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The Role of Echocardiography as a Predictor of the Incidence and Progression of Atrial Fibrillation

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Abstract

Atrial fibrillation is the most frequent sustained arrhythmia and is an independent risk factor for stroke and death. In recent years, major echocardiographic advances have been made with the development of new techniques and applications that can be extremely useful for the management of these patients. This paper describes the role of echocardiography as a predictor of the incidence and progression of atrial fibrillation. A detailed description of the most relevant studies and recognition of unresolved questions regarding this subject are presented here. A special emphasis will be given on new techniques that allow the assessment of myocardial deformation and their possible role in the way we treat these patients.

Introduction

Atrial fibrillation (AF) is the most frequent sustained arrhythmia and is an independent risk factor for stroke and death.[1] In recent years, major advances have been made in the field of echocardiography, with the development of new techniques and applications.

Transthoracic Echocardiography (TTE) is an easily accessible and non invasive technique. It presents no radiation hazard and has very few contraindications, which renders it ideal for the initial work-up of all patients presenting with AF.

In the following sections we will review most of the current applications of echocardiography concerning the prediction of the incidence and progression of AF and illustrate new findings and possible applications for the near future. There are two main parts in this article: the first, comprising sections 1 to 6, is about the natural course of atrial fibrillation and describes echocardiographic parameters that may predict its development and progression over time, from paroxysmal to persistent, and eventually permanent AF. The second part describes the predictors of AF relapse in procedures like cardioversion and radiofrequency ablation and the incidence and relapse in cardiac surgery (other than ablation).

A brief summary of the different echocardiographic parameters and the situations in which they can be used is present on Tables I and II.

Left Atrial Size as a Marker of the Incidence and Progression of AF

The Best Method for Measuring Left Atrial Size

Left atrial (LA) dilation can be assessed using

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Table 1 Echocardiographic parameters that predict the Development or Progression of Atrial Fibrillation

	Echocardiographic Parameter
Development of AF	LA size – diameter, area and indexed volume
	Atrial dissincrony (tissue Doppler strain)
Progression of AF	LA diameter
	Atrial conduction time (PA-TDI)

AF – atrial fibrillation; LA – left atrial; PA-TDI – time interval from P wave on ECG lead II to A´on lateral atrial pulsed tissue Doppler imaging

M-mode, two or three dimensional (2D or 3D, respectively) echocardiography. It is known that LA dilation spatially occurs in an asymmetric way, predominantly in the medial-lateral and superior-inferior axes since enlargement in the antero-posterior axis may be limited by the thoracic cavity. In face of this, and despite the fact that most classic studies have used this parameter, diameter is not an accurate way of assessing LA dimensions, because it frequently underestimates LA size. This is worrisome since underestimation is more pronounced in patients with enlarged LA.

The measurement of LA area using planimetry in apical four-chamber view can provide more consistent information regarding size and be used as part of the LA volume equation. Badano and colleagues suggested that 2D LA area may be an accurate method, however the available cut-off criteria are inappropriate and need redefinition.[2]

LA biplane volume measurement using either the area-length formula, or the modified Simpson's rule, is currently recommended by the European Society of Echocardiography (ESE) and American Society Echocardiography (ASE) guidelines as the preferred method, since it can more reliably reproduce the atrial geometry (as it relies on fewer geometric assumptions) and therefore has higher accuracy and prognostic value.[3, 4] These biplane methods have been successfully validated against cine computed tomography and magnetic resonance imaging.[5-7]

Nevertheless biplane volume measurement is not always feasible, as the apical two-chamber view may not provide optimal LA border visualization. Russo et al have demonstrated that single-plane modified Simpson's method for measuring LA volume has a high correlation with LA volume assessed by three-dimensional echocardiography ($r=0.93$, $p<0.001$). Similar findings were reported for the biplane area length method ($r=0.93$, $p<0.001$). Nevertheless, single-plane volumes were significantly larger than biplane volumes with an overall mean difference of 1.9ml/m2. This difference, albeit small, resulted in a significant misclassification when using the ASE cut-offs.[8] Similar findings were described by Badano and colleagues when comparing the single-plane area-length and biplane method of discs using 3D echocardiography as a reference standard.[2] They demonstrated that left atrial diameters and area measurements were poor predictors of 3D LA volume. Using M-mode antero-posterior diameter or LA area resulted in misclassification of the degree of left atrial dilation in 57 to 70% of patients. a good correlation was found between LA volumes assessed by 2D and 3D echocardiography. The biplane method seemed to be slightly more accurate than the single plane area-length method. Nevertheless, according to these authors, the additional accuracy obtained using a more technically demanding and time-consuming biplane method did not justify its usage.[2]

