Pharmacological Tests in Atrial Fibrillation Ablation

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Abstract

The invasive management of atrial fibrillation (AF) has been considerably changed by the identification of major sites of AF initiation and/or maintenance within the pulmonary vein antra. Percutaneous catheter ablation of these targets has become the standard of care for sustained maintenance of sinus rhythm. Long-term failure of ablation is related to an inability to create a durable transmural lesion or to identify all of the non-pulmonary vein arrhythmia triggers. Pharmacological challenges during catheter ablation have been suggested to improve outcomes in both paroxysmal and persistent AF. Herein we review the mechanism and evidence for the use of pharmacological adjuncts during the catheter ablation of AF.

Keywords

atrial fibrillation, catheter ablation, adenosine, isoproterenol, ibutilide, pulmonary vein isolation

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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia observed in clinical practice, occurring in approximately 2 % of the general population.[1–3] A progressive increase in both the prevalence and incidence of AF has been demonstrated in recent years, defining AF as a major economic and public health issue.[1]

The identification of sites of AF initiation and/or maintenance within the pulmonary veins (PVs) has led to the development of percutaneous procedures to electrically isolate the PVs from the left atrium (LA).[4] Large observational studies and multiple randomised-controlled trials have demonstrated that catheter ablation is universally superior to anti-arrhythmic drugs (AADs) for the maintenance of sinus rhythm (66–89 % versus 9–58 %, respectively) and results in a greater improvement in arrhythmia-related symptoms, exercise capacity and quality of life.[1,2,5–8] As a result, catheter ablation has become the 'standard of care' for the maintenance of sinus rhythm in symptomatic patients in whom drugs are ineffective or poorly tolerated.

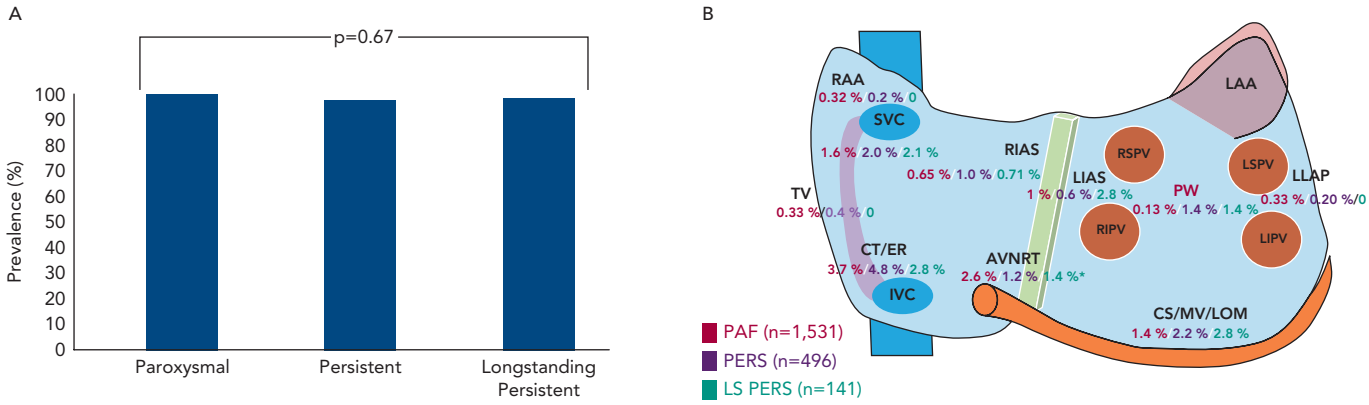
While the results of ablation are unequivocally superior to medical therapy, they are unfortunately not flawless: approximately 30 % of paroxysmal AF patients will experience arrhythmia recurrence after a single ablation procedure.[8] As most recurrences are in association with PV reconnection or as a result of non-PV triggers, several pharmacological challenges have been proposed to improve outcomes.[9–12] This article reviews the pathophysiological background and evidence for the use of pharmacological challenges during catheter ablation procedures.

Pathophysiology of Atrial Fibrillation and Atrial Fibrillation Catheter Ablation

Despite decades of progress, there is no comprehensive pathophysiological explanation of AF. Early hypotheses postulated that AF resulted from the co-existence of multiple independent wavelets propagating randomly throughout the left and right atria (the 'multiple wavelet hypothesis').[13,14] This hypothesis suggested that as long as the atria had a sufficient electrical mass, and an adequately short refractory period, AF could be initiated and indefinitely perpetuated.[15] Based on this theory, the early surgical interventions for AF were designed to reduce the excitable mass of atrial tissue by compartmentalising the atria into smaller regions incapable of sustaining a critical number of circulating wavelets.[16] Unfortunately this strategy has proved to be of limited efficacy and has been associated with a substantial risk of major complications.[17]

In the late 1990s, Haïssaguerre and colleagues demonstrated that AF is a triggered arrhythmia initiated by rapid repetitive discharges, predominantly from the proximal aspect of the PVs.[4] This discovery led to the development of percutaneous procedures to directly eliminate spontaneous focal ectopic activity within the PVs. However, early AF recurrences from the targeted and other non-targeted PVs led to modification of the ablation strategy to electrically isolate all of the PVs.[18,19] Over the past 17 years, the recognition that sites of AF initiation and/or maintenance (e.g. triggered activity and micro re-entry) are frequently located within the PV antrum has shifted the ablation target more proximally.[20–22] As such, the contemporary AF ablation procedure is a hybrid approach whereby circumferential ablative lesions are placed within the peri-venous left atrial myocardium, i.e. outside of the tubular veins with the goal of electrical pulmonary vein isolation (PVI). Successful electrical PVI is defined as a bidirectional conduction block documented using a circular mapping catheter placed at the PV ostia. Ablation is able to target both the initiating triggers, as well as the mass of electrically-active LA tissue capable of sustaining the fibrillatory

Figure 1: Triggers of Atrial Fibrillation During Second Catheter Ablation



*(A) Prevalence of pulmonary vein reconnection in paroxysmal (PAF), persistent (PERS) and longstanding persistent (LS PERS) atrial fibrillation (AF). (B) Prevalence of right and left non-pulmonary vein triggers. * = 2 patients with long-standing persistent AF; AVNRT = AV node reentrant tachycardia; CS = coronary sinus; CT = crista terminalis; ER = eustacian ridge; LAA = left atrial appendage; LLAP = left lateral accessory pathway; LOM = ligament of Marshall; MV = mitral valve; PW = posterior wall; RAA = right atrial appendage; SVC = superior vena cava; TV = tricuspid valve. Modified from Singh et al, 2016.[101]*

wavelets responsible for AF perpetuation.[3] It also has the advantage of limiting PV stenosis.[23]

While isolation of the PV antra has become the cornerstone of all contemporary AF ablation procedures, patients with more advanced forms of AF, e.g. persistent rather than paroxysmal AF, are known to be less dependent on the PV antra for arrhythmia initiation and perpetuation.[24–26] As the disease progresses, electrical and structural remodelling of the atrial substrate shifts the sites of AF perpetuation to regions outside the PV–LA junction and results in the emergence of non-PV triggers.[27–29] The ablation of these 'fibrotic atrial' forms of AF often requires adjunctive strategies targeting the abnormal LA substrate, such as linear LA ablation with the goal of compartmentalising the LA into smaller regions incapable of sustaining micro re-entry, or the ablation of complex fractionated atrial electrograms (CFAEs, or areas of abnormal substrate representing areas of slow conduction, conduction block or local 'pivot' points) that perpetuate AF re-entry.[20,30–33] However, the addition of such substrate-based ablation (either linear ablation or CFAE elimination) does not appear to reduce AF recurrence after PVI in patients with persistent AF.[34]

It has been suggested that ganglionated plexi may have a role in the initiation and maintenance of both paroxysmal and non-paroxysmal AF.[35–41] Localisation is usually performed on the endocardium either anatomically, by vagal response following high-frequency stimulation, or by Fourier transform in sinus rhythm.[35,37] Although ganglionated plexi ablation significantly reduces AF recurrence, the long-term success rate is lower than after PVI.[35–41] Interestingly, in addition to PVI, the suppression of ganglionated plexi response – particularly that observed during cryoablation – may reduce AF recurrence.[40,41]

Although many authors believe that additional ablations are required for non-paroxysmal AF or some paroxysmal AF, no randomised studies have consistently shown which strategy to use.

