JAFIB
Featured Review
Journal of Atrial Fibrillation
www. jafib.com

Improvements In Af Ablation Outcome Will Be Based More On Technological Advancement Versus Mechanistic Understanding

Chen-yang Jiang, MD[1], Ru-hong Jiang, MS[1]

[1]*Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China.*

Abstract

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias. Catheter ablation has proven more effective than antiarrhythmic drugs in preventing clinical recurrence of AF, however long-term outcome remains unsatisfactory. Ablation strategies have evolved based on progress in mechanistic understanding, and technologies have advanced continuously. This article reviews current mechanistic concepts and technological advancements in AF treatment, and summarizes their impact on improvement of AF ablation outcome.

Introduction

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias. The last 15 years witnessed advances in mechanistic understanding and technology that fueled the rapid development and refinement of catheter ablation therapy of refractory AF. Despite its status as gold standard and an increasing body of evidence on greater effectiveness over antiarrhythmic drug therapy in preventing clinical recurrence of AF,[1, 2] long-term success rates of catheter ablation remain unsatisfactory. This article highlights current mechanistic concepts and technological advances in AF treatment.

Mechanisms of Atrial Fibrillation

AF is a complex arrhythmia with multiple possible mechanisms[3] including, from an electrophysiological perspective, multiple propagating wavelets, focal electrical discharges, and local reentrant activity, among others.[4, 5] Great progress in mechanistic understanding came with demonstration by Haissaguerre and co-workers that pulmonary veins (PVs) play a critical role in AF generation in humans and that AF could be treated by ablation therapy.[6] PVs and surrounding atrial tissue consequently became the major focus of AF mechanistic research.

It is well accepted that onset and maintenance of AF require both a trigger and a substrate. P, transitional, and Purkinje cells endow human PVs[7, 8] with potential for ectopic beat initiation while muscular discontinuities and abrupt changes in fiber orientation in PVs and the PV-left atrium (LA) junction provide ideal substrates for reentry.[9]

Disclosures:
None.

Corresponding Author:
Chen-yang Jiang, M.D.
Department of Cardiology,
Sir Run Run Shaw Hospital,
Zhejiang University School of Medicine. 3 East Qingchun Road,
Hangzhou, Zhejiang,
310016,
P.R.China.

Although ectopic beats also can originate in other anatomical structures, including LA posterior wall, superior vena cava, crista terminalis, ligament of Marshall, coronary sinus ostium, and interatrial septum,[10] the PV-LA junction has the highest density of autonomic innervation,[9, 11] and autonomic nerve stimulation which is thought to play an important role in AF initiation[12, 13] can initiate PV firing.[14, 15] Clinically, abolition of vagal reflexes around PVs during circumferential pulmonary vein isolation (CPVI) benefits AF ablation outcome;[16] this has been further supported by studies directly targeting ganglionated plexi (GP).[17-19]

Self-perpetuation through induction of atrial structural and electrical remodeling also is an important mechanism for AF.[20-22] This mechanism undermines outcomes of ablation therapy for AF, as particularly reflected in higher recurrence rate after targeting PV and/or non-PV triggers alone in patients with persistent and long-standing persistent AF.[23, 24]

Ablation Strategies and Their Bottleneck

Based on progress in mechanistic understanding, ablation strategies have evolved from early attempts at replicating the surgical Maze procedure to modification of the trigger(s) and/or substrate for AF.[25]

Ablation Strategy Targeting PV

The crucial role of PVs in AF initiation has rendered ablation targeting PVs and/or PV surrounding atrial tissue as cornerstone procedure in AF treatment.[26] Because of infrequent AF inducibility, difficulty in mapping original triggers, and risk of PV stenosis, the ablation site however has shifted from the PV itself to the atrial tissue located in the antrum.[27] Of the two PV ablation strategies initially proposed, namely segmental and circumferential, the latter is more widely accepted and associated with higher success rate as shown in a randomized study.[28] The larger circumferential area of isolation around PVs not only eliminates PV foci but also contains more of the atrial myocardium surrounding the PVs, i.e., the area with autonomic innervation and substrates for reentry.

The recommended PV ablation endpoint of electrical isolation in PVs is achieved in most cases. However, there is high incidence of

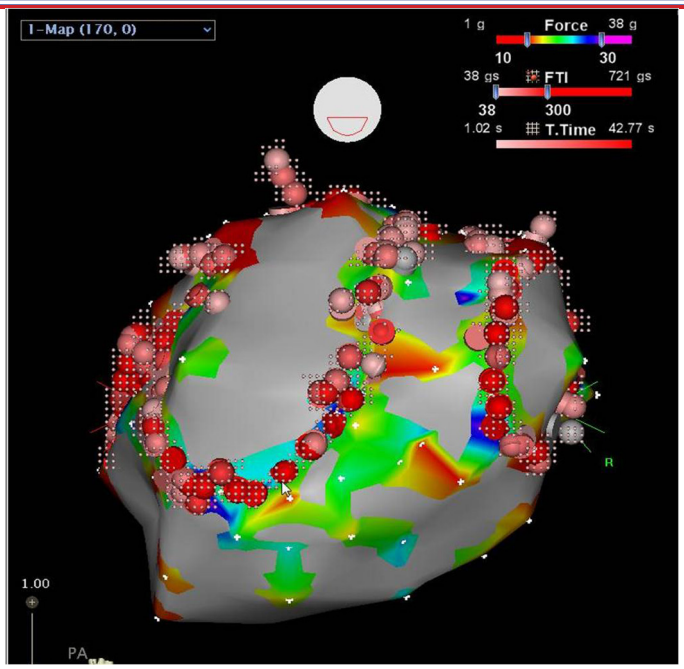

Figure 1: Circumferential PV isolation performed by contact-force sensing catheter. Contact force during mapping and ablation, and ablation time are shown in the 3D model of left atrium.

