Atrial Fibrillation

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Abstract

AF is the most common sustained arrhythmia seen in clinical practice with an overall prevalence of 700–750 per 100,000 of the population in North America (Chugh et al., Circulation 129:837–847, 2014). In addition to causing considerable adverse sequelae and an increase in hospitalizations, there is a five-fold increase in the risk of stroke associated with non-valvular AF (Wolf et al., Stroke 22:983–988, 1991) which increases by a factor of 17 in the presence of significant valvular heart disease (Fuster et al., Circulation 123:e269–e367, 2011). The risk of AF increases markedly with older age affecting approximately 5% of people over 65 years and 10% of people age over 80 years (Miyasaka et al., Circulation 2006; 12: 114–119, 2006).

Classification of AF

AF is classified as paroxysmal, persistent, long-standing persistent or permanent. Paroxysmal AF is defined as two or more episodes of AF, each of which terminate within 7 days and commonly within 24 h. Persistent AF is generally sustained for greater than 7 days (or less if a cardioversion was performed in this time) and requires chemical or electrical cardioversion for termination of the arrhythmia. Longstanding persistent AF refers to cases in which the arrhythmia has been present for more than 1 year and previously may have been designated as being permanent; however, an electrical cardioversion or ablation strategy is being pursued and therefore sinus rhythm may be achieved. Permanent AF also persists for more than 7 days and can no longer be terminated; thus, a rhythm control strategy has been unsuccessful or not appropriate.

Etiology

The incidence of AF is increased by other cardiovascular and metabolic conditions as well as several lifestyle factors. It may also be secondary to either acute reversible insults or to other arrhythmias.

The main cardiovascular causes of AF are shown on Fig. 8.1 and include hypertension, coronary artery disease and valvular heart dis-

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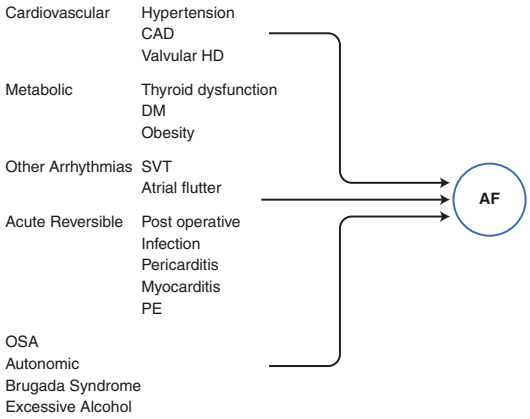


Fig. 8.1 Causes of Atrial Fibrillation. These can be divided into cardiovascular such as hypertension, coronary artery disease (CAD) and valvular heart disease (HD), metabolic, such as thyroid dysfunction, diabetes mellitus (DM) and obesity other arrhythmias such as SVT and atrial flutter and acute reversible causes such as post operative, infections, pericarditis, myocarditis and pulmonary embolism (PE). Other causes include OSA, autonomic, Brugada and excess alcohol

ease. Metabolic causes of AF include thyroid dysfunction and diabetes mellitus while lifestyle risk factors include obesity, excessive alcohol and obstructive sleep apnea. AF is frequently seen in the acute setting in post-operative patients as well as those who have infection, or in association with pulmonary embolism, pericarditis and myocarditis. AF may also occur in association with other supraventricular arrhythmias, such as AV nodal re-entry tachycardia, AV re-entry tachycardia and atrial flutter. It is important to perform an EP study in patients who are being considered for an AF ablation and in particular young patients to ensure that there is no underlying SVT. In patients who have undergone a successful ablation for typical atrial flutter the incidence of AF with 2.5 years post ablation is 50% (Chinitz et al. 2007). There has been some recent evidence to suggest that triggers from the pulmonary veins may also play a role in the initiation of typical atrial flutter (Schneider et al. 2015). Other less common causes of AF may be associated with autonomic activity, familial forms (particularly Brugada syndrome), and inflammatory mediators.

Hypertension

The odds ratio for developing AF in association with hypertension is 1.5 for men and 1.4 for women (Benjamin et al. 1994). Although this is not the highest risk for AF in an individual it is the most common cause of AF due to the high incidence of hypertension. Hypertension is often accompanied by left atrial remodeling due to pressure and volume overload as a result of a degree of left ventricular diastolic dysfunction. These changes may alter the electrical properties of the myocytes in the pulmonary veins, increasing their potential to act as triggers.

Effective treatment of hypertension in patients with AF has been shown to reduce all cause mortality (7.8%), cardiovascular mortality (4.3%), nonfatal myocardial infarction (5.3%) and stroke (2.2%), independent of blood pressure lowering effects (Dagenais et al. 2006). Additionally effective treatment of hypertension has been shown to reduce the overall risk of developing AF by 28% (Healey et al. 2005). Data supporting this has been inconsistent however, which may be a reflection of difficulties in optimal blood pressure control.

Coronary Artery Disease

AF is relatively common following an acute myocardial infarction (MI) occurring in approximately 15% of patients. Early reperfusion as well as the use of beta blockers appears to have an impact on lowering the incidence of AF post-MI. AF may result from occlusion to or proximal to the sinus node artery as well as the hemodynamic changes associated with left ventricular dysfunction. It may also occur as a result of changes in autonomic tone, particularly with an increase in adrenergic stimulation or as a result of pericarditis.

Of additional note, some patients with AF present with chest pain, an elevated cardiac troponin and no evidence of significant obstructive coronary artery disease. It has been suggested that this may be a result of AT1 receptor-mediated oxidative stress accompanied by a reduction in microvascular blood flow (Goette et al. 2009).

Valvular Heart Disease

The incidence of AF in patients with significant valvular heart disease is approximately 30% and in patients with mitral stenosis, approximately 50%. AF tends to be an early manifestation of mitral valve disease and tends to present later in aortic valve disease. Patients with significant mitral and aortic valve disease tend to have elevated left atrial pressure with left atrial dilatation and left atrial fibrosis which increases the possibility of re-entry circuits. The overall reduction in the incidence of rheumatic heart disease in the Western World has led to a significant reduction in valvular heart disease as an overall contributor to AF.

Diabetes Mellitus

Diabetes mellitus (DM) has been shown to be associated with an increased incidence of AF, whereby increasing risk is associated with diabetes duration and poor glycemic control (Dublin et al. 2010; Tesfaye et al. 2005). DM may result in a disturbance of cardiac autonomic function, in particular an increase in sympathetic tone, which may result in the initiation of AF (Dimmer et al. 1998). The cardiac autonomic dysfunction in patients with DM may also result in coronary microvascular dysfunction and diastolic dysfunction in diabetic subjects (Di Carli et al. 1999; Sacre et al. 2010; Pop-Busui et al. 2004) which may increase the potential for AF. There may also be inflammatory changes responsible for both conditions. CRP and interleukin 6 (IL-6) have been shown to be elevated in atrial biopsies in patients with lone AF which may also be elevated in DM (Chung et al. 2001; Frustaci et al. 1997).

Obesity and Obstructive Sleep Apnea (OSA)

Obesity is a significant public health concern with increasing prevalence. There is a 2.4-fold increased risk of AF in obese individuals versus those with a normal body mass index (BMI) (Frost et al. 2005). Furthermore this risk appears to increase with higher BMI values, as seen by a 1.2-fold increased risk in those with a BMI of 25–30 kg/m^2 and a 2.3-fold increase in those with a BMI greater than 40 kg/m^2 (Zacharias et al. 2005).

There are several potential explanations for an increased AF risk in patients who are overweight or obese. Indeed, AF may occur as a direct result of obesity or in association with other risk factors, which are more commonly associated with an elevated BMI.

There is a direct association between left atrial dilatation and obesity with a 2.4-fold 10-year risk of left atrial enlargement on echocardiogram (Stritzke et al. 2009).

In the settings of obesity and in particular, hypertension, left atrial pressure may also increase as a result of left ventricular hypertrophy and diastolic dysfunction. It has also been shown that obese patients have slower left atrial conduction times and shorter effective refractory periods in the left atrium and pulmonary veins even when adjusting for confounding variables including hypertension, DM and OSA (Munger et al. 2012). Overall these changes may result in atrial remodeling and atrial arrhythmias.

Atrial remodeling can be summarized as a heterogeneous process characterized by the disruption of atrial electrical integrity. Delayed interatrial conduction reflected as a broad and biphasic P wave in the inferior leads has been shown to increase with BMI and waist circumference (Magnani et al. 2012).

Increased pericardial fat occurs frequently with obesity, which may lead to a disturbance in atrial conduction. Variable expression of this adipose tissue may result in heterogeneity of atrial conduction. This has been shown to result in an increased risk of developing AF (Magnani et al. 2011).

OSA may be found in up to 90% of individuals with obesity (Frey and Pilcher 2003). If untreated, this is characterized by significant negative drops in intrathoracic pressure, intermittent hypercapnic hypoxia, and transient repeated wakening at the end of each episode. These drops in intrathoracic pressure may subsequently result in alterations of the left atrial chamber dimen-

sions which may, in itself, increase the risk of developing AF. Additionally, both hypercapnic hypoxia and frequent changes in sleep patterns may result in an increase in sympathetic tone. Overall, these changes may lead to an increase in the left atrial volume (Otto et al. 2007).

Effective treatment with CPAP in patients with OSA and no history of AF has been shown to reduce right and left atrial dimensions (Colish et al. 2012). OSA has been shown to be independently associated with failure of catheter ablation for AF (Patel et al. 2010). Ablation success rates are higher in patients with OSA who are treated with CPAP versus those not treated (Patel et al. 2010; Fein et al. 2013).

Obesity and its associated conditions are potentially modifiable risk factors for AF. In general, it is currently recommended that individuals with a BMI > 25 kg/m^2 with 1 associated comorbidity (diabetes, prediabetes, hypertension, dyslipidemia, elevated waist circumference) should be offered advice on dietary and lifestyle modification (Fein et al. 2013).

Aggressive risk factor modification in patients with a BMI > 27 kg/m^2 and at least one other risk factor (hypertension, DM, OSA, smoking and excessive alcohol consumption) in patients awaiting catheter ablation has been shown to result in an improvement in patient's symptoms, with 30% of patients avoiding the need for ablation (Abed et al. 2013). In patients undergoing catheter ablation for symptomatic AF, a significant improvement in symptoms was observed post-ablation as measured by the AF severity score (Pathak et al. 2014). AF-free survival after a single ablation procedure was 62% for patients with risk-factor-modification and only 26% for the control arm. After multiple ablations, AF-free survival increased to 87% in the risk-factor-modification group versus 48% in the control arm. Structural changes of the heart were also significantly better with left atrial volume and LV diastolic volume reduction.

Autonomic AF

An alteration in sympathetic activity may result in an increase in the potential for the initiation or maintenance of AF. This can occur either by direct effects on the action potential duration and refractory period of the cells in the pulmonary veins or left atrium or by structural changes.

An increase in adrenergic stimulation may result in an enhancement of focal automaticity which may act as a potential trigger for AF. Increased parasympathetic activation increases the action potential duration. However, its contribution to AF may result from its ability to shorten the atrial effective refractory period by varying degrees throughout the left atrium, which may contribute to a heterogeneity of conduction properties (Liu and Nattel 1997).

Both vagally induced and adrenergic AF tend to occur in younger patients with no other obvious risk factors. Vagally-induced AF is much more common than adrenergic AF and tends to occur after a preceding sinus pause or sinus bradycardia. Vagally induced AF may be partially responsive to flecainide and disopyramide and frequently worsens with beta blockers. Adrenergic AF is often provoked by exercise or increased emotional stress and tends to be preceded by an increase in sinus rate. This type of AF responds well to beta-adrenoceptor blockade.

