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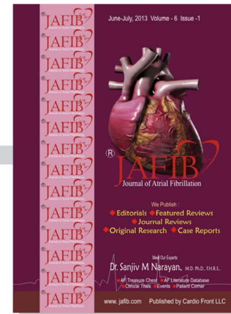

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Cardiac Remodeling After Atrial Fibrillation Ablation

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Abstract

Radiofrequency catheter ablation procedures are considered a reasonable option for patients with symptomatic, drug refractory atrial fibrillation (AF). Ablation procedures have been reported to effectively restore sinus rhythm and provide long-term relief of symptoms. Both electrical and structural remodeling occurs with AF. A reversal of the electrical remodeling develops within 1 week after restoration to sinus rhythm following the catheter ablation. The recovery rate is faster in the right atrium than the left atrium. Reverse structural remodeling takes longer and is still present 2 to 4 months after restoration of sinus rhythm. The left atrial transport function also improves after successful catheter ablation of AF. Left atrial strain surveys from echocardiography are able to identify patients who respond to catheter ablation with significant reverse remodeling after ablation. Pre-procedural delayed enhancement magnetic resonance imaging is also able to determine the degree of atrial fibrosis and is another tool to predict the reverse remodeling after ablation. The remodeling process is complex if recurrence develops after ablation. Recent evidence shows that a combined reverse electrical and structural remodeling occurs after ablation of chronic AF when recurrence is paroxysmal AF. Progressive electrical remodeling without any structural remodeling develops in those with recurrence involving chronic AF. Whether progressive atrial remodeling is the cause or consequence during the recurrence of AF remains obscure and requires further study.

Introduction

Atrial fibrillation (AF) is the most common cardiac dysrrhythmia encountered in the clinical practice.[1] It carries a significant risk to the patients and also brings a tremendous economic burden to the social and health care systems. AF initiates self-perpetuating changes in the electrophysiology, structure and functional properties of the atria, a phenomenon known as a remodeling.[2] The process can happen in both the atrium and ventricle. Catheter ablation of AF has evolved from being a novel, unproven procedure, to a commonly performed procedure for treatment in symptomatic patients over the past 15 years. Ablation does change the process of remodeling. In this paper, our aim was to review the recent understanding of the remodeling process that develops after catheter ablation of AF.

Remodeling Process During AF

The concept of 'AF begets AF' was postulated by Wijffels and coworkers in 1995 through long term rapid atrial pacing in healthy goats which created sustained AF in those animals.[3] Shortening of the atrial refractory period (-35%) was noted after 24 hours of rapid atrial pacing. A reversion of the physiological rate adaptation and an increase in the rate, inducibility and stability of AF were also reported. A decrease in the conduction velocity with shortening of the atrial refractory period was also demonstrated by Morillo and colleagues.[4] The remodeling process is secondary to ionic remodeling with an increase in the intracellular Ca^{2+}. Evidence from a canine study showed that chronic atrial pacing progressively reduces the density of the L-type Ca^{2+} current and transient outward current, and the action potential duration (APD) and APD adaptation to the rate are also decreased.[5]

In addition to electrical remodeling, structural remodeling also developed after the progression of AF. Macroscopic atrial enlargement and microscopic changes have also been previously documented. Mary-Rabine et al. reported a loss of myofilaments and that clusters of accumulated glycogen and lysosomal degeneration occur in patients with atrial arrhythmias.[6] Morrillo et al. also characterized an increase in the mitochondrial size and number, and disruption of the sarcoplasmic reticulum in a canine model.[4] Those changes may result in an inhomogeneous conduction and electrical uncoupling, which in turn may facilitate the maintenance of AF.