PV reconnection in patients with clinical recurrence, which is implicated as its predominant mechanism.[29,30] Achievement of durable PV isolation, likely requiring continuous and transmural lesion formation, therefore is considered an important goal of AF ablation.

Ablation Strategies Not Targeting PVs

Non-PV Triggers

Non-PV triggers, including LA posterior wall, superior vena cava, crista terminalis, and ligament of Marshall among others, can be identified in some patients during the ablation procedure.[10] Although it is recommended to eliminate them,[26] as is the case for PV foci they are infrequently induced and difficult to localize with positioned catheters during routine AF ablation procedures.

Ablation Of Complex Fractionated Atrial Electrograms (CFAEs)

CFAEs, initially reported by Nademanee et al, are defined as electrograms with highly fractionated potentials or with a very short cycle length (<120ms).[31] Areas with CFAEs are considered substrate for AF maintenance, and their ablation in addition to PVI or as a part of stepwise approach appears beneficial in treatment of non-paroxysmal but not of paroxysmal AF.[32, 33] However, definitions of CFAEs and endpoints of ablation are inconsistent among trials, extensive areas might be targeted and become arrhythmogenic, and CFAEs mechanism is not totally understood.[32-34]

Linear Ablation

The most common lines in AF ablation are the mitral isthmus (sometimes replaced by anterior line between roof line and mitral annulus), LA roof and cavotricuspid isthmus lines. Linear ablation, although not recommended for paroxysmal AF because of possible increased atrial tachycardia,[35] benefits outcome when added to PVI in patients with persistent AF.[36, 37] The key for linear ablation is line completeness with bi-directional block, which is sometimes challenging.

GP (ganglionated plexi) Ablation

Based on evidence from animal and clinical studies,[16, 38] recent studies have focused on ablation of GP identified by high-frequency electrical stimulation causing marked slowing of ventricular response during AF[39] or by an anatomic approach.[17] Clinical results are inconsistent among studies using GP ablation alone,[17, 40] while its addition to PVI increases AF-free survival in patients with paroxysmal AF,[19, 41, 42] and it is superior to PVI plus linear ablation in patients with persistent or long-standing persistent AF.[43] However, 14.7%[41] and 26%[19] of patients with paroxysmal AF experienced AF recurrence in the PVI plus GP ablation group at 12 and 24 months follow-up, respectively, while 66% of patients with persistent AF experienced AF recurrence at 3 years follow-up.[43]

Concerns about GP ablation include knowing which substrate is destroyed when ablation is performed endocardially; potential autonomic tone imbalance; autonomic reinnervation; and safety of high-power used.

Rotors

Using a recently developed physiologically-guided computational approach, Narayan et al. revealed sustained electrical rotors and repetitive focal beats during human AF; focal impulse and rotor modulation (FIRM)-guided ablation at patient-specific sources acutely terminated or slowed AF, and improved long-term outcome.[44,45] Their findings provide novel mechanistic insight into AF.

Technological Advances

Advances in RF (Radiofrequency) Ablation Systems

Radiofrequency is the most-commonly used energy for AF ablation.[26] As compared to ablation of atrioventricular reentry and non-reentry tachycardia, AF ablation requires multiple, larger and transmural lesions. To this end and relative to conventional 4mm tip ablation catheters, irrigated-tip catheters are more efficient by maintaining a low electrode-tissue interface temperature and impedance during RF application at high power;[46] and patients undergoing AF ablation with irrigated-tip catheters are less likely to experience AF recurrence.[47]

Most centers currently use irrigated-tip catheters in AF ablation procedures. Several electrode architectures have been developed with different tip dimensions, temperature sensor location and design of irrigation ports on the tip surface; however, only slight differences have been found in lesion size or safety profile among catheters tested in vitro.[48]

There is no definitive clinical evidence on which technology is associated with better outcomes or less complications, and all traditional irrigated catheters have been unsatisfactory in achieving long-term success in AF ablation. Besides mechanistic complexity of AF in humans, effect of RF ablation is influenced by transmurality and continuity of lesions created, and most AF recurrence is thought to be related with PV-LA reconnection after initially successful PVI.[49,50]

One of the most anticipated features of new-generation irrigated catheters has been contact-force sensing, which helps optimize electrode-tissue contact and provides the operator more quantifiable energy delivery.[51-53] In clinical trials, contact force information guidance reduced AF recurrence by 20 to 25 percent,[54, 55] and similarly important, yields more favorable procedural parameters, in particular procedural and fluoroscopy times, without increasing complications (Figure 1).[54-56]