Table 2 Echocardiographic parameters that predict atrial fibrillation relapse after procedures

Procedure	Echocardiographic Parameter
Cardioversion	LA size – diameter, area and indexed volume Systolic pulmonary venous flow LV systolic function LAA ejection fraction LAA peak emptying velocity LA strain and strain rate (Doppler derived and speckle tracking)
Percutaneous Radiofrequency Ablation	Indexed LA volume E/E´ratio LA strain and strain rate (Doppler derived and speckle tracking)
Surgical ablation	LA size – diameter, area and indexed volume
Other types of cardiac surgery	E/A ratio E/E´ratio indexed LA volume

LA – left atrial; LV - left ventricle; LAA – left atrial appendage; E - early transmitral flow velocity; A - late transmitral flow velocity; E' - early diastolic mitral annular velocity.

Incidence of AF in the Dilated Left Atrium

According to data from the Framingham Heart Study, during an 8-year follow-up of 1924 subjects, a 5mm increment on LA size (diameter on M-mode) was associated with a 39% increase in the risk for subsequent development of AF.[9] Psaty and colleagues demonstrated in a cohort of 5201 elderly subjects that the risk of developing AF during a 3 year follow-up period was increased about 4 times in those with LA diameter over 5 cm.[10]

In patients admitted due to congestive heart failure, LA size > 45mm and atrial dissincrony > 39ms assessed by strain were independent predictors of the incidence of new-onset atrial fibrillation.[11]
Lin and colleagues have found that LA area independently correlates with the incidence of paroxysmal AF in patients with sick sinus syndrome: each 1cm2 increase in LA area led to a 44% increase in the incidence of AF.[12]

In a cohort of 1655 elderly patients followed during an average of 3.97 years, a 30% increase in LA volume was associated with a 43% higher risk of developing AF.[13] In an elderly cohort of patients with no history or evidence of prior atrial arrhythmias, LA volume was an independent predictor of first AF episode or atrial flutter during a mean follow-up of 1.9±1.2 years.[14]

Progression of AF in the Dilated Left Atrium

LA enlargement was associated with progression to chronic AF in patients with newly diagnosed AF in the Canadian Registry of AF (CARAF).[15]

In a 14 years follow-up study, Kato et al have found that aging (HR 1.27 per 10 years, 95%CI 1.06-1.47), a dilated left atrium (HR 1.39 per 10mm, 95%CI 1.11-1.69), myocardial infarction (HR 2.33, 95%CI 1.13-4.81) and valvular heart disease (HR 2.29, 95%CI 1.22-4.30) were independent predictors of early progression of recurrent paroxysmal AF to chronic AF.[16] Kerr et al. have shown that left atrial enlargement, diagnosis of cardiomyopathy, significant aortic stenosis or mitral regurgitation, age and heart rate were independent predictors of progression of newly diagnosed AF to chronic AF over an 11 year period.[17]

Pillariseti et al. have supported these findings demonstrating that larger LA size (diameter), valvular heart disease (moderate to severe mitral and aortic valve disease) and cardiomyopathy (ischemic, non-ischemic or hypertrophic obstructive cardiomyopathy) predicted progression of paroxysmal AF to persistent or permanent AF. A larger LA size and the presence of valvular heart disease were also predictors of progression to permanent AF.[18] The role of cardiomyopathy and valvular heart disease is thought to be associated with the increase in LA stretch (see below).

