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Scar Homogenization in Atrial Fibrillation Ablation: Evolution and Practice

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Introduction

Atrial fibrillation (AF) ablation has emerged as the preferred rhythm control strategy for symptomatic paroxysmal AF refractory or intolerant to at least one class I or III antiarrhythmic medication[1],[2]. Since the initial observation by Haissaguerre and colleagues, of pulmonary vein triggers initiating atrial fibrillation (AF)[3], pulmonary vein isolation (PVI) has become the cornerstone for paroxysmal AF ablation therapy[4]. Despite technological advances and growing operator experience in performing percutaneous catheter ablation for AF, either by use of radiofrequency(RF) or cryotherapy, the long term procedural success rates for persistent AF and long standing persistent AF have not paralleled those of paroxysmal AF[5]-[8]. Due to the high recurrence rates observed in patients with persistent AF with PVI alone, efforts have been directed towards identifying additional strategies to improve the outcomes of persistent AF ablation. These strategies have included linear ablation lesions in the left and right atria, autonomic ganglionic plexi ablation, ablation directed by complex fractionated electrograms, ablation of non-pulmonary vein triggers, RF or ethanol ablation of the vein of Marshall and most recently, focal impulse and rotor modulation (FIRM). However, there is no consensus nor reproducible multicenter outcome data that would support one strategy over another. The randomized Substrate and Trigger Ablation for Reduction of AF Trial Part II (STAR AF II) failed to demonstrate any significant reduction in AF recurrences when linear ablation lines or complex fractionated electrogram based ablation was performed in addition to pulmonary vein antral isolation (PVAI) as compared to PVAI alone strategy[10]. Regardless of the approach, 40-50% failure rates with catheter ablation were observed over 12 months[10]. The results of this randomized trial form an impetus for researching newer percutaneous approaches for the treatment of persistent AF. The fundamental differences in the pathophysiology of paroxysmal and persistent AF cannot be overemphasized. Anisotropic conduction, triggered activity, autonomic innervation of the heart, embryogenesis of thoracic veins and interspersion of inhomogenous tissue (thoracic veins and heart) are believed to play a major role in initiation and pathogenesis of AF in paroxysmal AF. However, persistent AF pathogenesis is more complex and cannot be siloed into a pathogenic rubric. Observations of atrial substrate characteristics have pointed to a link between atrial fibrosis and AF progression. With rapidly emerging data on this association, ablation strategies have been developed to eliminate low voltage regions that may indicate scar and/or zones of non-uniform anisotropic conduction within the left atrium and convert them into electrically silent regions. This ablation strategy is known as scar homogenization. In this review, we discuss the evidence behind the use of scar homogenization in AF ablation, its evolution and scope in delivering optimal outcomes.

Key Words

Atrial fibrillation, atrial scar, cardiac ablation, scar homogenization, substrate ablation, arrhythmia mapping.

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Association between fibrosis and atrial fibrillation

There is growing evidence that atrial fibrosis plays a key role in maintenance of AF [11]-[13]. Atrial fibrosis may provide a substrate with electrophysiological properties of heterogeneity and nonuniform anisotropy which may help sustain the drivers for wavelet reentry. At a mechanistic level, Maesen et al[14] have shown with animal studies, that propagation of fibrillation waves is promoted by endocardial bundles in acute AF and by epicardial bundles in persistent AF. Remodeling of atrial fiber bundles result in endo to epicardial dissociation of electrical activity and the development of a 3-dimensional AF substrate. This process at least in part contributes to atrial structural remodeling and development of persistence of AF. In a study by Verma et al[15], out of a total of 700 consecutive patients undergoing first-time PVAI, preexisting left atrial (LA) scarring detected by contact voltage mapping with a multipolar circular catheter was a powerful independent predictor of procedural failure and was associated with a lower ejection fraction (EF), larger LA size, and increased inflammatory markers. Another study by Yamaguchi et al showed that the low voltage zone (LVZ) area (defined by bipolar voltage < 0.5 millivolts on electroanatomic mapping) was an independent predictor of recurrence after PVAI without any LA substrate modification[16]. There is growing evidence of significant association between progression of AF and atrial fibrosis as detected

by delayed enhancement MRI imaging (DE- MRI). The DECAAF study by Marrouche et al was a multicenter, prospective, observational cohort study of patients diagnosed with paroxysmal and persistent AF undergoing their first catheter ablation with PVAI[17]. Cardiac MRI was performed before ablation and atrial fibrosis was quantified and classified into stages with stage 1 (<10% of the atrial wall), 2 (≥10%-<20%), 3 (≥20%-<30%), and 4 (≥30%). Cumulative incidence of recurrent arrhythmia by day 325 for stage 1, 2, 3 and 4 fibrosis was 15.3%, 32.6%,45.9% and 51.1% respectively. In another study, atrial fibrosis was measured by late gadolinium enhancement (LGE) cardiac MRI imaging at baseline in patients undergoing PVAI. Patients with LGE ≤ 35% had favorable outcomes, whereas those with a higher LGE had higher AF recurrence rates in the first year after ablation, regardless of whether the initial rhythm was paroxysmal or persistent AF [18]. The studies listed above emphasize the importance of baseline imaging and quantification of atrial scar as a key predictor of procedural outcomes after PVAI. Appropriate patient selection and individualizing decision making based on preprocedural odds of success may be important to consider specifically if PVAI alone strategy is planned. These studies also lay down the platform for other investigations looking at substrate modification in addition to PVAI, specifically in patients with severe LA scarring as detected by MRI imaging or electroanatomic mapping. While there is an abundance of basic science and clinical data emphasizing association between AF and fibrosis, the concept behind ablation strategies targeting 'the atrial scar' seems reasonable, although some important questions remain unanswered, such as "What comes first- the chicken or the egg?, the scar or the AF?" and "To what degree is one required for the other to occur?" or "Are they coexistent but independent of each other?". If AF is the result of scar, does modifying the scar prevent further AF-induced scar formation, or harm by creating more scar?