Mechanism of Atrial Fibrillation Recurrence After Ablation

Unfortunately, the results of ablation can be unsatisfactory. In the case of paroxysmal AF, only about 70 % of patients will remain arrhythmia-free after a single ablation procedure without the use of AADs.[1,2,5–8] It is important to recognise that the reasons for long-term failure are largely centred on the relative inability to create a lasting transmural lesion using the contemporary ablation toolset. While electrical PVI may be achieved acutely, the combination of inadequate electrode–tissue contact, insufficient power delivery and tissue oedema may prevent radiofrequency (RF)-induced heating of the myocardium to lethal temperatures.[27,42–44] As the transient injury induced at the time of index ablation resolves, gaps in the initial line of ablation may emerge, allowing PV triggers to excite the adjacent LA and induce AF.[27] This is highlighted by the observation that >90 % of patients requiring a second catheter ablation procedure demonstrate one (or more) PV reconnections (see *Figure 1A*).[26,45]

For patients with more advanced forms of AF, recurrences may be due to the persistence of LA substrate abnormality as well as non-PV triggers (see *Figure 1B*). These triggers can be found in about 50 % of patients and originate in the superior vena cava, left atrial free wall or appendage, coronary sinus, crista terminalis or right atrial free wall.[27] Targeted ablation of these non-PV triggers has been shown to improve outcomes, but unfortunately is limited by non-inducibility at the time of the ablation procedure, as well as unreliable long-term behaviour over time.[9,33,46]

Pharmacological Challenges in Catheter Ablation of Atrial Fibrillation

Four pharmacological adjuncts have been proposed to improve the outcomes of AF ablation. These four agents – isoproterenol, adenosine, amiodarone and ibutilide – are mechanistically disparate and are used for different purposes: unmasking dormant conduction (DC), inducing non-PV triggers or identifying abnormal substrate for ablation.

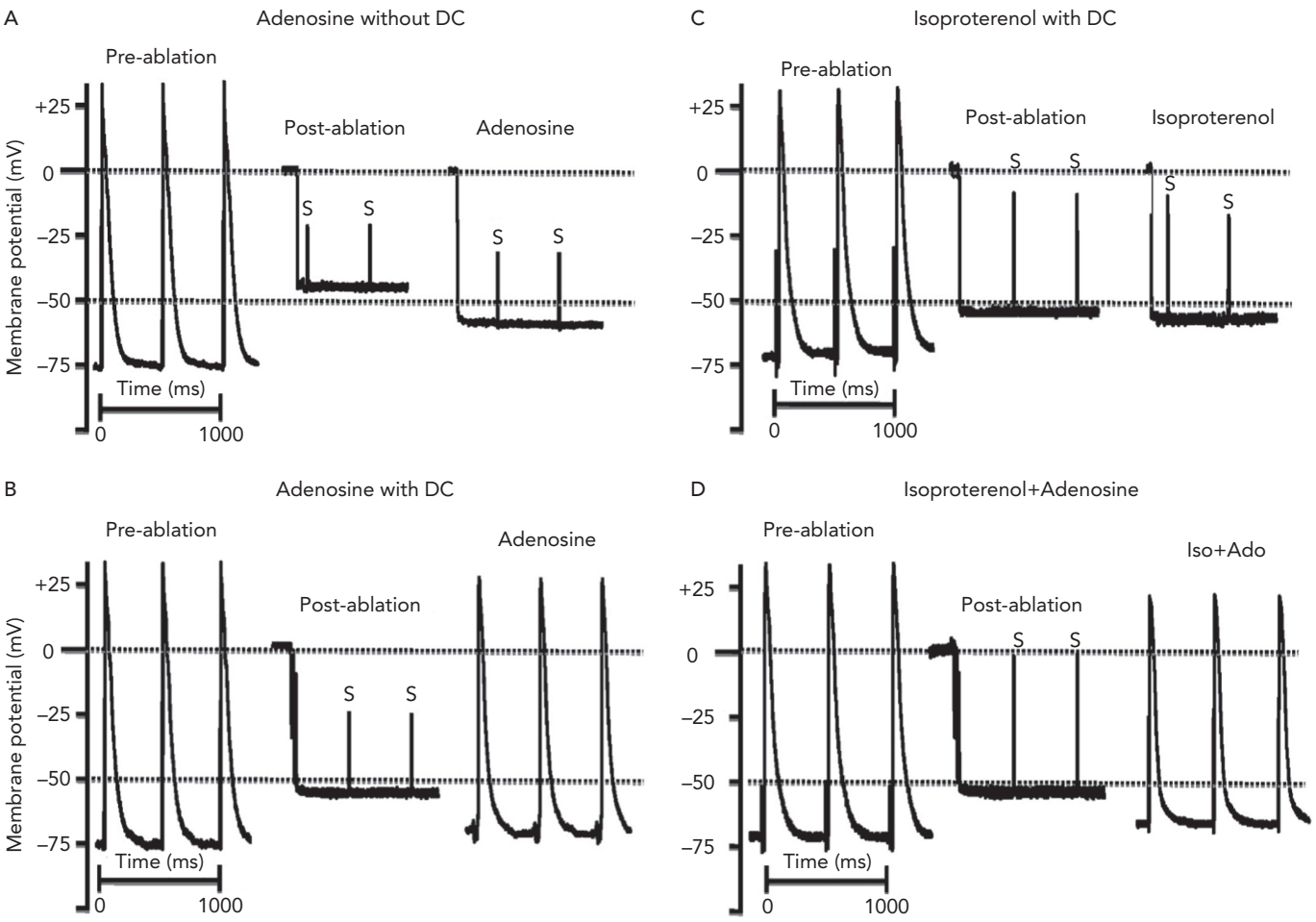
Adenosine

Adenosine is predominantly used to differentiate permanent PV-atrial conduction block from DC (i.e. viable but latently non-conducting tissue).

