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Imaging in atrial fibrillation: A way to assess atrial fibrosis and remodeling to assist decision-making

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Abstract The 2020 ESC atrial fibrillation (AF) guidelines suggest the novel 4S-AF scheme for the characterization of AF. Imaging techniques could be helpful for this objective in everyday clinical practice, and information derived from these techniques reflects basic aspects of the pathophysiology of AF, which may facilitate treatment decision-making, and optimal management of AF patients. The aim of this review is to provide an overview of the mechanisms associated with atrial fibrosis and to describe imaging techniques that may help the management of AF patients in clinical practice. Transthoracic echocardiography is the most common procedure given its versatility, safety, and simplicity. Transesophageal echocardiography provides higher resolution exploration, and speckle tracking echocardiography can provide incremental functional and prognostic information over conventional echocardiographic parameters. In addition, LA deformation imaging, including LA strain and strain rate, are related to the extent of fibrosis. On the other hand, multidetector-row computed tomography and cardiac magnetic resonance provide higher resolution data and more accurate assessment of the dimensions, structure, and spatial relationships of the LA. Imaging is central when deciding on catheter ablation or cardioversion, and helps in selecting those patients who will really benefit from these procedures. Moreover, imaging enhances the understanding of the underlying mechanisms of atrial remodeling and might assists in refining the risk of stroke, which help to select the best medical therapies/interventions.

In summary, evaluation of LA enlargement, LA remodeling and fibrosis with imaging techniques adds clinical and prognostic information and should be assessed as a part of routine comprehensive AF evaluation. (Am Heart J 2023;258:1–16.)

Background

Atrial fibrillation (AF) is the most common cardiac arrhythmia and it is associated with high mortality and morbidity and an increased risk of stroke.[1,2] By definition, AF is represented by a highly irregular atrial rhythm, maintained by regularly firing sources or drivers, whether single rapidly rotating re-entry circuits or rapidly firing ectopic foci, by virtue of fibrillatory conduction.[3]

Heart vulnerability to AF induction and maintenance is affected by atrial remodeling.[4] The principal pathophysiological mechanisms that promote AF development are electrical, functional and structural remodeling.[5] In addition, atrial fibrosis and remodeling are associated with the risk of left ventricular (LV) systolic dysfunction, left atrial appendage (LAA) thrombus formation, and stroke.[6]

For these reasons, the management of AF is complex and requires multiple treatment decisions about opti-

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Abbreviations: AERP, atrial effective refractory period; AF, atrial fibrillation; CMR, cardiac magnetic resonance; CRP, C-reactive protein; CT, computerized tomography; CTDI, colour-coded tissue Doppler imaging; ESUS, embolic stroke of undetermined source; IL6, interleukin 6; LA, left atrium; LAA, left atrial appendage; LAEF, left atrial emptying fraction; LAVi, left atrial volume indexed; LGE-CMRI, late gadolinium enhancement on cardiac magnetic resonance imaging; LV, left ventricular; MDCT, multidetector row computerized tomography; MMPs, matrix metalloproteinases; PVs, pulmonary veins; RA, right atrium; ROS, reactive oxygen species; STE, speckle tracking echocardiography; TDI, tissue Doppler imaging; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

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mal symptom control, thromboprophylaxis, identification and management of concomitant cardiovascular risk factors and prevention of AF progression. The 2020 ESC AF guidelines suggest using the novel 4S-AF scheme for the characterization of AF, including the evaluation of the substrate severity.[1] This should consider not only comorbidities/cardiovascular risk factors under clinical assessment, but also imaging modalities, which may facilitate treatment decision-making, and optimal management of AF patients. Indeed, changes in cardiac dimensions, and very probably in the function and tissue characteristics of the left atrium (LA), are important markers of LA structural remodeling and modification of the arrhythmogenic substrate. Imaging techniques could be helpful for proper AF characterization in everyday clinical practice, and information derived from these techniques reflects basic aspects of the pathophysiology of AF.

We are in a new era of AF management, where personalized medicine is gaining great interest. The search for an individualized approach for each patient requires the use of tools that provide newly added information. In this sense, multimodality imaging such as transthoracic echocardiography (TTE), transoesophageal echocardiography (TOE), computerized tomography (CT) and cardiac magnetic resonance (CMR), provide LA size and shape, and therefore may also help to the identification and characterization of LA enlargement, LA remodeling and fibrosis with subsequent LA dysfunction.[7] Thus, multimodality imaging may assist us to identify early those patients who will benefit from 1 or another therapy and may help to the assessment of the risk of AF recurrence and thromboembolism in each patient.

The aim of this review article is to provide an overview of the mechanisms associated with atrial fibrosis and to describe the main imaging techniques that may help the management of patients with AF in clinical practice.

Structural and electrical remodeling in AF

The association between AF and LA remodeling is well known, but remains as *'the chicken or the egg causality dilemma'*, ie it is not clear whether AF causes progressive LA tissue changes, or rather it is a consequence.

The AF substrate is complex and involves atrial dilation, inflammation, acute ischemia, and fibrosis; with a significant contribution of structural, contractile, and electrical remodeling in the atria.[8]

Atrial remodeling leads to increase the collagen content and a decrease of atrial myocytes.[9] The increase of collagen fibers constitutes electrical barriers, causing asynchronous propagation of electrical activation,[10] because under normal conditions, the myocardium is composed of thin tissues, allowing close contact between adjacent cardiomyocyte cells.[11] This process, therefore, produces fibrosis, LA dilation, and LA dysfunction with delayed electromechanical conduction, which contributes to the sustainability and persistence of the arrhythmia.[12] In fact, LA fibrosis has been considered an irreversible form of LA remodeling, which occurs in response to stretch, overload, and inflammation.[13]