Defining the 'Atrial Scar'

In a study by Kapa et al[19], LA bipolar voltage was measured in sinus rhythm (SR) and values lower than the amplitude of 95% of sampled points was used as the upper cutoff value for an abnormal signal. Delayed enhancement (DE) cardiac magnetic resonance imaging (CMRI) sequences were performed to validate voltage cutoffs. The authors showed that a voltage range of 0.2-0.45 mV can demarcate LA scar distribution during SR. Most studies have defined severely affected fibrotic areas as those with bipolar voltage on electroanatomic mapping of < 0.5 millivolts. However, the limitations of using bipolar voltage to define scar are well understood. Bipolar voltage amplitude depends on the type of mapping electrode, electrode tip size, orientation, interelectrode spacing and tissue contact[20]. Moreover, voltage in the same areas of the atrium do not follow the same cutoffs in AF as in SR or paced rhythm. Yagashita et al have shown that using electroanatomic mapping, mean bipolar voltage for same areas are lower in AF than in SR[21]. However, they found a linear voltage correlation between SR and AF, suggesting that LA fibrotic substrate may also be estimated in AF if the voltage cutoff is adjusted. In another study, there was no correlation between mean voltage or percentage low voltage during AF and paced rhythm[22]. Areas of complex fractionated electrograms and low voltage during AF frequently demonstrated normal atrial myocardial characteristics during SR. In addition, mean bipolar LA voltages, whether measured during AF, SR or pacing were lower in patients with persistent and long standing persistent AF than paroxysmal AF thereby correlating with AF severity and disease progression[23],[24],[25]. Recognizing the limitations of bipolar LA voltage as a marker of atrial scar is important as at least some of these limitations are avoidable. Standardization of mapping protocols, use of same catheter for building entire LA geometry and mapping with different voltage cutoffs based on the atrial rhythm as well as correlating with cardiac MRI when available include some of these measures that may potentially improve our ability to accurately define atrial scar.

Targeting the atrial substrate for AF ablation – Evidence 'For' and 'Against'

[Table 1] summarizes the studies assessing the role of substrate modification in AF ablation. Rolf et al in 2014[26] studied 178 patients with paroxysmal or persistent AF who first underwent voltage mapping during SR after circumferential pulmonary vein isolation. Subsequently substrate modification was performed in the same procedure and confined to the presence of low voltage zones (LVZ) defined by bipolar voltage<0.5mV. They identified LVZs in 35% and 10% of patients with persistent and paroxysmal AF respectively, most commonly in the LA roof followed by anterior, septal, and posterior wall. A twelve-month AF-free survival was 62% for patients without LVZs undergoing PVAI alone and 70% for patients with LVZs who also underwent tailored substrate modification (P=0.3). In addition, this success rate was significantly higher than in a control group of 26 patients with LVZ in whom no substrate modification was performed (27%, p value<0.001). The authors concluded that sinus rhythm voltage mapping is a useful tool to guide personalized AF substrate modification in patients undergoing AF ablation. Substrate modification in this study mostly involved posterior box isolation, roof lines and anterior mitral isthmus lines.

Jadidi et al[27] reported outcomes in 85 consecutive patients with persistent AF who underwent voltage mapping, PVI, and ablation at low-voltage zones (<0.5 millivolts while in AF) that were associated with electric activity lasting >70% of AF cycle. The procedural endpoint was AF termination. Freedom from arrhythmia was compared with a control group undergoing PVI only (66 patients). In the study population, 23 of 85 (27%) patients had small area of LVZ (<10% of left atrial surface area) and thus underwent PVI alone. In the remaining 62 patients with higher scar burden, PVI was performed followed by ablation of LVZs. In this subgroup, the procedural AF-termination rate was 73%. At a median follow-up of 13 months, arrhythmia free survival after single procedure was 69%, compared with a PVI-only approach (47%). In addition, there was no significant difference in the success rate of patients in the study group with a low amount of LVZ undergoing PVI only and patients requiring PVI + selective LVZ ablation.

Yamaguchi et al[28] performed voltage mapping of the LA during SR in 101 persistent AF patients. LVZ was defined as an area with bipolar electrograms <0.5 mV covering at least 5% of the left atrial surface excluding the pulmonary vein antrum. In patients with LVZs, PVI was performed along with substrate homogenization (LVZ-Abl) as opposed to PVI alone strategy in non-LVZ persistent AF patients. A historical control group included 16 patients who underwent PVI and left atrial scar mapping with the same method but without ablation of the scar areas (LVZ non-abl). During a mean follow-up period of 18 ± 7 months, the study reported an AF free survival of 72% in LVZ abl and 79% in PVI alone group, a statistically nonsignificant result. A second ablation procedure, when performed resulted in subsequent

Table 1: Studies of substrate guided AF ablation. See text for additional details.

Study (author/yr)	Design	Description	Follow up duration	Results	Favors Substrate modification
Rolf et al (2014)24	Nonrandomized, observational study	178 patients with paroxysmal or persistent AF underwent voltage mapping during sinus rhythm after circumferential PVI and then subsequent substrate modification confined to the presence of LVZ (<0.5 mV).	12 months	12 month AF-free survival - 62% for patients without LVZs undergoing PVAI alone - 70% for patients with LVZs who also underwent tailored substrate modification (P=0.3). -27% patients with LVZ in whom no substrate modification was performed	True
Jadidi et al (2016)25	Nonrandomized observational study	-85 consecutive patients with persistent AF underwent voltage mapping, PVI, and ablation at LVZ (<0.5 millivolts while in AF) associated with electric activity lasting >70% of AF cycle length. -Control group- PVI only	13 months	Study group with high-procedural AF termination rate. At follow up, arrhythmia free survival after single procedure was 69%, compared with a PVI-only approach (47%) in patients with persistent AF.	True
Yamaguchi et al (2016)26	Nonrandomized observational study	-101 persistent AF patients underwent voltage mapping to identify LVZ. -In patients with LVZs identified, PVI was performed along with substrate homogenization (LVZ-Abl) -PVI alone strategy in non-LVZ persistent AF patients. -A historical control group of 16 patients with PVI and left atrial scar mapping with the same method but without ablation of the scar areas (LVZ non-abl)	18+/-7 months	-AF free survival of 72% in LVZ abl and 79% in PVI alone group and AF free survival of 90% and 84% respectively with second procedure if required. -In LVZ-non Abl controls, AF free survival remained low (38% at mean follow-up 32 ± 7 months)	True
Yang et al (2016)27	Nonrandomized observational study	-86 consecutive patients with nonparoxysmal AF underwent PVI followed by LVZ guided substrate homogenization (Study) - 78 consecutive sex- and age-matched patients with nonparoxysmal AF who underwent stepwise ablation approach(Control)	24 months	The probability to maintain SR at 24 months was 69.8% versus 51.3% in the two groups respectively.	True
Kottkamp et al(2015)28	Nonrandomized observational	-10 patients with PAF with durable PVI for redo ablation underwent box isolation of fibrotic areas (BIFA). -31 patients with nonparoxysmal AF for first AF ablation underwent PVI alone (if no LVZ) or PVI + BIFA (if LVZ present)	Mean follow-up was 12.5 ± 2.4 months	In pts with paroxysmal AF despite durable PVI and in 60% of patients with nonparoxysmal AF, individually localized LVZ were identified and targeted successfully with the BIFA strategy.	True
Wang et al (2014)28	Randomized	One hundred and twenty-four patients were randomized to individualized substrate modification (ISM) group (n = 64) or stepwise ablation (SA) group (n = 60). All patients underwent PVAI first.	12- month	Sinus rhythm was maintained in 65.5% of patients in the ISM group and in 45.0% of patients in the SA group after a single procedure (P = 0.04)	True
Blandino et al (2017)29	Meta-analysis	-6 studies including 885 patients (517 in study group and 368 in control group). Aim to assess the impact of a voltage-guided substrate modification by targeting low-voltage zones (LVZ) in addition to pulmonary vein isolation (PVI). 92% patients with nonparoxysmal AF.	17 months	70% of patients in the study group vs. 43% in the control group were free from AF/atrial tachycardia (AT) recurrences (odds ratio [OR] = 3.41, 95% confidence interval [CI] 2.22-5.24).	True
Mohanty et al (2016)30	Nonrandomized observational study	-177 consecutive patients with PAF and severe LA scarring undergoing first AF ablation. - Success rates (no recurrence of AF while off antiarrhythmic drugs through average follow up.	27+/-5 months	-PVAI only (n=45), PVAI + scar homogenization (n=66) or PVAI + ablation of non-PV triggers (n=66) resulted in success rates of 18%, 21% and 61% respectively -Scar homogenization combined with PVAI did not provide any additional advantage compared with PVAI alone	False