Mechanism of Action

Following ablation, the resting membrane potential (RMP) of the targeted left atrial myocardial cells becomes depolarised due to cell membrane injury. This depolarisation of the RMP results in sodium-channel inactivation (when >–60mV), leading to inexcitability and

Figure 2: Effect of Pharmacological Challenge on Pulmonary Vein Potentials and Dormant Conduction After Pulmonary Vein Isolation



Pulmonary vein potentials are recorded immediately above the ablation line in the perfused heart of a dog. (A) After adding adenosine without dormant conduction (DC). (B) After adding adenosine in a case with DC. (C) After adding isoproterenol in a case with DC. (D) After adding isoproterenol plus adenosine (Iso+Ado) in a case with DC. S = stimulus artefacts without action potential responses. Modified from Datino et al., 2011.[50]

functional conduction block.[47,48] After a waiting period of 30–60 minutes, a slow hyperpolarisation can be observed leading to spontaneous PV reconnection, called DC.[49] The difference between dormant and non-dormant PVs lies primarily in the degree of RF-induced depolarisation. Non-dormant PVs are depolarised more severely (post-ablation RMPs positive to –50 mV) than dormant PVs (post-ablation RMPs of –50 to –60 mV).[49]

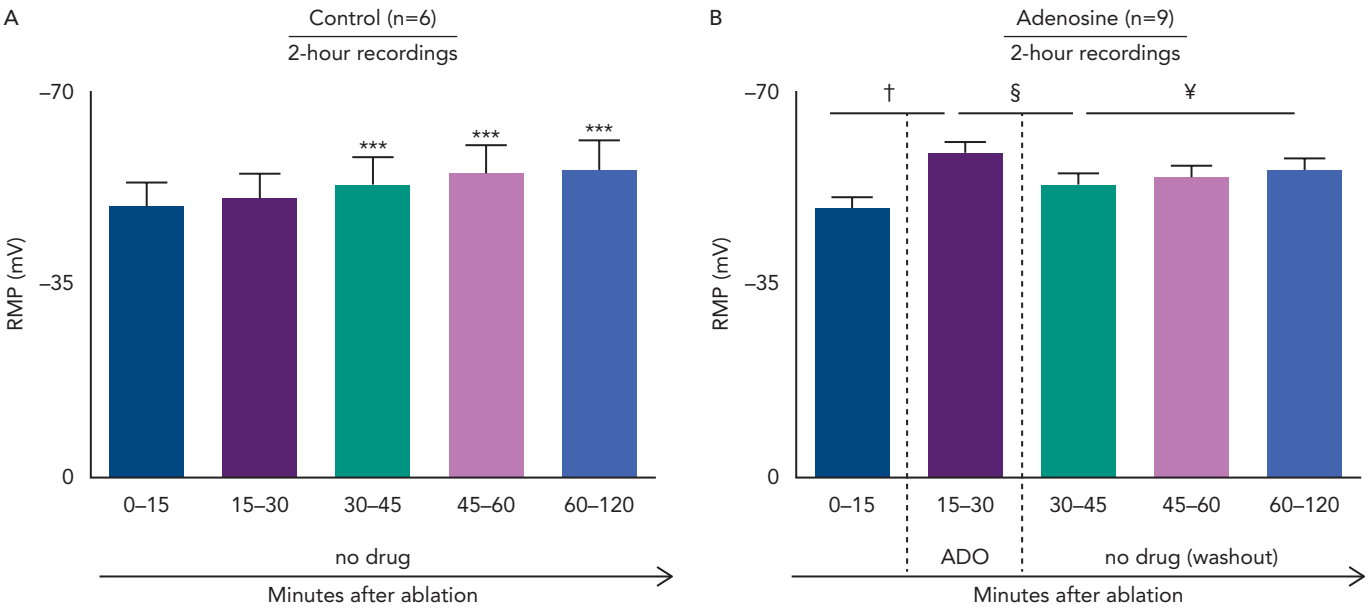
Adenosine has been proposed as a useful test of DC due to its differential effect on PV cells and LA cells.[50] In both the PV and LA cells adenosine is able to shorten the action potential duration, however it selectively hyperpolarises the RMP by about 10 mV and increases dV/dt (max) by selectively activating I_{KAdo} in PV cells (leading to an increase in the transient outward potassium currents; see *Figure 1*).[49,51,52] Moreover adenosine's effect on the PV sodium channel removes voltage-dependent I_{Na} inactivation, and further increases the dV/dt (maximum velocity of phase 0 of the action potential; see *Figure 2*).[49,51,52] Taken together, in the event of incomplete membrane damage after RF ablation, adenosine can facilitate membrane hyperpolarisation, restoring the excitability threshold see (*Figure 1*). Conversely, those cells that have sustained irreversible damage will not respond to adenosine infusion, i.e. the membrane will remain depolarised and unexcitable. Additionally, adenosine may reveal non-PV triggers secondary to post-bradycardia adrenergic simulation.[9,49]

Clinical Value

In 2004, Arentz et al. demonstrated that adenosine could be used to reveal DC.[53] Subsequent observational studies have demonstrated DC in 25–51 % of cases after PVI using RF. These studies have suggested that ablation guided by adenosine triphosphate (ATP)/adenosine administration can reduce AF recurrences at 1 year by 32–50 % (relative risk reduction).[53–57] Despite a lower incidence of DC (13–40 %), a similar effect has been suggested after cryoablation of the PV.[58,59]

The recently-published randomised Adenosine Following Pulmonary Vein Isolation to Target Dormant Conduction Elimination (ADVICE) study was the first to prospectively evaluate the impact of adenosine testing on clinical outcomes after AF ablation.[60] After PV isolation using an irrigated-tip RF catheter, adenosine revealed DC in 53 % of patients. Those with DC were randomised to additional adenosine-guided RF ablation until DC was eliminated or no further ablation. In this study a 56 % relative-risk reduction (27 % absolute risk reduction) in the recurrence of atrial tachyarrhythmias was observed with the elimination of DC. In contrast, the Unmasking Dormant Electrical Reconduction by Adenosine Triphosphate (UNDER-ATP) study and the study by Ghanbari et al. failed to demonstrate a significant difference in the reduction of AF recurrence between adenosine-guided PVI and conventional PVI (1-year event-free survival of 68.7 % with ATP-guided versus 67.1 % without ATP, p=0.25 in UNDER-ATP; and 61 % with

Figure 3: Evolution of the Resting Membrane Potential of the Pulmonary Vein After Ablation



*(A) Spontaneous evolution of resting membrane potential. ***p<0.001 versus 0–15 minutes. (B) Evolution with adenosine: †p<0.001 for adenosine versus 0–15 minutes by Bonferroni-adjusted t-tests; §p<0.001 for adenosine versus washout period of 30–45 minutes by Bonferroni-adjusted t-tests; ¥p <0.001 for washout period of 30–45 versus washout period of 60–120 minutes by Bonferroni-adjusted t-tests. ADO = adenosine, RMP = resting membrane potential. Modified from Datino et al., 2010.[11]*

adenosine plus isoproterenol versus 66 % with isoproterenol alone, p=0.83 in Ghanbari et al.).[61,62]

Differences in the studies' methodology and approach may explain these results. First, the endpoint of adenosine testing in the ADVICE study and Ghanbari et al. was based on titration of the adenosine dose until the intended electrophysiological effect (transient AV block or sinus arrest) was observed. Conversely, in the UNDER-ATP study the dose of adenosine was predetermined (0.4 mg/kg) and was not altered regardless of the observed effect. Given the lack of documentation of adenosine effect, it is possible that patients in the UNDER-ATP study were underdosed. Second, the waiting period between the achievement of index PVI and adenosine test varied between the studies. In the ADVICE study it was 20 minutes after isolation of the last PV, while in Ghanbari et al. it was 60 minutes, and in UNDER-ATP there was no specific protocol regarding the timing of adenosine administration. In effect this resulted in a median waiting period in UNDER-ATP and Ghanbari et al. that was more than double that of the ADVICE trial. This is relevant given the knowledge that spontaneous recovery of PV–LA conduction is a time-dependent process, with spontaneous RMP hyperpolarisation occurring approximately 30 minutes after ablation.[49,50] Mechanistically the administration of adenosine results in a more rapid hyperpolarisation, effectively predicting the spontaneous reconnections that occur between 20 and 60 minutes post-PVI (*Figure 3*).[60,63–66] Taken together it is not surprising that the UNDER-ATP trial and Ghanbari et al. had a higher rate of spontaneous PV reconnection (42.6 % in UNDER-ATP versus 27 % in ADVICE) and a lower rate of DC (27.6 % versus 53 % in the ADVICE study and 37 % in the Ghanbari et al study).[53–57,60] Third, as a result of the low prevalence of DC the UNDER-ATP trial was underpowered. Lastly, The ADVICE study only included patients with paroxysmal AF treated with PVI alone, while the UNDER-ATP study included patients with persistent AF (32.8 %) treated with PVI accompanied by additional linear lesions or complex electrogram ablation. While adenosine testing lacks substantial effect in the case of additional linear lesions or the ablation of non-PV triggers, the delivery of additional substrate-guided ablation (roof line, mitral isthmus line, superior vena cava isolation and CFAE elimination) would have conferred an even longer waiting period. Thus the pathophysiology of persistent AF, the longer post-PVI waiting period and the relative underdosing of adenosine could all explain the low rate of DC revealed with adenosine testing in the UNDER-ATP study. As such, we can conclude the use of adenosine testing for DC is useful in paroxysmal AF patients when an adequate adenosine dose (titrated to clinical effect) is administered after a fixed waiting period (20 minutes).