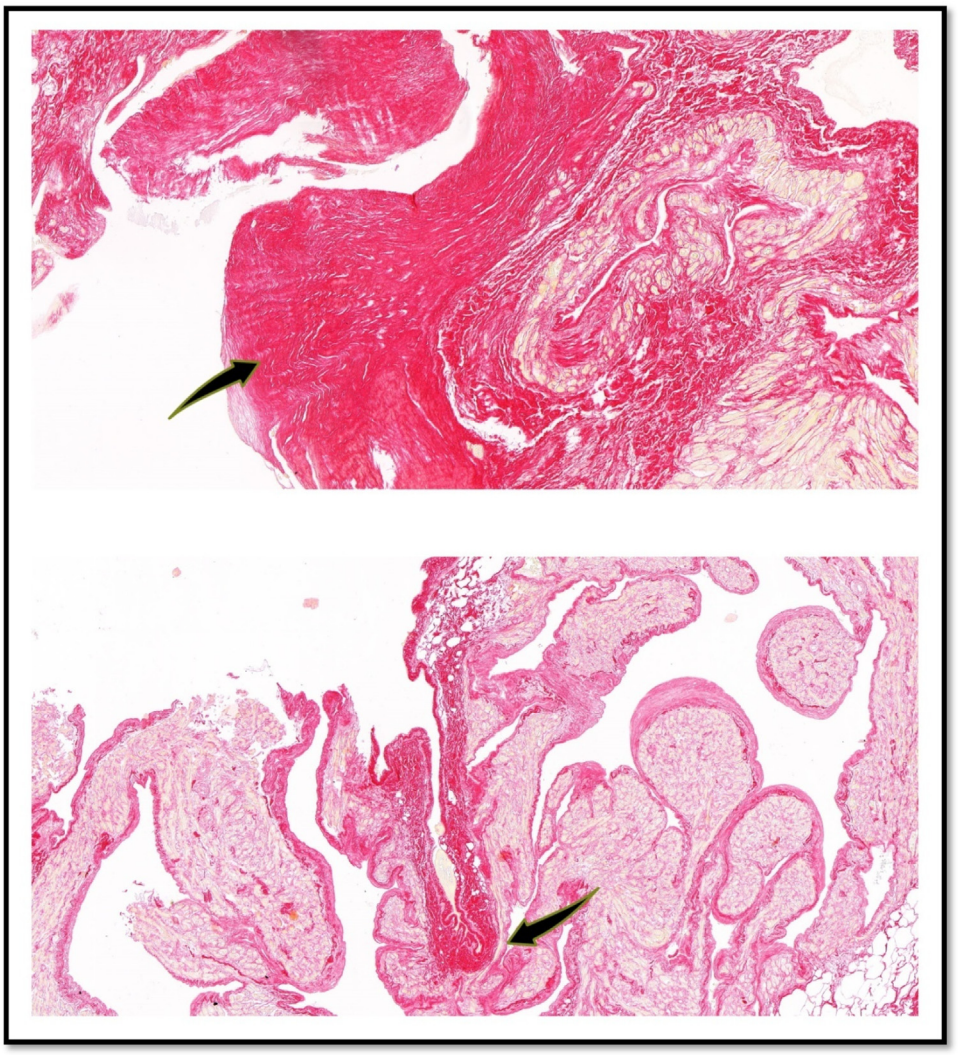
Histologically, structural atrial remodeling is characterized by increased connective tissue, fibroblast activation, and occurrence of different degrees of interstitial fibrosis (Figure 1), with glycogen accumulation and marked loss of sarcomere in the atrial cardiomyocytes, atrial fat infiltration, myocyte hypertrophy, necrosis, amyloidosis, and inflammatory infiltrates.[14–16]

In patients with AF, fibroblasts play an important role in atrial remodeling and fibrosis, as they may differentiate into myofibroblasts, proliferate and increase extracellular matrix production. When fibrosis is developed, intercellular conduction is affected due to a mismatch in the propagation of the electrical impulse between cardiomyocytes, leading to the appearance of heterogeneous fibrous myocardial tissue. This process takes place through the gap junction channels, connexins, which ensure the optimal interconnection of the cytoplasmic compartments of the cells.[11,17,18] Advanced interstitial fibrosis may render the atrial myocardium discontinuous, resulting in a branching structure and would show impairment of atrial conduction at the microscopic level. Thus, changes in matrix regulation of tissue inhibitors of metalloproteinases and several matrix metalloproteinases (MMPs) have been observed in AF patients.[5]

Another contributing factor in the development of cardiac remodeling could be the production of reactive oxygen species (ROS) due to abnormal oxidative stress. In the heart, ROS derived from several intracellular sources triggering mitochondrial DNA damage, cardiac fibroblast proliferation, activate MMPs and apoptosis.[19] Similarly, fibrosis markers with a regulatory role in myocardial fibrosis such as soluble ST2 and galectin-3 have been related with LA wall remodeling, and consequently with the presence of AF and poorer prognosis.[20–23] In addition, under conditions of tissue injury or infection, the cardiac immune cells are recruited and activated, which leads to the production of proinflammatory cytokines and the recruitment of several types of leukocytes involved in the generation, propagation, development of inflammation and tissue remodeling.[24,25] Indeed, interleukin 6 (IL6) and C-reactive protein (CRP) are 2 inflammatory cytokines commonly increased in patients with atrial remodeling that have been associated with incident AF.[22,26]

In conjunction with these pathophysiological mechanisms, Wijffels *et al.* described the electrical remodeling in a goat model of AF, characterized by a short atrial effective refractory period (AERP), heterogeneity of AERP, and rate maladaptation.[27] The shortening of AERP can lead to a reduction in wave length, thereby allowing the atria to contain an increased number of re-entry cir-

Figure 1



Evidence of fibrosis in right atrial tissue of two different patients with atrial fibrillation.

cuits, with a consequent enlarged in AF sustenance. Unlike AERP, in different atria substrates, increased conduction heterogeneity and slowing conduction have been reported, with progressive electrical and tissue structural remodeling.[28] However, these conduction abnormalities are probably due to the increase of atrial interstitial fibrosis. The mechanisms underlying the remodeling are complex, but the changes in electric activation are manifested as a decrease in the effective refractory period and a reduction in myocardial voltage.[29]