AF free survival of 90% and 84% (LVZ abl vs. PVI). In LVZ-non Abl controls, AF free survival remained low (38% at mean follow-up 32 ± 7 months). However, a significant decline in left atrial function in 13% of LVZ patients and higher procedural and fluoroscopy times were noted in LVZ-Abl cohort. Authors concluded that LVZ-based substrate modification after PVI improved the outcomes in persistent AF patients with LVZs, whereas PVI alone strategy worked well in patients without LVZs, even those with persistent AF. In another investigation by Yang et al[29], 86 consecutive patients with non-paroxysmal AF were studied. After circumferential pulmonary vein isolation, cavo-tricuspid isthmus ablation and cardioversion to SR, high-density electroanatomic mapping of left atrium was performed to identify LVZs and abnormal potentials in SR. Seventy eight consecutive sex- and age-matched patients with non-paroxysmal AF who underwent stepwise ablation (SA) approach were included in the historical control group. In the study group, patients underwent PVI followed by LVZ guided substrate homogenization. In control group, PVI was performed followed by linear ablation at LA roof,

mitral isthmus and cavo-tricuspid isthmus if AF persisted, followed by complex fractionated atrial electrograms (CFAEs) ablation and finally DCCV. The probability to maintain SR at 24 months was 69.8% versus 51.3% in the two groups respectively. Authors concluded that for non-paroxysmal AF, electrophysiological substrate-guided LA ablation during SR in addition to PVI, significantly improved single procedural success rates compared to the widely practiced stepwise approach. Kottkamp et al[30] reported high success rates with box isolation of fibrotic substrate (BIFA) in both non-paroxysmal AF patients and in patients with paroxysmal AF undergoing redo procedure. First, PVI was performed in all patients. Then, based on left atrial voltage mapping, the authors classified patients into different stages of fibrotic atrial cardiomyopathy (FACM). Left atria with no or very limited low-voltage areas were classified as fibrotic atrial cardiomyopathy (FACM) 0–1, left atria with regional areas of low voltage as FACM 2, and atria with large confluent areas as FACM 3. The procedure involved circumferential isolation of confluent LVZs identified by point-by-point voltage mapping. In 60% of the non-paroxysmal AF patients who were classified as FACM 2–3, BIFA ablation was performed. In this subgroup, single-procedure success rate measured 72% with a 1-year follow-up and 83% with only 1.2 procedures/patient. However, one limitation was that the study lacked a comparative group for the patients with FACM 2–3 (solely PVI without BIFA).

All the above studies were observational nonrandomized trials and hence suffer from limitations inherent to the study design; incorporating data from historical controls introduces further bias. In a randomized trial, Wang et al[31] reported success with a novel individualized substrate modification approach when compared to a stepwise approach in patients with long standing persistent AF. One hundred and twenty-four patients were randomized to individualized substrate modification (ISM) group (n = 64) or stepwise ablation group (n = 60). All patients underwent PVAI first. In ISM group, ablation strategy included creating LA roof line in all patients and substrate ablation based on the extent of scar. Only abnormal potentials (AP) within LVZs were ablated in patients with mild substrate abnormality (LVZ< 10%). In patients with moderate (LVZ =10—20%) and large substrate areas (LVZ>20%), AP within LVZ were ablated and additional individualized lines were created to connect scar areas with each other and/or to anatomical structures. In SA group, PVI was followed by linear ablation at the LA roof, mitral isthmus and cavo-tricuspid isthmus, followed by ablation of complex fractionated atrial electrograms (CFAE) with a goal to terminate AF. If AF did not terminate, DCCV was applied. At end of 12-month follow up, the intention-to-treat analysis showed that sinus rhythm was maintained in 65.5% of patients in the ISM group and in 45.0% of patients in the SA group after a single procedure (P = 0.04). The total procedural time was significantly shorter in ISM than that in SA group. This study highlights that even with extensive ablation performed in both groups, targeting the low voltage zone and individualizing scar modification strategy in patients may produce better outcomes with a shorter procedural time than PVI with additional lines and CFAE and non-PV trigger guided ablation strategy in patients with long standing persistent AF. However, the study results were limited by small sample size and short duration of follow up. Most recently, a meta-analysis, including 6 studies of 885 predominantly non-paroxysmal AF patients (92%), looked at outcomes of freedom from AF or AT in patients with PVI+LVZ ablation vs. PVI and other conventional ablation techniques (control). The results indicated that LVZ ablation in addition to PVI was more effective than PVI +/- traditional ablation (70% vs. 43%) with comparable rates of adverse events (2.5% vs. 6%) [32].