Concomitant use of dipyridamole has been suggested to prolong the transient effect of adenosine in DC and to reduce AF recurrence by facilitating the elimination of DC.[67,68] The global outcome of such a strategy, however, remains to be assessed.

Isoproterenol

Isoproterenol is used predominantly to identify non-PV triggers that have been associated with AF recurrence, particularly in those with persistent AF.[69–74] These triggers may originate from the superior vena cava, coronary sinus, interatrial septum, crista terminalis, Eustachian ridge, inferior mitral annulus, atrial appendages, persistent left superior vena cava and ligament of Marshall. When present, non-PV triggers have been associated with AF recurrence and a worse outcome after ablation.[69–74] Fortunately these sites can be revealed in patients with paroxysmal and persistent AF with the infusion of high-dose isoproterenol.[9,11,75]

Mechanism of Action

Isoproterenol is a cardiac beta$_1$ and beta$_2$ adrenoreceptor agonist with positive chronotropic, dromotropic and inotropic effects. Via the cyclic adenosine monophosphate mechanism, isoproterenol results in an increase in diastolic $[Ca^{2+}]_i$ and intracellular Ca^{2+}, decreasing the action potential duration and atrial refractory periods while facilitating slow diastolic depolarisation (abnormal automaticity) and triggered

activity.[76–79] The ability to reveal triggered activity is significantly greater with isoproterenol than adenosine.[9,49]

With respect to DC, isoproterenol induces a mild hyperpolarisation due to its summative effect on K^+ currents (particularly the inward rectifier current, or I_{K1}), cyclic adenosine monophosphate-activated Cl^- currents and the pacemaker current, I_f, as well as its secondary effects on L-type Ca^{2+} currents and the Na^+–Ca^{2+} exchanger.[80] The magnitude of the effect on the RMP is minimal, i.e. no different from controls, however, being significantly smaller than that observed with adenosine, and is insufficient to restore conduction in dormant veins (see *Figure 2*).[49,50]

Clinical Value

Observational studies have suggested that PVI accompanied by the ablation of non-PV triggers unmasked by isoproterenol infusion could improve the success rate of catheter ablation.[69–74,81–83] Non-PV trigger-ablation protocols generally involve burst-pacing protocols with isoproterenol infusion to induce the triggers, followed by mapping and elimination. Unfortunately the utility of non-PV trigger elimination is limited by the difficulty in inducing, identifying and eliminating these non-PV triggers. In different cohorts the prevalence of non-PV triggers varies between 9 and 19 % (9 % in Inoue et al.'s study of 263 persistent AF patients, 11 % in Santangelli et al.'s study of 2,168 patients with paroxysmal and persistent AF, and 19 % in Lin et al.'s study of 130 patients with long-standing persistent AF).[33,84,85] This incidence seems to increase with age, worse atrial substrate and in the presence of cardiomyopathy.[81,86] Despite the identification of non-PV trigger sites, however, only 30 % of these can be eliminated due to difficulties in localising them.[85] That said, a better arrhythmia-free outcome has been observed in patients in whom all PV and non-PV triggers are eliminated when compared with those in whom triggers are identified but cannot be eliminated (86 % versus 37 %; p=0.09).[85]

It is not clear whether current protocols are able to reliably identify all relevant non-PV trigger sites. As such, it has been postulated that empiric ablation of common non-PV trigger sites may improve outcomes. This has been examined in the Randomized Ablation Strategies for the Treatment of Persistent Atrial Fibrillation (RASTA) study, which compares: circumferential PVI plus ablation of non-PV triggers; circumferential PVI plus ablation of non-PV triggers plus empirical ablation at common non-PV trigger sites; and circumferential PVI plus ablation of non-PV triggers plus CFAE ablation.[87] The freedom from atrial arrhythmias after a single ablation procedure was significantly worse with the addition of CFAE (29 %) when compared with PVI plus non-PV triggers alone (49 %, p<0.040) and PVI plus non-PV triggers plus empirical trigger-site ablation (58 %, p<0.004).

Last, the relevance of targeting non-PV triggers remains a matter of debate. Most studies considered repetitive premature atrial contraction as the target for ablation.[9,33, 81–87] Several repetitive premature atrial contractions, however, will never induce AF. As such, an increased success rate has been achieved when targeting only the premature atrial contractions that induce AF.[9] Thus, non-PV AF trigger could explain the variation observed in the prevalence and outcomes in different groups.

Clinical Perspective

- Adenosine can prevent the need for a long observational time to identify dormant conduction that will increase the recurrence of AF after pulmonary vein isolation (PVI).
- The role of adenosine in a second ablation procedure for the treatment of paroxysmal AF and in the catheter ablation of persistent AF remains to be assessed.
- In patients with paroxysmal and persistent AF, the use of isoproterenol should be considered in appropriate cases as its ability to reveal non-PV triggers has been demonstrated.
- Amiodarone and ibutilide allow the organisation of electrical substrates in persistent AF but they do not appear to be efficient in reducing AF recurrence.

Amiodarone and ibutilide

Amiodarone and ibutilide are used to organise persistent AF.

Mechanism of Action

In advanced forms of AF, the abnormal atrial substrate is thought to act as a driver of arrhythmia perpetuation.[88,89] Although PVI can reduce the amount of substrate required for atrial re-entry, persistent AF seems to be less dependent on the PV antral region for arrhythmia initiation and perpetuation, relying more on perpetuating regions outside the PV–LA junction. It has been postulated that these CFAEs (local signals during AF that are either at a very short cycle length, or are fractionated with two or more components and/or a continuous perturbation of the baseline) represent areas of slow conduction, conduction block or 'pivot' points for AF perpetuating re-entry. It is thought that complete elimination of these abnormal substrate areas may improve outcomes.[90–92] Extensive ablation of atrial substrate may result in prolonged procedures, however, and increased risk of complications.[93,94] Moreover, while fractionation may be recorded close to the core of an AF-perpetuating rotor, it may also be recorded at sites not actively participating in the AF process, i.e. bystander sites of passive wavelet collision. It is postulated that the co-administration of amiodarone and ibutilide (both class III AADs) might facilitate the identification of CFAE sites critical to AF maintenance by eliminating areas of passive atrial activation. Mechanistically these agents differentiate active from passive CFAEs by lengthening the effective refractory period (e.g. global AF cycle length). Pre-treatment with amiodarone or the administration of ibutilide during catheter ablation to reduce active CFAE sites has been shown to reduce the amount of ablation in persistent AF without adversely affecting longer-term outcomes.[95,96]

Clinical Value

The Substrate Trigger Ablation for Reduction of Atrial Fibrillation II (STAR-AF II) study recently demonstrated that the addition of substrate-base ablation (either linear ablation or CFAE elimination) did not reduce AF recurrence after PVI in patients with persistent AF.[34] These negative results could be explained by the amount of ablation that increases the iatrogenic arrhythmia rate.[87,97–99] To reduce this arrhythmia rate, two recent randomised studies have investigated the effect of ibutilide and amiodarone with respect to PVI and CFAE ablation. Mohanty et al. described a 112-patient population treated with amiodarone for persistent AF.[100] Patients were randomised to either amiodarone continuation or amiodarone discontinuation 4 months prior to catheter ablation. The authors observed a higher organisation rate of AF, and a lower amount of RF energy required terminate AF in the amiodarone continuation group. Despite this, they observed an increase in AF recurrence with amiodarone continuation. In the

Modified Ablation Guided by Ibutilide Use in Chronic Atrial Fibrillation (MAGIC-AF) study, Singh et al. randomly assigned 200 patients with persistent AF to receive ibutilide during catheter ablation.[101] A higher AF organisation rate, a reduction in the number of CFAE sites and a higher rate of AF termination were observed during catheter ablation in the ibutilide group, similar to the study by Mohanty et al.[101] Likewise the clinical outcomes were unchanged. These results once again suggest the limited role of substrate ablation instead of PVI.