Remodeling Process After Restoration to Sinus Rhythm

Are those remodeling processes reversible if restoration to sinus

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rhythm is achieved? In an animal study, Wijffels et al. observed a restoration of all electrophysiologic changes within 1 week after sinus rhythm was restored.[3] Allessie demonstrated that the atrial effective refractory period returned completely to normal 2 months after restoration to sinus rhythm in a goat model.[7] Lee. et al. demonstrated that the recovery of the shortened atrial refractoriness was slower in the left atrium than in the right atrium or Bachmann's bundle.[8] In humans, by applying cardioversion in patients with long-standing AF (5 years), Yu and colleagues first reported that reverse remodeling did occur with a prolongation of the effective refractory period and progressively improved the rate adaptation response.[9] The reverse remodeling effect reached a stable level on the third day after restoration to sinus rhythm. A similar finding was also reported by Raitt et al. in which they observed that the atrial refractory period increases, sinus node function improves and atrial conduction velocity goes up in the first week after cardioversion of long-standing AF.[10] However, the recovery rate is faster in the right atrium than the left atrium. This transient dispersion of the atrial refractoriness may increase the risk for an early recurrence of AF. Therefore, recurrence occurs mostly within 3 to 5 days after restoration to sinus rhythm.

Reverse structural remodeling takes a longer time than reverse electrical remodeling. The remodeling process is still present 2 and 4 months post-AF. The severe myolysis returned to almost normal within 4 months after restoration of sinus rhythm, but mild myolysis still remained and significantly increased.[7] The reduction in the connexin 40 during AF completely reversed within 4 months after restoration to sinus rhythm.[7] In humans, a study in patients undergoing a surgical Maze procedure revealed that the atrial mechanical dysfunction improved over time (2 months).[11] The right atrium recovers faster than the left.[11] Choi et al. found that the left atrial dimension and mean late mitral annulus velocity also increased from 1 week to 3 months after electrical cardioversion of AF.[12]

Complex Remodeling Process After Catheter Ablation of AF

Reverse remodeling was observed after a surgical Maze or electrical cardioversion of AF. Because catheter ablation of AF has become an effective treatment for AF after the pioneering work of Haissaguerre et al. and Chen et al.[13,14], whether or not the reverse remodeling process develops after catheter ablation is an interesting issue. However, recurrence of AF still remains a prevalent issue after pulmonary vein isolation.[15-18] The atrial substrate turns into a more complex entity after the interventional procedure.

Electrical Properties After Catheter Ablation

Sino-atrial Node

Widespread atrial myopathy with areas of low voltage and slowed conduction throughout the right atrium were observed by Sanders et al., and Chang et al. further reported that advanced regional substrate remodeling with a lower bipolar voltage and slower conduction velocity in the sinus node region occurred in patients with AF and sick sinus syndrome.[19,20] Reverse remodeling developing after AF ablation was first reported by Hocini et al. when she observed that prolonged sinus pauses after paroxysms of AF could be eliminated by curative ablation of AF.[21] This phenomenon is accompanied by an improvement in the parameters of the sinus node function, suggesting reverse remodeling of the sinus node after catheter ablation of AF.[21]

Atrium

After the development of the 3D electroanatomic mapping system, Pappone and colleagues used it to map the patients who received repeat ablation procedures due to recurrence.[22] There was a significant decrease in the bipolar voltage and conduction velocity at the pulmonary vein-left atrial junction at the end of the index procedure. Recurrence after ablation was associated with an increase