Because outcome of ablation also is dependent on LA architecture and catheter stability, an auxiliary system for RF ablation mainly including a nonfluoroscopic three-dimensional mapping system and

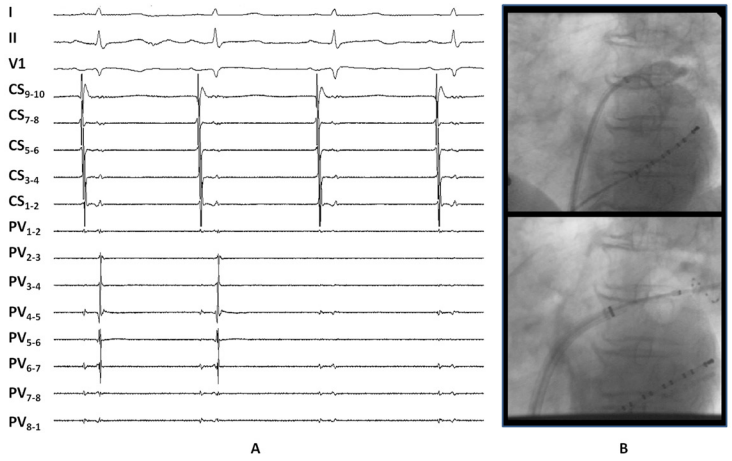

Figure 2: Example of LSPV isolation performed by cryoballoon ablation. A: PV potential disappeared during ablation; B: Fluoroscopic images of angiography of PVs and cryoballoon catheter position during ablation.

sheath to support the ablation catheter improved 1-year outcome after AF ablation.[57] The CARTO and the Ensite Navx 3-dimensional systems have been used extensively.[58,59] With system version updates, efficiency and precision both in atrial geometry reconstruction and catheter guidance have improved continuously, benefiting from technological advances in data collection rate, catheter visualization, gating and compensation technique, among others. The recently introduced sensor-based electromagnetic tracking system, the MediGuide technology, is easy to integrate into the workflow of AF ablation and allows high-quality nonfluoroscopic 4D catheter tracking while significantly reducing radiation exposure of patients and staff.[60] Also, steerable sheath technology designed to facilitate catheter access, stability, and tissue contact during AF catheter ablation might lead to higher clinical success rate.[57,61]

Advances In Other Ablation Systems

Although RF catheter ablation is used worldwide as standard of care in AF treatment, it leaves room for improvement. The RF catheter ablation procedure is time-consuming and highly dependent on operator's experience while major complications such as cardiac perforation, PV stenosis, stroke, atrioesophageal fistula and phrenic nerve injury cannot be completely avoided.[62-64]

Investigators therefore have conducted research on other energy ablation systems, most for PV isolation. Cryothermal energy is an alternative energy source that has been used for over 3 decades in cardiac arrhythmia treatment.[65] In early years, cryoablation was used in AF therapy on a limited basis because of prolonged procedure time and low success rate of point-to-point ablation;[66,67] it became a feasible approach with introduction of the cryoballoon ablation catheter (Figure 2).[68] Cryoballoon technology, developed to simplify and accelerate the procedure and used in patients with paroxysmal AF in most published studies,[69] has proven a safe and effective alternative to antiarrhythmic medication for the treatment of AF patients, with risks within accepted standards for ablation therapy.[70] Compared with RF ablation, cryoballoon-based ablation yields similar acute success and overall complication rates,[71] and in a case control study, similar success rate at 3 and 6 months post-ablation.[72] A second generation cryoballoon catheter appears to provide improved ablation efficiency with higher success rates at 12 months follow-up.[73,74]

Ablation procedures based on other energy forms, including balloon-based ultrasound ablation,[75] RF hot balloon catheter,[76] laser based ablation,[77] and visually guided RF ablation[78] have been developed, however, both efficacy and safety need to be evaluated in more clinical trials.

Advances In Imaging And Mapping Technologies

Conventional fluoroscopy-guided catheter mapping had been unsatisfactory in mapping complex arrhythmias such as AF and VTs, which require accurate navigation and combined anatomic and electrical information. Two electroanatomic mapping systems including CARTO mapping system and NavX mapping system are widely used in clinical practice as described above. The anatomic accuracy of the map could be improved by integration of 3D images by CT, MRI or ultrasound in both systems. 3D rotational angiography has been introduced recently, and proven to significantly reduce radiation exposure while used as a single tool or in combination with CARTO or NavX systems.[79-81] Besides providing anatomic guidance, atrial myocardial fibrosis can be visualized by technology with late gadolinium enhancement MRI,[82] and the real-time MRI-guided system has demonstrated advantage in atrial tissue lesion visualization during RF delivery.[83]

Several mapping catheters have been developed for AF ablation. Multipolar catheters, such as Double-loop catheter (Inquiry AFocus II™, St. Jude Medical, Minneapolis, MN, USA), and Pentaray catheter (PentaRay, Biosense-Webster, Diamond Bar, CA, USA), can improve electroanatomic information collection, which is beneficial for cardiac chamber building, activation analyzing, and voltage/substrate mapping. Another multipolar basket catheter (Constellation, Boston Scientific, MA, USA) has been recently used for FIRM mapping of AF, and along with a novel system (RhythmView, Topera Medical, Lexington, Massachusetts) found to improve long-term outcome of AF ablation.[44,45]

Conclusion:

The mechanism of AF is still not totally understood. Under the present mechanistic understanding, ablation therapy has been documented as an effective treatment, although its long-term outcome especially after the initial procedure remains unsatisfactory. Multiple procedures with current strategies appear to yield more acceptable outcome,[49,84] and technological advances appear to offer greater impetus to AF ablation outcome improvement than deeper mechanistic understanding. Although indeed we do not fully understand the mechanism of AF, we aim to develop tools to personalize AF treatment (when and what additional ablation is needed), improve outcomes and reduce complications. Technology has helped and will hopefully path the way to that direction.

