barrier to impulse propagation, impairing intermyocytes coupling.[18]

Atrial remodelling influences the natural course of AF; it is responsible for the perpetuation of the arrhythmia and its recurrence, characterizing the typical clinical history of these patients. Nowadays, identification of myocardial fibrosis by delayed contrast enhancement (DCE) represents the main application of cardiac magnetic resonance imaging (CMR) in many cardiac diseases. The use of DCE visualizes the altered washout kinetics of gadolinium relative to normal surrounding tissue, which reflects increased fibrosis or tissue remodelling of the myocardium. Therefore, myocardial damage appears as a hyperintense area, whereas normal myocardium appears as a hypointense ('nulled') area (*Figure 1C* and *F*).

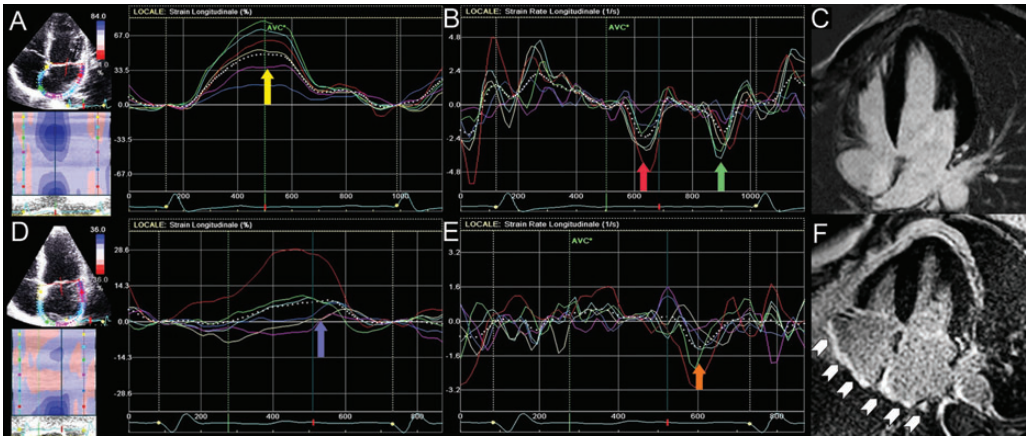

Figure 1 Transthoracic echocardiography in the four-chamber view showing global left atrial (LA) longitudinal strain in a normal subject. The positive peak (yellow arrow) represents an atrial preserved reservoir phase, which occurs during ventricular systole (*A*). Transthoracic echocardiography in the four-chamber view showing global LA longitudinal strain rate in a normal subject. During ventricular diastole it is possible to identify two negative peaks, the first corresponding to passive early LV filling (red arrow) and the second to atrial booster pump function (green arrow) (*B*). Cardiac magnetic resonance imaging in the four-chamber view showing a normal heart with no atrial delayed contrast enhancement and normal atrial volumes (*C*). Transthoracic echocardiography in the four-chamber view showing global LA longitudinal strain in a patient with permanent atrial fibrillation (AF). A reduction of positive curve during the reservoir phase (purple arrow) is expected in a patient with reduced LA compliance (*D*). Transthoracic echocardiography in the four-chamber view showing global LA longitudinal strain rate in the same patient. Loss of left atrial booster pump function occurs and a single negative deflection (orange arrow) can be observed during ventricular diastole, as the main pattern of AF (*E*). Cardiac magnetic resonance imaging in the four-chamber view showing delayed contrast enhancement in both atria (white arrow heads) and atrial dilatation in the same patient with permanent AF (*F*).

The first studies of CMR in the evaluation of atria were focused on the measurement of atrial volumes[24,25] in patients with AF before and after cardioversion. Eventually this technique was used to detect fibrosis in the atria as it could be performed in the ventricles. Moreover, evidence of a correlation between DCE-CMR images and histopathological reports of fibrosis after radiofrequency of lesions in dogs allowed a noninvasive characterization of scar tissue.[26] Furthermore, three-dimensional (3D) DCE-CMR revealed DCE of the atria or pulmonary vein wall 1–3 months after AF ablation in all patients with no preablation LA scar.[27] This proved a direct correlation between amount of LA fibrosis and DCE.