Using data from the Euro Heart Survey on AF, Vos et al. have developed the HATCH score for the prediction of AF progression. The multivariate logistic regression included clinical factors only: heart failure, age, previous ischemic attack or stroke, chronic obstructive pulmonary disease and hypertension. Still, patients with AF progression had larger LA size (diameter) and higher prevalence of valvular disease.[19]

Recently, Suzuki and colleagues have found that increased LA diameter is associated with a longer period in AF (6.5% increase in the number of days) and progression from paroxysmal to persistent AF (HR 1.84) in hypertensive patients from the Japanese Rhythm Management Trial II (J.RHYTHM II).[20]

Atrial Stretch and the Progression of AF

AF is self-regenerating and predisposes to the progression of AF ("AF begets AF")[21] due to electroanatomical remodeling. Accordingly, AF leads to left atrial dilation which subsequently leads to more AF episodes or progression to persistent and permanent forms. Therefore, left atrial dilation is a part of this vicious circle arising both as a cause for and a consequence of AF. Besides left atrial dilatation, the presence of pressure and volume overload in the atria, resulting in cardiomyocite elongation and increased atrial stretch, also seems to have a preponderant role in atrial remodeling and incidence and progression of AF.[22] Mitral regurgitation, arterial hypertension and diastolic dysfunction are some of the factors that lead to atrial stretching and cause structural remodeling. The role of atrial stretch, occuring independently of left atrial dilation needs to be further evaluated and the echocardiographic deformation assessment may have an important role in this field.

The Association of Pulmonary Vein Dilation with AF

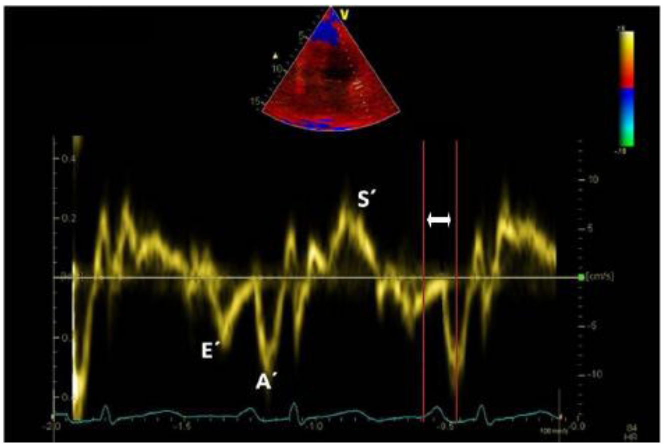
Pulmonary vein dilation may be another possible crosslink between LA enlargement and AF.[23] Isolated dilation of the pulmonary veins[24] or alongside with left atrial dilation[25] has been reported in patients with AF. However, it is not totally clear if pulmonary vein dilation precedes left atrial dilation or arises as a cause of it.[26] Unfortunately, echocardiography is not as accurate as other techniques (angiography, computed tomography or magnetic resonance imaging) to assess these structures.

Atrial Conduction Time and AF Progression

The use of tissue Doppler imaging (TDI) allows quantification of low-velocity, high-amplitude, long-axis intrinsic myocardial velocities, and provides information regarding systole and diastole in a load independent way.

A prolonged atrial conduction time measured through signal averaged ECG has been previously associated with history of AF[27] and progression of paroxysmal into permanent AF.[28] A new transthoracic echocardiographic tool has been recently described, the PA-TDI, which measures the time from the initiation of the P wave on the ECG in lead II to the late diastolic mitral annular velocity - A′ wave - on the lateral left atrial tissue by Doppler tracing and reflects the total atrial conduction time (Figure 1). A prolonged PA-TDI seems to predict a new-onset of AF,[29] AF after acute myocardial infarction[30] and recurrence of AF after radiofrequency catheter ablation.[31] This index has been proposed as an early marker of paroxysmal AF[32] and has also been shown to be associated with echocardiographic signs of diastolic dysfunction, valve incompetence and LA dilation.[33]

Figure 1: Measurement of the atrial conduction time: PA-TDI is obtained using pulsed tissue doppler imaging with the sample placed in lateral border of the mitral annulus and measuring the time interval from the begining of the P wave (ECG lead II) to the late diastolic mitral annular velocity (A′)



E´- early diastolic mitral annular velocity; S´- systolic annular velocity.

Left Atrial Mechanical Function and the Progression of AF

LA mechanical function can be assessed with pulsed wave Doppler measurement of transmitral inflow patterns. The peak transmitral A wave velocity is frequently used to provide information regarding LA mechanical function but is absent during AF. Other parameters of atrial function like the velocity time integral of the A velocity and the atrial fraction (ratio of the time velocity integral of the mitral A wave to that of the total diastolic transmitral flow) can also be used, but only in patients in sinus rhythm.[34] Atrial ejection force, defined as the force exerted by the LA to propel blood across the mitral valve into the LV during atrial systole, is another marker of atrial mechanical function.[35]

Since these markers are lacking in patients in AF, they have limited interest in the assessment of atrial mechanical function. Moreover, they are highly dependent on loading conditions (LA and LV pressures) and diastolic function.