References:

1. Jais P, Cauchemez B, Macle L, Daoud E, Khairy P, Subbiah R, Hocini M, Extramiana F, Sacher F, Bordachar P, Klein G, Weerasooriya R, Clementy J, Haissaguerre M. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: The a4 study. Circulation. 2008;118:2498-2505.
2. Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, Macle L, Daoud EG, Calkins H, Hall B, Reddy V, Augello G, Reynolds MR, Vinekar C, Liu CY, Berry SM, Berry DA. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: A randomized controlled trial. JAMA. 2010;303:333-340.
3. Allessie MA, Boyden PA, Camm AJ, Kleber AG, Lab MJ, Legato MJ, Rosen MR, Schwartz PJ, Spooner PM, Van Wagoner DR, Waldo AL. Pathophysiology and prevention of atrial fibrillation. Circulation. 2001;103:769-777.

4. Nattel S. New ideas about atrial fibrillation 50 years on. Nature. 2002;415:219-226.
5. Jalife J, Berenfeld O, Mansour M. Mother rotors and fibrillatory conduction: A mechanism of atrial fibrillation. Cardiovasc Res. 2002;54:204-216.
6. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Metayer P, Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998;339:659-666.
7. Ehrlich JR, Cha TJ, Zhang L, Chartier D, Melnyk P, Hohnloser SH, Nattel S. Cellular electrophysiology of canine pulmonary vein cardiomyocytes: Action potential and ionic current properties. J Physiol. 2003;551:801-813.
8. Chen YC, Pan NH, Cheng CC, Higa S, Chen YJ, Chen SA. Heterogeneous expression of potassium currents and pacemaker currents potentially regulates arrhythmogenesis of pulmonary vein cardiomyocytes. J Cardiovasc Electrophysiol. 2009;20:1039-1045.
9. Tan AY, Li H, Wachsmann-Hogiu S, Chen LS, Chen PS, Fishbein MC. Autonomic innervation and segmental muscular disconnections at the human pulmonary vein-atrial junction: Implications for catheter ablation of atrial-pulmonary vein junction. J Am Coll Cardiol. 2006;48:132-143.
10. Lin WS, Tai CT, Hsieh MH, Tsai CF, Lin YK, Tsao HM, Huang JL, Yu WC, Yang SP, Ding YA, Chang MS, Chen SA. Catheter ablation of paroxysmal atrial fibrillation initiated by non-pulmonary vein ectopy. Circulation. 2003;107:3176-3183.
11. Chevalier P, Tabib A, Meyronnet D, Chalabreysse L, Restier L, Ludman V, Alies A, Adeleine P, Thivolet F, Burri H, Loire R, Francois L, Fanton L. Quantitative study of nerves of the human left atrium. Heart Rhythm. 2005;2:518-522.
12. Coumel P. Autonomic influences in atrial tachyarrhythmias. J Cardiovasc Electrophysiol. 1996;7:999-1007.
13. Scherlag BJ, Yamanashi W, Patel U, Lazzara R, Jackman WM. Autonomically induced conversion of pulmonary vein focal firing into atrial fibrillation. J Am Coll Cardiol. 2005;45:1878-1886.
14. Patterson E, Po SS, Scherlag BJ, Lazzara R. Triggered firing in pulmonary veins initiated by in vitro autonomic nerve stimulation. Heart Rhythm. 2005;2:624-631.
15. Po SS, Scherlag BJ, Yamanashi WS, Edwards J, Zhou J, Wu R, Geng N, Lazzara R, Jackman WM. Experimental model for paroxysmal atrial fibrillation arising at the pulmonary vein-atrial junctions. Heart Rhythm. 2006;3:201-208.
16. Pappone C, Santinelli V, Manguso F, Vicedomini G, Gugliotta F, Augello G, Mazzone P, Tortoriello V, Landoni G, Zangrillo A, Lang C, Tomita T, Mesas C, Mastella E, Alfieri O. Pulmonary vein denervation enhances long-term benefit after circumferential ablation for paroxysmal atrial fibrillation. Circulation. 2004;109:327-334.
17. Pokushalov E, Romanov A, Shugayev P, Artyomenko S, Shirokova N, Turov A, Katritsis DG. Selective ganglionated plexi ablation for paroxysmal atrial fibrillation. Heart Rhythm. 2009;6:1257-1264.
18. Po SS, Nakagawa H, Jackman WM. Localization of left atrial ganglionated plexi in patients with atrial fibrillation. J Cardiovasc Electrophysiol. 2009;20:1186-1189.
19. Katritsis DG, Pokushalov E, Romanov A, Giazitzoglou E, Siontis GC, Po SS, Camm AJ, Ioannidis JP. Autonomic denervation added to pulmonary vein isolation for paroxysmal atrial fibrillation: A randomized clinical trial. J Am Coll Cardiol. 2013;62:2318-2325.
20. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation. 1995;92:1954-1968.