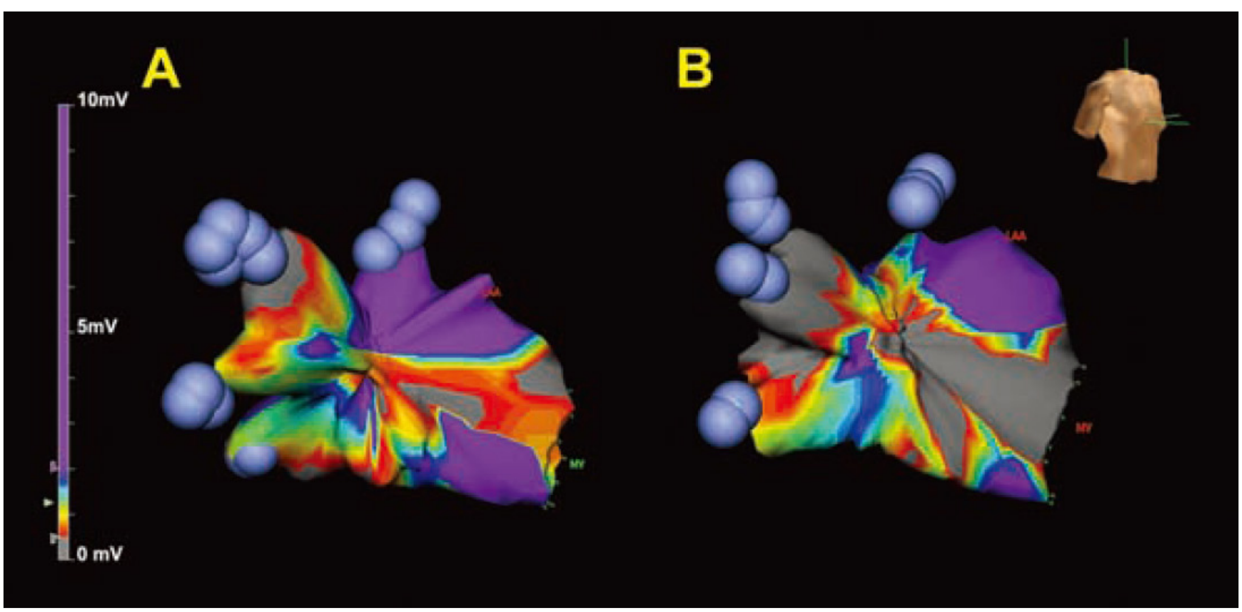

Figure 1: **Electroanatomic bipolar voltage mapping in a patient with paroxysmal AF undergoing an initial catheter ablation and a repeat ablation of AF which recurred as paroxysmal AF**

Panels A and B denote the right anterior oblique view of the left atrium in the first and second procedures. The color annotation shows a range of colors with a bipolar voltage of ≤0.5 mV shown in gray, all the way through to a voltage of > 2.0 mV shown in purple. During the second procedure (B), a newly developed low voltage zone occurred over the mid-to-lower anterior wall of the left atrium and right superior pulmonary vein antrum of the left atrium, and the high voltage area shown in purple decreased. LAA: left atrial appendage, MV: mitral annulus. (Reproduced with permission from Lo LW, et al. J Cardiovasc Electrophysiol 2007;18:258-265.[23])

in the voltage and conduction velocity to an intermediate value in all left atrial sites.[22] In this study, the recurrence of atrial arrhythmias was associated with a reverse process across the ablated area. In our laboratory, we further discovered that a progressive electrical remodeling occurred with a decreasing left atrial voltage in the paroxysmal AF patients with recurrent AF and a similar arrhythmic burden.[23] The low voltage zone also increased during recurrence. Figure 1 is an example of an electroanatomic bipolar voltage map in a patient with paroxysmal AF who received an ablation and had a recurrence of paroxysmal AF. The low voltage area increased in the second procedure. Mesas et al. observed the development of a low voltage area over the left atrial posterior wall and mitral isthums during recurrent AF.[22]

The pattern of remodeling varies in patients with chronic AF after ablation. Electrical reverse remodeling occurs with a greater left atrial bipolar voltage and smaller low voltage area in patients with a decreased AF burden during recurrence.[24] Progressive electrical remodeling was noted in the patients with a similar or higher AF burden during recurrence. Figure 2 shows examples of electroanatomic bipolar voltage mapping for two different procedures. Panel A is a patient with a decreased AF burden during the recurrence, whereas panel B is a patient with a similar AF burden during the recurrence. Progressive electrical remodeling was noted in the second procedure in this patient.

Whether progressive atrial remodeling is the cause or consequence during a recurrence of AF remains obscure. Kalman et al. evaluated the patients with lone AF undergoing catheter of AF and compared the electrical properties before and more than 6 months after the ablation.[25] Unfortunately, the electrical substrate does not appear to reverse after a successful catheter ablation with a lower bipolar voltage and either no improvement or further slowing of the conduction velocity. However, there was a prolongation of the regional refractoriness and reversal of the left atrial dilation. This study indicated that progressive electrical remodeling still continued in spite of a curative ablation, and the remodeling process after ablation might be much more complex than the structural remodeling and may require a longer observational period and further investigation.