Non-invasive functional quantification of LA deformation properties provides functional information that is independent of cardiac rotational motion and from tethering of contiguous segments of the heart. The rhythm, sinus or AF, during strain imaging does not seem to affect the analysis of LA strain or strain rate. Tissue Doppler velocities measure global tissue motion, whereas strain and strain rate respectively represent the extent and rate of regional deformation that the tissue experiences.

Regional left atrial function assessed by tissue Doppler velocity and strain imaging is markedly compromised in patients with AF.[36] Wang et al.

compared 52 patients with AF for less than 1 year with 27 matched normal control subjects and found that LA early diastolic strain rate was lower in the AF group.[37] Di Salvo et al. have also described compromised atrial myocardial properties assessed by tissue Doppler myocardial velocity, strain rate and strain in AF patients when compared to normal subjects.[38]

Schneider et al described differences in the left atrial deformation properties assessed by TDI in patients before undergoing catheter ablation of AF. Both paroxysmal and persistent AF patients had compromised deformation of the LA, but persistent AF patients presented even lower values .[39] Changes were also found in the left atrial appendage (LAA) pulsed wave TDI with reduction of late systolic wave (upward) and late diastolic wave (downward) and disappearance of initial upward velocity wave during early ventricular diastole.[40]

Angle-dependence, signal artifacts, suboptimal reproducibility and lack of information about the atrial roof and other atrial regions are some of the limitations that have been pointed out to Doppler-derived strain. To overcome these limitations, the use of speckle tracking has been proposed. It is not derived from Doppler but rather from 2D echocardiography. It is angle-independent and allows the measurement of global as well as regional atrial strain.[41]

The Role of Fibrosis as a Marker of Disease Progression

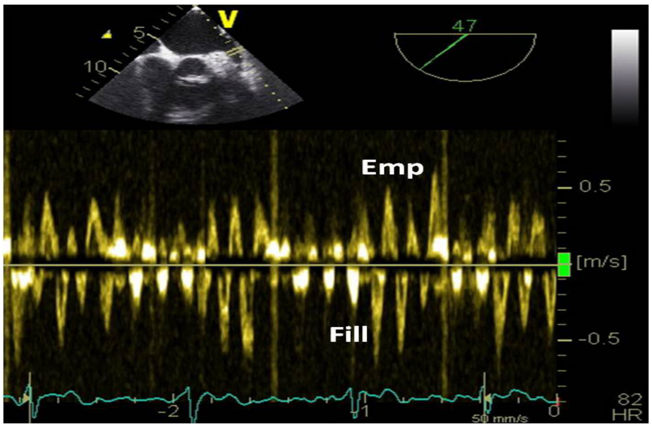
LA enlargement and fibrosis cause disruption of normal electric conduction and establish reentry circuits that lead to increased susceptibility and predisposition to maintenance of AF.[42] The extent of this histologically determined remodelling process has been shown to correlate with the persistence of AF.[43] Oakes and colleagues have described a method using delayed-enhancement MRI (DE-MRI) to assess what is presumed to be LA wall fibrosis.[54] Kuppahally and colleagues have demonstrated that LA wall fibrosis assessed by DE-MRI is inversely related to strain and strain rate derived from vector velocity imaging echocardiography[45] mostly in patients with persistent AF. Patients with persistent AF had significantly more DE (marker of fibrosis) alongside with decreased strain and strain rate compared to those with paroxysmal AF, supporting the concept that there is a progressive remodelling process once AF develops.[46] LA relaxation and lengthening during ventricular systole (markers of LA compliance) are translated by a positive strain and strain rate that seem to be impaired in AF due to fibrosis.