21. Morillo CA, Klein GJ, Jones DL, Guiraudon CM. Chronic rapid atrial pacing. Structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. Circulation. 1995;91:1588-1595.
22. Goette A, Honeycutt C, Langberg JJ. Electrical remodeling in atrial fibrillation. Time course and mechanisms. Circulation. 1996;94:2968-2974.
23. Hayward RM, Upadhyay GA, Mela T, Ellinor PT, Barrett CD, Heist EK, Verma A, Choudhry NK, Singh JP. Pulmonary vein isolation with complex fractionated atrial electrogram ablation for paroxysmal and nonparoxysmal atrial fibrillation: A meta-analysis. Heart Rhythm. 2011;8:994-1000.
24. Assasi N, Xie F, Blackhouse G, Gaebel K, Robertson D, Hopkins R, Healey JS, Goeree R. Comparative effectiveness of catheter ablation strategies for rhythm control in patients with atrial fibrillation: A meta-analysis. J Interv Card Electrophysiol. 2012;35:259-275.
25. Haissaguerre M, Jais P, Shah DC, Gencel L, Pradeau V, Garrigues S, Chouairi S, Hocini M, Le Metayer P, Roudaut R, Clementy J. Right and left atrial radiofrequency catheter therapy of paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol. 1996;7:1132-1144.
26. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, Crijns HJ, Damiano RJ, Jr., Davies DW, DiMarco J, Edgerton J, Ellenbogen K, Ezekowitz MD, Haines DE, Haissaguerre M, Hindricks G, Iesaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim YH, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay BD, Mansour M, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Nakagawa H, Natale A, Nattel S, Packer DL, Pappone C, Prystowsky E, Raviele A, Reddy V, Ruskin JN, Shemin RJ, Tsao HM, Wilber D. 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. Europace. 2012;14:528-606.
27. Marrouche NF, Martin DO, Wazni O, Gillinov AM, Klein A, Bhargava M, Saad E, Bash D, Yamada H, Jaber W, Schweikert R, Tchou P, Abdul-Karim A, Saliba W, Natale A. Phased-array intracardiac echocardiography monitoring during pulmonary vein isolation in patients with atrial fibrillation: Impact on outcome and complications. Circulation. 2003;107:2710-2716.
28. Arentz T, Weber R, Burkle G, Herrera C, Blum T, Stockinger J, Minners J, Neumann FJ, Kalusche D. Small or large isolation areas around the pulmonary veins for the treatment of atrial fibrillation? Results from a prospective randomized study. Circulation. 2007;115:3057-3063.
29. Ouyang F, Antz M, Ernst S, Hachiya H, Mavrakis H, Deger FT, Schaumann A, Chun J, Falk P, Hennig D, Liu X, Bansch D, Kuck KH. Recovered pulmonary vein conduction as a dominant factor for recurrent atrial tachyarrhythmias after complete circular isolation of the pulmonary veins: Lessons from double lasso technique. Circulation. 2005;111:127-135.
30. Verma A, Kilicaslan F, Pisano E, Marrouche NF, Fanelli R, Brachmann J, Geunther J, Potenza D, Martin DO, Cummings J, Burkhardt JD, Saliba W, Schweikert RA, Natale A. Response of atrial fibrillation to pulmonary vein antrum isolation is directly related to resumption and delay of pulmonary vein conduction. Circulation. 2005;112:627-635.
31. Nademanee K, McKenzie J, Kosar E, Schwab M, Sunsaneewitayakul B, Vasavakul T, Khunnawat C, Ngarmukos T. A new approach for catheter ablation of atrial fibrillation: Mapping of the electrophysiologic substrate. J Am Coll Cardiol. 2004;43:2044-2053.
32. Li WJ, Bai YY, Zhang HY, Tang RB, Miao CL, Sang CH, Yin XD, Dong JZ, Ma CS. Additional ablation of complex fractionated atrial electrograms after pulmonary vein isolation in patients with atrial fibrillation: A meta-analysis. Circ Arrhythm Electrophysiol. 2011;4:143-148.
33. Wu SH, Jiang WF, Gu J, Zhao L, Wang YL, Liu YG, Zhou L, Gu JN, Xu K, Liu X. Benefits and risks of additional ablation of complex fractionated atrial electrograms for patients with atrial fibrillation: A systematic review and meta-analysis. Int J Cardiol. 2013;169:35-43.
34. Ban JE, Chen YL, Park HC, Lee HS, Lee DI, Choi JI, Lim HE, Park SW, Kim YH. Relationship between complex fractionated atrial electrograms during atrial fibrillation and the critical site of atrial tachycardia that develops after catheter