It has been suggested that ganglionic plexi denervation may have a role in the treatment of AF. Indeed, left atrial ablation may have some impact by its effects on the autonomic innervation of the heart. One of the main restrictions in ganglionic plexus denervation using an ablation catheter is the difficulty in optimal access to the nerves which are not easily ablated from the endocardium.

Familial AF

Approximately 5% of cases of AF may have a genetic component (Darbar et al. 2003). This may be even higher in patients who develop AF at a younger age and those with no other obvious risk factors for AF. The risk of developing AF in an individual who has a parent with a history of AF is increased by a factor of 1.85 times that of the population (Fox et al. 2004). Additionally an

increased incidence of AF has been noted in long QT4, short QT and Brugada syndrome.

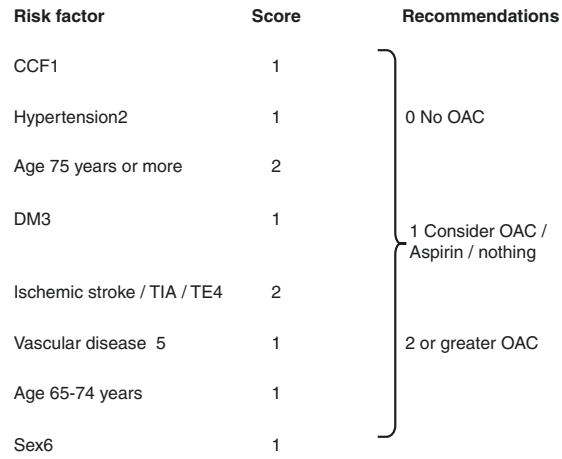
Several genetic mutations have been implicated in AF. A missense mutation in the KCNQ1 gene has been shown to result in an alteration of the activity of the voltage gated delayed potassium current (IKS) (Chen et al. 2003). In addition to other mutations in the KCNQ1 gene, SHOX2, TBX3 and PITX2 gene mutations have been linked to enhanced susceptibility to familial AF.

Mutations have also been detected in the KCNN3 gene, which encodes calcium activated potassium channels within in the atria (Ellinor et al. 2010).

Oral Anticoagulation

The issue of oral anticoagulation is one of the more complex issues in clinical cardiology. Most risk stratifying scores have been designed to be simple and easy to remember. Currently the most widely used risk scoring system is the CHA2DS2VASc, which is shown in Fig. 8.2. This was based on the CHADS2 score with a greater emphasis on age as well as the addition of vascular disease (prior MI or peripheral vascular disease), female gender and diabetes mellitus. It is generally recommended that oral anticoagulation should be considered in patients with a CHA2DS2VASc of greater than or equal to 2 (Class I Indication, Level of Evidence B) with either Coumadin or a direct oral anticoagulant. In patients with a CHA2DS2VASc score of greater than or equal to 1 oral anticoagulation, aspirin or no antithrombotic therapy can be considered (Class IIb Indication, Level of Evidence C). For patients with a CHA2DS2VASc of 0 no antithrombotic therapy is generally recommended. In general, female gender in a patient with no other risk factor for stroke would not result in the institution of oral anticoagulation although this clearly has to be reviewed with increasing age. It should also be remembered that each individual risk factor does not confer an equal percentage risk for stroke.

Although CHA2DS2VASc is more sensitive for predicting low event rates in low-risk patients, it is only modestly effective in terms of its positive predictive value with an area under the



1 Signs/symptoms of LV/RV/Biventricular dysfunction confirmed with objective testing
2 Resting SBP > 140 mmHg and/or DBP > 90 mmHg on 2 or more measurements or patients receiving antihypertensive medication
3 Fasting plasma glucose greater than or equal to 7.0mmol/L /126 mg/dL or treatment with oral hypoglycemic agent or insulin
4 Ischemic stroke is defined as a sudden focal neurological deficit diagnosed by a neurologist and found to be due to an ischemic orgin lasting greater than 24 hours
TIA is a sudden focal neurological deficit diagnosed by a neurologist and lasting less than 24 hours
5 Vascular disease is considered a prior MI/PVD/aortic plaque
6 Female gender with no other risk factors is not considered sufficient for commencing OAC

Fig. 8.2 Summarizing the CHA2DS2VASc Scoring system for Non-Valvular AF. *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TIA* transient ischemic attack, *TE* thromboembolism, *MI* myocardial infarction, *PVD* peripheral vascular disease

receiver-operating characteristic curve of approximately 0.6 (Troughton and Crozier 2013).

Additional factors which have been examined in order to help calculate the risk of stroke include the use of biomarkers as well as LAA morphology. Biomarkers such as NT-pro-BNP, von Willebrand levels, d-dimers and troponin have been studied. Although they appear to have some merit they have yet to be incorporated into the guidelines. LAA morphology appears to correlate to an extent with the risk of thromboembolism. It has been proposed that an increase in trabeculations, number of bends and narrowness of the LAA orifice may also increase the risk of thrombus formation. Although this can be documented on TEE or CT, this is not recommended for decision making regarding oral anticoagulation therapy.

Vitamin K Antagonist

Warfarin acts by inhibiting the cyclic interconversion of vitamin K and vitamin K epoxide, thereby reducing the vitamin K-dependent clotting factors II, VII, IX and X. When compared with placebo, adjusted dose warfarin maintaining an INR or 2.0–2.9 results in an absolute reduction in ischemic and hemorrhagic strokes of 2.7% per year (Hart et al. 2007). Warfarin has also been shown to be superior to aspirin in patients considered to be at an increased risk of stroke.

Several major limitations concerning warfarin exist. The time within the therapeutic range is often less than 75% exposing patients to the risk of thrombo-embolism for significant periods of time. Warfarin administration is associated with several drug-drug interactions; therefore, food and dose adjustments are frequently required. Despite these considerations, there is still a role for warfarin in clinical practice particularly in patients with valvular heart disease and AF. The non-vitamin K antagonist agents are contraindicated in the presence of valvular AF and also need to be used with extreme caution in the setting of renal impairment. The widespread use of warfarin combined with antiplatelet agents has been clinically documented and the ability to monitor the effect of the drug may provide a reasonable indication of patient compliance. Warfarin is also relatively easily, albeit slowly, reversed with vitamin K.

Non-vitamin K Antagonist Oral Anticoagulation Therapy (OAC's)

These agents act by either directly suppressing thrombin or the conversion of prothrombin to thrombin by blocking the activated Xa factor. They have several theoretical advantages over warfarin such as a rapid onset and offset of action, reasonably predictable pharmacokinetics that do not require ongoing monitoring, and fewer interactions overall. It is important to monitor renal function particularly in patients where the baseline eGFR is below normal limits.

Direct Thrombin Inhibitors

Direct thrombin inhibitors bind to both soluble and fibrin-bound thrombin. The most commonly used agent in this group is the pro-drug dabigatran etexilate which was evaluated against warfarin in the RELY study. This prospective, randomized trial compared either 150 mg or 110 mg twice daily with warfarin (INR 2.0–3.0) for the prevention of stroke and systemic embolism in patients with non-valvular AF (Connolly et al. 2009).

Dabigatran at a dose of 150 mg has been shown to be superior to warfarin with no significant difference in the primary safety endpoint of major bleeding. At a dose of 110 mg, dabigatran was non-inferior to warfarin, with fewer major bleeds. The incidence of intracranial haemorrhage and haemorrhagic stroke were lower with both doses of dabigatran.

Based on these results, dabigatran etexilate has been approved by the Food and Drug Administration (FDA) at 150 mg twice daily with 75 mg twice daily in patients with renal impairment. The European Medicines Association (EMA) has approved both doses of 110 mg twice

daily and 150 mg twice daily in patients with non-valvular AF.

Factor Xa Inhibitors

The three available factor Xa inhibitors in clinical practice are edoxaban, apixaban and rivaroxaban.

Edoxaban has been shown to be noninferior to warfarin in the largest of all the clinical trials and also appears to have a very favorable side effect profile when compared with warfarin.

Rivaroxaban has a plasma half life of 7–11 h with a flat dose response resulting in a once daily administration. Rivaroxaban was compared with warfarin for the prevention of stroke or systemic embolism among patients with nonvalvular AF who were at moderate-to-high risk for stroke in the Rocket AF Trial (Patel et al. 2011). This double-blind trial compared rivaroxaban 20 mg once daily (15 mg daily for those with an estimated creatinine clearance of 30–49 mL/min) with warfarin in 14,264 patients. Rivaroxaban was found to be noninferior compared with warfarin for the primary endpoint of stroke and systemic embolism with a significant reduction in haemorrhagic stroke and intracranial haemorrhage. Rivaroxaban has a distinct advantage in being a once daily preparation. Additionally, the ROCKET AF study enrolled older patients (mean age 73 years), with at least two risk factors (congestive heart failure, hypertension, stroke or TIA), higher mean values of CHADS2 score (3.5) and lower median values for therapeutic INR's compared to other trials which are more comparable to real life conditions.

Approximately one-third of active rivaroxaban is renally excreted and a dose reduction from 20 mg once daily to 15 mg once daily is recommended for patients with moderate to severe renal impairment with periodic monitoring of renal function. A sub-study of the ROCKET AF study demonstrated that this lower dose was safe and effective in patients with a creatinine clearance between 30 and 49 mL min^{-1}. Rivaroxaban has been approved by both the FDA and the EMA for stroke prevention in non-valvular AF.

Apixaban has been shown to reduce the risk of stroke (predominantly through its effects on a reduction in hemorrhagic stroke) or systemic embolism, major bleeding and mortality in comparison with warfarin (Granger et al. 2011). Moreover, in patients for whom vitamin K antagonist therapy was considered unsuitable, apixaban compared with aspirin, reduced the risk of stroke or systemic embolism without a significant increase in the risk of major bleeding (Connolly et al. 2011). Apixaban has gained clinical approval with the FDA and EMA in patients with nonvalvular AF. Although the usual dose is 5 mg BiD, this should be reduced to 2.5 mg BiD if two out of the following three criteria are present: age greater than or equal to 80 years, weight less than or equal to 60 kg or a serum creatinine greater than or equal to 133 mmol/L. The details associated with the major trials in the NOACs are summarized on Table 8.1.