Conclusion

PVI remains the cornerstone of catheter ablation for the treatment of both paroxysmal and persistent AF, but the durability of electrical isolation remains a challenge. Both longer observational time (>30 minutes) and adenosine testing (>20 minutes after successful PVI with dose titration to achieve transient atrioventricular conduction block) are efficient and should be considered after PVI to decrease long-term PV reconnection and AF recurrences in paroxysmal AF.

Isoproterenol may unmask non-PV triggers in appropriate cases. The benefit seems to be relatively greater during a second ablation procedure, particularly if one or more PVs have reconnected. Limited data are available to support the use of amiodarone and ibutilide; despite their role in substrate organisation, the lack of impact on clinical outcome does not suggest a relevant use in catheter ablation of AF. ■

1. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide Epidemiology of Atrial Fibrillation A Global Burden of Disease 2010 Study. *Circulation* 2014;**129**:837–47. DOI: 10.1161/CIRCULATIONAHA.113.005119; PMID: 24345399
2. Svennberg E, Engdahl J, Al-Khalili F, et al. Mass Screening for Untreated Atrial Fibrillation: The STROKESTOP Study. *Circulation* 2015;**131**:2176–84. DOI: 10.1161/CIRCULATIONAHA.114.014343; PMID: 25910800
3. Andrade J, Khairy P, Dobrev D, et al. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. *Circ Res* 2014;**114**:1453–68. DOI: 10.1161/CIRCRESAHA.114.303211; PMID: 24763464
4. Haïssaguerre M, Jaïs P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998;**339**:659–66. DOI: 10.1056/NEJM199809033391003; PMID: 9725923
5. Wazni OM, Marrouche NF, Martin DO, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. *JAMA* 2005;**293**:2634–40. DOI: 10.1001/jama.293.21.2634; PMID: 15928285
6. Jaïs P, Cauchemez B, Macle L, et al. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. *Circulation* 2008;**118**:2498–505. DOI: 10.1161/CIRCULATIONAHA.108.772582; PMID: 19029470
7. Morillo CA, Verma A, Connolly SJ, et al.; RAAFT-2 Investigators. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. *JAMA* 2014;**311**:692–700. DOI: 10.1001/jama.2014.467; PMID: 24549549
8. Piccini JP, Lopes RD, Kong MH, et al. Pulmonary vein isolation for the maintenance of sinus rhythm in patients with atrial fibrillation a meta-analysis of randomized, controlled trials. *Circ Arrhythm Electrophysiol* 2009;**2**:626–33. DOI: 10.1161/CIRCEP.109.856633; PMID: 20009077
9. Elayi CS, Di Biase L, Bai R, et al. Administration of isoproterenol and adenosine to guide supplemental ablation after pulmonary vein antrum isolation. *J Cardiovasc Electrophysiol* 2013;**24**:1199–206. DOI: 10.1111/jce.12252; PMID: 24020649
10. Andrade JG, Pollak SJ, Monir G, et al. Pulmonary vein isolation using a pace-capture-guided versus an adenosine-guided approach effect on dormant conduction and long-term freedom from recurrent atrial fibrillation – a prospective study. *Circ Arrhythm Electrophysiol* 2013;**6**:1103–8. DOI: 10.1161/CIRCEP.113.000454; PMID: 24097372
11. Kurotobi T, Shimada Y, Kino N, et al. Residual arrhythmogenic foci predict recurrence in long-standing persistent atrial fibrillation patients after sinus rhythm restoration ablation. *Can J Cardiol* 2014;**30**:1535–40. DOI: 10.1016/j.cjca.2014.10.013; PMID: 25475458
12. Verma A, Kilicaslan F, Pisano E, et al. Response of atrial fibrillation to pulmonary vein antrum isolation is directly related to resumption and delay of pulmonary vein conduction. *Circulation* 2005;**112**:627–35. DOI: 10.1161/CIRCULATIONAHA.104.533190; PMID: 16061753
13. Moe G. On multiple wavelet hypothesis of atrial fibrillation. *Arch Int Pharmacodyn Ther* 1962;**140**:183–8.
14. Moe GK, Rheinboldt WC, Abildskov JA. A computer model of atrial fibrillation. *Am Heart J* 1964;**67**:200–20. DOI: 10.1016/0002-8703(64)90371-0; PMID: 14118488
15. Mandapati R, Skanes A, Chen J, et al. Stable microreentrant sources as a mechanism of atrial fibrillation in the isolated sheep heart. *Circulation* 2000;**101**:194–9; PMID: 10637208
16. Cox JL. The surgical treatment of atrial fibrillation. IV. Surgical technique. *J Thorac Cardiovasc Surg* 1991;**101**:584–92. PMID: 2008096
17. Jaïs P, Shah DC, Haïssaguerre M, et al. Efficacy and safety of septal and left-atrial linear ablation for atrial fibrillation. *Am J Cardiol* 1999;**84**:139R–46R. PMID: 10568673
18. Haïssaguerre M, Shah DC, Jaïs P, et al. Electrophysiological breakthroughs from the left atrium to the pulmonary veins. *Circulation* 2000;**102**:2463–5. DOI: 10.1161/01.CIR.102.20.2463; PMID: 11076817
19. Haïssaguerre M, Jaïs P, Shah DC, et al. Electrophysiological end point for catheter ablation of atrial fibrillation initiated from multiple pulmonary venous foci. *Circulation* 2000;**101**:1409–17. DOI: 10.1161/01.CIR.101.12.1409; PMID: 10736285
20. Nishida K, Datino T, Macle L, et al. Atrial fibrillation ablation: translating basic mechanistic insights to the patient. *J Am Coll Cardiol* 2014;**64**:823–31. DOI: 10.1016/j.jacc.2014.06.1172; PMID: 25145528
21. Lee G, Spence S, Teh A, et al. High-density epicardial mapping of the pulmonary vein–left atrial junction in humans: insights into mechanisms of pulmonary vein arrhythmogenesis. *Heart Rhythm* 2012;**9**:258–64. DOI: 10.1016/j.hrthm.2011.09.010; PMID: 21907170
22. Nilsson B, Chen X, Pehrson S, et al. Recurrence of pulmonary vein conduction and atrial fibrillation after pulmonary vein isolation for atrial fibrillation: a randomized trial of the ostial versus the extraostial ablation strategy. *Am Heart J* 2006;**152**:537.e1-8. DOI: 10.1016/j.ahj.2006.05.029; PMID: 16923426
23. Tamborero D, Mont L, Nava S, et al. Incidence of pulmonary vein stenosis in patients submitted to atrial fibrillation ablation: a comparison of the selective segmental ostial ablation vs the circumferential pulmonary veins ablation. *J Interv Card Electrophysiol Int J Arrhythm Pacing* 2005;**14**:21–5. DOI: 10.1007/s10840-005-4513-6; PMID: 16311935
24. Oral H, Knight BP, Tada H, et al. Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. *Circulation* 2002;**105**:1077–81. DOI: 10.1161/hc0902.104712; PMID: 11877358
25. Oral H, Pappone C, Chugh A, et al. Circumferential pulmonary-vein ablation for chronic atrial fibrillation. *N Engl J Med* 2006;**354**:934–41. DOI: 10.1056/NEJMoa050955; PMID: 16510747