Echocardiographic Predictors of Successfull Cardioversion and Sinus Rhythm Maintenance

Evidence suggests that LA diameter assessed through echocardiography is inversely related to the success of cardioversion (CV).[47-59] Subjects with enlarged LA are more prone to present AF recurrences after CV.[48, 50, 51] An increase in LA area has also been associated with AF relapse after successful CV.[48, 52, 53] According to Marchese et al. the same can be observed with the indexed LA volume, where each ml/m2 increase independently associates with a 21% increase in the risk of AF recurrence (OR 1.21 $p<0.001$). The area under receiver operating characteristic (ROC) curve regarding indexed LA volume as predictor of AF recurrence was 0.85, which was far superior to the one obtained for LA diameter (AUC 0.59; $p<0.001$).[53]

Systolic pulmonary venous flow is a marker of atrial compliance and reservoir function. Low values before or early after CV seem to predict relapse at 6 and 12 months.[54, 55]

Figure 2: Measuring of left atrial appendage flow velocities: placing the pulsed wave Doppler sample 1 cm from the entry of the LAA into the body of the LA. Emptying (Emp – positive defletion, towards the probe) and filling (Fill – negative deflection, away from the probe) velocities should be estimated from an average of five well-defined waves



Preserved LAA peak emptying velocity (high values)[49, 56] has been associated with restoration and maintenance of sinus rhythm in subjects underdoing electrical CV.[47, 56, 57]

In a study by Okçün et al a LAA ejection fraction <30% was the only independent predictor of relapse of AF at 6 months after CV.[54]

Higher values of LA inferior wall peak systolic strain rate and LA septal peak systolic strain assessed through colour Doppler myocardial imaging before electrical CV have also been associated with a greater likelihood of maintaining patients in sinus rhythm. In multivariate analysis, traditional parameters like atrial appendage flow velocity (Figure 2) had no additional predictive value when added to those two parameters (both $p<0.0001$).[38] Wang T et al. have shown that a lower early diastolic strain rate and larger LA transverse diameter were independent predictors of failure of both CV and maintenance of sinus rhythm at 4 weeks.[37]

Echocardiographic Predictors of Sinus Rhythm Maintenance After Percutaneous Catheter Ablation

Shin and colleagues have reported that LA volume measured through echocardiography was a strong independent predictor of AF recurrence after catheter ablation.[58]

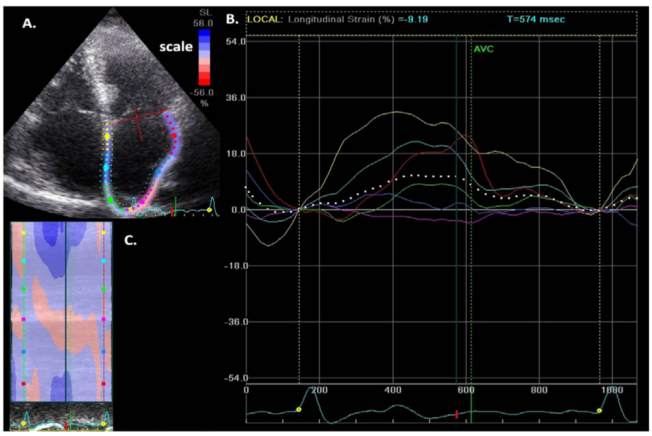
An increased ratio of early transmitral flow velocity (E) to early diastolic mitral annular velocity (E´) (over 11.2) has been associated with AF recurrence after catheter ablation.[59]

Schneider et al. described significantly different atrial myocardial properties (LA strain and strain rate assessed by TDI) after catheter ablation of AF in patients with persistent AF when compared to healthy controls. Using data from the echocardiographic assessment after ablation, septal systolic strain rate ($p<0.0001$) and inferior systolic strain ($p<0.0001$) were the best predictors on logistic regression analysis for sinus rhythm maintenance. These authors have shown that there are specific parts of the cardiac cycle and segments of the LA wall that can provide more relevant information for this endpoint. Additionally, in patients who maintained sinus rhythm in the 3 months period following ablation, an improvement in deformation properties of the LA and decrease in LA size was also found in contrast to patients with recurrent AF ($p=0.001$).[39]

Hammerstingl el al. have used speckle tracking for the measurement of LA strain and strain rate (Figure 3) and found that global LA strain and strain rate displayed better results than regional LA function analysis (despite the fact that LA-septal wall strain was an independent predictor for AF recurrence after ablation).[60] Moreover, average systolic strain was the only independent predictor of AF relapse after catheter ablation on multivariate analysis. Other independent predictors on univariate analysis, as LA volume index, did not add predictive value to this variable.[61]

Some limitations should be mentioned regarding speckle tracking: it strictly depends on the frame rate, image quality (with potential errors in epicardial/endocardial border tracing if suboptimal) and the need for an appropriate learning curve to achieve adequate experience in using the analysis software. Moreover, the currently available software is not dedicated to LA analysis, as it has been originally developed for left ventricle study.[41]

