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Clinical utility of left atrial strain in predicting atrial fibrillation recurrence after catheter ablation: An up-to-date review

Yu ZX *et al.* Atrial strain, atrial remodeling and AF

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Abstract

Rhythm control is the core part of the integrated management of atrial fibrillation (AF), especially in the early stages. Despite advances in catheter ablation (CA), the recurrence rate of AF after CA remains high. As a result, stratification and early management of AF recurrence after CA are critical. Currently, predictors of recurrence of AF after CA are mostly based on dysfunction caused by structural remodeling, apart from traditional risk factors. Atrial strain is a recently developed important parameter for detecting the deformability of atrial myocardium during the cardiac cycle prior to atrial remodeling. Although there is only preliminary evidence, atrial strain is still a promising parameter in predicting the recurrence of AF after CA at an early stage. This review focuses on the evaluation of atrial strain, the current applications of atrial strain in assessing atrial function, and predicting the recurrence of AF after CA. We summarize the contents related as follows: (1) CA for rhythm control in AF; (2) Evaluation methods of atrial strain; (3) Atrial strain in the remodeling and reverse remodeling of AF; and (4) Clinical applications of atrial strain in predicting the recurrence of AF after CA. Although there is accumulating evidence on the role of decreased atrial strain in the early prediction of AF recurrence, atrial strain is limited in clinical practice for lacking exact cut-off values and difficulty in distinguishing specific function phases of the atrium. More research is needed in the future to add strength to the early prediction value of atrial strain in AF recurrences.

Key Words: Atrial strain; Atrial remodeling; Speckle tracking image; Catheter ablation; Atrial fibrillation recurrence

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Core Tip: Atrial fibrillation (AF) is the most common arrhythmia, and rhythm control, especially catheter ablation (CA) is the core part of the integrated management of AF. Despite protocol and devices advances in CA, the recurrence rate of AF after CA is still high. Atrial strain, the parameter of atrial deformation during the cardiac cycle, is closely related to atrial remodeling and atrial function. Furthermore, accumulating evidence showed the role of decreased atrial strain in the early prediction of AF recurrence. Further studies are needed to add strength to the early prediction value of atrial strain in AF recurrences.

INTRODUCTION

Atrial fibrillation (AF) is the most common chronic arrhythmia, with an estimated incidence of 2%–4% in adults worldwide[1]. According to the Global Burden of Disease Study 2017[2], there are 37.6 million cases globally, resulting in approximately 287200 deaths in 2017. With the population aging and prolonged survival of chronic disease, the burden of AF is still increasing rapidly. Besides, AF is associated with a higher incidence of ischemic stroke and cardiac mortality.

Rhythm control is the core part of the integrated management of AF[3], especially in the early stage. Catheter ablation (CA) targeting for the pulmonary vein–left atrium (PV-

LA) conjunction area, known as PV isolation (PVI), is the most common way of restoring sinus rhythm. However, despite the enormous advances in the protocol and devices in PVI, the recurrence rate of AF after CA is still high[4].

Atrial remodeling is considered to be one potential mechanism for AF recurrence. Left atrial strain is related to structural remodeling in paroxysmal AF (PAF) and persistent AF (PeAF)[5]. Speckle tracking echocardiography (STE), commonly used in early left ventricular (LV) dysfunction assessment, has also been used in left atrial (LA) strain evaluation[6]. This article highlights the accumulating evidence on AF recurrence after CA and the role of LA strain assessment in the prediction of atrial remodeling and AF recurrence.

CA FOR RHYTHM CONTROL IN AF AND AF RECURRENCE AFTER CA

CA for rhythm control

Whether rhythm control reduces cardiovascular risk in patients with AF has been debated for decades. Previous trials of rate control *vs* rhythm control in AF, such as the Atrial Fibrillation Rhythm Management Follow-up Study (AFFIRM) study[7], have not demonstrated the superiority of rhythm control in patients with AF. The recent EAST-AFNET 4 study[8] showed that compared to rate control, early rhythm control therapy (including antiarrhythmic drugs and/or CA) can significantly reduce the risk of major adverse cardiovascular outcomes (MACE) in patients with early-stage AF (diagnosis ≤ 1 year).

Since then, the treatment of AF has entered the era of rhythm control[9]. On the basis of adequate anticoagulation and management of cardiovascular risk factors and comorbid diseases, patients who are suitable for rhythm control should be converted and maintained in sinus rhythm to improve the prognosis of patients.