Structural Properties After Catheter Ablation

There are conflicting results regarding the reversibility of the atrial structural remodeling after catheter ablation. Reverse structural remodeling varies in different parts of the myocardium.

Atrium

Several studies have shown decreases in the left atrial volume (-8% to -15%) after catheter ablation of AF regardless of whether echocardiography or computed tomographic imaging was used for the measurements. Reverse structural remodeling is considered to be the mechanism of the decrease in the atrial size. Another possibility is that the scar formation from the ablation lesions decreases the atrial size. The study from Wylie et al. used the cardiac imaging to evaluate the patients receiving ablation and found a linear correlation between the decline in the left atrial systolic function and volume of radiofrequency ablation scar.[26] But the study from Tsao et al. found the reverse electrical remodeling with a smaller low voltage area and scar were detected in the patients with a decreasing AF burden following the catheter ablation.[25] From current evidences, it is still not sufficient to ignore the damage of the left atrial function caused by ablation. Avoidance of over-ablating the unnecessary atrial myocardium is important.

Tsao et al. reported an improvement in the left atrial transport function (+9%) after a successful catheter ablation of AF.[27] The linear lesion applied in the procedure may influence the local motility of

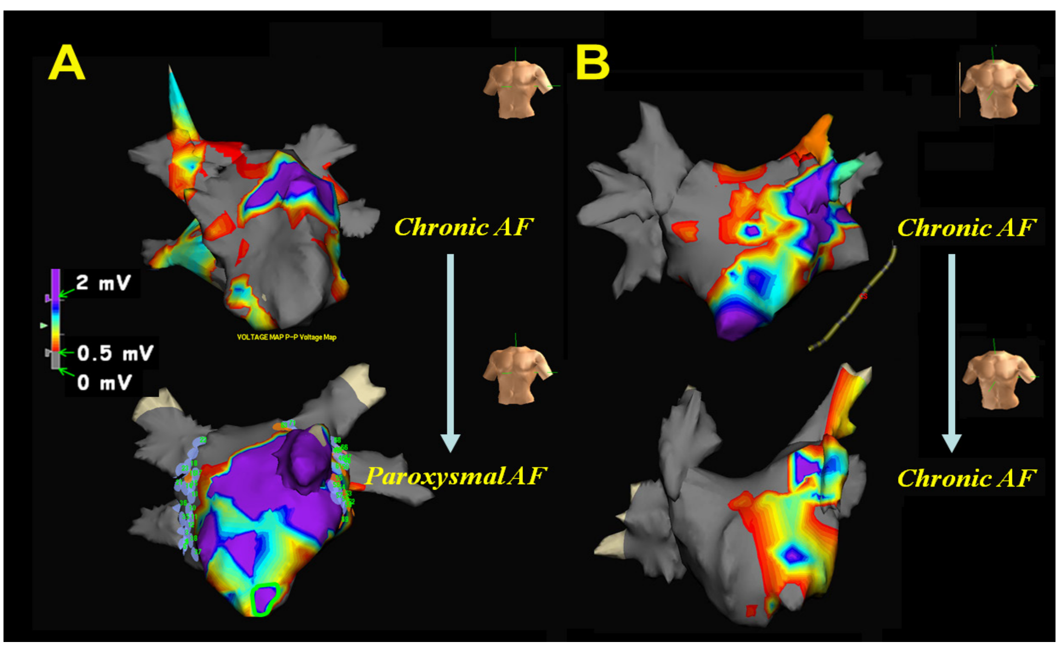

Figure 2: **Electroanatomic bipolar voltage maps in patients with chronic AF undergoing catheter ablation in which one recurred as paroxysmal AF (A), and the other as persistent AF (B). Both panels represent the anterioposterior view of the left atrium in the first and second procedures**