Figure 3: Left atrial deformation assessment using speckle tracking derived longitudinal strain. Six segments identified by different colours (red, blue, pink, green, light blue and yellow) are seen in the apical 4 chamber view image (A.). The corresponding segment strain and its variation during the cardiac cycle can be seen in the corresponding curves to the left (B.) and colour graph beneath the echocardiogram image (C.). The curves show a predominant positive strain (reflecting stretching). Different strain values can be observed in the different regions. The scale shows that positive strain in A. and C. is represented by the blue colour scale and negative strain by the red colour scale



AVC – aortic valve closure

Echocardiographic Predictors of Success After Surgical Ablation of AF

In patients treated with the Cox maze IV procedure an enlarged left atrial diameter was a risk factor for AF relapse at medium (12 months)[62] and long-term (38 months)[63] follow-up. Chen et al. described a preoperative left atrial area cuttof point, 56.25cm^2, with 50.5% sensitivity and 86.2% specificity for predicting conversion to sinus rhythm after surgery.[63] Furthermore, in patients undergoing mitral valve surgery plus radiofrequency ablation maze operation a 6 cm cutoff value of preoperative left atrial diameter was predictive of persistent atrial fibrillation at 6 months (100% sensitivity and 73.6% specificity).[64]

The role of left atrial diameter as a predictor of long-term sinus rhythm maintenance in patients undergoing open-heart procedures and concomitantly with a radiofrequency modified maze procedure has been demonstrated by other authors.[65, 66]

Finally, in a recent review of 12 papers[67] concerning the impact of left atrial size on maze surgery in terms of recurrence of AF the following cutoff points were found: left atrial volume index > 135 ml/m2 had 100% specificity[68] and left atrial diameter > 60mm a 100% sensitivity for procedure failure; conversely a left atrial diameter < 48.3mm conferred 100% sensitivity for sinus conversion.

Echocardiographic Predictors of AF After Cardiac Surgery

According to Gibson et al, the transmitral early (E) to late (A) diastolic filling velocity ratio and the early diastolic myocardial velocity (E´) predicted AF after isolated CABG on univariate analysis. However, no echocardiographic parameters remained significant on multivariate analysis.[69]

In 205 patients underdoing cardiac surgery, an indexed LA volume > 32ml/m2 increased the risk of postoperative AF around five fold, independently of age and clinical risk factors (adjusted HR 4.84 95%CI 1.93-12.17, p=0.001). The area under the ROC-curve for indexed LA volume was 0.729 (p<0.0001).[70]

Unsolved Questions

The development of a score using echocardiographic parameters, alongside with other data, in order to predict recurrences after cardioversion might help us redefine treatment decisions for patients with AF. It could be an effective and accurate method of deciding between further cardioversions or a rate control strategy. The same might apply to AF catheter ablation.

The debate remains open regarding the best way (more accurate, reproducible and easy to use) for LA volume assessment.[2, 8] Morevoer, there seems to be a need to redefine reference values for single-plane LA volume and LA area measurement, and to establish new cut-off values for category classification .

The best way of assessing LA deformation also needs to be clarified. Further investigations are needed to define which is the best technique (Doppler derived, speckle tracking or vector velocity imaging) or method (strain, strain rate or both), where to place the sample for data measurement (regional vs. global deformation; if regional, which wall provides the best information) and the best portion of the cardiac cycle to retrieve information.

Also, more studies will be necessary to reproduce findings correlating LA deformation and MRI delayed-enhancement, namely with other techniques (speckle tracking and Doppler derived strain and strain rate).

Conclusions

The use of 2D and Doppler echocardiography for anatomic and functional study should be the starting point of evaluation in all patients with AF in order to diagnose concomitant cardiac disease (myocardial, pericardial, valvular or congenital heart disease, LV systolic or diastolic compromise) predisposing to AF. Furthermore, this technique would be extremely helpful in guiding treatment decisions and providing prognostic information. Conversely, transesophageal echocardiography is an invasive and poorly tolerated technique that should be reserved for other specific clinical settings.

Left atrial and left atrial appendage deformation assessment is a field of very active research that warrants further validation before potential implementation in clinical practice.

Disclosures

No disclosures relevant to this article were made by the authors.

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