Antiarrhythmic drugs to maintain sinus rhythm often require long-term use, which increases the risk of side effects and limits the indications. CA targeting for PV-LA conjunction area, known as PVI, is the cornerstone way of restoring sinus rhythm.

Compared to drug therapy, CA can lighten the AF burden, and improve quality of life[10,11].

Moreover, there have been enormous advances and optimizations in the protocol and devices in PVI, including cryoballoon ablation and additional atrial ablations *etc.*[3,9]. These advances have substantially improved the safety and efficacy of PVI. However, the high recurrence rate of AF after CA is still a concern in clinical practice[4]. As a result, stratification and early management of AF recurrence after CA are critical.

Predicators for AF recurrence after CA

Technological advances have improved the success rate of CA for both PAF and PeAF. Still, recurrence of AF is a concern for both the patients and the cardiologists in clinical practice. Due to inconsistency in the definitions of procedural success and post-procedural recurrences, the estimation of CA success rate is challenging[3,12]. The commonly accepted AF recurrence as the occurrence of any symptomatic or asymptomatic atrial tachyarrhythmia lasting > 30 s 3 mo after the procedure[13]. Accordingly, the long-term success rate of CA for AF is between 50% and 80%[12,14].

The recurrence of AF after CA is the result of a complex interaction of many factors. However, aging, female gender, hypertension, PeAF, impairment of atrial function, *etc.*[15] are assumed to be related to AF recurrence after CA[16]. Apart from clinical risk factors, predictors of the recurrence of AF after CA are mostly based on the dysfunction caused by structural remodeling. Increasing attention has been attracted to the predictive role of atrial functional assessment and remodeling in the recurrence of AF after CA. Parameters for assessing left atrial (LA) remodeling and LA function[17,18], including biomarkers, electrocardiogram (ECG), and imaging parameters, are summarized in Table 1.

Patients with AF, especially those undergoing CA, are recommended to check transthoracic echocardiography (TTE) during routine follow-up. Apart from cardiac function, TTE can provide LA parameters that can represent the extent of LA remodeling and function. LA diameter, volume and ejection fraction are parameters that can be used in LA remodeling assessment and AF recurrence prediction[18]. In the meta-analysis by

D'Ascenzo *et al*[19] that included 19 studies and 4357 AF patients, valve defect and LA diameter > 50 mm predicted AF recurrence after CA.

Owing to the low sensitivity, LA volume measurement to evaluate atrial function lacks accuracy and is limited in the prediction of recurrence of AF after CA, especially in the early stage. Parameters that can potently predict the recurrence of early AF are still needed. STE, commonly used in early LV dysfunction assessment, is also an important assessment method[20], in the quantification of LA myocardial deformation and remodeling[21].

Recently, LA strain has been proven to be superior to LA size as a predictor for AF recurrence after CA[22,23]. An increased LA strain, representing the decline in the deformability of LA, is related to a higher AF recurrence rate. Moreover, Sílvia *et al*[24] indicate LA strain is reliable in predicting the success of the CA procedure in AF, especially for the second CA.

EVALUATION METHODS OF ATRIAL STRAIN

Myocardial strain is a change in the distance between two points of the myocardium occurring in the cardiac cycle, expressed as a percentage, representing the fractional change in length of a myocardial segment. Strain is initially used to analyze ventricular function, and the resulting atrial strain provides a highly reproducible measurement of atrial myocardial deformation. Thus, subsequent research focuses on the LA strain.

Normal range and measurement of atrial strain

The left atrium is a functional complex chamber, that plays an integral role in maintaining physiological hemodynamic and electrical stability of the heart. Apart from acting as a booster pump during late ventricular diastole to augment LV filling, it also serves as a reservoir to adapt the inflow volume from pulmonary veins during ventricular systole and isovolumic relaxation as well as serves as a passive conduit during early ventricular diastole[25]. In healthy people, the contribution of the LA reservoir, conduit, and booster pump to left ventricular filling is roughly 50%, 30% and 20% respectively[26]. The strains in the heart are longitudinal, circumferential and radial, but because of the fiber orientation and thinness of the atrial wall, only longitudinal strains are generally measured in the left atrium.