HAS-BLED Score

This is a scoring system used to predict the 1-year risk of major bleeding defined as intracranial bleeding, hospitalization, blood transfusion or a drop in hemoglobin of greater than 2 g/L. The components of this scoring system are:

Hypertension: uncontrolled systolic blood pressure >160 mm Hg

Abnormal renal or liver function: a serum creatinine greater than 200 mmol/L, need for long-term dialysis or history of a renal transplant. Abnormal liver function is defined as an elevation of transaminases greater than three times the upper limit of normal or a history of chronic liver disease

Stroke

Bleeding

Labile INR: in the therapeutic range less than 60% of the time

Elderly

Drugs or alcohol: the use of non-steroidal anti-inflammatory or antiplatelet agents

Table 8.1 Showing a summary of randomized clinical trial data supporting NOAC's

Parameter	Dabigatran (Rely)	Rivaroxaban (Rocket-AF)	Apixaban (Averroes)	Edoxaban (Engage AF)
Drug Dose	150 mg BID or 110 mg BID versus Warfarin (INR 2.0–3.0)	20 mg QD 15 mg QD in patients with creatinine clearance 30–49 mL/min) versus Warfarin (INR 2.0–3.0)	5 mg BID versus Aspirin 81–315 mg OD	60 mg Edoxaban versus Warfarin or 30 mg Edoxaban OD
Study Design	Randomized, open label	Randomized double-blind, double Dummy	Randomized, double-blind	Randomized double blind
Inclusion Criteria	AF within 6 mths + 1 risk factor	AF within 6 mths + 2 risk factors	AF within 6 mths + 1 risk factor	AF within 12 mths + 2 risk factors
Number of Patients	18,113	14,000	5600	21,105
Mean Age	71.5 years	73 years	70 years	72 years
Prior Stroke/TIA	20%	55%	13.5%	28.5%
Mean CHADS2 score	2.1	3.5	2.1	2.8
Stroke and Systemic Embolism (percent/year)	1.71% warfarin 1.54% dabigatran 110 mg ($p = 0.34$) 1.11% dabigatran 150 mg ($p < 0.001$)	2.42% warfarin 2.12% rivaroxaban ($p = 0.117$)	3.9% aspirin 1.7% apixaban ($p < 0.001$)	1.50% warfarin 1.18% Edoxaban
Major Bleeding	3.57% warfarin 2.87% dabigatran 110 mg ($p = 0.003$) 3.32% dabigatran 150 mg ($p = 0.31$)	3.45% warfarin 3.6% rivaroxaban ($p = 0.576$)	1.2% aspirin 1.4% apixaban ($p = 0.33$)	3.43% warfarin 2.75% edoxaban ($p < 0.001$)
Intracranial Haemorrhage Rate (percent/year)	0.74% warfarin 0.23% dabigatran 110 mg ($p < 0.001$) 0.3% dabigatran 150 mg ($p < 0.001$)	0.74% warfarin 0.49% rivaroxaban ($p = 0.019$)	0.3% aspirin 0.4% apixaban ($p = 0.83$)	0.85% warfarin 0.39% edoxaban ($p < 0.001$)

The maximum score is 9 with a score of ≥3 indicative of a high bleeding risk, where increased caution and regular review should be performed. This scoring system should not be used solely to exclude administration of oral anticoagulation therapy but may be used to highlight patients at a higher risk of bleeding for the modification of controllable risk factors.

Catheter Ablation for AF

Catheter ablation for the treatment of AF emerged as a viable treatment option when it was discovered that ectopic foci, which originate from sleeves of myocardium extending into the pulmonary veins, may initiate AF (Haissaguerre et al. 1998). This resulted in the concept that isolation of these foci by catheter ablation may reduce the likelihood of developing AF. Although the foci themselves were initially targeted, this resulted in a high incidence of pulmonary vein stenosis, which has now been largely replaced with wide antral circumferential ablation (WACA). This technique has been shown to be associated with a lower incidence of arrhythmia recurrence compared with segmental antral ablation (Proietti et al. 2014). This may be due to the isolation of regions of the left atrial PV junction where micro re-entry may occur. Additionally, WACA may have a greater effect on the elimination of other non-PV triggers in the posterior LA wall, debulk the left atrium, and have a greater effect on autonomic denervation.

Pulmonary vein isolation (PVI) is currently considered the mainstream catheter approach for

paroxysmal AF. It also is a very reasonable approach for the management of persistent AF, albeit, with the need for additional options to be considered. Some centers perform PVI in all patients with a history of persistent AF followed by an electrical cardioversion for the first ablation procedure. If the patient presents with further AF, then either linear lesions, CFAE ablation or rotor ablation can be considered at that stage. Other centers perform more ablation for the first procedure although this may increase the potential for developing AT.

Risks of Catheter Ablation of AF

The risk of a significant complication associated with an AF ablation is approximately 2.9% (Gupta et al. 2013). The most common complication is vascular (approximately 1%) which is largely related to groin hematoma and occasionally femoral pseudoaneurysm formation. The risk of stroke and TIA is 0.6%, cardiac tamponade (1%) and clinically evident PV stenosis 0.5%. The incidence of phrenic nerve palsy is approximately 0.4% and although esophageal injury is common, atrio-oesophageal fistula is unusual occurring in 0.1% of cases. The overall mortality is 0.06%.

How to Perform a PVI

Patient Preparation

A PVI can be performed either with the patient under general anesthesia or with intravenous sedation and analgesia. There are several advantages to either strategy. General anesthesia often results in a quicker procedure with less patient discomfort and less patient movement. However, this may not always be available, and some operators prefer sedation as there is more patient feedback during the procedure.

A TEE may be performed in order to rule out a LAA thrombus particularly in patients who are in AF and have not been anticoagulated prior to the procedure. In most cases where the patient is receiving warfarin, this can be continued throughout the procedure with an upper INR cut off of 3.5 above which the risk of bleeding is increased by a factor of 6 (Kim et al. 2013).

If the patient is receiving a non vitamin K antagonist OAC (NOAC), a decision must be made whether to stop the agent or not.

Some data suggests that uninterrupted dabigatran compared with uninterrupted warfarin is associated with an increased risk of bleeding and thrombo-embolic complications (Lakkireddy et al. 2012). Dabigatran increases the effects of heparin often doubling the effects, an effect not seen to the same degree with rivaroxaban and apixaban (Walenga and Adiguzel 2010). It is therefore, standard practice to interrupt dabigatran prior to performing an AF ablation. The decision of when to hold dabigatran is dependent on the patient's renal function. In patients with normal renal function, the drug may be held either the morning of the procedure or the evening prior but not for more than 24 h pre-procedure (Providência et al. 2014). Dabigatran should be stopped earlier if renal function is reduced.

In patients with normal renal clearance, the best option may be drug suspension on the morning of the procedure, or the night before, but always <24 h before the procedure. A target ACT of greater than 350 s should be achieved during the procedure. Dabigatran can then be recommenced 3–4 h following removal of the sheaths (Providência et al. 2014). The dosage of dabigatran following this should be based on renal function and the potential risk of bleeding.

Recent data has shown that uninterrupted rivaroxaban therapy appears to be as efficacious as uninterrupted warfarin in preventing thromboembolic and bleeding complications in patients undergoing AF ablation (Lakkireddy et al. 2014). If the decision is made to hold rivoroxaban for an AF ablation, the dose on the morning of the procedure may be held. There is currently limited data regarding the use of apixaban in patients undergoing an AF ablation although it may seem reasonable to hold a dose the morning of or the evening before the procedure.

It is common practice to administer the final dose of the OAC 24 h prior to the ablation and

perform a pre-procedure TEE. Heparin is then administered throughout the procedure and the OAC is recommenced 3 h following removal of the venous sheaths which are removed at the end of the case with no reversal of heparin.

If the patient is receiving a general anesthetic the TEE probe can be left in position in order to help facilitate the transseptal access and monitor for pericardial effusion.

Venous access is generally achieved via the femoral vein with two 8 Fr sheaths and a 6 Fr sheath. A decapolar is positioned in the coronary sinus to help with the transseptal puncture and may also be useful for mapping and pacing particularly if an AT develops during the procedure.

Two transseptal sheaths are then positioned over 0.032 wires into the superior vena cava and flushed with heparinized saline. Heparin is then administered at a dose of 100 iu/kg in order to achieve an ACT of greater than 300 s in patients who are either not on warfarin or have an INR less than 2.0 (Calkins et al. 2012). For patients who are receiving warfarin and have a therapeutic INR 75 iu/kg of heparin should be administered in order to achieve an ACT of greater than 300 s. ACT should be checked every 20 min at which time, either further boluses or an infusion can be administered.

Transseptal Access

A posterior location in the fossa ovalis is chosen in order to facilitate access to all regions around the pulmonary veins. Although his can be performed under fluoroscopic guidance the addition of echocardiographic data is oftentimes helpful particularly if the fossa is difficult to cross or is aneurysmal.

A range of sheaths and transseptal needles are available. A BRK1 needle often results in a good location and is useful in patients who have enlarged atria. If this is tenting the fossa without crossing, then the flexion can be slightly reduced or a BRK or Baylis needle can be considered. Transseptal access can generally be achieved using a combination of a PA, left lateral, RAO and LAO views. Generally, for PVI, standard sheaths are sufficient although deflectable sheaths may help with contact and occasionally with access to the right superior pulmonary vein. Deflectable sheaths may be useful for a linear lesion joining the mitral isthmus to the left inferior pulmonary vein. If a non-standard sheath is to be switched to a deflectable sheath, a 0.032 wire can be extended out to the left superior pulmonary vein for an over the wire switch.

Notwithstanding the choice of sheath, it is very important that the side arms are flushed with heparinized saline in a closed circuit and that no air bubbles enter the system.

Anatomic Reconstruction of the Left Atrium

The anatomy of the LA is generally constructed using a multipolar circular catheter. This may be merged with a pre-procedure CT, which could be helpful in determining the presence of aberrant pulmonary veins as well as the presence of variants such as common ostia. MRI of the LA can also be performed but is more time consuming. Either of these modalities can be merged with the electroanatomic image. Carto-Merge (Biosense Webster) uses fiducial points taken from selected anatomical structures such as the pulmonary vein ostia. The image is then rotated in order to compare the anatomic shells of both structures for comparison. If there is a difference between the two images further points can be taken on the electro anatomic map.

NavX Fusion (St Jude Medical) can also be used to integrate the electroanatomic map onto a baseline CT scan. Following acquisition of the anatomic shell, this system utilizes a field scaling algorithm which adjusts for the non-linearity of the geometry and takes into account the measured inter-electrode spacing for all locations within the geometry. Four fiducial points are then taken on the CT and the electroanatomic map and secondary fusion is used to reduce mismatch between the two images (Brooks et al. 2008).

Although these systems may be helpful the LA dimensions vary with rhythm status and are also dependent on the intravascular volume.

Overall, there remains no convincing data to suggest that image integration increases success or reduces complications. IT may, however, reduce fluoroscopy times.

Ablation Technique

Following anatomic reconstruction of the LA, a circular mapping catheter is positioned within the ostia in one of the pulmonary veins where it should record nearfield pulmonary vein potentials and farfield left atrial potentials. If a contact force catheter is being used for ablation, this should be positioned in the middle of the left atrium where there is no contact and a zero is set on the catheter.

The catheter should then be positioned so that it is on the atrial side of the pulmonary vein ostia. The ostia can be difficult to locate precisely on fluoroscopy or even on an electroanatomic map and there is an overlap between left atrial myocytes extending into the pulmonary veins and venous tissue extending into the left atrium. If the demarcation is unclear, the ablation catheter can be placed on the venous side of the ostia while pacing and capturing the pulmonary veins. The point at which pulmonary vein capture no longer occurs is a reasonable estimate of the ostia.

Point by point ablation is generally performed using a 3.5–4.0 mm irrigated catheter. Power is delivered at 30–35 W anterior to the pulmonary veins and 25–30 W along the posterior wall in order to limit energy delivery to the esophagus and branches of the vagus nerve. A target temperature of less than 40 °C and irrigation at 17 mL/min are set. If contact force is used, then a minimum of 10 g of force should be targeted. The catheter is typically moved every 30–60 s.

Certain regions around the pulmonary veins may be technically more challenging than others and require different catheter manipulations. The ridge between the left pulmonary veins and the left atrial appendage is an infolding of the lateral atrial wall (Fig. 8.3). It is at its narrowest at the border of the left superior pulmonary vein measuring 2.2–6.3 mm to its broadest aspect at the boundary of the left inferior pulmonary vein measuring 6.2–12.3 mm (Ho et al. 2012). It is at its thickest at the anterosuperior region.