There is emerging data that additional substrate guided ablation may not add much benefit to conventional PVAI alone strategy. A nonrandomized prospective study of 177 consecutive patients with paroxysmal AF and severe LA scarring (scar >60% of LA area as defined by electroanatomic voltage mapping during procedure) underg oing first AF ablation showed that PVAI only (n=45), PVAI + scar homogenization (n=66) or PVAI + ablation of non-PV triggers (n=66) resulted in success rates (no recurrence of AF while off antiarrhythmic drugs through average follow up duration of 27+/-5 months) of 18%, 21% and 61% respectively33. Scar homogenization combined with PVAI did not provide additional benefit when compared with PVAI alone and both approaches had very low-success rate after single procedure in patients with extensive scarring. Interestingly, a PVAI + trigger based ablation strategy was not only safe but also provided significantly higher success rate than PVAI alone or PVAI + scar homogenization. Non-PV trigger ablation is yet another extensively studied strategy for persistent AF ablation which is beyond the scope of this review.

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However, the results of STAR AF II trial do merit some discussion[10]. Five hundred and eighty nine patients with persistent AF were randomized to PVI alone (67 patients), PVI plus CFAE ablation (263 patients), or PVI and linear ablation across the left atrial roof and mitral valve isthmus (259 patients). After 18 months, AF free survival was 59%, 49% and 46% in group 1, 2 and 3 respectively (P=0.15). There was no significant difference among the three groups in freedom from AF even after a redo procedure. Procedure time was significantly shorter for PVI alone than for the other two procedures (P<0.001). From this study, it appears that neither complex electrograms nor linear ablation lines are the correct ancillary targets for ablation. Thus, the authors concluded that the role of more extensive ablation in persistent AF patients is of dubious benefit. It is very important to remember that in this study, scar modification or homogenization was not performed in either study group. Ablation targeting CFAE or roof/isthmus lines cannot be equated with individualized substrate modification approach. The

results of the trial emphasize the need for future research looking at selective ablation targets based on an individual patient's specific arrhythmic substrate.

In the 2017 HRS expert consensus document[34], the usefulness of mapping and ablation of areas of abnormal myocardial tissue identified with voltage mapping or MRI as an initial or repeat ablation strategy for persistent or longstanding persistent AF was given a class IIb recommendation. A class IIb recommendation was given to creation of linear ablation lines (in absence of documented macro-reentrant flutter), CFAE ablation, rotor ablation, extensive posterior wall ablation or targeting of autonomic ganglionic plexi in persistent AF. The document did however give a class IIa recommendation to ablation of non-PV triggers, if found.

Pitfalls of a substrate guided approach

Scar modification/homogenization approach is not without pitfalls. Some of these include

1. Variation in accuracy and reproducibility of scar maps by electroanatomic mapping or MRI

We have discussed the pitfalls of bipolar voltage mapping earlier in this review. Voltage maps may look different in the same patient with different mapping catheters and in different rhythms. Specific cutoffs for different catheters, mapping systems and rhythms may apply which are yet to be identified. The same problem is noted with MRI imaging where considerable differences in operator and center experience exists. Recent data regarding use of MRI for fibrosis imaging is conflicting. Most recently, a prospective single center experience of 149 consecutive patients (64 persistent, 85 paroxysmal) undergoing AF ablation showed that delayed enhancement detected by cardiac MRI within LA walls using standard clinical scanners and typical pulse sequence parameters was uncommon (five patients, prevalence 3%) and when present, did not correlate with AF type or risk of AF recurrence.[35] These results are contrary to other investigational data.[17],[18] Developing standardized fibrosis specific protocols and uniform cutoffs for fibrosis detection may lead to improved accuracy and reproducibility.

2. What are the end points of substrate modification?

End point of substrate modification is not well established and best ablation approach would likely depend on the distribution and extent of the fibrosis. For example, it may be reasonable to expect to completely homogenize a scar that comprises 5% of the atrium but it is unreasonable to do so if the scar is 40% or more. In those cases, a box lesion set may be more feasible but anatomic location of the scar could further complicate the task, an example would be a septal extension of the scar. The power, duration, extent and end-point of scar-homogenization ablation may also have to be tailored to the adjacent structures such as the esophagus and posterior wall to minimize risk of damage.

3. Is atrial scar really a 'static' substrate?

Targeting the scar at the time of AF ablation may potentially eliminate the 'electrical substrate' at that time point but scar recovery and progression of fibrosis should be considered. In one study, atrial fibrosis quantified by LGE-MRI was stable in the majority of AF patients at one-year follow-up[36]. However, about one third of patients evaluated in the study exhibited progression of atrial fibrotic disease over time. Specific risk predictors for progression of fibrosis could not be identified in this study. In another report by the same group[37], scar recovery and presence of new fibrosis as detected by LGE MRI scans were significant risk factors for late recurrence of AF after initial ablation. If the substrate is not static, scar progression should be considered as a potential risk factor and whether modifying this process can be a long term solution remains to be seen. It is uncertain as to what may be the best approach for ablation in patients with large atrial scars and what would be the endpoint of ablation. Additionally, to what extent right atrial scars correlate with AF progression and whether these need to be targeted remains to be determined.

4. Does scar define all the abnormal substrate? What about the' hidden' substrate?

Even if we consider that imaging or voltage mapping can accurately define the scar and that scar represents the static substrate, it must be understood that fibrosis may just be the final step of a remodeling cascade including myocyte architectural changes, ion channel dysfunction, connexin disarray and disruption of fiber orientation all of which may precede scarring but may not be seen on voltage mapping or imaging. However, it is possible that these areas may still exhibit properties of electrical heterogeneity and may sustain reentrant drivers. This may be referred to as the hidden substrate and at this time remains non-quantifiable. Whether or not this hidden substrate can be detected or targeted to make a clinically relevant difference remains to be seen.

5. Procedural times and fluoroscopy times with additional substrate mapping and modification are longer than PVAI alone

This is a particularly concerning issue at the present time when minimizing fluoroscopy exposure is a principle safety goal during AF ablation procedure. However, as 'low' fluoroscopy and 'no' fluoroscopy techniques for AF ablation become widespread, this issue may not remain as important.

6. Risk–benefit ratio of additional ablation

The risk- benefit ratio of substrate modification would conceivably vary depending on extent of fibrosis, classification and duration of AF, operator and center experience, and expected chances of success with PVAI alone strategy. For example, in a paroxysmal AF patient with first ablation of AF and mild scar, considering that PVAI alone may have high success rates, it may be better to stay away from additional ablation. On the contrary, during redo ablation in long standing persistent AF patients with extensive scar, an individualized substrate modification approach may be necessary. However, a risk benefit model may be most useful in patients such as those with long standing persistent AF going for first AF ablation with moderate scar or paroxysmal AF patients with severe LA scarring. At this time, evidence from large randomized trials is not available to answer these questions.