The first positive peak in the sinus rhythm strain curve corresponds to the phase before P wave in the ECG and represents LA reservoir strain (LASr) (Figure 1), reflecting the reserve function of the left atrium. The second negative peak (LASct) represents LA strain during contraction. The first negative peak and plateau reflect the LA strain when the atrium works as a conduit (LAScd). In a nutshell, LASr, LASct and LAScd respectively represent the reservoir, contractile and conduit functions of the left atrium. The specific measurements are as follows: (1) LASr: Strain change over reservoir phase in the cardiac cycle, expressed as the strain value at mitral valve opening minus the strain value at ventricular end diastole (positive value); (2) LAScd: Strain change over conduit phase in the cardiac cycle, expressed as the strain value at the beginning of atrial contraction minus the strain value at mitral valve opening (negative value); and (3) LASct: Only in patients with sinus rhythm is strain during the contraction phase measured as the difference between the strain value at ventricular end diastole and the onset of atrial contraction (negative value)[27].

Positive values are typically assigned to lengthening, thickening or clockwise rotation, whereas negative values are assigned to shortening, thinning or counterclockwise rotation. The baseline could be the electrocardiographic P wave or QRS complex, but patients with AF need measurements from the QRS complex.

Besides, the peak atrial longitudinal strain (PALS), which corresponds to the peak of the positive strain during left ventricular systole, is a crucial indicator of atrial compliance[27]. Furthermore, global atrial longitudinal strain (GALS) is a term that describes the average change in muscle length for visible segments[27,28].

With preliminary evidence of clinical applications of STE in atrial cardiomyopathy and valvular heart disease, the consensus on STE confirmed the ability of STE for assessing atrial function[29]. When feasible, atrial strain and three-dimensional (3D) atrial size and function assessment are used as part of the standard examination[30].

There has not been an accurate normal range for atrial strain parameters since the lack of standardization of measurement software and data processing software. Some preliminary research has led to the normal range of STE as a reference for evaluating atrial function. Pathan *et al*[31] performed a meta-analysis on 40 studies involving 2038 healthy subjects and tested the normal range of strain in the three functional states of the LA. The normal reference ranges were: LASr 39.4% (95% CI: 38.0%-40.8%), LAScd 23.0% (95% CI: 20.7%-25.2%), and LASct 17.4% (95% CI: 16.0%-19.0%). In 2019, Haji *et al*[32] described eight practical steps in measuring LA strain with TTE and strain software, and stressed the comprehensive clinical applications of LA strain in heart failure and AF.

Sun *et al*[33] noted that atrial strain significantly correlated with a few two-dimensional (2D) Doppler LV diastolic and LA function parameters. Peak strain and strain rate during LA contraction had a modest correlation with LA volumes and LV diastolic function.

Assessment methods of LA strain

There are distinct advantages and disadvantages to assessing LA strain after CA procedure in AF patients using 2D-STE and 3D-STE, cardiac computed tomography (CT) and cardiac magnetic resonance imaging (MRI) *etc.*

The use of cardiac CT is limited in the assessment of LA strain due to radiation exposure. For better visualization of the LA border, CT angiography has also been used, which can result in renal function impairment by using the iodine contrast agent. As a result of short data acquisition duration (PR interval 120-200 ms), it is difficult to distinguish LA volume changes over the functional phases[34]. In a small study of Szilveszter *et al*[35] cardiac CT slightly but consistently underestimated both LV and LA absolute global strain values.

Cardiac MRI is rarely used in clinical practice in LA strain assessment due to its high cost and lengthy examination time, making it unsuitable for heart disease patients, such as heart failure. Feature-tracking cardiac MRI is a novel and practical approach to assessing LA deformation that uses standard cine images and does not require additional tagging sequences[36]. Cardiac MRI can directly detect pathological features such as myocardial scars and fibrosis by late gadolinium enhancement imaging, thus accurately displaying the endocardial boundary, and providing details beyond structure and function[37]. Kuppahlly *et al*[5] have confirmed a negative correlation between myocardial fibrosis level and LA strain by cardiac MRI in AF patients. Moreover, PeAF patients have more myocardial fibrosis than PAF patients, implying a link between atrial remodeling, LA mechanical dysfunction, and AF prognosis.

Echocardiography is still the most commonly used examination to assess cardiac function because of its simplicity and convenience[21]. Tissue Doppler imaging (TDI) has traditionally been used in clinical practice. TDI evaluates the LA function using volume measurement, susceptible to angle dependence, noise interference, artifacts, and other factors[22].