As previously commented, structural remodeling is characterized by tissue fibrosis and atrial enlargement, a key determinant of re-entry persistence to maintain AF. Indeed, higher AF burden and LA remodeling are known to be closely related.[30] The role of atrial fibrosis in AF perpetuation was actually demonstrated by Li *et al.* in 1999 by experimental congestive heart failure induced in a canine model, whereby the percentage of fibrosis was significantly greater in all atrial regions and overall fibrosis was highly increased.[31] "Lone" AF can also contribute to atrial fibrosis independently of the underlying cardiovascular conditions,[32] especially for its apparent structural stability and negligible regression after restoration of sinus rhythm.[33]

Importantly, fibrosis could also be a marker of progressive atrial cardiomyopathy.[34] In another study of 30 atrial samples of patients with a different history of AF, fatty infiltration and fibrosis extent were 2 to threefold higher

in patients with a history of AF and correlated with lymphomononuclear infiltration compared to patients without AF history. Moreover, patients with permanent AF had larger extent of fibrosis compared to patients with paroxysmal AF.[35] The authors also provided histological evidence of an association between major atrial conduction pathways and structural changes in LA walls, with AF history and clinical type.

In addition, the association between inflammatory cell count and extent of fibrosis in AF patients is strong and suggested the important role of inflammation in the creation of an AF substrate. Similar studies examined LA and right atrium (RA) tissue samples of patients without previous history of AF who underwent cardiac surgery and reported that LA fibrosis was higher in patients developing AF compared with those who remained in normal sinus rhythm.[36] Thus, the accumulation of fibrosis modifies the electrophysiologic properties of the atrium, reducing the velocity of the impulse and providing a substrate for reentry and AF initiation.

More recent studies show that the distribution of LA fibrosis is different depending on the chronicity of AF, and LA fibrosis is primarily observed within the posterior LA wall around pulmonary veins (PVs) ostia.[37,38] Histological studies on LA tissue have confirmed the presence of fibrosis in low-voltage tissue regions, but without invasive techniques, it has not been possible to determine the location and extent of fibrosis in LA.[39] The degree of fibrosis/low-voltage tissue and spatial distribution can influence the variability and location of wave-front breakthroughs and fibrillary dynamics. It is considered that myocardial fibrosis is the consequence of microvascular ischemia, which triggers apoptosis and collagen deposition.[40]

Multimodality imaging in AF

Basic echocardiographic parameters

The importance of left atrial size, volume and function

As described above, there are a number of physiological and biological changes related to LA fibrosis and remodeling mechanisms. However, these aspects require a more complex and invasive assessment, sometimes nonspecific (eg when using biomarkers). Then, how to determine the presence of LA fibrosis with some degree of precision in everyday clinical practice? The answer is imaging. Therefore, the characterization of the anatomy, geometry and function of the LA with imaging techniques is central and should be assessed in all patients with AF.

LA enlargement or dilation may be a marker of the severity of underlying structural heart diseases including hypertension, coronary artery disease, heart failure, or valvular heart disease. But LA size may also act as a marker of long lasting LV diastolic dysfunction, and LA enlargement has been related to hospitalization, cardiovascular outcomes,[41,42] and higher risk of new-onset AF.[43–46] In patients without permanent AF, progression of AF is independently associated with LA dilation, so adding this parameter to clinical scores (eg HATCH score) might improve prediction of progression to permanent AF.[47] The recent AF A-Recur, an ESC EORP AFA-LT registry machine-learning web calculator for predicting AF recurrence after ablation, also includes LA diameter as 1 of their items.[48] However, LA enlargement is present even in patients with paroxysmal AF which suggests that cardiac remodeling may occur very early in the natural history of AF.[49]

In addition, echocardiographic variables might improve thromboembolic risk stratification.[50] Thus, remodeling of the LA characterized by an enlarged LA diameter is a risk factor of thrombosis,[51] and several studies have now demonstrated how enlarged LA is an independent risk factor for LAA thrombus and ischemic stroke in AF patients.[52–54] Severe LA enlargement is even associated with increased risk of recurrent ischemic events after an ischemic stroke/transient ischemic attack (TIA) in patients with AF.[55] In particular, there is evidence showing that LA enlargement is significantly related to thromboembolic events in AF patients at low/moderate thromboembolic risk (ie CHA_2DS_2-VASc score: 0 to 1 in males, 1 to 2 in females),[56] and that enlarged LA *per se* was independently associated with the presence of LAA thrombus or spontaneous echo contrast in AF patients with low CHA_2DS_2-VASc score.[57,58]

However, the echocardiographic assessment of LA size has some limitations. This method is based on the measurement of LA size in an anteroposterior linear dimension by M-mode or 2D echocardiography in parasternal long-axis view and assumes the constant relationship between all LA dimensions. Thus, it could be an unreliable representation of the true LA size, particularly when LA dilatation is present, resulting in an asymmetric shape of the LA. For this reason, linear methods are not the preferred method and instead, LA-indexed volumes should be assessed for quantification of LA size.[59,43] Indeed, LA volume further refines risk stratification for new-onset AF in patients with normal LA diameter,[44] and LA volume indexed for the body surface area (LAVi) is associated with new-onset AF and stroke recurrence in patients with Embolic Stroke of Undetermined Source (ESUS).[60,61] Moreover, in elderly AF patients without anticoagulation therapy, LAVi may identify thromboembolic events, all-cause and cardiovascular mortality.[62] Similarly, a recent systematic review and meta-analysis found that a higher LAVi was significantly associated with the risk of MACE in AF patients (relative risk 1.01, 95% CI 1.00-1.02; $P = .03$).[42] Another study demonstrated that LAVi increased significantly in patients with higher CHA_2DS_2-VASc, which may suggest that high LA pressure favors thrombogenic propensity.[63] Indeed, patients with AF and an enlarged

LA assessed by LAVi have shown a higher risk of LAA thrombi and thromboembolism.[64,65]

Another parameter specifically associated with atrial remodeling is the LA emptying fraction (LAEF).[66] Thus, reduced LAEF increased the risk for new onset AF,[67] and it is associated with worse cardiovascular outcomes, rehospitalization and mortality.[41,68] Overall, LA dilation processes are complex and not always seem concordant to histologic and electrophysiologic changes so dilation may occur with relatively benign histology and electrophysiology. This also emphasizes why imaging could be useful in this context, independent of other complex and invasive assessment methods to determine the potential presence of remodeling and fibrosis.