26. Ganesan AN, Shipp NJ, Brooks AG, et al. Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *J Am Heart Assoc* 2013;**2**:e004549. DOI: 10.1161/JAHA.112.004549; PMID: 23537812
27. Hussein AA, Saliba WI, Martin DO, et al. Natural history and long-term outcomes of ablated atrial fibrillation. *Circ Arrhythm Electrophysiol* 2011;**4**:271–8. DOI: 10.1161/CIRCEP.111.962100; PMID: 21493959
28. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014;**64**:e1–e76. DOI: 10.1016/j.jacc.2014.03.022
29. Camm AJ, Lip GYH, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Europace* 2012;**14**:1385–1413. DOI: 10.1093/europace/eus305
30. Haissaguerre M, Hocini M, Denis A, et al. Driver domains in persistent atrial fibrillation. *Circulation* 2014;**130**:530–8. DOI: 10.1161/CIRCULATIONAHA.113.005421; PMID: 25028391
31. Scherr D, Khairy P, Miyazaki S, et al. Five-year outcome of catheter ablation of persistent atrial fibrillation using termination of atrial fibrillation as a procedural endpoint. *Circ Arrhythm Electrophysiol* 2015;**8**:18–24. DOI: 10.1161/CIRCEP.114.001943; PMID: 25528745
32. Hirsh BJ, Copeland-Halperin RS, Halperin JL. Fibrotic atrial cardiomyopathy, atrial fibrillation, and thromboembolism: mechanistic links and clinical inferences. *J Am Coll Cardiol* 2015;**65**:2239–51. DOI: 10.1016/j.jacc.2015.03.557; PMID: 25998669
33. Santangeli P, Zado ES, Hutchinson MD, et al. Prevalence and distribution of focal triggers in persistent and long-standing persistent atrial fibrillation. *Heart Rhythm* 2016;**13**:374–82. DOI: 10.1016/j.hrthm.2015.10.023; PMID: 26477712
34. Verma A, Jiang C, Betts TR, et al.; STAR AF II Investigators. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med* 2015;**372**:1812–22. DOI: 10.1056/NEJMoa1408288; PMID: 25946280
35. Calò L, Rebecchi M, Sciarra L, et al. Catheter ablation of right atrial ganglionated plexi in patients with vagal paroxysmal atrial fibrillation. *Circ Arrhythm Electrophysiol* 2012;**5**:22–31. DOI: 10.1161/CIRCEP.111.964262; PMID: 22147839
36. Katritsis DG, Giazitzoglou E, Zografos T, et al. Rapid pulmonary vein isolation combined with autonomic ganglia modification: a randomized study. *Heart Rhythm* 2011;**8**:672–8. DOI: 10.1016/j.hrthm.2010.12.047; PMID: 21199686
37. Pachon M JC, Pachon M EI, Pachon M JC, et al. A new treatment for atrial fibrillation based on spectral analysis to guide the catheter RF-ablation. *Europace* 2004;**6**:590–601. DOI: 10.1016/j.eupc.2004.08.005; PMID: 15519263
38. Sairaku A, Yoshida Y, Hirayama H, et al. Impact of pulmonary vein isolation on fractionated atrial potentials and ganglionated plexi in patients with persistent atrial fibrillation. *Int Heart J* 2014;**55**:494–8. PMID: 25310931
39. Mikhaylov E, Kanidieva A, Sviridova N, et al. Outcome of anatomic ganglionated plexi ablation to treat paroxysmal atrial fibrillation: a 3-year follow-up study. *Europace* 2011;**13**:362–70. DOI: 10.1093/europace/euq416
40. Yorgun H, Aytemir K, Canpolat U, et al. Additional benefit of cryoballoon-based atrial fibrillation ablation beyond pulmonary vein isolation: modification of ganglionated plexi. *Europace* 2014;**16**:645–51. DOI: 10.1093/europace/eut240
41. Kurotobi T, Shimada Y, Kino N, et al. Features of intrinsic ganglionated plexi in both atria after extensive pulmonary isolation and their clinical significance after catheter ablation in patients with atrial fibrillation. *Heart Rhythm* 2015;**12**:470–6. DOI: 10.1016/j.hrthm.2014.11.033; PMID: 25433142
42. Andrade JG, Monir G, Pollak SJ, et al. Pulmonary vein isolation using "contact force" ablation: the effect on dormant conduction and long-term freedom from recurrent atrial fibrillation – a prospective study. *Heart Rhythm* 2014;**11**:1919–24. DOI: 10.1016/j.hrthm.2014.07.033; PMID: 25068575
43. Fujiwara R, Imamura K, Kijima Y, et al. The importance of catheter stability evaluated by Visitag(TM) during pulmonary vein isolation. *J Interv Card Electrophysiol Int J Arrhythm Pacing* 2016;**46**:161–6. DOI: 10.1007/s10840-016-0103-z; PMID: 26781786
44. Anter E, Tschabrunn CM, Contreras-Valdes FM, et al. Radiofrequency ablation annotation algorithm reduces the incidence of linear gaps and reconnection after pulmonary vein isolation. *Heart Rhythm* 2014;**11**:783–90. DOI: 10.1016/j.hrthm.2014.02.022; PMID: 24583098
45. Cappato R, Negroni S, Pecora D, et al. Prospective assessment of late conduction recurrence across radiofrequency lesions producing electrical disconnection at the pulmonary vein ostium in patients with atrial fibrillation. *Circulation* 2003;**108**:1599–604. DOI: 10.1161/01.CIR.0000091081.19465.F1; PMID: 12963643
46. Takigawa M, Takahashi A, Kuwahara T, et al. Impact of non-pulmonary vein foci on the outcome of the second session of catheter ablation for paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol* 2015;**26**:739–46. DOI: 10.1111/jce.12681; PMID: 25845757
47. Ehrlich JR, Cha T-J, Zhang L, et al. Cellular electrophysiology of canine pulmonary vein cardiomyocytes: action potential and ionic current properties. *J Physiol* 2003;**551**:801–13. DOI: 10.1113/jphysiol.2003.046417; PMID: 12847206
48. Melnyk P, Ehrlich JR, Pourrier M, et al. Comparison of ion channel distribution and expression in cardiomyocytes of canine pulmonary veins versus left atrium. *Cardiovasc Res* 2005;**65**:104–16. DOI: 10.1016/j.cardiores.2004.08.014; PMID: 15621038
49. Datino T, Macle L, Qi X-Y, et al. Mechanisms by which adenosine restores conduction in dormant canine pulmonary veins. *Circulation* 2010;**121**:963–72. DOI: 10.1161/CIRCULATIONAHA.109.893107; PMID: 20159830
50. Datino T, Macle L, Chartier D, et al. Differential effectiveness of pharmacological strategies to reveal dormant pulmonary vein conduction: A clinical-experimental correlation. *Heart Rhythm* 2011;**8**:1426–33. DOI: 10.1016/j.hrthm.2011.04.011; PMID: 21699824
51. Belardinelli L, Shryock JC, Song Y, et al. Ionic basis of the electrophysiological actions of adenosine on cardiomyocytes. *FASEB J* 1995;**9**:359–65. PMID: 7896004
52. Workman AJ, Kane KA, Rankin AC. Ionic basis of a differential effect of adenosine on refractoriness in rabbit AV nodal and atrial isolated myocytes. *Cardiovasc Res* 1999;**43**:974–84. DOI: 10.1016/S0008-6363(99)00166-2. PMID: 10615425
53. Arentz T, Macle L, Kalusche D, et al. "Dormant" pulmonary