STE is a new angle-independent quantitative technology that evaluates myocardial function by analyzing points on 2D gray-scale ultrasound images. In 2015, American/European Society of Echocardiography guidelines recommended the use of 2D-STE to analyze LA volume[38]. Among the techniques for evaluating atrial strain 2D-STE and 3D-STE have better predictive ability in AF recurrence after CA[39]. Because of the 3D nature of the technology, 3D-STE provides novel deformation parameters that have the potential for a more accurate assessment of overall and regional myocardial function[40] (Figure 2). However, the reconstruction of 3D images depends on a stable cardiac cycle, which is difficult to be achieved in AF.

Hwang *et al*[41] reported that applying artificial intelligence algorithms to the STE radial strain of the left atrium can assess outcome status after AF ablation more accurately and sensitively. They developed a deep convolutional neural networks (CNN) model based on curved M-mode STE images, which may be a novel approach to evaluate the LA dysfunction. CNN may accurately classify the curved M-mode images of global strain in patients and provide detailed spatiotemporal information about the deformation sufficiently.

Although STE may not be possible to track accurately the LA deformation, because of the thinner atrial wall, being interrupted by the LA appendage and the four pulmonary vein openings, and shortening and extending uniformly[42], it is still a convenient and practical method in assessing LA strain compared to other assessment methods.

CLINICAL UTILITY OF LA STRAIN IN AF PATIENTS AFTER CA

LA Strain in atrium remodeling and reverse remodeling

Atrial remodeling, including electrical and structural remodeling[43], is a common pathophysiological feature of AF, interacting with one another and ultimately causing dysfunction. Electrical remodeling includes changes in the properties of ion channels that affect atrial myocardium activation and conduction, resulting in longer atrial conduction times. Structural remodeling refers to microscopic structural changes such as myocardial hypertrophy, fibrosis, and muscle fiber arrangement disorder, leading to decreased atrial compliance and contractility. An electrophysiological study with detailed biatrial electroanatomic mapping has demonstrated that right atrial remodeling could accurately correlate with LA remodeling[44]. The imbalance between collagen synthesis and degradation and a fibrotic atrial substrate has consequences for LA electromechanical function, eventually leading to the occurrence of AF[45,46]. In contrast, atrial electrophysiological remodeling, cellular structure remodeling, myocardial lysis, interstitial fiber deposition, and extra-atrial matrix changes occur shortly after the onset of AF[47,48]. These changes cause a slow and gradual remodeling of the atrium and promote the recurrence and continuous occurrence of arrhythmia.

Extensive fibrosis is the cause of atrial arrhythmia, atrial stiffness increases, and atrial activities decrease, which is only seen in a small percentage of PeAF patients[49]. Atrial fibrosis occurs before changes in the macroscopic structure of the atrium[50,51], which is used to predict the outcome of CA. It takes a long time for the atrium to regain normal contractile function after cardioversion[52].

LA presents reservoir, conduit and contractile functions in sequence during the cardiac cycle. The compliance or stiffness of the atrial wall determines the deformability of the atrial muscle[53]. Kuppahally *et al*[5] proposed that LASr is a surrogate for fibrosis in patients with PeAF. In AF, increased atrial stiffness, weakened elasticity, decreased atrial compliance, and contractility result in lower strain and dysfunction of atrial reservoir function when compared to sinus rhythm[54]. Patients with AF have less strain, which reduces their atrial myocardial deformability. It is assumed that the deformability of the myocardium is further compromised during the development of AF.

Due to changes in atrial structure, the contractile function is almost lost in AF, and reservoir and conduit functions are both reduced. As a result, the strain curves in AF differ from those in sinus rhythm (Figure 3).

Reverse remodeling improves the response to medical or nonmedical intervention, whereas LA remodeling represents a state of maladaptive deterioration[55]. The reverse modeling increase, or anti-remodeling, is confirmed after restoring sinus rhythm through medical treatment and cardioversion[56]. The reduced baseline LA deformability assessed by STE has been shown to help identify patients at high risk of AF recurrence after CA in both PAF and PeAF[57]. While the CA is successful, the left atrium may undergo reverse remodeling, improving its function. Although the exact pathophysiology of LA reverse remodeling is unknown, it is critical in determining the prognosis of the left atrium, which may help to reduce the risk of AF recurrence. LV function can be improved by sinus rhythm recovery after CA, and LA strain and strain rate improve as LV systolic pressure strain improves. The LA strain may improve in the 3 mo following a successful CA procedure for AF[58]. Similarly, patients with AF had lower PLAS than healthy subjects, but it increased significantly at 3 and 12 mo after CA[59]. Furthermore, 63% of patients had reversal remodeling of AF after CA, accompanied by an improvement in LA strain. The baseline LA strain is a reliable predictor of LA reverse reconstruction[60].