7. Substrate based ablation may potentially affect LA diastolic function- The "Stiff left atrial syndrome"

Gibson et al[38] first reported the syndrome of dyspnea, congestive heart failure, pulmonary hypertension, and large V waves recorded on PCWP or LA pressure tracings in the absence of significant mitral regurgitation. This syndrome is seen despite absence of pulmonary vein stenosis and is a result of abnormal LA diastolic function due to extensive ablation. Small LA size, obstructive sleep apnea, diabetes mellitus, atrial scarring, and high LA pressure were predictors of this complication of AF ablation. It is conceivable that the syndrome may become more important if operators were to perform extensive ablations beyond PVI alone as the LA diastolic function is more

likely to be affected. While there is data suggesting abnormalities of LA diastolic function after substrate ablation[28], whether this difference is clinically relevant between PVI alone versus PVI with substrate homogenization remains to be seen.

The 'Future role' of substrate guided ablation in management of AF

Voltage and MRI guided substrate modification in addition to pulmonary vein isolation during AF ablation have been performed successfully. However, data is confined to small, mostly non-randomized observational studies. In face of conflicting results from these studies, longer procedural times and possible increased risk of complications with extensive ablation, the rates at which this strategy is employed have remained low, even for repeat ablation in persistent and long standing persistent AF[33]. The currently ongoing large, multicenter randomized DECAAF II trial is designed to study the efficacy of DE-MRI detected fibrosis guided AF ablation strategy (involving PVI +/-scar homogenization based on fibrosis extent) in comparison to conventional catheter ablation of AF. The results of this trial will likely provide further insight in substrate guided AF ablation and more specifically, the role of scar homogenization in AF. However, as previously mentioned in this manuscript, there is lack of consistent reproducibility of MRI detected scar in the atrium and results from recent data regarding use of MRI for LA fibrosis imaging using current standard MRI equipment and protocols have not been entirely encouraging.

Results of a recent investigation indicate that a wholly patient tailored approach may be successful in trigger based ablation in all AF types. In a recent prospective nonrandomized pilot study of 105 patients undergoing AF ablation, Seitz et al[39] have shown that spatiotemporal dispersion of electrograms may represent an electrical footprint of waves that emanate from AF drivers and that these areas may further represents sites of interstitial fibrosis and atrial muscle heterogeneity. The authors demonstrated a novel approach involving recording regions exhibiting spatiotemporal electrogram dispersion by multipolar catheter mapping (Pentaray, Biosense Webster) during AF and then targeting such regions without additional PVI or any other anatomy-based ablation lines. An average of 49 ± 21 mins ablation duration and a mean of 1.4 ± 0.5 procedures resulted in a 95% rate of acute AF termination and 85% AF free survival during an 18 months follow-up. These results showed that the novel approach allowed for efficacious, nonextensive, and wholly patient-tailored ablation in all AF types. The nonrandomized design of this pilot study limited author conclusions. There were other limitations including comparison to a historical cohort and high use of anti-arrhythmic drug (44%). However, the study provides a new hypothesis that needs to be further tested and which may provide a significant step forward in the field of trigger based ablation. It also brings forth evidence supporting an overlap between anatomic substrate and electrical drivers of AF. A larger randomized trial to study this approach against conventional approaches of AF ablation is now warranted.

Since the results of the randomized Fire and ICE trial[40] which showed cryoballoon ablation was noninferior to radiofrequency ablation with respect to efficacy and safety for the treatment of patients with drug-refractory paroxysmal atrial fibrillation, there is growing use of cryoablation for pulmonary vein isolation worldwide. Multiple small nonrandomized studies[41]-[45] have been conducted to assess the efficacy and safety of this technique in persistent AF patients and initial results have been encouraging. Shorter procedural and fluoroscopy times have been reported[45] when compared with RF ablation in persistent AF patients. Larger randomized trials of cryoablation in persistent and long standing persistent AF ablation are underway. As the role of substrate modification in AF ablation remains controversial and pulmonary vein isolation by cryoablation is a growing trend, willingness of operators to perform additional ablation which may require a different ablation technique altogether or a different catheter will be important factors that may determine the future of substrate or trigger based ablation as a first line therapy, even with growing evidence in support of these techniques. There is increasing emphasis on fluoroless ablation techniques and shorter procedural times and hence the benefits of substrate guided ablation will need to be weighed against safety profile and long term outcomes that will determine whether these techniques gain widespread acceptability among electrophysiologists.

Conclusions

Despite technological advances and growing operator experience in performing percutaneous catheter ablation for AF, the long term procedural success rates for persistent AF and long standing persistent AF have not paralleled those of paroxysmal AF. A thorough understanding of the AF substrate requires standardized techniques for defining the static and dynamic substrates of AF. Our most-studied modalities for scar mapping include electroanatomic mapping and cardiac MRI. Currently, the use of either of these techniques has significant pitfalls. In the future, the ability to integrate imaging information with emerging technologies like body surface mapping, ripple mapping and very high-density mapping with closely spaced bipoles and improving the spatial resolution and accuracy of cardiac MR imaging with development of fibrosis specific protocols might provide further understanding of the pathophysiologic interrelation between "scar" and abnormal electrophysiologic substrate in persistent and long standing persistent AF. Multiple studies have reported success with novel trigger and substrate based ablation techniques and larger randomized trials are underway. However, due to lack of data from large multicenter randomized trials, these techniques have not yet gained widespread acceptability. Even as evidence of benefit from substrate based ablation in persistent AF patients grows, there will be practical barriers that will need to be overcome before these techniques can become standard of care (risk-benefit ratio, operative training and experience, requirement for additional ablation techniques in case cryoablation used for PVI, procedural times, fluoroscopy times). Nevertheless, as we embark on our efforts to improve outcomes of AF ablation, especially in patients with persistent and long standing persistent AF, the role of substrate guided AF ablation strategies remains promising.

Disclosures

The authors do not have any conflicts of interest in relation to this manuscript.

References

1. January Craig T, WannL Samuel, AlpertJoseph S, CalkinsHugh, CigarroaJoaquin E, ClevelandJoseph C, ContiJamie B, EllinorPatrick T, EzekowitzMichael D, FieldMichael E, MurrayKatherine T, SaccoRalph L, StevensonWilliam G, TchouPatrick J, TracyCynthia M, YancyClyde W. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society.