What is the best echocardiography technique to assess LA size?

As highlighted above, LA size is related with the risk of thromboembolism, and may also impact the success of catheter ablation, depending on the presence of severe LA dilatation, as a marker of atrial remodeling. For this reason, an echocardiographic examination is recommended for all AF patients, to assess cardiac structure and function.

However, a remaining question is about the appropriate tool for this assessment of the LA. TTE is the most common procedure in everyday clinical practice owing to its versatility, safety, and ability to assess myocardial and valvular structure and function, and provides linear and volumetric measurements of the LA. Thus, the LA anteroposterior diameter, using linear methods such as the M-mode, is frequently used in several studies and clinical trials, and has good reproducibility. Unfortunately, this method may underestimate the LA size, particularly in the presence of severely enlarged LA. Therefore, volumetric measures for quantification of LA volumes, for example by the biplane Simpson's rule, are accurate and currently recommended.[6,69]

On the other hand, TOE provides a higher resolution exploration of the posterior cardiac structures, including the atria, atrial septum, PVs, and atrial appendages for thrombus detection. Hence, TOE is the more reliable test for AF patients at high risk of thromboembolism, to rule-out the presence of LAA thrombus before early cardioversion, in AF patients with history of LAA thrombus or stroke/TIA, or in those with valvular disease[1,70,71] (Table I).

However, 2D imaging techniques that may underestimate LA dimension as compared with 3D imaging, since use geometric assumptions and are operator dependent. In contrast, real-time transthoracic 3D echocardiography allows a more accurate assessment of LA volumes and provides direct identification of the LA endocardial border.[59,69,72] Other 3D imaging techniques, such as real-time multidetector row CT (MDCT), and CMR, may provide more exact and detailed assessment of the dimensions, structure, and spatial relationships of the LA, critical for risk stratification and clinical decision-making of patients with AF.[73]

How to solve limitations of conventional echocardiographic indices?

We have previously discussed that LA size and LA volume have some limitations when evaluating LA function since they depend on hemodynamic loading conditions, geometric assumptions, and on the subjective image interpretation. These problems could be solved by using more sophisticated echocardiographic techniques.

For example, pulse-wave Doppler echocardiography at the tips of mitral valve leaflets and at PVs ostia provides information on hemodynamics between the LA and LV, and upstream to the LA. Indeed, peak transmitral A-wave velocity and velocity-time integral in late diastole with pulsed-wave Doppler echocardiography serve as indexes of LA function. Moreover, peak transmitral E-wave velocity and peak mitral annular tissue velocity in early diastole ratio (E/e´ratio) is a non-invasive measure of LV filling pressure, thus indirectly reflecting the pressure overload of the LA. Similarly, the E/A ratio which represents the ratio of peak velocity blood flow from LV relaxation in early diastole (the E-wave) to peak velocity flow in late diastole caused by atrial contraction (the A-wave), is very large in AF since in these patients the late phase is dependent upon atrial contraction and absent due to the lack of effective atrial contraction.[70,73] Additionally, tissue Doppler imaging (TDI) depicts myocardial tissue velocity at specific locations in the heart, which has the advantage of lower load-dependency.[74] Both pulse-wave TDI and color-coded TDI (CTDI) can be applied to generate a myocardial velocity curve to assess a regional LA function. However, CTDI offers the possibility to process images offline and present simultaneous multi-segment analyses of velocities; hence different LA walls can be compared and assessed.[75]

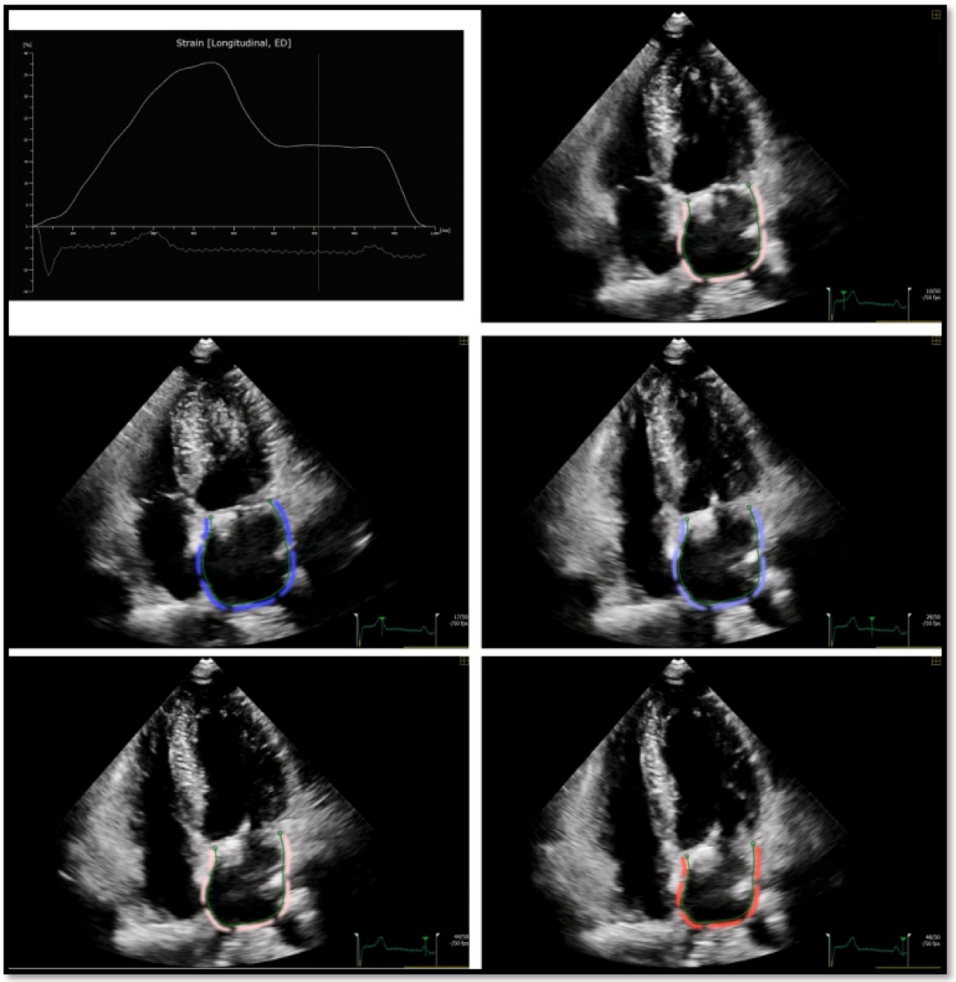
Speckle tracking echocardiography (STE) is a useful tool for the quantitative evaluation of myocardial performance. It is a reproducible, more objective and less loading and operator-dependent method to quantify LA function. Technically, STE records consecutive cardiac cycles in apical 4-, 3- and 2-chamber views to measure longitudinal deformation and in the parasternal short axis view for circumferential and radial deformation.[76] LV torsion can also be assessed by capturing the short axis view at the level of the mitral valve, the papillary muscles and the apex.[77] The software detects unique myocardial pixel patterns in greyscale images, so-called "speckles" and traces those acoustic markers throughout the analyzed cardiac cycle. Vectors are measured and deformation parameters are subsequently calculated. By this way, regional and global myocardial deformation can be assessed throughout cardiac cycle for both left and right ventricles and atria.[78,79] Thus, LA dysfunction