In order to ablate along the ridge, the ablation catheter can be withdrawn from the left superior pulmonary vein with counterclockwise rotation so that the catheter is moving anterior in the direction of the LAA. This should maximize contact with this region. Excess counterclockwise torque results in the catheter moving into the LAA, which often needs to be counteracted with clockwise rotation. Given the significant autonomic innervation of the lateral ridge, ablation in this region commonly results in a slowing of the sinus rate.

Flexion and extension of the ablation catheter is required for ablation inferior and superior to the left sided PV's. Ablation starting on the roof superior to the left superior pulmonary vein often results in separation of local pulmonary vein signals and LAA farfield signals.

Ablation superior and inferior to the right sided PV's can be performed often with a combination of rotation with flexion and extension of the catheter. Occasionally a deflectable sheath may be useful in these regions although the use of a bidirectional catheter through a standard sheath is generally suitable to reach all regions. When ablation is performed inferior to the right inferior pulmonary vein within a small left atrium, it is important to flex with an acute angle in order to minimize the risk of losing transseptal access.

Ablation may be required in the carina between the pulmonary veins despite WACA being performed. This may be explained by endocardial to epicardial connections in this region resulting in continued conduction. Additionally, connections exist between ipsilateral PV's resulting in several isthmuses which may be an important consideration when performing PVI and may in part explain why segmental ablation was previously shown to have limited efficacy (Cabrera et al. 2009).

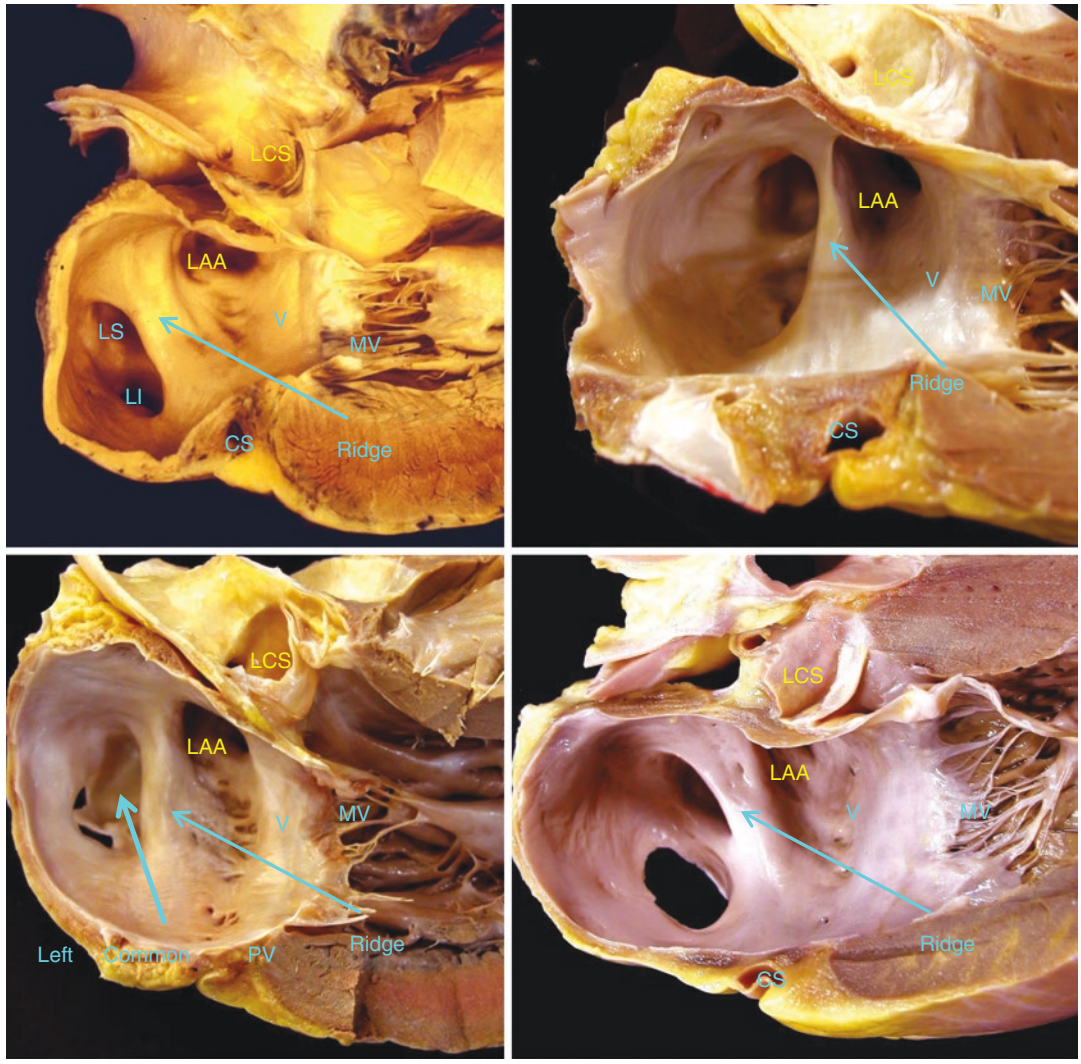


Fig. 8.3 The ridge between the left superior (LS) pulmonary vein, the left inferior (LI) pulmonary vein and the left atrial appendage (LAA). This ridge can vary significantly from being broad and extending anterior to the LS and LI pulmonary veins (top left image) to a more narrow structure (top right image) or may be anterior to a left common pulmonary vein (bottom left) or may be broad and move anterior as it extends inferior so as to have less of a direct relationship with the LI pulmonary vein. Also seen in these images are the mitral valve (MV), the vestibule of the mitral valve (V) and the coronary sinus (CS)

Pulmonary Vein Potentials and Farfield Signals

Electrograms recorded from the ostia of the pulmonary veins show an initial non circumferential lower amplitude atrial signal followed by an isoelectric period and finally, by sharp pulmonary vein potentials (Patel et al. 2003). Depending on the overlap between the left atrium and the surrounding structures as well as the orientation of the mapping catheter there is a variable delay between the farfield electrogram and the pulmonary vein potentials. An example of this is shown in Fig. 8.4 in which the first component is farfield left atrial followed by an isoelectric line followed by a PVP which is a sharp high frequency signal.

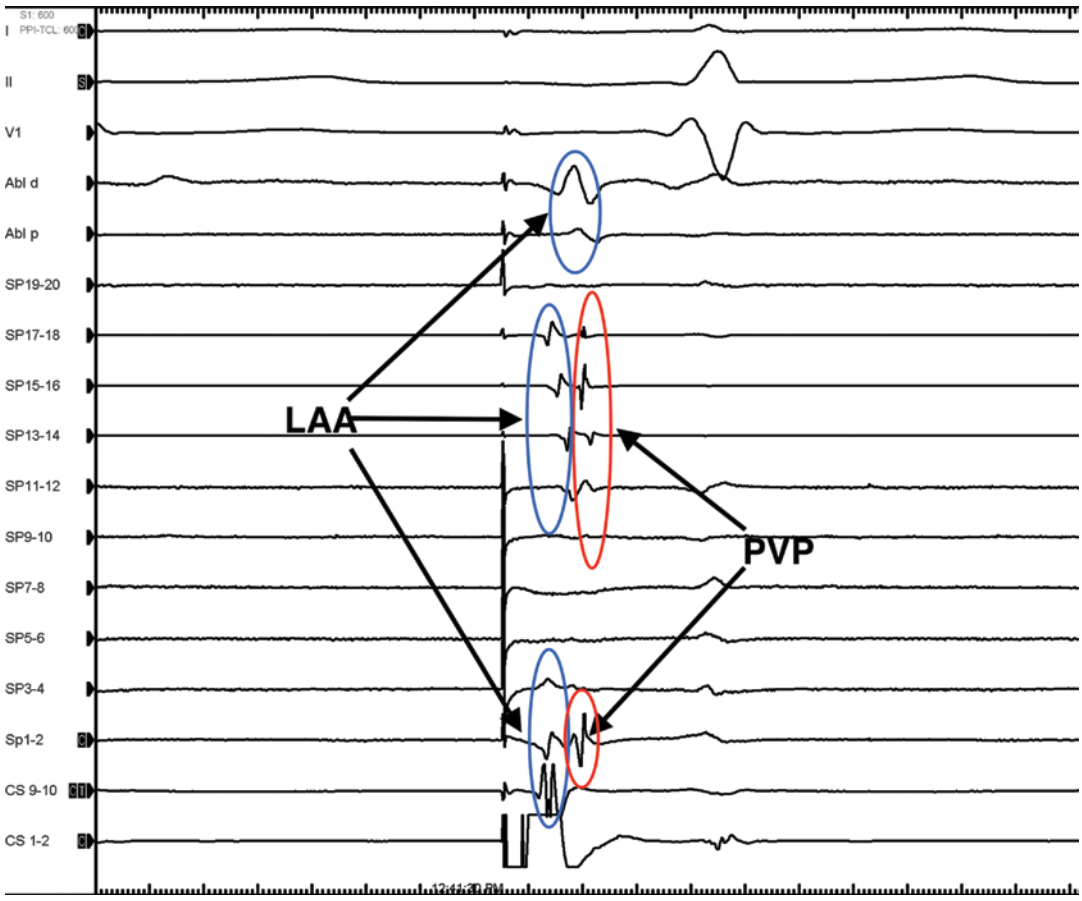


Fig. 8.4 The circular catheter (SP 1–20) is in the left superior pulmonary vein. Pacing is performed from the distal coronary sinus (CS 1–2). The first deflection is farfield from the left atrial appendage (circled in blue) followed by an isoelectric line followed by a sharp pulmonary vein potential (circles in red)

The LAA is anterior to the left superior pulmonary vein. As a result, sharp pulmonary vein potentials can often be merged within LAA signals. In order to separate LAA signals from PV potentials, CS pacing can be used as shown in Fig. 8.4. Additionally, direct pacing may be performed from the LAA. For the left superior and inferior pulmonary veins, pacing from the distal coronary sinus or left atrial appendage can be performed in order to increase the isoelectric line between the farfield and nearfield signals. Although pacing from the distal coronary sinus is reasonably simple, it is somewhat dependent on the variable connections between the coronary sinus and the left atrium. Left ventricular farfield may also be recorded in the left inferior pulmonary vein.