vein conduction revealed by adenosine after ostial radiofrequency catheter ablation. *J Cardiovasc Electrophysiol* 2004;**15**:1041–7. DOI: 10.1046/j.1540-8167.2004.04031.x. PMID: 15363077
54. Tritto M, Ponti RD, Salerno-Uriarte JA, et al. Adenosine restores atrio-venous conduction after apparently successful ostial isolation of the pulmonary veins. *Eur Heart J* 2004;**25**:2155–63. DOI: 10.1016/j.ehj.2004.08.023
55. Hachiya H, Hirao K, Takahashi A, et al. Clinical implications of reconnection between the left atrium and isolated pulmonary veins provoked by adenosine triphosphate after extensive encircling pulmonary vein isolation. *J Cardiovasc Electrophysiol* 2007;**18**:392–8. DOI: 10.1111/j.1540-8167.2006.00753.x; PMID: 17286569
56. Matsuo S, Yamane T, Date T, et al. Reduction of AF recurrence after pulmonary vein isolation by eliminating ATP-induced transient venous re-conduction. *J Cardiovasc Electrophysiol* 2007;**18**:704–8. DOI: 10.1111/j.1540-8167.2007.00842.x; PMID: 17506857
57. Kumagai K, Naito S, Nakamura K, et al. ATP-induced dormant pulmonary veins originating from the carina region after circumferential pulmonary vein isolation of atrial fibrillation. *J Cardiovasc Electrophysiol* 2010;**21**:494–500. DOI: 10.1111/j.1540-8167.2009.01667.x; PMID: 20021515
58. Ciconte G, Chierchia G-B, DE Asmundis C, et al. Spontaneous and adenosine-induced pulmonary vein reconnection after cryoballoon ablation with the second-generation device. *J Cardiovasc Electrophysiol* 2014;**25**:845–51. DOI: 10.1111/jce.12421; PMID: 24678900
59. Kumar N, Dinh T, Phan K, et al. Adenosine Testing after Second-Generation Cryoballoon Ablation (ATSCA) study improves clinical success rate for atrial fibrillation. *Europace* 2015;**17**:871–6. DOI: 10.1093/europace/euu352; PMID: 25972302
60. Macle L, Khairy P, Weerasooriya R, et al. Adenosine-guided pulmonary vein isolation for the treatment of paroxysmal atrial fibrillation: an international, multicentre, randomised superiority trial. *Lancet Lond Engl* 2015;**385**:672–9. DOI: 10.1016/S0140-6736(15)60026-5; PMID: 26211828
61. Kobori A, Shizuta S, Inoue K, et al.; UNDER-ATP Trial Investigators. Adenosine triphosphate-guided pulmonary vein isolation for atrial fibrillation: the UNmasking Dormant Electrical Reconduction by Adenosine TriPhosphate (UNDER-ATP) trial. *Eur Heart J* 2015;**36**:3276–87. DOI: 10.1093/eurheartj/ehv457; PMID: 26321237
62. Ghanbari H, Jani R, Hussain-Amin A, et al. Role of adenosine after antral pulmonary vein isolation of paroxysmal atrial fibrillation: A randomized controlled trial. *Heart Rhythm* 2016;**13**:407–15. DOI: 10.1016/j.hrthm.2015.10.016; PMID: 26455342
63. Cheema A, Dong J, Dalal D, et al. Incidence and time course of early recovery of pulmonary vein conduction after catheter ablation of atrial fibrillation. *J Cardiovasc Electrophysiol* 2007;**18**:387–91. DOI: 10.1111/j.1540-8167.2007.00760.x; PMID: 17394453
64. Nakamura K, Naito S, Kaseno K, et al. Optimal observation time after completion of circumferential pulmonary vein isolation for atrial fibrillation to prevent chronic pulmonary vein reconnections. *Int J Cardiol* 2013;**168**:5300–10. DOI: 10.1016/j.ijcard.2013.08.011; PMID: 23998548
65. Wang X, Liu X, Sun Y, et al. Early identification and treatment of PV re-connections: role of observation time and impact on clinical results of atrial fibrillation ablation. *Europace* 2007;**9**:481–6. DOI: 10.1093/europace/eum101; PMID: 17522081
66. Bänsch D, Bittkau J, Schneider R, et al. Circumferential pulmonary vein isolation: wait or stop early after initial successful pulmonary vein isolation? *Europace* 2013;**15**:183–8. DOI: 10.1093/europace/eus205; PMID: 22764199
67. De Potter TJR, Eisenberger M, McCann C, et al. Adenosine plus dipyridamole: a novel strategy to enhance adenosine-induced conduction recovery after pulmonary vein isolation. *Europace* 2012;**14**:1567–71. DOI: 10.1093/europace/eus159; PMID: 22622141
68. Miyazaki S, Taniguchi H, Uchiyama T, et al. Impact of low-dose dipyridamole injection on adenosine test after pulmonary vein isolation. *Pacing Clin Electrophysiol* 2013;**36**:1451–9. DOI: 10.1111/pace.12220; PMID: 23875810
69. Lee S-H, Tai C-T, Hsieh M-H, et al. Predictors of non-pulmonary vein ectopic beats initiating paroxysmal atrial fibrillation: implication for catheter ablation. *J Am Coll Cardiol* 2005;**46**:1054–9. DOI: 10.1016/j.jacc.2005.06.016; PMID: 16168291
70. Arruda M, Mlcochova H, Prasad SK, et al. Electrical isolation of the superior vena cava: an adjunctive strategy to pulmonary vein antrum isolation improving the outcome of AF ablation. *J Cardiovasc Electrophysiol* 2007;**18**:1261–6. DOI: 10.1111/j.1540-8167.2007.00953.x; PMID: 17850288
71. Johnson N, Danilo P, Wit AL, et al. Characteristics of initiation and termination of catecholamine-induced triggered activity in atrial fibers of the coronary sinus. *Circulation* 1986;**74**:1168–79. PMID: 3769174
72. Elayi CS, Fahmy TS, Wazni OM, et al. Left superior vena cava isolation in patients undergoing pulmonary vein antrum isolation: impact on atrial fibrillation recurrence. *Heart Rhythm* 2006;**3**:1019–23. DOI: 10.1016/j.hrthm.2006.05.024; PMID: 16945794
73. Biase LD, Burkhardt JD, Mohanty P, et al. Left atrial appendage: an underrecognized trigger site of atrial fibrillation. *Circulation* 2010;**122**:109–18. DOI: 10.1161/CIRCULATIONAHA.109.928903; PMID: 20606120
74. Tsai C-F, Tai C-T, Hsieh M-H, et al. Initiation of atrial fibrillation by ectopic beats originating from the superior vena cava electrophysiological characteristics and results of radiofrequency ablation. *Circulation* 2000;**102**:67–74. DOI: 10.1161/01.CIR.102.1.67; PMID: 10880417
75. Kurotobi T, Iwakura K, Inoue K, et al. Multiple arrhythmogenic foci associated with the development of perpetuation of atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010;**3**:39–45. DOI: 10.1161/CIRCEP.109.885095; PMID: 19996379
76. Liang BT, Frame LH, Molinoff PB. Beta 2-adrenergic receptors contribute to catecholamine-stimulated shortening of action potential duration in dog atrial muscle. *Proc Natl Acad Sci* 1985;**82**:4521–5. PMID: 2989829