Table I. Role of different imaging modalities in atrial fibrillation.

	TTE	TOE	MDCT	CMRI
Assessment of LA size	+ +	+ +	+ + +	+ + +
Assessment of LA function*	+ +	+ +	+ +	+ +
Assessment LA deformation (LA strain and strain rate)	+ + +	+ + +	-	-
Evaluation of underlying heart disease	+ +	+ +	+ + +	+ + +
Identification of LA thrombus	-	+ + +	+ +	+ +
Visualization of anatomy pre-ablation procedure	+	+ +	+ + +	+ + +

CMRI, cardiac magnetic resonance imaging; LA, left atrial; MDCT, multidetector row computed tomography; TTE, transthoracic echocardiography.
*Assessment of LA function LA volumes by echocardiography could be improved by using 3D assessment of LA volume.

Figure 2



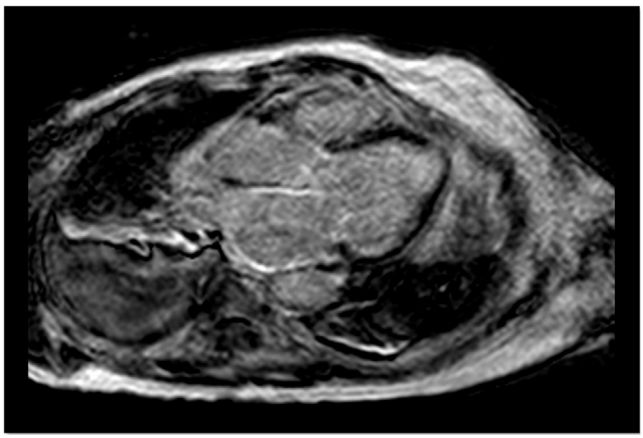
Global longitudinal strain of the left atrium by transthoracic echocardiography.

determined by STE can provide incremental prognostic information to conventional echocardiographic parameters in patients with cardiovascular diseases and appears to be a promising technique for diagnosis and therapeutic decision-making.[80]

LA deformation imaging

Novel modalities for the assessment of LA remodeling include LA strain (or deformation) and strain rate. Both may be measured by either TDI or STE, and provide direct information of LA myocardial properties

Figure 3



Cardiac magnetic resonance in four-chamber plane. Late gadolinium enhancement sequence.

LA strain is the deformation of the LA wall, and it is significantly and independently associated with AF, providing incremental predictive value over clinical and standard echocardiographic parameters.[81-83] TDI allows the estimation of LA strain in TTE, yet it depends on the angle of insinuation and considerably limits its use because the analysis provided is mainly regional.[84] LA strain by STE is a postprocessing algorithm that allows the assessment of LA function in each phase of the cardiac cycle (Figure 2), although its determinants and relation with LV function have not yet been fully described.[85] Reservoir, conduction, and pump functions can be measured by the LA strain, which are inversely correlated with the degree of fibrosis. Thus, a reduced LA strain is a marker of fibrous atria with decreased contractile capacity.[70]

An EACVI/ASE/Industry Task Force consensus document recommends taking into account variations in LV function during the evaluation of LA strain, and also states that LA strain during late diastole might be more informative than LA strain during LV systole.[86] In brief, this document suggests that LA strain should be evaluated in the booster pump phase and not only in the reservoir phase after adjustment for LV longitudinal systolic function.[86] However, a LA strain independently associates with incident AF in the general population, even in participants with normal-sized LA and normal LV systolic function.[87]

On the other hand, strain rate could be of great interest in the assessment of LA function. While LA strain evaluates LA deformation alone, LA strain rate examines the rate of change in strain, and can be measured throughout the cardiac cycle, thereby enabling the evaluation of LA reservoir function (in systole) as well as the conduit and contractile function (in diastole).[88] On the other hand, in patients with paroxysmal or persistent AF referred for TTE, there was an inverse correlation between lower strain during the reservoir phase in the mid-septal and mid-lateral LA and the greater extension of LA enhancement with late gadolinium enhancement on CMRI (LGE-CMRI). Multivariable analysis showed that mid-lateral strain ($r = -0.5$, $P = .006$) and strain rate ($r = -0.4$, $P = .01$) inversely correlated the extent of fibrosis independently of other echocardiographic parameters.[89]

In summary, TTE and TOE are the most widely performed techniques for the evaluation of LA, and the study of LA wall deformation analysis is becoming more reliable. These methods should be implemented for all AF patients, and could be practical and meaningful in everyday clinical practice. TTE is the first-choice technique for both anatomical and functional analysis of the LA, with the anteroposterior atrial diameter as the most accepted parameter for the evaluation of atrial size. TOE is usually used to study some morphological characteristics of the LA, particularly in the preparation and performance of invasive treatments such as LAA closure. Nevertheless, it is currently recommended to assess the LA with 3D echocardiography techniques, since they provide greater accuracy.[84] Of note, TDI and STE allows us to obtain LA strain and strain rate, thus also providing information about LA deformation which could be of clinical relevance in AF.