This cannot be performed if the patient is in AF as differentiation of farfield LAA signals from local PV potentials can be somewhat more complex. An example of isolation of the LSPV during AF is shown in Fig. 8.5. In this example the circular catheter is positioned in the LSPV during ablation along the ridge between the LAA and the vein. The earliest activation is recorded on poles 13–14 where ablation is performed. This results in isolation of the vein with farfield LAA potentials being recorded on poles 9–10, 11–12 and 19–20 which are all in anterior locations. Another example of isolation of the RSPV is

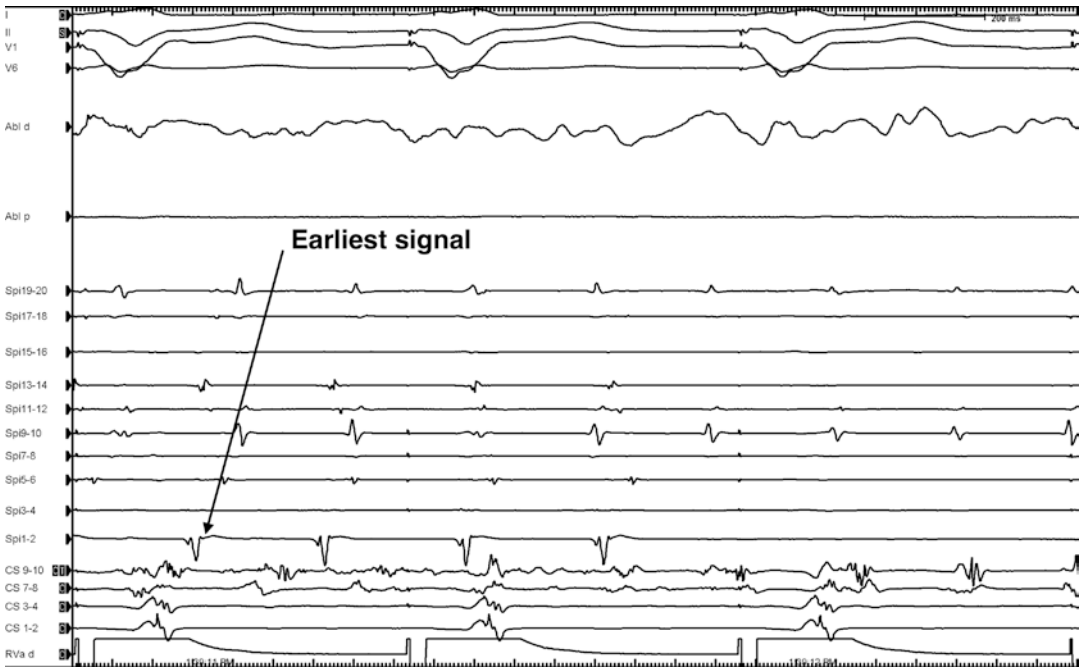


Fig. 8.5 Isolation of the LSPV. The circular catheter is positioned in the LSPV. The earliest nearfield activation is recorded on Spi poles 1–2 followed by 13–14. These poles are almost overlapping and are located along the lower junction between the LSPV and the LAA along the ridge (near to where the ablation catheter is positioned). Ablation in this region results in isolation of the vein with only LAA farfield recorded on the circular catheter. (CS 9–10 is in the proximal coronary sinus and CS 1–2 is in the distal CS). Ventricular pacing from the RV apex is performed as the patient became bradycardic during RF ablation

shown in Fig. 8.6. As ablation is performed, local PVP's in the vein slow considerably and then disappear with only farfield atrial activation recorded.

As shown in the anatomic image in Fig. 8.7, the superior vena cava is anterior to the right superior pulmonary vein. In order to differentiate superior vena cava potentials from pulmonary vein potentials, the signal can be measured relative to the surface p wave. As the superior vena cava is so close to the sinus node, signals will be very early if they originate from the superior vena cava. If this is within 30 ms of the onset of the p wave, it is likely to reflect superior vena cava activity. There is generally no significant farfield recorded in the right inferior PV. The PV potentials recorded on the circular catheter have slowed considerably during ablation. Further ablation results in loss of PV potentials with only farfield atrial signals.

Confirming Pulmonary Vein Isolation

PVI may be confirmed by proving bidirectional block with or without the administration of intravenous adenosine as well as pacing along the ablation line around the pulmonary veins. Of note, **entrance block without exit block may occur in up to 40% of the patients** (Takahashi et al. 2002).

Entrance block may be observed either during normal sinus rhythm or with atrial pacing during sinus rhythm. The circular catheter is positioned in the PV antra just distal to the line of ablation. The most important principle is to distinguish between PV potentials and LA or RA signals detected as farfield on the circular catheter. Although PV potentials are sharp and of a much higher frequency than farfield atrial potentials, they may be superimposed. Pacing the structure or close to the structure where the atrial signals

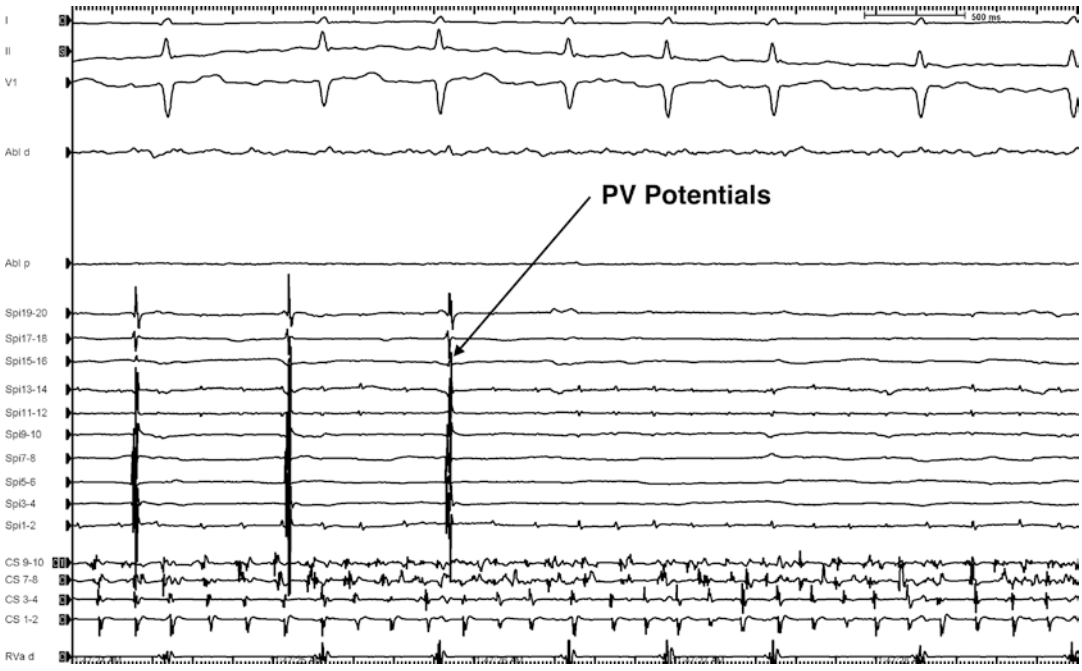


Fig. 8.6 Loss of local PV potentials during isolation of the RSPV. These signals are slowed considerably during ablation and following further ablation only farfield atrial signals are detected. The spiral (Spi) catheter is located in the RSPV. (CS 9–10 is positioned in the proximal coronary sinus and CS 1–2 is located in the distal CS)

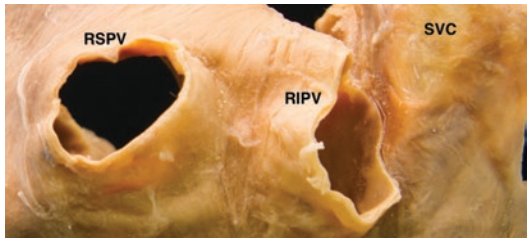


Fig. 8.7 Anatomic specimen showing a posterior view of the right superior pulmonary vein (RSPV) and right inferior pulmonary vein (RIPV). The superior vena cava (SVC) is anterior and close to both of these structures and farfield electrical activity from the SVC may be detected when mapping these veins

are originating from should result in these signals becoming earlier if they are originating from that structure. For potentials coming from the LAA either the LAA can be paced directly or the distal CS if the catheter is positioned appropriately. An example of 2:1 conduction from the left atrium to the LSPV is seen in Fig. 8.8 in which a potential with the vein is recorded after every second atrial electrogram. This represents slow conduction with conduction through SP 3–4, which was positioned posterior to the LSPV. Ablation in this region resulted in isolation of the vein.

In order to prove exit block, the ablation catheter can be positioned in the same pulmonary vein as the circular mapping catheter. Although pacing can be performed from either the ablation catheter alone or the circular catheter alone, it is often easier to discern pulmonary vein potentials from a separate catheter which has closely spaced poles without superimposed pacing artifact. Pacing can be performed using a decremental output until there is only pulmonary vein capture. This avoids capture of adjacent structures, which may mimic intact conduction. Lack of conduction from the pulmonary veins to the left atrium proves that the ablation line is resulting in conduction block. An example of this is shown in Fig. 8.9.

Although the presence of dissociated PV potentials is a useful indicator of exit block, conduction may still be present in 10% of patients

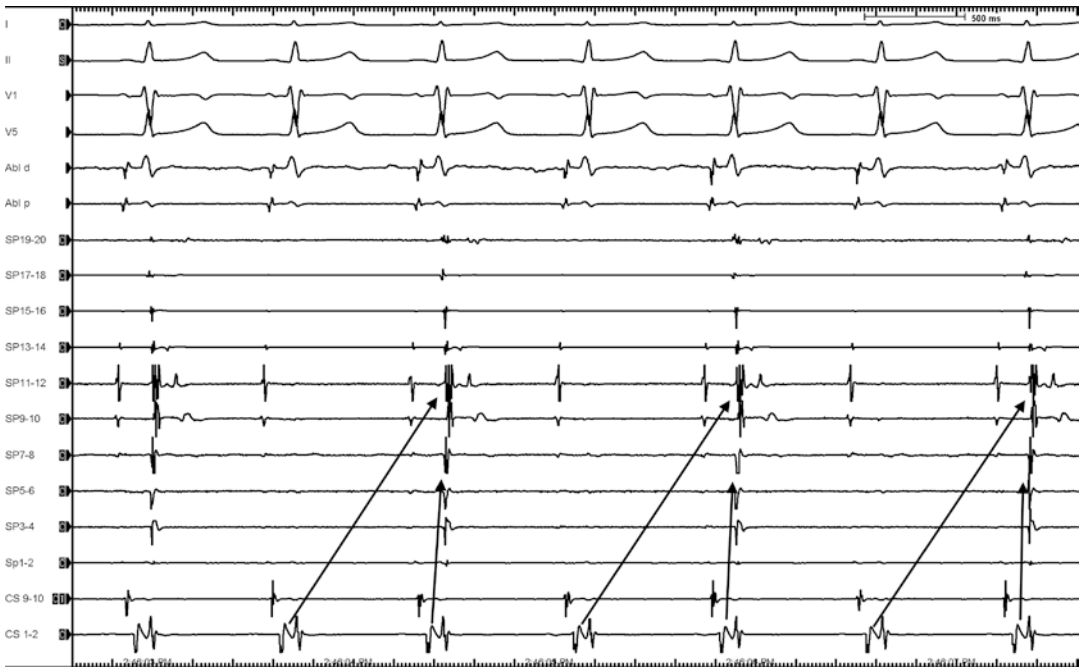


Fig. 8.8 2:1 conduction from the left atrium to the left superior pulmonary vein. A potential is recorded in the vein after every second atrial electrogram. This signified continued conduction in the posterior region of the LSPV (SP 3–4) which required further ablation for isolation of the vein

who display these (Europace 2009). An example of dissociated potentials from the RIPV is shown in Fig. 8.10. Pacing is performed from the high right atrium (HRA). Farfield atrial potentials are seen on the circular catheter with intermittent PV potentials which are not conducted to the atrium.

Another useful technique to help confirm an intact line around the pulmonary veins is to assess for unexcitability to pacing. Following ablation, the catheter is positioned along the line during sinus rhythm at an output of 10 mA and a pulse width of 2 ms (Steven et al. 2013). If lack of local capture occurs, the catheter is moved a further 5 mm along the line and pacing is repeated. If local capture occurred, then further ablation was performed in this region and pacing is performed at the same output.