The main clinical application of noninvasive atrial fibrosis assessment is the possibility of predicting risk of AF recurrence on the basis of post-radiofrequency ablation DCE. A larger amount of fibrosis, and so of DCE in the ablation sites, represents a more complete isolation of the AF focus and less chance of recurrence.[28] Moreover, some authors[29,30] demonstrated that not only the degree of postablation fibrosis within the LA is useful in predicting the outcome of patients, but also that the amount of preablation fibrosis is strongly associated with AF recurrence after pulmonary vein isolation. They observed an AF recurrence rate of 14% in patients with minimal enhancement, 43% in those with moderate enhancement, and 75% in those with extensive enhancement before the procedure.

These data are confirmed by Mahnkopf *et al.*[31] who evaluated LA fibrosis before catheter ablation by DCE-CMR, and produced a new classification, the Utah classification, which divides patients into four groups according to degree of fibrosis: Utah I (≤5% LA wall DCE), Utah II (>5 to ≤20% LA wall DCE), Utah III (>20 to ≤35% LA wall DCE), and Utah IV (>35%). Catheter ablation proved successful in suppressing AF in all of Utah I, 81.8% of Utah II, in 62.5% of Utah III patients, and none of Utah IV patients. No recurrence of the arrhythmia occurred in Utah I patients and the rate of recurrence of the arrhythmia was progressively higher according to the increasing amount of fibrosis (28% in Utah II, 35% in Utah III, and 56% in Utah IV).[32,33] This finding shows how Utah classification integrated with LA strain evaluation could help in clinical practice to perform a more patient-tailored approach to the arrhythmia (*Figure 2*).

Vergara and Marrouche[34] also demonstrated how postablation DCE-CMR could help identify breaks in lesion sets, and how its correlation with conduction recovery could be used successfully to guide repeat procedures. They affirmed that real-time CMR-based ablation has the potential advantage of tissue lesion visualization during radiofrequency delivery, and that this could be a substantial help in obtaining complete pulmonary vein isolation.

McDowell *et al.*[35] presented a new method for constructing a patient-specific model of atrial fibrosis as a substrate for AF by DCE-CMR images acquired *in vivo*. In the era of noninvasive multimodality cardiac imaging, comprehensive evaluation of LA fibrosis is leading to more appropriate management of patients with AF.

Noninvasive assessment of atrial fibrosis: histology to function

Kuppahally *et al.*[36] effectively demonstrated that a larger extension of LA enhancement on DCE-CMR is related to lower atrial reservoir performance, expressed by a reduced atrial strain peak during this phase of the cardiac cycle. After dividing patients with AF according to duration of the arrhythmia (paroxysmal and persistent), the amount of fibrosis and concordant reduction of atrial strain was significantly greater in patients with chronic AF than in those with paroxysmal AF, showing a continuum of ultrastructural abnormalities affecting the atria.

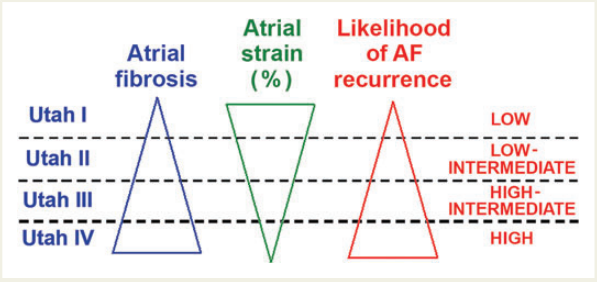

Figure 2 Schematic showing the use of atrial fibrosis and strain to determine the likelihood of atrial fibrillation (AF) recurrence. The blue triangle represents the degree of atrial fibrosis according to Utah classification, the green triangle represents atrial longitudinal strain and the red triangle represents the likelihood of AF recurrence. The chance of AF recurrence correlates directly to atrial performance during reservoir phase and inversely correlates to degree of atrial fibrosis.

Furthermore, it has been recently demonstrated that LA strain is a better predictor than traditional parameters of the degree of fibrosis detected in histological specimens of the atrial wall from a specific subset of patients with severe primary mitral regurgitation undergoing mitral valve surgery.[37] This finding definitively correlates the histopathological report of fibrosis with loss of function, and enlightens on the relationship between atrial remodelling and functional alterations in patients with AF.