Does multi-slice computed tomography or cardiac magnetic resonance add value?

MDCT allows imaging of the anatomic characteristics of the PVs and LA, hence helping to understand the morphological remodeling of PVs and LA.[6,59,69] Compared to conventional CT, MDCT has a high acquisition speed

Table II. Risk factors and scoring system included in different schemes for predicting atrial fibrillation.

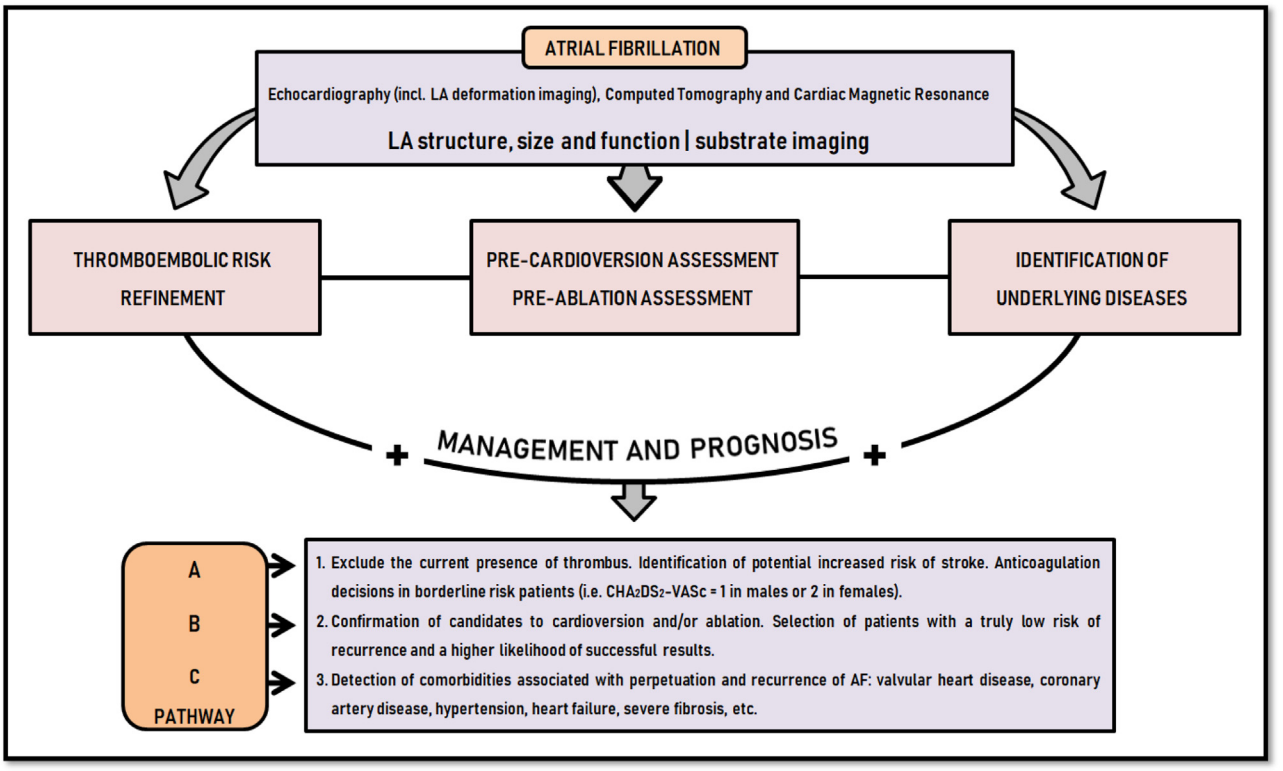
	CHA_2DS_2-VASc	BASE-AF2	APPLE	MB-LATER	CAAP-AF	HATCH	POAF	COM-AF	C_2HEST
Age									
50-59 years					**1**				
60-69 years					**2**		**1**		
>65 years			**1**						
65-74 years	**1**							**1**	
>69 years					**3**				
70-79 years							**2**		
>75 years*	**2**					**1**		**2**	**2**
>79 years							**3**		
Sex									
Male				**1**					
Female	**1**				**1**			**1**	
AF-related factors									
AF type									
Non-paroxysmal		**1**							
Persistent			**1**	**1**	**2**				
Long-standing persistent				**2**	**2**				
AF history									
>6 years		**1**							
Comorbidities									
Hypertension	**1**					**1**		**1**	**1**
Vascular disease	**1**								
Coronary artery disease					**1**				**1**
Heart failure	**1**					**2**		**2**	**2**
Ejection fraction <30%							**1**		
Ejection fraction <50%			**1**						
Diabetes mellitus	**1**							**1**	
Chronic kidney disease									
eGFR <15 ml/min/1.73 m^2							**1**		
eGFR <60 ml/min/1.73 m^2			**1**						
Smoking		**1**							

	CHA_2DS_2-VASc	BASE-AF2	APPLE	MB-LATER	CAAP-AF	HATCH	POAF	COM-AF	C_2HEST
Stroke/TIA	**2**					**2**		**2**	
Body mass index									
>28 kg/m^2		**1**							
COPD						**1**	**1**		
Hyperthyroidism									**1**
Bundle branch block				**1**					
Echocardiographic results									
LA diameter									
>40 mm		**1**							
40-44 mm					**1**				
>42 mm			**1**						
45-49 mm					**2**				
>46 mm				**1**					
50-54 mm					**3**				
>54					**4**				
Factors related to restoration of sinus rhythm									
Post-ablation early recurrence		**1**		**1**					
Failed AAD									
1 or 2					**1**				
>2					**2**				
Surgical-related factors									
Emergency surgery							**1**		
Preoperative IABP							**1**		
Valve surgery							**1**		
Total score	**9**	**6**	**5**	**6**	**13**	**7**	**9**	**9**	**8**
High risk	**≥2**	**≥3**	**≥3**	**≥2**	**ND**	**≥5**	**≥3**	**>2**	**>3**

AF = atrial fibrillation; eGFR = estimated glomerular filtration rate; TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease; LA = left atrium; AAD = anti-arrhythmic drugs; IABP = intra- aortic balloon pump; NR = non-declared.