Atrial strain is essential in detecting an increase in atrial stress early on, which other indexes can hardly accomplish. The strain is useful in determining the recurrence of AF following the CA procedure. Unfortunately, no clear strain value exists to predict the occurrence of a recurring event, and a large amount of data is still required to complete the evidence.

LA strain in AF recurrence after CA

The clinical use of the LA strain has grown rapidly in recent years. The application of LA strain in AF patients not only includes assessing LA fibrosis and dysfunction, calculating thrombosis risk, *etc.*, but also in predicting the presence/recurrence of AF. Table 2 shows the specifics of clinical application in atrial strain after CA.

Decreased LA strain is generally accepted to be related to AF recurrence after cardioversion or CA. LA strain is superior in early detection of LA functional impairment than other structural change parameters by TTE. Patients with AF recurrence had significantly lower LA strain when compared to those who maintained sinus rhythm after CA[61-63]. Moreover, in patients with AF and atrial flutter, atrial function impairment, reduction in LA strain, and atrial compliance impairment all come before structural reconstruction and LA size changes[23].

PALS and GALS are two indexes used to represent LA strain changes over the cardiac cycle. Several studies have shown that GALS in the basal, midseptal, or midlateral walls of patients with AF recurrence after CA decreased significantly[39,57,64]. The baseline GALS is related to the rhythm maintenance after CA, and GALS < 23.2% shows a higher rate of AF recurrence[39]. The global and regional LA strains were both reduced in patients with AF recurrence[24] .

PALS is frequently an independent predictor of LA fibrosis[6] and arrhythmia recurrence[63,65,66]. PALS is significantly reduced in patients with recurrence of AF[63]. Nielsen *et al*[67] conducted research on a meta-analysis of 12 studies involving 1025 subjects, revealing that lower PALS is associated with an increased risk of AF recurrence following CA. They determined that 12.8% was the cut-off value for PALS to predict AF recurrence, with a weighted mean sensitivity of 80% (range 74%-86%) and specificity of 87% (range 71%-98%). Also, in another recent study, it has been confirmed that LA strain and strain rate are more independent than other parameters in predicting the possibility of AF recurrence after CA[68,69]. Similarly, Bajraktari *et al*[70] did the meta-analysis of 85 studies including 16126 patients and verified that LA diameter > 50 mm, volume > 150 mL, and strain < 19%, have a negative effect on maintaining sinus rhythm after CA.

Consistent with GALS and PALS changes, LA strain in the different phases, LASr, LAScd and LASct are all significantly reduced in PAF patients after CA[6].

When it comes to a specific phase, LASr is decreased in patients with AF recurrence after CA. Physiologically, LASr reduction is related to the increase in LA pressure, compromised LA compliance and high fibrosis status[24,71-76]. Decreased LAScd, has also been found related to AF recurrence after CA in limited evidence due to the difficulty in discrimination and vulnerability to be affected by atrial remodeling[71]. LASct is a more sensitive parameter that reflects the structure of the atrium. Decreased LASct is also related to AF recurrence after CA. Besides, it can predict the AF recurrence during long-term follow-up[77].

Still, the evaluation of LA strain is restricted in AF rhythm. Also, due to the limited evidence, the exact cut-off value of LA strain in a specific phase has not been proposed. Compared to LA strain, right atrial strain is more commonly used in the atrial assessment of potential right heart disease. Peak right atrial longitudinal strain, peak LA longitudinal strain, and the combination of the two have also been reported can predict the recurrence of AF after CA in patients with chronic lung disease[78].

CONCLUSION

Rhythm control is the core part of the integrated management of AF. Despite protocol and devices advances in CA, the recurrence rate of AF after CA is still high. Atrial strain, the parameter of atrial deformation during the cardiac cycle, is closely related to atrial remodeling and atrial function. Furthermore, accumulating evidence shows the role of decreased atrial strain in the early prediction of AF recurrence. Further studies are needed to add strength to the early prediction value of atrial strain in AF recurrences.

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