Why obtain atrial strain?

Atrial dilation is considered the best predictor of AF onset and recurrence.[38–40] For this reason, echocardiographers initially focused on early detection of atrial geometrical abnormalities through monodimensional atrial diameter quantification and then bidimensional areas and volume estimation.[6,38,41–43] However, LA volume assessment with 3D echocardiography has been validated against magnetic resonance imaging, and follow-up assessment in daily practice appears feasible and reliable with both 2D and 3D approaches.[44] Bidimensional transoesophageal echocardiography remains one of the best tools for thrombus detection and left atrial appendage flow velocity assessment.[6,45]

Although it is well demonstrated that patients with AF who tend to maintain sinus rhythm after cardioversion present with remarkably smaller LA size if compared with patients who revert to the arrhythmia,[46–48] it is well known that all structural changes are late markers of the disease. As a consequence, the challenge for cardiologists is to detect early functional remodelling before anatomical alterations occur. Atrial fibrosis and reduced atrial strain detection, especially during the reservoir phase of cardiac cycle, might have a relevant role in the management of patients with AF. One possible major

application of strain is the possibility of predicting the rate of cardioversion success and risk of AF recurrence.

Low atrial strain and strain rate calculation during the reservoir phase proved to be very sensitive and reliable markers for the recurrence of the arrhythmia as demonstrated by Di Salvo[49] *et al*., who confirmed the prognostic value of strain imaging in maintaining sinus rhythm in a group of patients with lone AF. In 65 patients with recent-onset AF, strain and strain rate imaging by transthoracic and transoesophageal echocardiography was performed before successful external cardioversion and at 9-month follow-up to compare those who maintained sinus rhythm with those with AF recurrence. They found that atrial myocardial properties assessed by strain and strain rate were significantly reduced in patients with AF, and that the only effective predictors of sinus rhythm maintenance were atrial appendage flow velocity assessed by transoesophageal echocardiography and precardioversion atrial strain peak systolic values. Similar results were obtained by Mirza *et al*.,[50] who demonstrated that regional LA lateral wall strain was a preprocedural determinant of AF recurrence in patients who underwent cardioversion, independent of LA enlargement.

In the clinical management of patients with AF, given the close relationship between morphology and function, a reduced atrial deformation during the reservoir phase of cardiac cycle may be an early and noninvasive marker of the amount of atrial wall fibrosis. Moreover, postprocedural LA strain during reservoir phase holds promise to be a remarkably reliable predictor of successful AF ablation,[51–53] allowing stratification of patients on the basis of the likelihood of maintaining sinus rhythm after the procedure. Strain and strain rate also are good tools to quantify atrial remodelling as demonstrated by Thomas *et al*.,[54] who reported that strain rate in the AF cohort was significantly lower than in controls immediately after cardioversion, and that atrial function improved over time, with maximum change observed in the initial 4 weeks after cardioversion.

Recently, 3D speckle tracking became available, but it is not yet well known and little used in clinical practice. Some studies[55,56] have demonstrated that it enables the measurement of LA strain with excellent reproducibility, and it appears to be beneficial, compared with 2D speckle tracking, for stratifying patients with AF.

Conclusions

In an era of noninvasive cardiac imaging, tissue characterization together with functional strain analysis will play a pivotal role in the overall assessment and prognostic stratification of patients with the aim of tailoring patient-specific treatment. Nonetheless, atrial strain analysis and LA fibrosis detection cannot be considered as part of the routine 'work up' of patients with AF in current clinical practice, and modulation of antiarrhythmic therapy according to the chance of AF recurrence based on strain analysis or atrial fibrosis evaluation needs further study. However, development of accurate noninvasive imaging techniques enabling the identification of AF patients with different prognoses will probably generate different therapeutic approaches to the disease and influence timing of follow-up for these patients. In conclusion, though many attempts have been made to understand the real mechanisms underlying AF, it seems clear that it cannot be considered a unique disease but a heterogeneous entity, and still a challenging issue for cardiologists.

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