The administration of intravenous adenosine appears to be of some use in assessing for dormant conduction following isolation of the PV's due to the hyperpolarization of myocytes which have been acutely ablated. This can be administered after a period of monitoring post-ablation whereby further ablation should be performed if there is any evidence of dormant conduction. An example of this is shown in Fig. 8.11.

Assessing for Non PV Triggers

Non pulmonary vein triggers may contribute to AF in some cases and are worth examining particularly in redo ablations where the pulmonary veins have remained isolated. As shown in Fig. 8.12, potential locations include the superior vena cava, coronary sinus, crista terminalis, fossa ovalis, ligament of Marshall and left atrial appendage.

In order to map for non pulmonary vein triggers a multipolar catheter is positioned in the coronary sinus and another along the posterolareral right atrium extending into the superior vena cava. Intravenous isoprenaline is administered in incremental doses from 3 to 20 μg/min. If AF is not inducible, decremental atrial pacing can be performed. Using the earliest sites of activation,

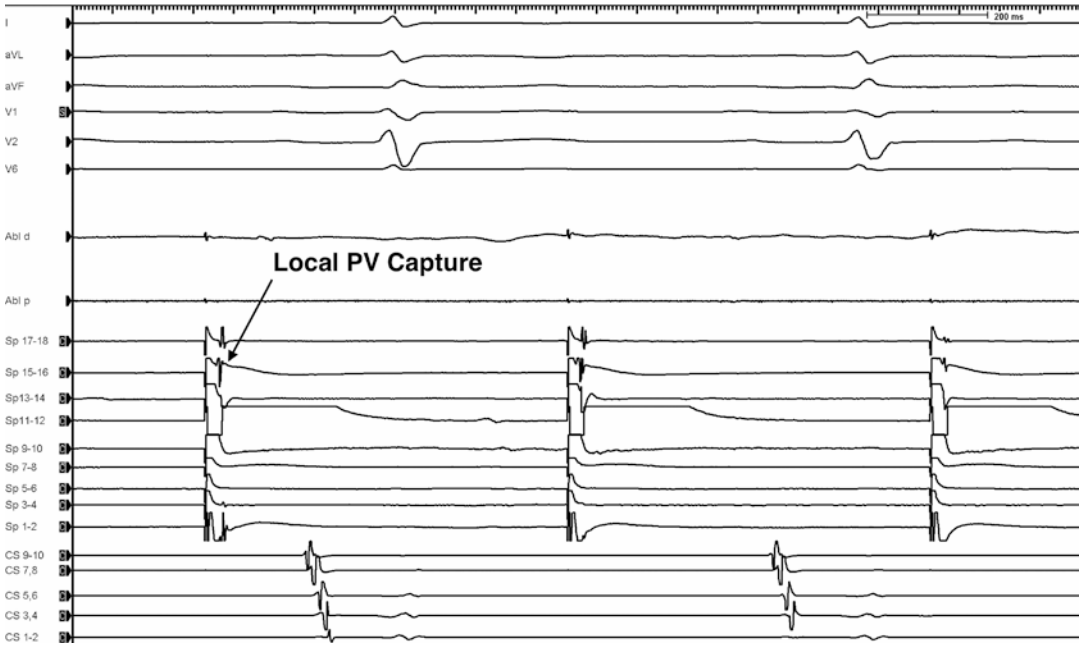


Fig. 8.9 Circular catheter (SP 1–18) in the right superior pulmonary vein with pacing from poles 15–16 showing local capture with sharp local PV potentials which do not capture the left atrium. (CS 9–10 is located in the proximal coronary sinus while CS 1–2 is located in the distal coronary sinus)

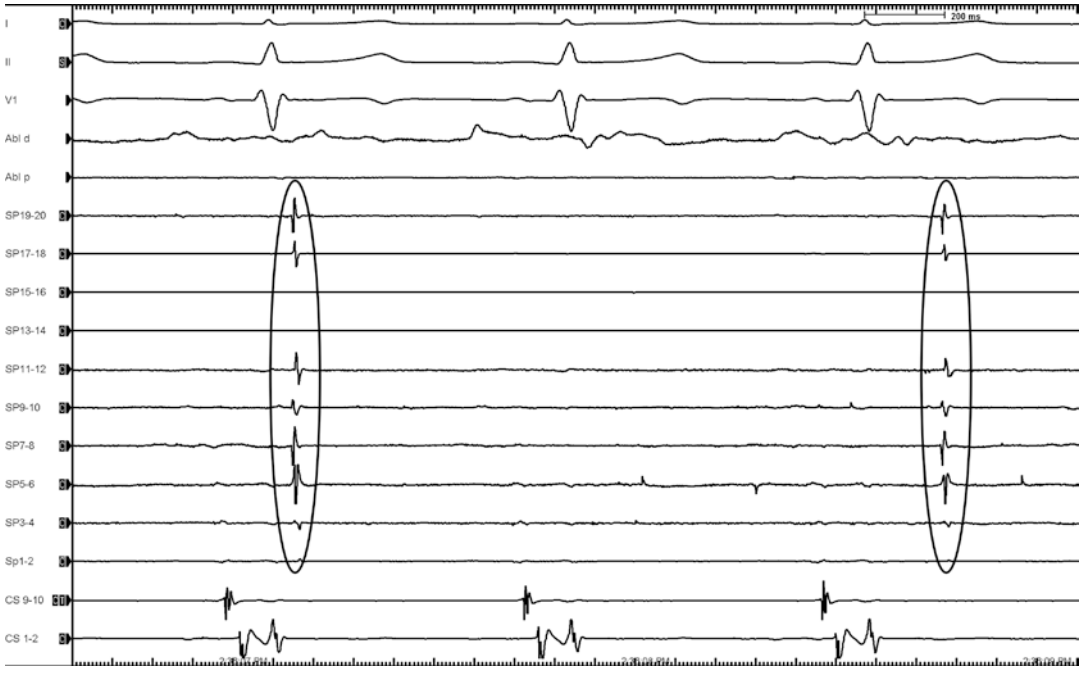


Fig. 8.10 Dissociated PV potentials (circled) recorded on a circular catheter (Sp 1–20) positioned in the right superior pulmonary vein (RSPV). Pulmonary vein potentials are seen which do not conduct into the left atrium. The ablation catheter is positioned in the RSPV. CS 9–10 is in the proximal CS while CS 1–2 is in the distal CS

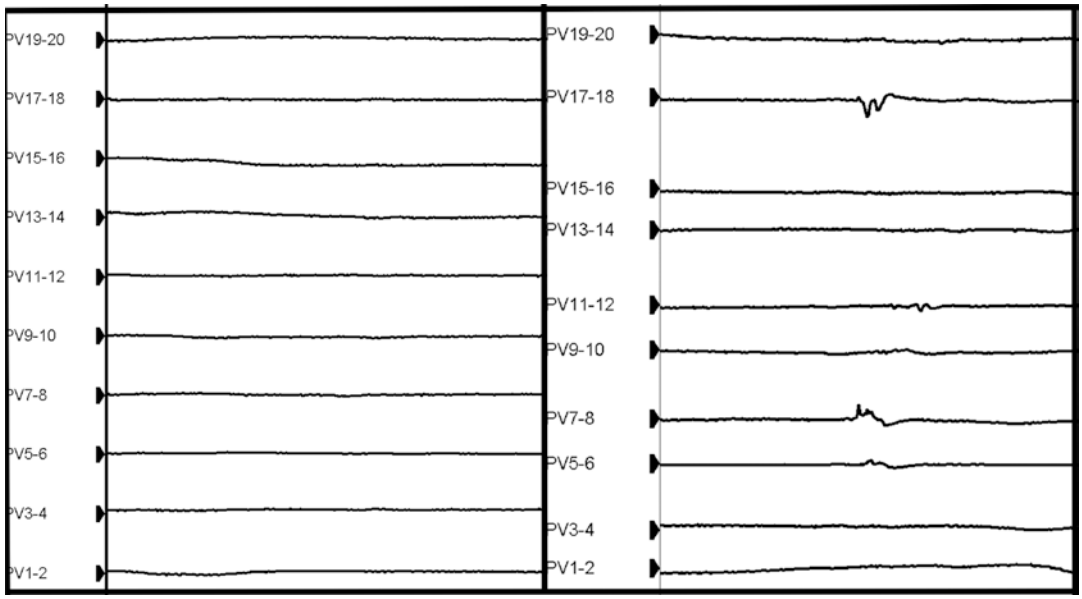


Fig. 8.11 The circular catheter (PV 1–20) is in the right superior pulmonary vein. The image on the right shows the potentials recorded following ablation and before the administration of adenosine. The pulmonary vein appears to be isolated. The image on the right is recorded following the administration of adenosine. This shows early activation in PV 7–8 followed by 5–6, 17–18, 9–10 and 11–12. This region was anterior to the right superior pulmonary vein at the level of the carina. Further ablation was delivered here and the vein was retested with adenosine and found to be isolated

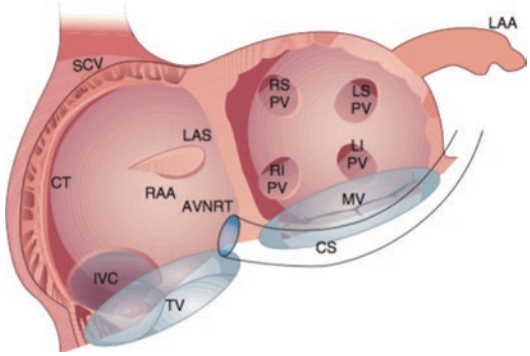


Fig. 8.12 Potential locations of Non-Pulmonary Venous Triggers (*RSPV* right superior pulmonary vein, *RIPV* right inferior pulmonary vein, *LSPV* left superior pulmonary vein, *LIPV* left inferior pulmonary vein, *MV* mitral valve, *CS* coronary sinus, *LAA* left atrial appendage, *LAS* left anterior septum, *RAA* right atrial appendage, *AVNRT* AV nodal re-entry tachycardia, *TV* tricuspid valve, *SVC* superior vena cava, *IVC* inferior vena cava)

focal ablation can be performed and further triggers can then be mapped. Given the increasing width of WACA, many triggers may be incorporated into the original lesions.

Cryoablation

Cryoablation utilizes a system (Arctic Front Cardiac CryoAblation, Medtronic, Inc) which pumps the refrigerant N20 into an inflatable balloon as shown in Fig. 8.13. This is positioned at the PV orifice. Contrast is injected into the PV in order to assess for good contact and applications are generally performed over a period of 4 min. A circular catheter assesses for electrical isolation of the PV's and further applications are performed if required. This procedure generally requires a single transseptal access with a 15 Fr sheath. The balloon is advanced over a guidewire and positioned at the PV ostia. The balloon diameter is available in either 23 or 28 mm. The size can be determined on CT or ICE. Cryoablation has been shown to be non-inferior to point by point RF ablation with regards to freedom from AF and an absence of persistent complications (Luik et al. 2015). The second generation cryoballoon has an inner mapping guidewire and an increased number of emission ports.