* ≥75 years in CHA_2DS_2-VASc, COM-AF and C_2HEST scores.

Figure 4



Integration of imaging in decision-making process of atrial fibrillation in relation to the ABC pathway.

and records volume data instead of individual slice data. Therefore, MDCT allows 3D assessment of LA size and offers higher spatial and temporal resolution with better diagnostic image quality. In addition, as MDCT enables the visualization of the PVs, this is of particularly interest in AF since these are the main target during the ablation procedure.

However, MDCT has the disadvantage of the need for iodinated contrast and radiation exposure and for this reason it is currently not the first choice for assessment of LA size.[59,69] Nevertheless, ECG-gated cardiac scanning MDCT systems can scan large volumes at high speed so that the temporal and spatial resolution significantly improves and enables visualization of small and moving structures,[90]and led to a significant reduction in effective radiation doses compared with retrospective acquisition modes.[6] Indeed, a meta-analysis found that prospectively triggered examinations provided image quality and diagnostic accuracy comparable with retrospectively gating, but at a much lower radiation dose,[91] with considerable reduction of radiation exposure in coronary CT angiography during the last decade.[92]

Alternatively, CMR also provides 3D imaging with high spatial resolution which gives accurate assessment of the LA, mostly by the modified Simpson's method using LA areas from subsequent cross-sectional images.[59] During recent years, CMR has become the gold standard for volumetric analysis and quantification of LA size, avoiding exposure to ionizing radiation and allowing tissue characterization.[59,93] In particular, LGE-CMRI uses gadolinium contrast agents that remain trapped within the expanded extracellular matrix, which is visualized as hyperenhanced areas (bright) (Figure 3).[69] Thus, LGE-CMRI has emerged as a promising tool to obtain mechanistic insights into structural alterations of the atrial wall in patients with AF.[94] Indeed, AF patients had higher LGE and lower LA functional parameters compared with healthy volunteers.[95] LGE-CMRI and custom image analysis software may identify, quantify, and characterize atrial fibrosis, and has been used to characterize areas of LA fibrosis in AF patients.[96–98] As mentioned above, LA fibrosis is the cornerstone of LA remodeling, and is associated with new-onset AF, perpetuation of AF, and recurrence of AF after catheter ablation. For this reason, the degree of LA fibrosis quantified by LGE-CMRI might be useful to stratify recurrence risk and therefore personalize the therapeutic strategy to each patient.[6,96] As limitations of this technique, the acquisition of images is prolonged and ar-

tifacts related to patient's movement or atypical respiratory patterns are frequent. In addition, post-processing of the images is complex and requires segmentation of the walls of the LA, determination of fibrosis through signal intensity thresholds, and specific export formats of the 3D reconstructions.

In summary, MDCT and LGE-CMRI provide high spatial resolution data and clear definitions of the endocardium improving the accuracy of 3D measurements of the .LA[69,99] (Table I), with good correlations for LA volume assessment between the 2 techniques.[100]

Multimodality imaging: from atrial substrate characterization to clinical practice

AF is a complex, multifaceted and heterogeneous disease that requires multiple treatment decisions and a holistic management. For this reason, the use of appropriate imaging techniques should no longer be considered as optional or additional tests but as a central part of AF management to aid decision-making (Figure 4). In patients with AF, an assessment of cardiac function and structure is necessary to complement the clinical evaluation, and to provide insights into the etiology and pathophysiology. This is central to assist the decision about stroke risk stratification and the use of rate or rhythm control management strategies.

Although echocardiography has been well recognized in AF, its use was mainly limited to rule out the presence of LA thrombus prior to ablation or cardioversion procedure. Thus, pre-procedure TOE is commonly performed to exclude LA thrombus since it is a temporal contraindication for an AF ablation.[6] While this is undoubtedly relevant, more precise imaging techniques also facilitate visualization of LA, PVs size and anatomy, as well as surrounding structures including coronary veins, coronary arteries, and the course of the oesophagus. Moreover, LA enlargement adds clinical and prognostic information and should be assessed as a part of routine comprehensive AF evaluation. Consequently, MDCT and CMR are now preferred and used for anatomical guidance during the procedure, and provide relevant additional information of the LA.

Over the last few years, new horizons have been opened in the use of imaging techniques to improve the overall management of AF patients. The EAST-AFNET 4 trial demonstrated that early rhythm control was associated with a lower risk of adverse cardiovascular outcomes than usual care among AF patients,[101] which was consistent in asymptomatic and symptomatic patients.[102] For this reason, it is essential to properly evaluate AF patients who may benefit from a rhythm control strategy, especially from AF ablation.

In this regard, the 4S-AF scheme was recently described as a novel approach to in-depth characterization of AF and includes 4 AF-related domains (*S*troke risk, *S*ymptom severity, *S*everity of AF burden, *S*ubstrate severity).[103] Importantly, the *S*ubstrate severity domain in the 4S-AF scheme requires the assessment of LA enlargement/dysfunction and LA fibrosis by TTE, TOE, MDCT or CMR hence putting imaging in the frontline of the AF management decision-making. For example, when deciding on ablation, imaging may help in selecting those patients who will really benefit from this procedure since extreme LA enlargement and long-standing permanent AF are relative contra-indications because of the low probability of successful outcome.[59]

Thus, LA remodeling assessed by 3D echocardiography predicted AF recurrence after cryoballoon ablation even in patients with non-dilated LA by M-Mode and 2D echocardiography, which suggests that 3D echocardiography might be considered for systematic use to evaluate AF recurrence risk.[104] Furthermore, extensive LA remodeling (≥30% LA wall enhancement) identified on LGE-CMRI brought a poor response to catheter ablation therapy for AF.[105]