ablation for atrial fibrillation. J Cardiovasc Electrophysiol. 2013.
35. Sawhney N, Anousheh R, Chen W, Feld GK. Circumferential pulmonary vein ablation with additional linear ablation results in an increased incidence of left atrial flutter compared with segmental pulmonary vein isolation as an initial approach to ablation of paroxysmal atrial fibrillation. Circ Arrhythm Electrophysiol. 2010;3:243-248.
36. Willems S, Klemm H, Rostock T, Brandstrup B, Ventura R, Steven D, Risius T, Lutomsky B, Meinertz T. Substrate modification combined with pulmonary vein isolation improves outcome of catheter ablation in patients with persistent atrial fibrillation: A prospective randomized comparison. Eur Heart J. 2006;27:2871-2878.
37. Knecht S, Hocini M, Wright M, Lellouche N, O'Neill MD, Matsuo S, Nault I, Chauhan VS, Makati KJ, Bevilacqua M, Lim KT, Sacher F, Deplagne A, Derval N, Bordachar P, Jais P, Clementy J, Haissaguerre M. Left atrial linear lesions are required for successful treatment of persistent atrial fibrillation. Eur Heart J. 2008;29:2359-2366.
38. Lu Z, Scherlag BJ, Lin J, Yu L, Guo JH, Niu G, Jackman WM, Lazzara R, Jiang H, Po SS. Autonomic mechanism for initiation of rapid firing from atria and pulmonary veins: Evidence by ablation of ganglionated plexi. Cardiovasc Res. 2009;84:245-252.
39. Lemery R, Birnie D, Tang AS, Green M, Gollob M. Feasibility study of endocardial mapping of ganglionated plexuses during catheter ablation of atrial fibrillation. Heart Rhythm. 2006;3:387-396.
40. Katritsis D, Giazitzoglou E, Sougiannis D, Goumas N, Paxinos G, Camm AJ. Anatomic approach for ganglionic plexi ablation in patients with paroxysmal atrial fibrillation. Am J Cardiol. 2008;102:330-334.
41. Katritsis DG, Giazitzoglou E, Zografos T, Pokushalov E, Po SS, Camm AJ. Rapid pulmonary vein isolation combined with autonomic ganglia modification: A randomized study. Heart Rhythm. 2011;8:672-678.
42. Zhou Q, Hou Y, Yang S. A meta-analysis of the comparative efficacy of ablation for atrial fibrillation with and without ablation of the ganglionated plexi. Pacing Clin Electrophysiol. 2011;34:1687-1694.
43. Pokushalov E, Romanov A, Katritsis DG, Artyomenko S, Shirokova N, Karaskov A, Mittal S, Steinberg JS. Ganglionated plexus ablation vs linear ablation in patients undergoing pulmonary vein isolation for persistent/long-standing persistent atrial fibrillation: A randomized comparison. Heart Rhythm. 2013;10:1280-1286.
44. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: Confirm (conventional ablation for atrial fibrillation with or without focal impulse and rotor modulation) trial. J Am Coll Cardiol. 2012;60:628-636.
45. Narayan SM, Krummen DE, Rappel WJ. Clinical mapping approach to diagnose electrical rotors and focal impulse sources for human atrial fibrillation. J Cardiovasc Electrophysiol. 2012;23:447-454.
46. Nakagawa H, Yamanashi WS, Pitha JV, Arruda M, Wang X, Ohtomo K, Beckman KJ, McClelland JH, Lazzara R, Jackman WM. Comparison of in vivo tissue temperature profile and lesion geometry for radiofrequency ablation with a saline-irrigated electrode versus temperature control in a canine thigh muscle preparation. Circulation. 1995;91:2264-2273.
47. Thomas SP, Aggarwal G, Boyd AC, Jin Y, Ross DL. A comparison of open irrigated and non-irrigated tip catheter ablation for pulmonary vein isolation. Europace. 2004;6:330-335.
48. Guerra JM, Jorge E, Raga S, Galvez-Monton C, Alonso-Martin C, Rodriguez-Font E, Cinca J, Vinolas X. Effects of open-irrigated radiofrequency ablation catheter design on lesion formation and complications: In vitro comparison of 6 different devices. J Cardiovasc Electrophysiol. 2013.
49. Ouyang F, Tilz R, Chun J, Schmidt B, Wissner E, Zerm T, Neven K, Kokturk B, Konstantinidou M, Metzner A, Fuernkranz A, Kuck KH. Long-term results of catheter ablation in paroxysmal atrial fibrillation: Lessons from a 5-year follow-up. Circulation. 2010;122:2368-2377.