The color annotation is the same as in Figure 1. In Panel A, there is a decrease in the low voltage area and an increase in the high voltage areas noted in the second procedure. In Panel B, a progressive electrical remodeling with an increase in the low voltage areas is noted in the second procedure. (Reproduced with permission from Lo LW, et al. J Cardiovasc Electrophysiol 2011;22:385-393.[24])

the left atrial roof, but it could be offset by the reverse remodeling of the rest of the left atrium after a successful ablation. Recently, Tops and coworkers used the left atrial strain to identify the patients who responded to catheter ablation with significant left atrial reverse remodeling after ablation.[28] Sixty-three percent of the patients exhibited a reverse structural remodeling after ablation with a concomitant improvement in the left atrial strain. The left atrial strain at baseline was an independent predictor of the left atrial reverse remodeling (odds ratio: 1.813). However, a recent study demonstrated that left atrial diastolic dysfunction and pulmonary hypertension developed in limited patients (1.4% incidence) following catheter ablation. It is the so-called stiff left atrial syndrome and should be carefully monitored in patients with severe left atrial scarring, a left atrial diameter of less than 45 mm, diabetes mellitus and obstructive sleep apnea syndrome undergoing catheter ablation.[29]

Delayed enhancement magnetic resonance imaging (de-MRI) is another tool to predict the reverse remodeling after ablation. Atrial fibrosis is a hallmark of atrial structural remodeling and Marrouche's group had reported that mild (<10%) hyper-enhanced areas in the de-MRI, suggestive of a pathologic myocardium (presumed to be fibrosis), indicated that the preablation structural remodeling determined by de-MRI predicts a favorable structural and functional reverse remodeling and long-term success after catheter ablation of AF, irrespective of a paroxysmal or non-paroxysmal nature of AF.[30]

The structural changes in patients during a recurrence after catheter ablation exhibited controversial results in different studies. Reant et al. found that the left atrial area decreased during the recurrence of AF 11 months after the index ablation procedure, and Teh et al. reported the reversal of the left atrial dilation 10 months after the index procedure.[25,31] Tsao et al. reported a increase in the left atrial volume and Chang et al. showed a increase in the left atrial appendage orifice area during a recurrence 21 months after the index procedure.[32,33] Lemola et al. and Beukema et al. did not observe any left atrial structural changes during recurrences 4-6 months after the index procedure.[34,35] Lo et al. reported that the left atrial volume decreased if the AF burden decreased during recurrences, but remained the same if the burden increased after the index procedure.[24] Table 1 shows the conflicting results published by different studies. The structural remodeling was not consistent with the changes in the electrical remodeling during recurrent AF. In addition, by using a wall motion analysis of the 18 segments of the left atrium , Tsao et al. demonstrated the dynamic motion of the left atrium remained reduced in patients with recurrent AF.[27] Figure 3 shows a Bull's-eye plot in two patients without (A) and with (B) AF recurrences following ablation. The wall motion and volume of the left atrium were similar before and after the ablation in the patients with recurrences following ablation.

Pulmonary Veins and the Left Atrial Appendage

It has been reported that in patients with AF, there is significant dilation of both superior pulmonary veins.[36] The structural remodeling process of the superior pulmonary veins was reversible after a successful ablation without an AF recurrence 1 year after ablation. A geometric alteration toward a round shape was noted in the ostia of the superior pulmonary veins during follow-up.[32] A similar finding with a decrease (-10%) in the pulmonary vein ostial area was reported by the Michigan group.[34] Recently, Tsao et al. reported the improvement in the pulmonary venous dynamic function using

Table 1: Structural remodeling of the left atrium and pulmonary veins after catheter ablation of atrial fibrillation