77. Chen P-S, Maruyama M, Lin S-F. Arrhythmogenic foci and the mechanisms of atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010;**3**:7–9. DOI: 10.1161/CIRCEP.110.936385
78. Chen Y-J, Chen Y-C, Yeh H-I, et al. Electrophysiology and arrhythmogenic activity of single cardiomyocytes from canine superior vena cava. *Circulation* 2002;**105**:2679–85. DOI: 10.1161/01.CIR.0000016822.96362.26; PMID: 12045176
79. Wit AL, Boyden PA. Triggered activity and atrial fibrillation. *Heart Rhythm* 2007;**4**:S17–S23. DOI: 10.1016/j.hrthm.2006.12.021; PMID: 17336878
80. Wang T-M, Luk H-N, Sheu J-R, et al. Inducibility of abnormal automaticity and triggered activity in myocardial sleeves of canine pulmonary veins. *Int J Cardiol* 2005;**104**:59–66. DOI: 10.1016/j.ijcard.2004.10.016; PMID: 16137511
81. Zhao Y, Di Biase L, Trivedi C, et al. Importance of non-pulmonary vein triggers ablation to achieve long-term freedom from paroxysmal atrial fibrillation in patients with low ejection fraction. *Heart Rhythm* 2016;**13**:141–9. DOI: 10.1016/j.hrthm.2015.08.029; PMID: 26304713
82. Hayashi K, An Y, Nagashima M, et al. Importance of nonpulmonary vein foci in catheter ablation for paroxysmal atrial fibrillation. *Heart Rhythm* 2015;**12**:1918–24. DOI: 10.1016/j.hrthm.2015.05.003; PMID: 25962801
83. Hsu L-F, Jaïs P, Keane D, et al. Atrial fibrillation originating from persistent left superior vena cava. *Circulation* 2004;**109**:828–32. DOI: 10.1161/01.CIR.0000116753.56467.BC; PMID: 14757689
84. Lin D, Frankel DS, Zado ES, et al. Pulmonary vein antral isolation and nonpulmonary vein trigger ablation without additional substrate modification for treating longstanding persistent atrial fibrillation. *J Cardiovasc Electrophysiol* 2012;**23**:806–13. DOI: 10.1111/j.1540-8167.2012.02307.x; PMID: 22509772
85. Inoue K, Kurotobi T, Kimura R, et al. Trigger-based mechanism of the persistence of atrial fibrillation and its impact on the efficacy of catheter ablation. *Circ Arrhythm Electrophysiol* 2012;**5**:295–301. DOI: 10.1161/CIRCEP.111.964080
86. Santangeli P, Di Biase L, Mohanty P, et al. Catheter ablation of atrial fibrillation in octogenarians: safety and outcomes. *J Cardiovasc Electrophysiol* 2012;**23**:687–93. DOI: 10.1111/j.1540-8167.2012.02293.x; PMID: 22494628
87. Dixit S, Marchlinski FE, Lin D, et al. Randomized ablation strategies for the treatment of persistent atrial fibrillation: RASTA study. *Circ Arrhythm Electrophysiol* 2012;**5**:287–94. DOI: 10.1161/CIRCEP.111.966226; PMID: 22139886
88. Roux J-F, Gojraty S, Bala R, et al. Complex fractionated electrogram distribution and temporal stability in patients undergoing atrial fibrillation ablation. *J Cardiovasc Electrophysiol* 2008;**19**:815–20. DOI: 10.1111/j.1540-8167.2008.01133.x; PMID: 18373601
89. Hunter RJ, Diab I, Tayebjee M, et al. Characterization of fractionated atrial electrograms critical for maintenance of atrial fibrillation: a randomized, controlled trial of ablation strategies (the CFAE AF trial). *Circ Arrhythm Electrophysiol* 2011;**4**:622–9. DOI: 10.1161/CIRCEP.111.962928; PMID: 21844156
90. Jadidi AS, Cochet H, Shah AJ, et al. Inverse relationship between fractionated electrograms and atrial fibrosis in persistent atrial fibrillation: combined magnetic resonance imaging and high-density mapping. *J Am Coll Cardiol* 2013;**62**:802–12. DOI: 10.1016/j.jacc.2013.03.081; PMID: 23727084
91. Rostock T, Rotter M, Sanders P, et al. High-density activation mapping of fractionated electrograms in the atria of patients with paroxysmal atrial fibrillation. *Heart Rhythm* 2006;**3**:27–34. DOI: 10.1016/j.hrthm.2005.09.019; PMID: 16399048
92. Viles-Gonzalez JF, Gomes JA, Miller MA, et al. Areas with complex fractionated atrial electrograms recorded after pulmonary vein isolation represent normal voltage and conduction velocity in sinus rhythm. *Europace* 2013;**15**:339–46. DOI: 10.1093/europace/eus321; PMID: 23148118
93. Roux J-F, Gojraty S, Bala R, et al. Effect of pulmonary vein isolation on the distribution of complex fractionated electrograms in humans. *Heart Rhythm* 2009;**6**:156–60. DOI: 10.1016/j.hrthm.2008.10.046; PMID: 19187903
94. Lin Y-J, Chang S-L, Lo L-W, et al. A prospective and randomized comparison of limited versus extensive atrial substrate modification after circumferential pulmonary vein isolation in nonparoxysmal atrial fibrillation. *J Cardiovasc Electrophysiol* 2014;**25**:803–12. DOI: 10.1111/jce.12407; PMID: 24628987
95. Miwa Y, Minamiguchi H, Bhandari AK, et al. Amiodarone reduces the amount of ablation during catheter ablation for persistent atrial fibrillation. *Europace* 2014;**16**:1007–14. DOI: 10.1093/europace/eut399; PMID: 24446509
96. Singh SM, D'Avila A, Kim SJ, et al. Intraprocedural use of ibutilide to organize and guide ablation of complex fractionated atrial electrograms: preliminary assessment of a modified step-wise approach to ablation of persistent atrial fibrillation. *J Cardiovasc Electrophysiol* 2010;**21**:608–16. DOI: 10.1111/j.1540-8167.2009.01671.x; PMID: 20039991
97. Providência R, Lambiase PD, Srinivasan N, et al. 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**:1017–29. DOI: 10.1161/CIRCEP.115.003019; PMID: 26082515
98. Sawhney N, Anousheh R, Chen W, et al. 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**:243–8. DOI: 10.1161/CIRCEP.109.924878; PMID: 20339034
99. Oral H, Chugh A, Yoshida K, et al. A randomized assessment of the incremental role of ablation of complex fractionated atrial electrograms after antral pulmonary vein isolation for long-lasting persistent atrial fibrillation. *J Am Coll Cardiol* 2009;**53**:782–9. DOI: 10.1016/j.jacc.2008.10.054; PMID: 19245970
100. Mohanty S, Di Biase L, Mohanty P, et al. Effect of periprocedural amiodarone on procedure outcome in patients with longstanding persistent atrial fibrillation undergoing extended pulmonary vein antrum isolation: results from a randomized study (SPECULATE). *Heart Rhythm* 2015;**12**:477–83. DOI: 10.1016/j.hrthm.2014.11.016; PMID: 25460855
101. Singh SM, d'Avila A, Kim Y-H, et al. The modified stepwise ablation guided by low-dose ibutilide in chronic atrial fibrillation trial (The MAGIC-AF Study). *Eur Heart J* 2016;**37**:1614–21. DOI: 10.1093/eurheartj/ehw003.