Chapter 5

Implanted Devices and Atrial Fibrillation

Federico Guerra, Michela Brambatti,
Maria Vittoria Matassini and Alessandro Capucci

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/47449

1. Introduction

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function. On the electrocardiogram (ECG), AF is characterized by the replacement of consistent P waves with rapid oscillations or fibrillatory waves associated with an irregular ventricular response. AF is the most common arrhythmia in clinical practice: its prevalence varies from 0.4% to 1% in the general population and increases with age, reaching 8% in patients older than 80 years [1]. AF may occur in a temporary causing condition setting, such as acute myocardial infarction, cardiac surgery, pericarditis, myocarditis, hyperthyroidism and pulmonary embolism, or in association with underlying cardiac disease such as valvular disease, coronary artery disease, hypertensive cardiomyopathy and others cardiomyopathies, especially those associated with left ventricular dysfunction and heart failure (HF). AF may also occur in younger patients without underlying cardiovascular disease and it is often referred to as "lone AF". AF may develop in isolation or in association with other tachyarrhythmias, most commonly atrial flutter or atrial tachycardia, or bradyarrhtythmias especially due to sinus node dysfunction [1].

Atrial fibrillation is very common in pacemaker recipients because of the wide range of conditions that could require device implantation and promote AF development.

1.1. Patients implanted with dual chamber pacemaker

Paced patients could develop AF for several reasons. On average, half of patients with dual chamber pacemaker have sinus node disease (SND) that is in turn associated with the development of AF in 20-50% of patients, defining the clinical picture of bradycardia-tachycardia (brady-tachy) syndrome [2,3]. Moreover, nearly one third of all patients with complete atrioventricular (AV) block also shows tachy-brady syndrome. Right ventricular (RV) pacing has been demonstrated to increase the risk of developing AF in patients with

permanent pacemaker implantation for both SND or AV block [4,5], because of its association with a number of pathophysiological changes which reduce left ventricular function and may promote AF. These changes include: an abnormal activation sequence (intraventricular and interventricular dyssynchrony), depressed left ventricular ejection fraction (EF), diastolic abnormalities and reduced myocardial perfusion [6]. As in general population, in paced patients aging is associated with a higher prevalence of AF, irrespectively of the pacing mode.

1.2. Patients implanted with Implantable Cardioverter Defibrillator (ICDs)

AF is particularly common in patients with left ventricular dysfunction and its prevalence depends on the severity of the underlying pathology. Prevalence is usually 10%-20% in mild to moderate HF, and up to 50% in patients with more advanced disease [7]. Therefore, AF is frequent in ICD recipients, the vast majority of whom have structural heart disease. Approximately 25% of patients who receive an ICD have documented atrial tachyarrhythmias before implantation. Furthermore, a large proportion of patients without prior history of atrial tachyarrhythmias will develop AF after ICD implantation. AF occurs in about 25% of the patients with secondary prevention indication while its prevalence in patients with primary prevention indication is more difficult to define. Prevalence seems to be higher in patients with left ventricular dysfunction due to non-ischemic etiology (ranging from 15% to 25%), and lower in patients with ischemic cardiomyopathy (about 5-10%). Management of atrial tachyarrhythmias in patients with ICDs is important because of the increased morbidity and mortality and the increased cost of medical care.

1.3. Patients implanted with Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT) has emerged as an important and established therapy for patients with end-stage drug refractory HF due to systolic dysfunction and cardiac dyssynchrony. Several clinical trials have demonstrated the efficacy of CRT; however, the vast majority of patients included in all major trials were in sinus rhythm (SR) [8,93]. The low prevalence of AF patients in these trials is justified for several reasons. First, patients with AF are usually patients with more comorbidities and therefore less likely to be included in a clinical trial. On the other hand, in the absence of atrioventricular node ablation, AF reduces the likelihood of obtaining adequate pacing percentage and introduces a reasonable element of confusion when interpreting study results. Daily clinical practice is however quite different: approximately one-fifth of all patients receiving CRT in Europe has permanent AF, as reported in a recent ESC survey [9]. Patients suffering from AF are typically older, more likely to receive a CRT with pacemaker function (CRT-P), and have higher morbidity and mortality rates than patients in SR.