Trial (Ref)	Patients (n)	Diagnostic tools (n)	Arrhythmia type (n)	AF duration (years)	Ablation sites	Follow-up (months)	AF recurrence n (%)	Atrial/PV remodeling	
								No recurrence group	Recurrence group
Lemola et al. (34)	41	CT (41)	PAF/PeAF 25/16	5±3	4PVs+MI+ Posterior LA	4±2	3 (7)	LA volume↓15%↓ PV ostial area↓10%↓	LA volume↓↑ PV ostial area ↓↑
Beukema et al. (35)	105	TTE (105)	PAF/PeAF 52/53	6.0±5.1/7.6±6.0 (PAF/PeAF)	4PVs±MI± Posterior LA±CTI	6	23(22)	LAD↓7.4%↓ (PAF) ↓9.1%↓ (PeAF)	LAD↓↑(PAF) ↑8.9%† (PeAF)
Tsao et al. (32)	45	MRI (45)	PAF 45	N/A	4PVs	21±11	10 (22)	LA volume↓7.9%* PV ostial area↓9.1-10%**	LA volume↑28%† PV ostial area↓↑
Chang et al. (33)	40	MRI (40)	PAF 40	N/A	4PVs	20±11	10 (25)	LAA orifice area↓12.5%↓ LAA neck area↓16.8%↓ LAA length↓8.7%↓	LAA orifice area↑14.4%* LAA neck area↑17.4%* LAA length↑6.0%*
Reant et al. (31)	48	TTE (48)	PAF/PeAF 37/11	6.1±5.6/12±8.8 (PAF/PeAF)	4PVs+CTI±MI±LA roof	11	13 (27)	LA area↓19%**(PAF), ↓24%* (PeAF)	LA area↓5%* (PAF), ↓7%(PeAF)
Teh et al. (25)	11	TTE (11)	PAF/PeAF 7/4	5.6±4.8	4PVs±LA roof	10±13	0 (0)	LAD↓6.7%↓ LA area↓7.4%↓ LA volume↓17%*	N/A
Lo et al. (24)	36	TTE (36) CT (36)	PeAF 36	N/A	4PVs+CTI±MI±LA roof± CFE	27±3	N/A	N/A	LA volume↓20% (PAF) † LA volume↓↑ (PeAF)

AF = atrial fibrillation, CFE = complex fractionated atrial electrogram, CT = computed tomographic imaging, CTI = cavotricuspid isthmus, LA = left atrium, LAA = left atrial appendage, LAD = LA dimension, MI = mitral isthmus, MRI = magnetic resonance imaging, N/A = not available, PAF = paroxysmal atrial fibrillation, PeAF = persistent atrial fibrillation, pts = patients, PV = pulmonary vein, SVC = superior vena cava, TEE = transesophageal echocardiography, TTE = transthoracic echocardiography.
↑ means an increase in the parameter compared to the value before the catheter ablation.
↓ means a decrease in the parameter compared to the value before the catheter ablation.
↓↑ means no significant change compared to the value before the catheter ablation.
* p ≤ 0.05, † p ≤ 0.01, ** p ≤ 0.001

multi-detector computed tomographic images. The contractile function of the superior pulmonary veins was impaired in patients with paroxysmal AF especially at the posterior wall. The hypokinesia improved after circumferential isolation of the pulmonary veins in the patients without a recurrence after a follow-up of 6 months.[37]

The left atrial appendage is also an important structure in AF. Di Biase and Natale had reported cauliflower and cactus type morphologies of the appendage are associated with a higher incidence of stroke.[38] By applying magnetic resonance angiography, Chang et al. reported the morphometric remodeling of the left atrial appendage reversed after a successful ablation of AF. The morphology of the neck of the appendage became more eccentric during reverse remodeling after a follow up of 20 months.[33] In addition, the appendage velocity also improved after AF ablation.[39] Similar results were also reported from echocardiographic findings with an improvement in the left atrial appendage wall velocity after a follow-up of 18 months, and the left atrial appendage wall velocity before ablation predicted sinus rhythm maintenance following ablation.[40]