Circulation. 2014;130 (23):2071–104

2. Calkins Hugh, ReynoldsMatthew R, SpectorPeter, SondhiManu, XuYingxin, MartinAmber, WilliamsCatherine J, SledgeIsabella. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. Circ Arrhythm Electrophysiol. 2009;2 (4):349–61
3. Haïssaguerre M, JaïsP, ShahD C, TakahashiA, HociniM, QuiniouG, GarrigueS, Le MourouxA, Le MétayerP, ClémentyJ. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N. Engl. J. Med. 1998;339 (10):659–66
4. Calkins Hugh, KuckKarl Heinz, CappatoRiccardo, BrugadaJosep, CammA John, ChenShih-Ann, CrijnsHarry J G, DamianoRalph J, DaviesD Wyn, DiMarcoJohn, EdgertonJames, EllenbogenKenneth, EzekowitzMichael D, HainesDavid E, HaissaguerreMichel, HindricksGerhard, IesakaYoshito, JackmanWarren, JalifeJosé, JaisPierre, KalmanJonathan, KeaneDavid, KimYoung-Hoon, KirchhofPaulus, KleinGeorge, KottkampHans, KumagaiKoichiro, LindsayBruce D, MansourMoussa, MarchlinskiFrancis E, McCarthyPatrick M, MontJ Lluis, MoradyFred, NademaneeKoonlawee, NakagawaHiroshi, NataleAndrea, NattelStanley, PackerDouglas L, PapponeCarlo, PrystowskyEric, RavieleAntonio, ReddyVivek, RuskinJeremy N, SheminRichard J, TsaoHsuan-Ming, WilberDavid. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society. Heart Rhythm. 2012;9 (4):632–696.e21
5. Elayi Claude S, VermaAtul, Di BiaseLuigi, ChingChi Keong, PatelDimpi, BarrettConor, MartinDavid, RongBai, FahmyTamer S, KhaykinYaariv, HongoRichard, HaoSteven, PelargonioGemma, Dello RussoAntonio, CasellaMichela, SantarelliPietro, PotenzaDomenico, FanelliRaffaele, MassaroRaimondo, ArrudaMauricio, SchweikertRobert A, NataleAndrea. Ablation for longstanding permanent atrial fibrillation: results from a randomized study comparing three different strategies. Heart Rhythm. 2008;5 (12):1658–64
6. Brooks Anthony G, StilesMartin K, LaborderieJulien, LauDennis H, KuklikPawel, ShippNicholas J, HsuLi-Fern, SandersPrashanthan. Outcomes of long-standing persistent atrial fibrillation ablation: a systematic review. Heart Rhythm. 2010;7 (6):835–46
7. Tilz Roland Richard, RilligAndreas, ThumAnna-Maria, AryaAnita, WohlmuthPeter, MetznerAndreas, MathewShibu, YoshigaYasuhiro, WissnerErik, KuckKarl-Heinz, OuyangFeifan. Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the Hamburg Sequential Ablation Strategy. J. Am. Coll. Cardiol. 2012;60 (19):1921–9
8. Providência Rui, LambiasePier D, SrinivasanNeil, Ganesh BabuGirish, BronisKonstantinos, AhsanSyed, KhanFakhar Z, ChowAnthony W, RowlandEdward, LoweMartin, SegalOliver R. Is There Still a Role for Complex Fractionated Atrial Electrogram Ablation in Addition to Pulmonary Vein Isolation in Patients With Paroxysmal and Persistent Atrial Fibrillation? Meta-Analysis of 1415 Patients. Circ Arrhythm Electrophysiol. 2015;8 (5):1017–29
9. Cox J L, BoineauJ P, SchuesslerR B, KaterK M, LappasD G. Five-year experience with the maze procedure for atrial fibrillation. Ann. Thorac. Surg. 1993;56 (4):814–823
10. Verma Atul, JiangChen-yang, BettsTimothy R, ChenJian, DeisenhoferIsabel, MantovanRoberto, MacleLaurent, MorilloCarlos A, HaverkampWilhelm, WeerasooriyaRukshen, AlbenqueJean-Paul, NardiStefano, MenardiEndrj, NovakPaul, SandersPrashanthan. Approaches to catheter ablation for persistent atrial fibrillation. N. Engl. J. Med. 2015;372 (19):1812–22
11. Heijman Jordi, AlgalarrondoVincent, VoigtNiels, MelkaJonathan, WehrensXander H T, DobrevDobromir, NattelStanley. The value of basic research insights into atrial fibrillation mechanisms as a guide to therapeutic innovation: a critical analysis. Cardiovasc. Res. 2016;109 (4):467–79
12. Zahid Sohail, CochetHubert, BoylePatrick M, SchwarzErica L, WhyteKaitlyn N, VigmondEdward J, DuboisRémi, HociniMélèze, HaïssaguerreMichel, JaïsPierre, TrayanovaNatalia A. Patient-derived models link re-entrant driver localization in atrial fibrillation to fibrosis spatial pattern. Cardiovasc. Res. 2016;110 (3):443–54
13. Andrade Jason, KhairyPaul, DobrevDobromir, NattelStanley. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. Circ. Res. 2014;114 (9):1453–68
14. Maesen Bart, ZeemeringStef, AfonsoCarlos, EcksteinJens, BurtonRebecca A B, van HunnikArne, StuckeyDaniel J, TylerDamian, MaessenJos, GrauVicente, VerheuleSander, KohlPeter, SchottenUlrich. Rearrangement of atrial bundle architecture and consequent changes in anisotropy of conduction constitute the 3-dimensional substrate for atrial fibrillation. Circ Arrhythm Electrophysiol. 2013;6 (5):967–75
15. Verma Atul, WazniOussama M, MarroucheNassir F, MartinDavid O, KilicaslanFethi, MinorStephen, SchweikertRobert A, SalibaWalid, CummingsJennifer, BurkhardtJ David, BhargavaMandeep, BeldenWilliam A, Abdul-KarimAhmad, NataleAndrea. Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation: an independent predictor of procedural failure. J. Am. Coll. Cardiol. 2005;45 (2):285–92
16. Yamaguchi Takanori, TsuchiyaTakeshi, NagamotoYasutsugu, MiyamotoKoji, MurotaniKenta, OkishigeKaoru, TakahashiNaohiko. Long-term results of pulmonary vein antrum isolation in patients with atrial fibrillation: an analysis in regards to substrates and pulmonary vein reconnections. Europace. 2014;16 (4):511–20
17. Marrouche Nassir F, WilberDavid, HindricksGerhard, JaisPierre, AkoumNazem, MarchlinskiFrancis, KholmovskiEugene, BurgonNathan, HuNan, MontLluis, DenekeThomas, DuytschaeverMattias, NeumannThomas, MansourMoussa, MahnkopfChristian, HerwegBengt, DaoudEmile, WissnerErik, BansmannPaul, BrachmannJohannes. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. JAMA. 2014;311 (5):498–506
18. Khurram Irfan M, HabibiMohammadali, Gucuk IpekEsra, ChrispinJonathan, YangEunice, FukumotoKotaro, DewireJane, SpraggDavid D, MarineJoseph E, BergerRonald D, AshikagaHiroshi, RickardJack, ZhangYiyi, ZipunnikovVadim, ZimmermanStefan L, CalkinsHugh, NazarianSaman. Left Atrial LGE and Arrhythmia Recurrence Following Pulmonary Vein Isolation for Paroxysmal and Persistent AF. JACC Cardiovasc Imaging. 2016;9 (2):142–8
19. Kapa Suraj, DesjardinsBenoit, CallansDavid J, MarchlinskiFrancis E, DixitSanjay. Contact electroanatomic mapping derived voltage criteria for characterizing left atrial scar in patients undergoing ablation for atrial fibrillation. J. Cardiovasc. Electrophysiol. 2014;25 (10):1044–52
20. Tschabrunn Cory M, RoujolSebastien, DormanNicole C, NezafatReza, JosephsonMark E, AnterElad. High-Resolution Mapping of Ventricular Scar: Comparison Between Single and Multielectrode Catheters. Circ Arrhythm Electrophysiol. 2016;9 (6)
21. Yagishita Atsuhiko, DE OliveiraSamer, CakulevIvan, GimbelJ Rod, SparanoDina, ManyamHarish, Manrique-GarciaAlvaro, ArredondoMichael, MackallJudith, ArrudaMauricio. Correlation of Left Atrial Voltage Distribution Between