50. Reichlin T, Michaud GF. Our approach to maximizing the durability of pulmonary vein isolation during a paroxysmal atrial fibrillation ablation procedure. J Cardiovasc Electrophysiol. 2012;23:1272-1276.
51. Haldar S, Jarman JW, Panikker S, Jones DG, Salukhe T, Gupta D, Wynn G, Hussain W, Markides V, Wong T. Contact force sensing technology identifies sites of inadequate contact and reduces acute pulmonary vein reconnection: A prospective case control study. Int J Cardiol. 2013;168:1160-1166.
52. Squara F, Latcu DG, Massaad Y, Mahjoub M, Bun SS, Saoudi N. Contact force and force-time integral in atrial radiofrequency ablation predict transmurality of lesions. Europace. 2014;16:660-667.
53. Reddy VY, Shah D, Kautzner J, Schmidt B, Saoudi N, Herrera C, Jais P, Hindricks G, Peichl P, Yulzari A, Lambert H, Neuzil P, Natale A, Kuck KH. The relationship between contact force and clinical outcome during radiofrequency catheter ablation of atrial fibrillation in the toccata study. Heart Rhythm. 2012;9:1789-1795.
54. Marijon E, Fazaa S, Narayanan K, Guy-Moyat B, Bouzeman A, Providencia R, Treguer F, Combes N, Bortone A, Boveda S, Combes S, Albenque JP. Real-time contact force sensing for pulmonary vein isolation in the setting of paroxysmal atrial fibrillation: Procedural and 1-year results. J Cardiovasc Electrophysiol. 2013:[Epub ahead of print].
55. Wutzler A, Huemer M, Parwani AS, Blaschke F, Haverkamp W, Boldt LH. Contact force mapping during catheter ablation for atrial fibrillation: Procedural data and one-year follow-up. Arch Med Sci. 2014;10:266-272.
56. Stabile G, Solimene F, Calo L, Anselmino M, Castro A, Pratola C, Golia P, Bottoni N, Grandinetti G, De Simone A, De Ponti R, Dottori S, Bertaglia E. Catheter-tissue contact force for pulmonary veins isolation: A pilot multicentre study on effect on procedure and fluoroscopy time. Europace. 2014;16:335-340.
57. Hutchinson MD, Garcia FC, Mandel JE, Elkassabany N, Zado ES, Riley MP, Cooper JM, Bala R, Frankel DS, Lin D, Supple GE, Dixit S, Gerstenfeld EP, Callans DJ, Marchlinski FE. Efforts to enhance catheter stability improve atrial fibrillation ablation outcome. Heart Rhythm. 2013;10:347-353.
58. Khongphatthanayothin A, Kosar E, Nademanee K. Nonfluoroscopic three-dimensional mapping for arrhythmia ablation: Tool or toy? J Cardiovasc Electrophysiol. 2000;11:239-243.
59. Novak PG, Macle L, Thibault B, Guerra PG. Enhanced left atrial mapping using digitally synchronized navx three-dimensional nonfluoroscopic mapping and high-resolution computed tomographic imaging for catheter ablation of atrial fibrillation. Heart Rhythm. 2004;1:521-522.
60. Rolf S, John S, Gaspar T, Dinov B, Kircher S, Huo Y, Bollmann A, Richter S, Arya A, Hindricks G, Piorkowski C, Sommer P. Catheter ablation of atrial fibrillation supported by novel nonfluoroscopic 4d navigation technology. Heart Rhythm. 2013;10:1293-1300.
61. Piorkowski C, Eitel C, Rolf S, Bode K, Sommer P, Gaspar T, Kircher S, Wetzel U, Parwani AS, Boldt LH, Mende M, Bollmann A, Husser D, Dagres N, Esato M, Arya A, Haverkamp W, Hindricks G. Steerable versus nonsteerable sheath technology in atrial fibrillation ablation: A prospective, randomized study. Circ Arrhythm Electrophysiol. 2011;4:157-165.
62. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, Kim YH, Klein G, Natale A, Packer D, Skanes A, Ambrogi F, Biganzoli E. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circ Arrhythm Electrophysiol. 2010;3:32-38.
63. Gupta A, Perera T, Ganesan A, Sullivan T, Lau DH, Roberts-Thomson KC, Brooks AG, Sanders P. Complications of catheter ablation of atrial fibrillation: A systematic review. Circ Arrhythm Electrophysiol. 2013;6:1082-1088.
64. Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, Williams CJ, Sledge I. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: Two systematic literature reviews and meta-analyses. Circ Arrhythm Electrophysiol. 2009;2:349-361.