Tops *et al.* showed that baseline LA deformation assessed by TDI-derived LA strain was associated with subsequent reverse structural LA remodeling following AF ablation, which may reflect the underlying extent of LA fibrosis, and impact the ability of the LA to reverse remodeling after successful catheter ablation.[106] Similarly, Kuppahally *et al.* demonstrated that LA fibrosis by LGE-CMRI was inversely related to LA strain and strain rate, and both were associated with AF burden, independently of other echocardiographic measurements.[89] More recently, CMR-derived baseline LA reservoir strain was independently associated with AF recurrence post AF ablation.[107]

Certainly, the Delayed-Enhancement MRI Determinant of Successful Radiofrequency Catheter Ablation of Atrial Fibrillation (DECAAF) study demonstrated that among AF patients undergoing catheter ablation, atrial tissue fibrosis estimated by LGE-CMRI was independently associated with AF recurrence.[108] Such observations are also valid for patients undergoing electrical cardioversion. Indeed, TTE and TOE might detect markers of mechanical remodeling associated with sinus rhythm maintenance after electrical cardioversion in AF,[109,110] and LA strain by STE predicted arrhythmia recurrence at 6-month after electrical cardioversion.[111]

Along the same lines, visualization of atrial fibrosis as a potential target for catheter ablation of AF is gaining attention. The DECAAF II trial was the first prospective, randomized, multicenter trial of patients with persistent AF to use LGE-CMRI defined atrial fibrosis as a treatment goal.[112] The trial demonstrated that LGE-CMRI guided fibrosis ablation plus PV isolation, compared with PV isolation catheter ablation alone, did not result in significant difference in atrial arrhythmia recurrences among patients with persistent AF. Therefore, these findings do

Table III. Patients subgroups who may benefit from more sophisticated techniques and in-depth imaging study.

Prior to electrical cardioversion in AF patients with suspected significant structural damage.
Prior to ablation in AF patients with suspected significant structural damage.
Patients who develop post-operative AF.
Patients who develop secondary AF due to an acute condition (eg pneumonia, sepsis, acute coronary syndrome)
Patients with AF detected by wearables without diagnostic ECG.

not support the use of LGE-CMRI guided fibrosis ablation for the treatment of persistent AF.[113] Thus, atrial fibrosis could be a potential and useful risk marker but not necessarily an ideal electrophysiological end point for catheter ablation.

Despite the observations derived from the DECAAF II, imaging techniques are still needed for a proper integrated and patient-centered assessment of AF. This more individualized management and substrate-based approach is aligned with the use of the 4S-AF scheme, so that the proper characterization of AF may help in deciding the correct management, leading to a reduction of AF symptoms and recurrence. Moreover, imaging enhances our understanding of the underlying mechanisms of atrial remodeling.[114] These added data will help us to select the best medical therapies and interventions. For example, modifying cardiovascular risk factors such as hypertension, obesity or heart failure can reverse –at least partially– the remodeling process, particularly in the early stages of LA structural and functional remodeling,[93,115] in order to reduce AF burden and AF-associated complications. Indeed, a systematic review and meta-analysis has shown that substrate modification based on LA low-voltage areas could improve the risk of arrhythmia recurrence in AF patients after a first conventional ablation procedure (OR 0.30, 95% CI 0.15-0.62).[116] Imaging techniques (and particularly the assessment of LA diameter), have been used to predict AF, thus highlighting the need to appraise the severity of the LA substrate (Table II).[117-125] More sophisticated imaging beyond LA diameter could be especially useful in different clinical situations where patient management and clinical decisions are less clear (Table III).

Additionally, cardiac imaging to assess LA remodeling/fibrosis might help in refining the risk of stroke and choosing the appropriate oral anticoagulation therapy. On the 1 hand, the use of imaging techniques may provide information that would improve the predictive ability of clinical risk scores such as CHA_2DS_2-VASc.[43, 82,126] Current clinical practice guidelines recommend the use of non-vitamin K antagonist oral anticoagulants (NOACs) in preference to warfarin for stroke prevention in AF patients;[1,71,127,128] indeed, NOACs are associated with reduced ischemic stroke/systemic embolism and all-cause death compared with warfarin in elderly AF patients with LA enlargement.[129]

Limitations and contra of multimodality imaging

The imaging techniques discussed above are promising techniques that might provide additional information for clinical practice. However, they are not exempt from limitations that may hinder their application in different contexts.

First, the usefulness of identifying fibrosis as a target for ablation outcome is not completely clear. This warrants further research to determine whether AF patients with highly remodeled or fibrotic atria should be predominately entered into an ablation programme. On the other hand, many of these techniques are sophisticated and required from a technology not always available in several centers. In addition, they imply higher costs, and require adequate training by the health care personnel in charge of performing them. Another pending issue is the quality, which could be variable. Indeed, the discrepancy in the amount of LA fibrosis quantified by different 3D LGE-CMRI analysis methods could be substantial, may have clinical implications when patients are classified according to their fibrotic burdenb[130] The need of contrast agents, or even ionizing radiation, may limit also the use of these techniques in some patients. Finally, many AF patients are cared for and followed in very resource-limited environments, where even TTE or TOE may not be available, or where the lack of software for 3D assessment may prevent a more accurate and precise assessment of LA or restrict its use in routine clinical practice.

Conclusions

Atrial remodeling and fibrosis are common in AF. To do an appropriate selection of rhythm/rate control strategies, address symptom improvement, assess risk profile and stroke prevention in a personalized manner, a comprehensive characterization is needed. The evaluation of the AF substrate complexity is therefore central, and includes the presence and extent of LA enlargement, impaired atrial function, LA deformation and fibrosis of the atrial myocardium. Thus, the management of AF requires a multidisciplinary and integrated approach to facilitate decision-making and imaging techniques such as TTE, TOE, MDCT or LGE-CMRI, might help to assess the AF substrate in everyday clinical practice, hence providing a better characterization of patients with AF.

Data availability Statement

No new data were generated or analyzed in support of this research.

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