Sinus Rhythm and Atrial Fibrillation: Identifying Structural Remodeling by 3-D Electroanatomic Mapping Irrespective of the Rhythm. J. Cardiovasc. Electrophysiol. 2016;27 (8):905–12

22. Teh Andrew W, KistlerPeter M, LeeGeoffrey, MediCaroline, HeckPatrick M, SpenceSteven J, SparksPaul B, MortonJoseph B, SandersPrashanthan, KalmanJonathan M. The relationship between complex fractionated electrograms and atrial low-voltage zones during atrial fibrillation and paced rhythm. Europace. 2011;13 (12):1709–16
23. Teh Andrew W, KistlerPeter M, LeeGeoffrey, MediCaroline, HeckPatrick M, SpenceSteven J, SparksPaul B, MortonJoseph B, KalmanJonathan M. Electroanatomic remodeling of the left atrium in paroxysmal and persistent atrial fibrillation patients without structural heart disease. J. Cardiovasc. Electrophysiol. 2012;23 (3):232–8
24. Lin Yazhou, YangBing, GarciaFermin C, JuWeizhu, ZhangFengxiang, ChenHongwu, YuJinbo, LiMingfang, GuKai, CaoKejiang, CallansDavid J, MarchlinskiFrancis E, ChenMinglong. Comparison of left atrial electrophysiologic abnormalities during sinus rhythm in patients with different type of atrial fibrillation. J Interv Card Electrophysiol. 2014;39 (1):57–67
25. Fiala Martin, WichterleDan, ChovancíkJan, BulkováVeronika, WojnarováDorota, NevralováRenáta, JanuskaJaroslav. Left atrial voltage during atrial fibrillation in paroxysmal and persistent atrial fibrillation patients. Pacing Clin Electrophysiol. 2010;33 (5):541–8
26. Rolf Sascha, KircherSimon, AryaArash, EitelCharlotte, SommerPhilipp, RichterSergio, GasparThomas, BollmannAndreas, AltmannDavid, PiedraCarlos, HindricksGerhard, PiorkowskiChristopher. Tailored atrial substrate modification based on low-voltage areas in catheter ablation of atrial fibrillation. Circ Arrhythm Electrophysiol. 2014;7 (5):825–33
27. Jadidi Amir S, LehrmannHeiko, KeylCornelius, SorrelJérémie, MarksteinViktor, MinnersJan, ParkChan-Il, DenisArnaud, JaïsPierre, HociniMélèze, PotocnikClemens, AllgeierJuergen, HochholzerWillibald, Herrera-SidlokyClaudia, KimSteve, OmriYoussef El, NeumannFranz-Josef, WeberReinhold, HaïssaguerreMichel, ArentzThomas. Ablation of Persistent Atrial Fibrillation Targeting Low-Voltage Areas With Selective Activation Characteristics. Circ Arrhythm Electrophysiol. 2016;9 (3)
28. Yamaguchi Takanori, TsuchiyaTakeshi, NakaharaShiro, FukuiAkira, NagamotoYasutsugu, MurotaniKenta, EshimaKenichi, TakahashiNaohiko. Efficacy of Left Atrial Voltage-Based Catheter Ablation of Persistent Atrial Fibrillation. J. Cardiovasc. Electrophysiol. 2016;27 (9):1055–63
29. Yang Gang, YangBing, WeiYouquan, ZhangFengxiang, JuWeizhu, ChenHongwu, LiMingfang, GuKai, LinYazhou, WangBenqi, CaoKejiang, KojodjojoPipin, ChenMinglong. Catheter Ablation of Nonparoxysmal Atrial Fibrillation Using Electrophysiologically Guided Substrate Modification During Sinus Rhythm After Pulmonary Vein Isolation. Circ Arrhythm Electrophysiol. 2016;9 (2)
30. Kottkamp Hans, BergJan, BenderRoderich, RiegerAndreas, SchreiberDoreen. Box Isolation of Fibrotic Areas (BIFA): A Patient-Tailored Substrate Modification Approach for Ablation of Atrial Fibrillation. J. Cardiovasc. Electrophysiol. 2016;27 (1):22–30
31. Wang Xin-Hua, LiZheng, MaoJia-Liang, HeBen. A novel individualized substrate modification approach for the treatment of long-standing persistent atrial fibrillation: preliminary results. Int. J. Cardiol. 2014;175 (1):162–8
32. Blandino Alessandro, BianchiFrancesca, GrossiStefano, Biondi-ZoccaiGiuseppe, ConteMaria Rosa, GaidoLuca, GaitaFiorenzo, ScaglioneMarco, RamettaFrancesco. Left Atrial Substrate Modification Targeting Low-Voltage Areas for Catheter Ablation of Atrial Fibrillation: A Systematic Review and Meta-Analysis. Pacing Clin Electrophysiol. 2017;40 (2):199–212
33. Mohanty Sanghamitra, MohantyPrasant, Di BiaseLuigi, TrivediChintan, MorrisEli Hamilton, GianniCarola, SantangeliPasquale, BaiRong, SanchezJavier E, HranitzkyPatrick, GallinghouseG Joseph, Al-AhmadAmin, HortonRodney P, HongoRichard, BeheirySalwa, ElayiClaude S, LakkireddyDhanunjaya, Madhu ReddyYaruva, Viles GonzalezJuan F, BurkhardtJ David, NataleAndrea. Long-term follow-up of patients with paroxysmal atrial fibrillation and severe left atrial scarring: comparison between pulmonary vein antrum isolation only or pulmonary vein isolation combined with either scar homogenization or trigger ablation. Europace. 2017;19 (11):1790–1797