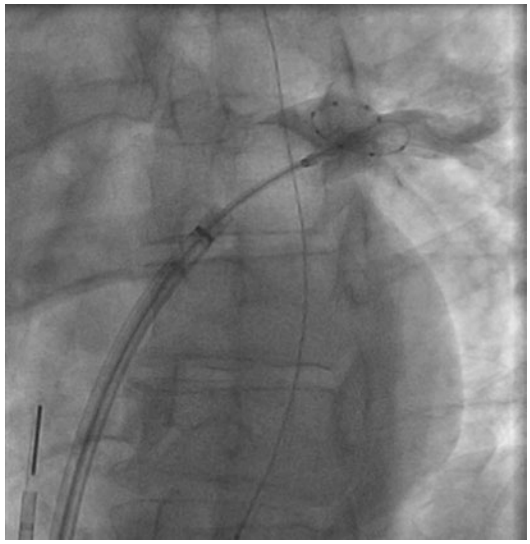


Fig. 8.13 Showing the new generation Cryoballoon used for antral pulmonary vein isolation. On this fluoroscopic image the cryoballoon is positioned in the left superior pulmonary vein. (© Medtronic plc 2015)

Hybrid Ablation of AF

Surgical ablation for AF has evolved from the Cox Maze procedure to a minimally invasive epicardial approach. These methods can be used to deliver RF around the PV antra as well as create a roof and floor line resulting in a posterior box lesion. Although this holds moderate effectiveness in cases of paroxysmal AF, freedom from AF for cases of persistent AF is relatively low due to complex AF propagation patterns which arise from progressive AF modeling. As a result, a hybrid approach combining endocardial and epicardial ablation has been developed. During hybrid ablation, thoracoscopic isolation of the PVs may be confirmed using circular mapping catheters. These endocardial catheters can verify the completeness and transmurality of the epicardial lesions and identify any macro or microreentrant circuits that may be treated through the creation of additional ablation lines. Although endocardial-epicardial ablation can be performed at the same time it is often considered reasonable to delay endocardial ablation for several months in order to assess conduction block after a period of time. This may be a useful option in patients with persistent AF and dilated atria.

Ablation of Persistent AF

Ablation strategies in persistent AF are imperfect. Several techniques have been developed for ablation for persistent AF. Linear lesions may be performed until sinus rhythm is restored or until an electrical cardioversion is performed and the lines checked for conduction block. CFAE ablation may be performed in the left and right atria and rotors ("drivers") may be mapped either invasively or non-invasively and selectively targeted.

Linear Lesions

Following isolation of the pulmonary veins, linear lesions can be performed. The most common of these involve a linear lesion along the left atrial roof joining the right superior pulmonary vein to the left superior pulmonary vein. A mitral isthmus line may also be performed although it may be difficult to achieve successful and permanent block as the wall may be relatively thick and require epicardial ablation via the coronary sinus (at a lower power). Rather than performing linear lesions in all cases of AF, these are often performed in cases where the patient develops an atrial flutter either during the ablation or has a documented history of an atrial flutter which is then induced. In such cases the CTI is often mapped first followed by the pulmonary veins. If these are silent then entrainment in certain anatomic locations can then be performed as well as mapping of local signals. The most common locations to map are the mitral annulus and the LA roof as the majority of macro re-entry atrial flutters involve these regions. If there is a significant variability in the tachycardia cycle length (greater than 15%) then the mechanism is more likely to represent a focal AT. In our experience both a focal AT and a macro re-entry atrial flutter may have a tachycardia cycle length less than

15% and therefore, this may not serve as a reliable discriminator.

Roof Dependent Left Atrial Flutter

In order to map roof dependent left atrial flutter, the catheter is positioned anterior to the roof and then more inferiorly close to the anterior mitral annulus. This is repeated by positioning the ablation catheter along the roof in the posterior direction and then towards the coronary sinus which generally marks the general direction of the posterior mitral annulus. If the activation is in the reverse direction (i.e. earlier inferior than superior on the anterior wall and earlier superior to inferior on the posterior wall or vice versa), this is likely to be a roof dependent atrial flutter. If entrainment is performed in the anterior and posterior regions of the roof, then a PPI-TCL <30 ms further helps to confirm roof dependent atrial flutter. In the setting of a prior roof line or PVI with WACA mapping of fractionated potentials in the region of the roof is also helpful. An example of an activation map of roof dependent atrial flutter is shown in Fig. 8.14.

A roof line connecting the LSPV and the RSPV should be performed in the setting of a macro re-entry atrial tachycardia circulating around the PV's and involving the roof. In order to perform this, the sheath is directed towards the right superior pulmonary vein while the catheter is flexed over to the left superior PV. Using 30–35 W the catheter flexion can then be slowly released staying at each point for approximately 30–60 s. A superior and a PA view help to ensure that the line is performed along the roof rather than the posterior wall. In order to evaluate the roof line, the LAA is paced during sinus rhythm. Roof line block is demonstrated by the presence of double potentials along the line during pacing as well as caudocranial activation of the posterior wall.

Mitral Isthmus Dependent Atrial Flutter

This is a relatively common cause of post PVI atrial arrhythmias and generally occurs as a result of slow conduction inferior to the LIPV from a prior mitral isthmus ablation or PVI. With this arrhythmia, CS activation is either proximal to

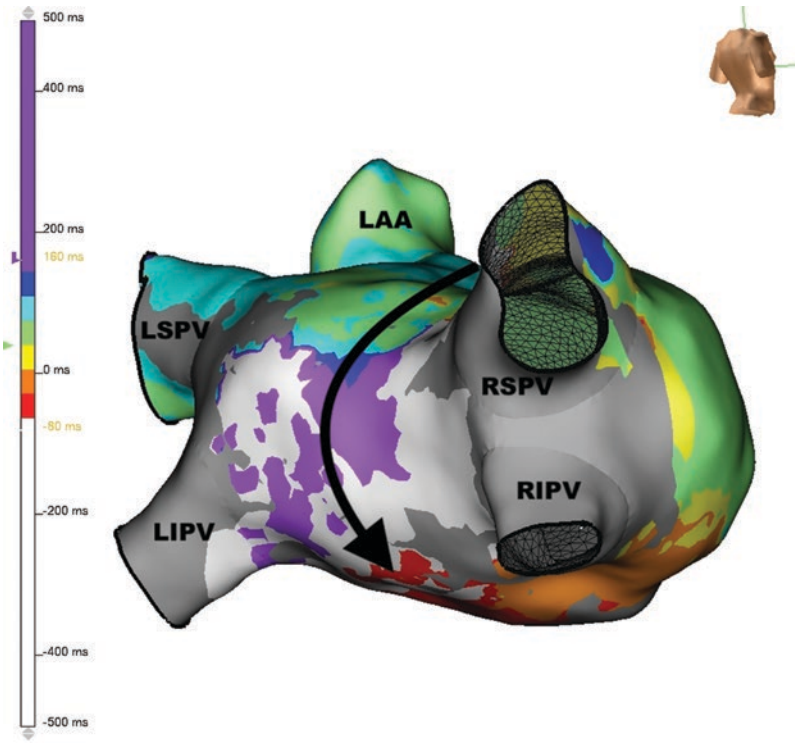


Fig. 8.14 Activation map of roof dependent atrial flutter showing propagation of early (white) at the inferior posterior wall of the left atrium to red, yellow, green indigo, navy and then purple which is the latest region (*LSPV* left superior pulmonary vein, *LIPV* left inferior pulmonary vein, *LAA* left atrial appendage, *RSPV* right superior pulmonary vein, *RIPV* right inferior pulmonary vein)

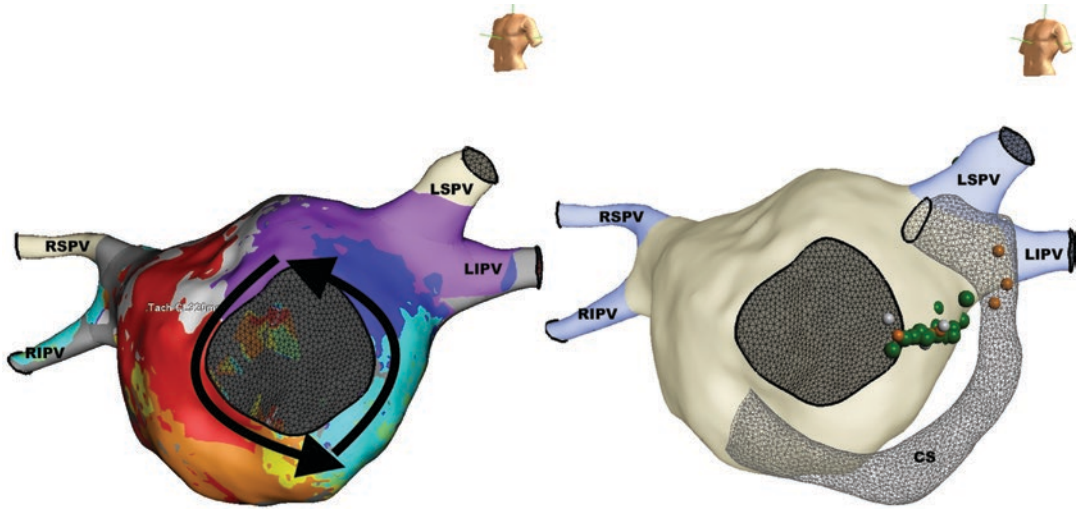


Fig. 8.15 Activation map (left image) showing counter-clockwise mitral isthmus atrial flutter with endocardial ablation (green lesions on right image) and epicardial ablation (brown lesions) within the coronary sinus (CS) resulting in termination of mitral isthmus dependent atrial flutter with block along the line of ablation (*RSPV* right superior pulmonary vein, *RIPV* right inferior pulmonary vein, *LSPV* left superior pulmonary vein, *LIPV* left inferior pulmonary vein)

distal or distal to proximal. It is useful to use the ablation catheter to map the anterior mitral annulus. If CS activation is proximal to distal then anterior activation should be from lateral to septal. If the CS activation is distal to proximal, then the anterior mitral annular activation should be from septal to lateral.

A posterior mitral isthmus line may be performed which connects the LIPV to the posterior mitral annulus close to the coronary sinus. A deflectable sheath is used and the ablation catheter is positioned at the ventricular side of the lateral mitral annulus with an AV ratio of either 1:1 or 2:1 (Jais et al. 2004).

During proximal CS pacing the catheter and sheath are then rotated clockwise towards the left inferior PV with delivery at 30 W for 90–120 s applied at each location. The catheter is moved whenever there is splitting of the local electrograms. The mitral isthmus varies in thickness along its length being thinner at the annular end and thicker at the medial end.

In order to prove block for a posterior mitral isthmus line, pacing is performed from the CS and activation is measured in the LAA. Normally pacing from the distal CS should result in a shorter conduction time to the LAA than pacing from a less distal pole. In the event of posterior mitral isthmus block the more distal location will take longer to travel to the LAA. The presence of double potentials along the entire ablation line with coronary sinus pacing is also a useful endpoint. As shown in Fig. 8.15 ablation sometimes has to be performed at 20 W from the coronary sinus in order to block epicardial activation. An alternative approach is to perform an anterior mitral isthmus line joining the anterior mitral annulus to the LSPV.

CFAE Mapping and Ablation

CFAE's are defined as local electrograms which are fractionated with at least two components and with cycle lengths less than 120 ms recorded during AF and lasting for at least 10 s (Nademanee et al. 2004). These are frequently recorded during AF within the regions of the LA close to the pulmonary vein antral regions and therefore may be ablated and electrically isolated during a pulmonary vein isolation.

In persistent atrial fibrillation, CFAE's may be located anywhere within the left and right atrium with a propensity for the septum, inferoposterior wall of the LA and the LAA.

There are various theories as to what CFAE's actually represent with suggestions such as anchor points in rotors, regions of conduction slowing or autonomic activation. The long-term results of CFAE ablation are not impressive and certainly this does not appear to represent a very effective strategy for the treatment of persistent AF.