Left Ventricle

Ventricular remodeling that develops during AF presents as systolic or diastolic dysfunction. Whether those changes are the cause or consequence of the arrhythmias remains debatable. Isolated paroxysmal AF is commonly associated with left ventricular diastolic dysfunction but normal systolic function. From the echocardiographic study, the Bourdeaux group demonstrated an improvement in the left ventricular diastolic and systolic function after restoration of sinus rhythm by catheter ablation. The left ventricular ejection fraction improved significantly at 1 month after ablation in the patients with nonparoxysmal AF.[41] Further, it was evident in paroxysmal AF patients only at 11 months after the ablation. Improvement in the diastolic dysfunction was also greater in the patients with nonparoxysmal than paroxysmal AF.[40] Similar findings with reverse remodeling were also report using a 2D strain technique and cardiac magnetic resonance imaging.[42-44] That evidence suggested that AF may be partly the cause rather than the consequence of the systolic and diastolic dysfunction.

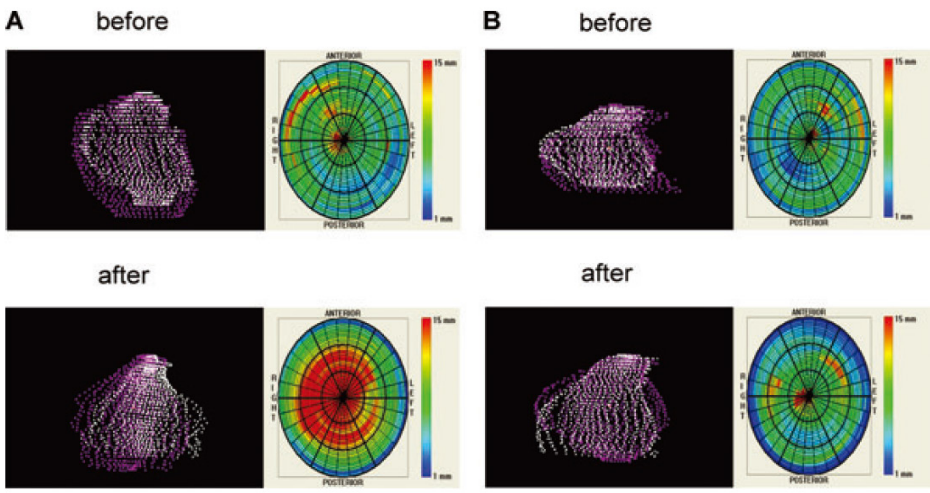

Figure 3: **Wall motion analysis with a Bull's-eye plot showing examples without (A) and with (B) recurrences after the AF ablation**

The purple dots represent the end-diastolic left atrium and white dots the end-systolic left atrium. In the Bull's-eye figures, the blue parts indicate the areas with minimal wall motion (~1-3 mm) and the red parts indicate the areas with greater wall motion (~12-15 mm). There is a decreased wall motion of the anterior roof (segment 1,2,3), and an increased wall motion of the rest of the left atrium can be demonstrated in the patient without recurrence (Panel A). In Panel B, the wall motion and volume of the left atrium were similar before and after the ablation because a recurrence occurred in this patient. (Reproduced with permission from Tsao HM et al. J Cardiovasc Electrophysiol 2010;21:270-277.[27])

Recently, study from Pennsylvania group also reported the atrial functional mitral regurgitation did develop in AF, which improved after restoration to sinus rhythm following catheter ablation.[45] Similar report also published by Anselmino et al. that the grading of mitral regurgitation decreased after AF ablation in patients with impaired left ventricular systolic function during a follow-up of more than 4 years.[46]

Conclusions:

AF maintenance is promoted by an atrial substrate that is suitable for the initiation and perpetuation of the re-entering wavelet. Both electrical and structural remodeling go hand in hand during the progression of AF. Electrical remodeling develops within hours to days and structural remodeling is a much slower process. It is possible to stop and reverse the remodeling process electrically and structurally with catheter ablation of AF. Both reverse electrical and structural remodeling do occur after the successful elimination of AF without any recurrence. In the circumstances of recurrent AF following ablation, the electrical and structural remodeling changes are much more complex and require further investigation in those with recurrences after AF ablation.

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