2. International recommendations for pacemaker and defibrillator implants in AF patients

Implantable devices are being commonly used for patients with AF. First of all, AF can occur in patients with SND. In SND, a wide range of cardiac arrhythmias such as sinus

bradycardia, sinus arrest, sinoatrial block and junctional rhythm, often coexist with concomitant episodes of supraventricular tachyarrhythmias, generally AF. This peculiar clinical entity is also called brady–tachy syndrome. AF is often triggered by sudden deceleration in heart rate, sinus arrest and, in other cases, by long-short cycle sequence induced by extrasystoles. Sometimes a prolonged sinus arrest or severe bradycardia may follow the end of AF and this phenomenon is probably due to the prolonged suppression of sinus node induced by tachyarrhythmia. Patients with SND may be symptomatic for both bradyarrhythmias (fatigue, exercise intolerance, dizziness, syncope or pre-syncope) and tachyarrhythmia (palpitations, dyspnea, angina, heart failure). In these clinical situations, the implantation of a pacemaker may be necessary in order to prevent AF recurrence and control the symptoms related to bradyarrhythmia. Cardiac pacing can also facilitate the use of optimal dosages of antiarrhythmic drugs, thus preventing the bradycardia induced by the drugs themselves. Moreover, the activation of rate-responsive and dedicated algorithms can increase the benefits of antiarrhythmic atrial stimulation especially during exercise.

Permanent AF with low ventricular rate is another important clinical condition requiring pacemaker implantation. The degenerating process culminating into long-standing AF may be associated to a spontaneous disturbance of the atrio-ventricular conduction or it could be due to a scarce adherence to therapy. In this instance, the implantation of a single-chamber rate-responsive PM is indicated in presence of symptoms, such as fatigue, dizziness, presyncope, syncope or heart failure.

In patients with permanent or paroxysmal AF, in which adequate control of ventricular rate cannot be achieved with drug therapy, device implantation may be also beneficial. Patients with symptoms related to rapid ventricular rates during AF require prompt medical management, and cardioversion should be considered if symptomatic hypotension, angina, or HF occurs. A sustained, uncontrolled tachycardia may lead to deterioration of ventricular function, the so-called tachycardia-induced cardiomyopathy, which tends to resolve within 6 months of rate or rhythm control. When tachycardia recurs, LV ejection fraction declines faster and HF develops over a shorter period. In this case, when pharmacologic antiarrhythmic treatment fails, atrioventricular junction ablation and pace-maker implantation and substrate catheter ablation are reasonable non-pharmacologic alternatives. A meta-analysis of 21 studies published between 1989 and 1998 that included a total of 1181 patients concluded that AV nodal ablation and permanent pacemaker implantation significantly improved cardiac symptoms, quality of life, and healthcare utilization for patients with symptomatic AF refractory to medical treatment [10].

The last issue concerns AF patients eligible to CRT. The European Society of Cardiology guidelines were the first to include patients with AF between the candidates for CRT in 2007 [11], and were recently revised and updated [12]. Nowadays, it is reasonable to implant a CRT-P in patients with LVEF≤35%, QRS duration≥130 ms and NYHA III-IV despite optimal pharmacological treatment with level of evidence B for patients dependent on ventricular pacing and C for those with slow ventricular response who are expected to achieve an adequate percentage of biventricular pacing.

3. Pacemakers and ICDs in detecting AF

3.1. Definition, prevalence and prognosis of asymptomatic AF

AF can manifest itself through symptoms or it can be silent and consequently subclinical. The true prevalence of AF is dependent upon the method used for the diagnosis of this arrhythmia [13]: in general, current data showed an increased AF detection rate with longer monitoring durations. Twelve leads electrocardiogram controls are not very sensitive, detecting less than 30% of all AF episodes [14], whereas more AF paroxysms can be unmasked by using Holter recordings, telemedicine techinques, and loop recorders. Implanted devices, whether pacemakers or ICDs, further enhance the diagnostic yield of asymptomatic atrial arrhythmias by providing continuous rhythm monitoring.