65. Harrison L, Gallagher JJ, Kasell J, Anderson RH, Mikat E, Hackel DB, Wallace AG. Cryosurgical ablation of the a-v node-his bundle: A new method for producing a-v block. Circulation. 1977;55:463-470.
66. Tse HF, Reek S, Timmermans C, Lee KL, Geller JC, Rodriguez LM, Ghaye B, Ayers GM, Crijns HJ, Klein HU, Lau CP. Pulmonary vein isolation using transvenous catheter cryoablation for treatment of atrial fibrillation without risk of pulmonary vein stenosis. J Am Coll Cardiol. 2003;42:752-758.
67. Wong T, Markides V, Peters NS, Davies DW. Percutaneous pulmonary vein cryoablation to treat atrial fibrillation. J Interv Card Electrophysiol. 2004;11:117-126.
68. Sarabanda AV, Bunch TJ, Johnson SB, Mahapatra S, Milton MA, Leite LR, Bruce GK, Packer DL. Efficacy and safety of circumferential pulmonary vein isolation using a novel cryothermal balloon ablation system. J Am Coll Cardiol. 2005;46:1902-1912.
69. Andrade JG, Khairy P, Guerra PG, Deyell MW, Rivard L, Macle L, Thibault B, Talajic M, Roy D, Dubuc M. Efficacy and safety of cryoballoon ablation for atrial fibrillation: A systematic review of published studies. Heart Rhythm. 2011;8:1444-1451.
70. Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG, Dubuc M, Reddy V, Nelson L, Holcomb RG, Lehmann JW, Ruskin JN. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: First results of the north american arctic front (stop af) pivotal trial. J Am Coll Cardiol. 2013;61:1713-1723.
71. Schmidt M, Dorwarth U, Andresen D, Brachmann J, Kuck KH, Kuniss M, Lewalter T, Spitzer S, Willems S, Senges J, Junger C, Hoffmann E. Cryoballoon versus rf ablation in paroxysmal atrial fibrillation: Results from the german ablation registry. J Cardiovasc Electrophysiol. 2014;25:1-7.
72. Linhart M, Bellmann B, Mittmann-Braun E, Schrickel JW, Bitzen A, Andrie R, Yang A, Nickenig G, Lickfett L, Lewalter T. Comparison of cryoballoon and radiofrequency ablation of pulmonary veins in 40 patients with paroxysmal atrial fibrillation: A case-control study. J Cardiovasc Electrophysiol. 2009;20:1343-1348.
73. Giovanni GD, Wauters K, Chierchia GB, Sieira J, Levinstein M, Conte G, C DEA, Baltogiannis G, Saitoh Y, Ciconte G, Julia J, Mugnai G, Irfan G, Brugada P. One-year follow-up after single procedure cryoballoon ablation: A comparison between the first and second generation balloon. J Cardiovasc Electrophysiol. 2014.
74. Straube F, Dorwarth U, Schmidt M, Wankerl M, Ebersberger U, Hoffmann E. Comparison of the first and second cryoballoon: High-volume single-center safety and efficacy analysis. Circ Arrhythm Electrophysiol. 2014;7:293-299.
75. Neven K, Metzner A, Schmidt B, Ouyang F, Kuck KH. Two-year clinical follow-up after pulmonary vein isolation using high-intensity focused ultrasound (hifu) and an esophageal temperature-guided safety algorithm. Heart Rhythm. 2012;9:407-413.
76. Sohara H, Takeda H, Ueno H, Oda T, Satake S. Feasibility of the radiofrequency hot balloon catheter for isolation of the posterior left atrium and pulmonary veins for the treatment of atrial fibrillation. Circ Arrhythm Electrophysiol. 2009;2:225-232.
77. Metzner A, Schmidt B, Fuernkranz A, Wissner E, Tilz RR, Chun KR, Neven K, Konstantinidou M, Rillig A, Yoshiga Y, Mathew S, Koester I, Ouyang F, Kuck KH. One-year clinical outcome after pulmonary vein isolation using the novel endoscopic ablation system in patients with paroxysmal atrial fibrillation. Heart Rhythm. 2011;8:988-993.
78. Ahmed H, Neuzil P, Skoda J, Petru J, Sediva L, Kralovec S, Reddy VY. Initial clinical experience with a novel visualization and virtual electrode radiofrequency ablation catheter to treat atrial flutter. Heart Rhythm. 2011;8:361-367.
79. Li JH, Haim M, Movassaghi B, Mendel JB, Chaudhry GM, Haffajee CI, Orlov MV. Segmentation and registration of three-dimensional rotational angiogram on live fluoroscopy to guide atrial fibrillation ablation: A new online imaging tool. Heart Rhythm. 2009;6:231-237.
80. Nolker G, Asbach S, Gutleben KJ, Rittger H, Ritscher G, Brachmann J, Sinha AM. Image-integration of intraprocedural rotational angiography-based 3d reconstructions of left atrium and pulmonary veins into electroanatomical mapping: Accuracy of a novel modality in atrial fibrillation ablation. J Cardiovasc Electrophysiol. 2010;21:278-283.
81. Carpen M, Matkins J, Syros G, Gorev MV, Alikhani Z, Wylie JV, Natan SR, Griben A, Hicks A, Armstrong J, Orlov MV. First experience of 3d rotational angiography fusion with navx electroanatomical mapping to guide catheter ablation of atrial fibrillation. Heart Rhythm. 2013;10:422-427.
82. Oakes RS, Badger TJ, Kholmovski EG, Akoum N, Burgon NS, Fish EN, Blauer JJ, Rao SN, DiBella EV, Segerson NM, Daccarett M, Windfelder J, McGann CJ, Parker D, MacLeod RS, Marrouche NF. Detection and quantification of left atrial structural remodeling with delayed-enhancement magnetic resonance imaging in patients with atrial fibrillation. Circulation. 2009;119:1758-1767.
83. Vergara GR, Vijayakumar S, Kholmovski EG, Blauer JJ, Guttman MA, Gloschat C, Payne G, Vij K, Akoum NW, Daccarett M, McGann CJ, Macleod RS, Marrouche NF. Real-time magnetic resonance imaging-guided radiofrequency atrial ablation and visualization of lesion formation at 3 tesla. Heart Rhythm. 2011;8:295-303.
84. Ganesan AN, Shipp NJ, Brooks AG, Kuklik P, Lau DH, Lim HS, Sullivan T, Roberts-Thomson KC, Sanders P. Long-term outcomes of catheter ablation of atrial fibrillation: A systematic review and meta-analysis. J Am Heart Assoc. 2013;2:e004549.