Re-Entry Mapping

A rotor is defined as an unexcited core, termed a phase singularity, resulting in reverberations which radiate at very high velocity into the surrounding tissue (Pandit and Jalife 2013). Phase singularities are surrounded by different phases of the cardiac action potential and may be considered useful targets for ablation as they may be considered regions of tissue which can support rotors. They may occur on the endocardium, mid myocardium or epicardium or indeed span all layers. The theory is that following initiation of atrial fibrillation from PV and non-PV sources, rotors result in maintenance of atrial fibrillation.

Rotors differ from re-entry circuits in several ways. In a rotor, the core is the active component with secondary spiral activity. The rotor core is functional and does not appear to be related to a detectable structural obstacle. Rotors are not stationary and may move over a considerable area (Narayan et al. 2013a). Spiral waves also collide with each other altering the overall activation pattern. Additionally, there does not appear to be a close correlation between rotors and CFAE's (Narayan et al. 2013a).

Some of these features actually make mapping of rotors very complex. Rotor activation is complex, can change during the mapping process and may involve different regions of the endocardium, myocardium and epicardium. There are currently two systems which may be used for mapping rotors. These involve either invasive mapping using a multi-electrode basket catheter called the Focal Impulse and Rotor Modulation system and a non-invasive multi electrode vest which is superimposed on a cardiac CT.

Focal Impulse and Rotor Modulation of Atrial Fibrillation

This system uses a 64-electrode basket with eight splines which is positioned in either the right, left or both atria as shown in Fig. 8.16. If the patient is in atrial fibrillation the unipolar electrograms are recorded and exported for analysis. If the patient is in sinus rhythm, atrial fibrillation is induced with rapid atrial pacing and the signals are then recorded and analyzed after 10 min of sustained atrial fibrillation. It is critical that there is excellent electrode contact. The correct size of basket should be chosen, and this may prove to be difficult in larger atria. Catheter orientation should be optimized on fluoroscopy and with the aid of a 3-D mapping system in order to record vital areas of the left atrium including the pulmonary veins and the left atrial appendage as well as septal, roof, anterior and posterior activity.

The signals are then processed using RhythmView™ (Topera Inc.). This system is based on restitution monophasic action potential data acquired during rapid atrial pacing and atrial fibrillation. This displays the activation signals on a 2-dimensional image where the operator can then visualize potential rotors or focal sources. The image of each atria is opened so that for the right atrium the tricuspid annulus is inferior with the septal component to the right of the image and the lateral component to the left. For the left atrium the mitral annulus is at the bottom of the image and is divided. The electrodes of interest where a rotor core is believed to exist can then be referenced off an electroanatomic system and ablation can then be performed.

It has been shown that focal sources and rotors may be recorded in almost all patients with atrial fibrillation. Approximately one third of these can be recorded in the right atrium (Narayan et al. 2012), and more than one half of all rotors are recorded outside of the regions where a wide area circumferential ablation would be performed (Narayan et al. 2013b). Results suggest that the addition of ablation of rotors using this technique

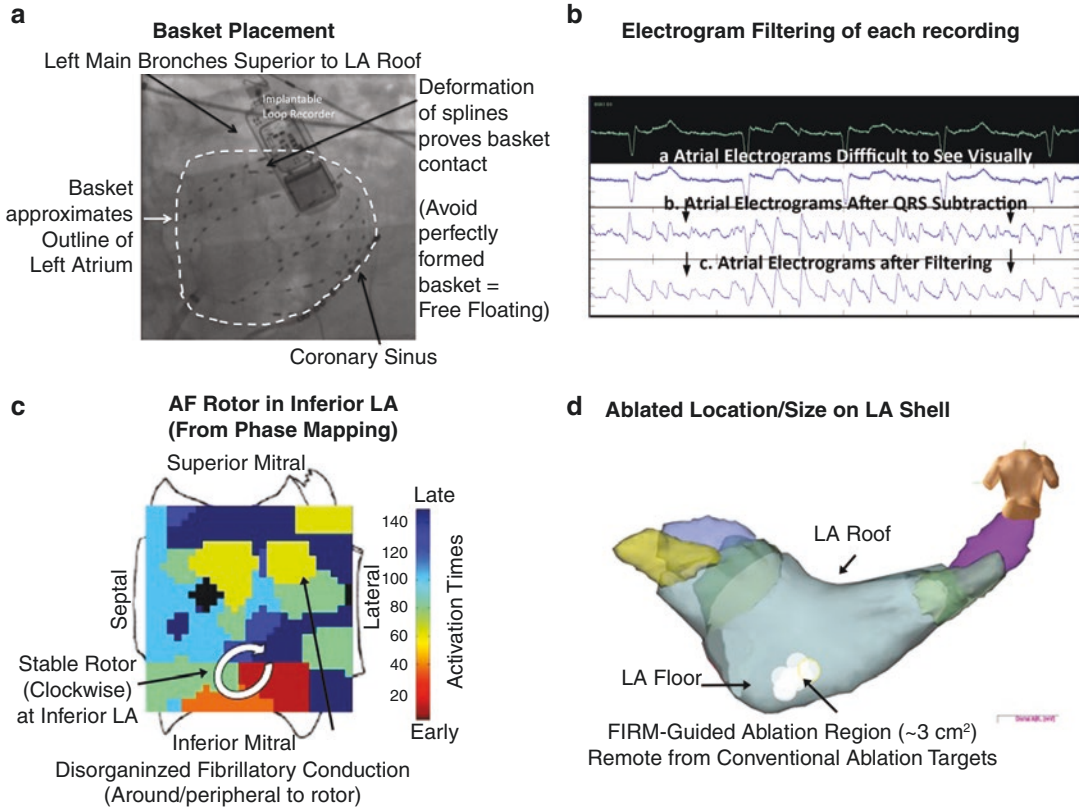


Fig. 8.16 Approach to FIRM (Focal Impulse and Rotor Mapping) Guided Ablation of Atrial Fibrillation. (Courtesy of Dr. Sanjiv Narayen). (**a**) **Baskets placed in left atrium (shown)** and also in right atrium to map both chambers sequentially. Good positioning results in deformation of the highly compliant basket, proving electrode contact, and splines that approximate the LA roof and floor. In contrast, a spherical shape when deployed indicates an undersized basket with poor contact. (**b**) **Electrogram filtering** using well-established methods enables detection of atrial signals which are sometimes difficult to identify visually. (**c**) **Rotor during human AF in left atrium**, revealed by spatial phase mapping of filtered atrial electrograms, depicted as clockwise 'snapshot' (isochrone) where early and late activation meet, surrounded by fibrillatory disorganization. Phase mapping is used since activation mapping during dynamically changing activation in AF is challenging. Intraprocedurally, diagnosis is actually made from animated 'FIRM movies" which better convey rotor precession and their dynamic interaction with the fibrillatory milieu. (**d**) **FIRM-guided ablation zone,** in inferior left atrium guided by map, typically of ≈3 cm^2 areas

increases the success when compared with pulmonary vein isolation alone.

Non-Invasive Multi Electrode Mapping

Using this technique a 252 electrode vest (CardioInsight, © Medtronic plc 2015) is applied to the patient during AF. This is used to record unipolar surface potentials. Anatomic data is then acquired by performing a noncontrast cardiac CT with the vest in place so that each electrode position can be calculated relative to the cardiac chambers. The system then performs a calculation in order to calculate and display electrical data on the surface of the heart from the surface unipolar electrograms. Activation sequences are then calculated by looking at the most negative dV/dT. This can then be displayed on a 3-D reconstruction of the right and left atria using colors to animate various phases of depolarization

and repolarization as shown in Fig. 8.16. This can be analyzed for focal sources as well as rotors. There are several advantages of this system since it simultaneously maps both atria and therefore can help to differentiate between active rotors and passive activation. It also does not rely on contact to record the electrograms. Given that data is acquired prior to an ablation there may be a question of changes in activation or changes related to the ablation itself.

Important Points to Remember

1. AF is classified as paroxysmal, persistent, longstanding persistent or permanent. Paroxysmal AF is defined as two or more episodes of AF each of which terminate within 7 days and commonly within 24 h. Persistent AF is sustained generally for greater than 7 days (or less if a cardioversion was performed in this time) and requires chemical or electrical cardioversion for termination of the arrhythmia. Longstanding persistent refers to cases in which AF has been present for more than 1 year and previously may have been designated as being permanent; however, an electrical cardioversion or ablation strategy is being pursued and therefore sinus rhythm may be achieved. Permanent AF also continues for more than 7 days and cannot be terminated anymore thus a rhythm control strategy has been unsuccessful or is not appropriate.
2. The main cardiovascular causes of AF are hypertension, coronary artery disease and valvular heart disease. Metabolic causes of AF include thyroid dysfunction and diabetes mellitus while lifestyle risk factors include obesity, excessive alcohol and obstructive sleep apnea. AF is frequently seen in an acute setting in post operative patients as well as those who have infection, or in association with pulmonary embolism, pericarditis and myocarditis. AF may also occur in association with other supraventricular arrhythmias, such as AV nodal re-entry tachycardia, AV re-entry tachycardia and atrial flutter.
3. PVI is considered to be a reasonable strategy in patients with paroxysmal AF in whom medication has been ineffective, poorly tolerated or in cases of patient preference. This may be performed using a point-by-point technique or a ‘single shot’ device. PVI may also be useful in patients with persistent AF as a method of isolating the potential triggers.
4. Electrograms recorded from the ostia of the pulmonary veins show an initial non circumferential lower amplitude atrial signal followed by an isoelectric period and finally by sharp pulmonary vein potentials. Depending on the overlap between the left atrium and the surrounding structures as well as the orientation of the mapping catheter there is a variable delay between the farfield electrogram and the pulmonary vein potentials. For the LSPV and to a lesser degree the LIPV, farfield electrograms from the LAA may be recorded. These can be separated from the PV potentials by pacing from the LAA or the distal CS. For the RSPV farfield electrograms may be recorded from the SVC. If the signal is within 30 ms of the onset of the p-wave then these are likely to represent SVC farfield.
5. Entrance block may be observed either during normal sinus rhythm or with atrial pacing during sinus rhythm. The circular catheter is positioned in the PV antra just distal to the line of ablation.

6. In order to prove exit block the ablation catheter can be positioned in the same pulmonary vein as the circular mapping catheter. Although pacing can be performed from either the ablation catheter alone or the circular catheter alone it is often easier to discern pulmonary vein potentials from a separate catheter which has closely spaced poles without a superimposed pacing artifact.
7. An additional useful technique to help prove an intact line around the pulmonary veins is to assess for unexcitability to pacing. Following ablation, the catheter is positioned along the line during sinus rhythm at an output of 10 mA and a pulse width of 2 ms. If lack of local capture occurs the catheter is moved a further 5 mm along the line and pacing repeated. If local capture occurred, then further ablation was performed in this region and pacing performed at the same output.
8. In some cases, non pulmonary vein triggers may contribute to AF. Potential locations include the superior vena cava, coronary sinus, crista terminalis, fossa ovalis, ligament of Marshall and left atrial appendage.
9. Post-PVI atrial arrhythmias may involve the CTI, gaps around the PV's, the mitral annulus or the LA roof. Activation mapping using the ablation catheter relative to a stable CS electrogram may help to distinguish these.
10. Newer mapping techniques including the potential mapping of rotors may help to further understand the mechanism for AF.

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