34. Calkins Hugh, HindricksGerhard, CappatoRiccardo, KimYoung-Hoon, SaadEduardo B, AguinagaLuis, AkarJoseph G, BadhwarVinay, BrugadaJosep, CammJohn, ChenPeng-Sheng, ChenShih-Ann, ChungMina K, NielsenJens Cosedis, CurtisAnne B, DaviesD Wyn, DayJohn D, d'AvilaAndré, de GrootN M S Natasja, Di BiaseLuigi, DuytschaeverMattias, EdgertonJames R, EllenbogenKenneth A, EllinorPatrick T, ErnstSabine, FenelonGuilherme, GerstenfeldEdward P, HainesDavid E, HaissaguerreMichel, HelmRobert H, HylekElaine, JackmanWarren M, JalifeJose, KalmanJonathan M, KautznerJosef, KottkampHans, KuckKarl Heinz, KumagaiKoichiro, LeeRichard, LewalterThorsten, LindsayBruce D, MacleLaurent, MansourMoussa, MarchlinskiFrancis E, MichaudGregory F, NakagawaHiroshi, NataleAndrea, NattelStanley, OkumuraKen, PackerDouglas, PokushalovEvgeny, ReynoldsMatthew R, SandersPrashanthan, ScanavaccaMauricio, SchillingRichard, TondoClaudio, TsaoHsuan-Ming, VermaAtul, WilberDavid J, YamaneTeiichi. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: Executive summary. J Arrhythm. 2017;33 (5):369–409
35. Bois John P, GlocknerJames, YoungPhillip M, FoleyThomas A, SheldonSeth, NewmanDarrell B, LinGrace, PackerDouglas L, BradyPeter A. Low incidence of left atrial delayed enhancement with MRI in patients with AF: a single-centre experience. Open Heart. 2017;4 (1)
36. Yamaji K, FujimotoS, YutaniC, IkedaY, MizunoR, HashimotoT, NakamuraS. Does the progression of myocardial fibrosis lead to atrial fibrillation in patients with hypertrophic cardiomyopathy?. Cardiovasc. Pathol. 2002;10 (6):297–303
37. Kottkamp Hans. Human atrial fibrillation substrate: towards a specific fibrotic atrial cardiomyopathy. Eur. Heart J. 2013;34 (35):2731–8
38. Gibson Douglas N, Di BiaseLuigi, MohantyPrasant, PatelJigar D, BaiRong, SanchezJavier, BurkhardtJ David, HeywoodJ Thomas, JohnsonAllen D, RubensonDavid S, HortonRodney, GallinghouseG Joseph, BeheirySalwa, CurtisGuy P, CohenDavid N, LeeMark Y, SmithMichael R, GopinathDevi, LewisWilliam R, NataleAndrea. Stiff left atrial syndrome after catheter ablation for atrial fibrillation: clinical characterization, prevalence, and predictors. Heart Rhythm. 2011;8 (9):1364–71
39. Seitz Julien, BarsClément, ThéodoreGuillaume, BeurtheretSylvain, LelloucheNicolas, BremondyMichel, FerracciAnge, FaureJacques, PenarandaGuillaume, YamazakiMasatoshi, AvulaUma Mahesh R, CurelLaurence, SiameSabrina, BerenfeldOmer, PisapiaAndré, KalifaJérôme. AF Ablation Guided by Spatiotemporal Electrogram Dispersion Without Pulmonary Vein Isolation: A Wholly Patient-Tailored Approach. J. Am. Coll. Cardiol. 2017;69 (3):303–321
40. Kuck Karl-Heinz, BrugadaJosep, FürnkranzAlexander, MetznerAndreas, OuyangFeifan, ChunK R Julian, ElvanArif, ArentzThomas, BestehornKurt, PocockStuart J, AlbenqueJean-Paul, TondoClaudio. Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. N. Engl. J. Med. 2016;374 (23):2235–45
41. Ciconte Giuseppe, OttavianoLuca, de AsmundisCarlo, BaltogiannisGiannis, ConteGiulio, SieiraJuan, Di GiovanniGiacomo, SaitohYukio, IrfanGhazala, MugnaiGiacomo, StortiCesare, MonteneroAnnibale Sandro, ChierchiaGian-Battista, BrugadaPedro. Pulmonary vein isolation as index procedure for persistent atrial fibrillation: One-year clinical outcome after ablation using the second-generation cryoballoon. Heart Rhythm. 2015;12 (1):60–6
42. Lemes C, WissnerE, LinT. One-year clinical outcome after pulmonary vein isolation in persistent atrial fibrillation using the second-generation 28 mm

cryoballoon: a retrospective analysis. Europace. 2015;18:201–205

43. Koektuerk Buelent, YorgunHikmet, HengeoezOezlem, TuranCem H, DahmenAlina, YangAlexander, BansmannPaul M, GorrEduard, HoppeChristian, TuranRamazan G, HorlitzMarc. Cryoballoon Ablation for Pulmonary Vein Isolation in Patients With Persistent Atrial Fibrillation: One-Year Outcome Using Second Generation Cryoballoon. Circ Arrhythm Electrophysiol. 2015;8 (5):1073–9
44. Guhl Emily N, SiddowayDonald, AdelsteinEvan, VoigtAndrew, SabaSamir, JainSandeep K. Efficacy of Cryoballoon Pulmonary Vein Isolation in Patients With Persistent Atrial Fibrillation. J. Cardiovasc. Electrophysiol. 2016;27 (4):423–7
45. Ciconte Giuseppe, BaltogiannisGiannis, de AsmundisCarlo, SieiraJuan, ConteGiulio, Di GiovanniGiacomo, SaitohYukio, IrfanGhazala, MugnaiGiacomo, HunukBurak, ChierchiaGian-Battista, BrugadaPedro. Circumferential pulmonary vein isolation as index procedure for persistent atrial fibrillation: a comparison between radiofrequency catheter ablation and second-generation cryoballoon ablation. Europace. 2015;17 (4):559–65