In a study of patients with paroxysmal AF and conventional indication for permanent pacemakers, Israel et al. found that more than one third of all device documented AF of at least 48 hours duration were asymptomatic [15]. A multicenter study on pacemaker diagnostics also reported a high incidence of atrial arrhythmia in the pacemaker population, with atrial high rate episodes (AHRE) documented in 89% and 46% of patients with and without prior history of atrial tachyarrhythmia by 24 months of follow-up, respectively [16]. This study demonstrated that patients with prior history of atrial arrhythmia had higher arrhythmia burden and, again, most device-detected AHRE were asymptomatic.

However, silent AF and symptomatic AF share exactly the same risk for cardiovascular death and cardiovascular events [1]. A major concern with the onset of AF that progresses without any symptoms is the risk of cerebral embolism, with acute stroke its first manifestation. In about 25% of patients who have ischemic strokes, no etiologic factor is identified but subclinical AF is often suspected to be the cause. In the AFFIRM trial, which tested rate control versus rhythm control, stroke occurred in both groups, particularly in patients among whom anticoagulants were discontinued on the assumption that sinus rhythm was successfully maintained [17]. Recently, the ASSERT study found that pacemaker patients who have no history of atrial tachycardia AT or AF, but do have device-detected arrhythmias, are approximately 2.5 times more likely to have a stroke than patients who do not have device-detected arrhythmias [18]. Nevertheless, it is currently unknown if treatment of asymptomatic episodes detected by the device should be the similar to what already recommended for symptomatic AF.

Another relevant aspect related to the absence of symptoms is the development of atrial remodeling. Intermittent asymptomatic AF episodes can cause changes in the electrophysiological and histological matrix of the atria, thereby facilitating the creation of appropriate conditions for degenerating AF into permanent type.

3.2. Usefulness of implanted device in AF detection – New diagnosis, relapse monitoring, event recording, fibrillation burden and rate-control

All implanted devices (pacemakers, ICDs and CRTs) including loop recorders are capable of identification, recording and transmission of electrocardiographic data. Among all the data

available, a modern device can store total number of episodes, time of onset and duration of each episode, the overall burden of arrhythmia and the ventricular electrocardiogram morphology (VEGM) associated with each detected episode. These continuous monitoring modalities have improved knowledge into the characteristics of AF.

As previously underlined, implanted devices are useful to detect new episodes of AF. Ricci et al. detected AF in 42 of 166 patients using implanted pacemakers or ICD over a period of 18 months. Interestingly enough, AF was not known before device implantation in more than half of these patients [19].

In patients without a definitive device implant indication implantable leadless loop recorders may be useful in order to detect AF and quantify its burden. The XPECT trial tested an AF detection algorithm incorporated into an implantable leadless loop recorder against traditional monitoring through 48-h ECG Holter [20]. The results of this study indicated a higher sensitivity of loop recorder for detecting AF. However, specificity was limited by falsely stored AF episodes in 15% of the patients. In addition, continuous monitoring can contribute to better therapy management, through better rate control therapy or monitoring of rhythm control especially after catheter ablation. In the latter case, continuous assessment of freedom from tachyarrhythmia recurrences may lead to discontinuation of oral anticoagulation after a successful procedure in selected patients.

3.3. Supraventricular tachycardia or ventricular tachycardia? Discriminating algorithms in modern devices

The MADIT-II, SCD-HeFT, and MUSTT trials indicate that ICD therapy improves survival with a significant reduction in mortality [21-23]. However, nearly half of all shocks experienced by ICD patients are inappropriate, an outcome resulting in poorer quality of life, pain, psychological distress, shorter battery life and device-induced arrhythmias. To reduce inappropriate therapy of supraventricular tachycardia (SVT), ICDs include algorithms engineered to discriminate ventricular tachycardia (VT) from SVT. Programming of discrimination algorithms varies from single chamber to dual chamber ICDs, and should be tailored according to the patient's specific needs, comorbidity and previous history of SVT such as paroxysmal AF.

3.3.1. Single-Chamber SVT-VT discriminators

Most single chamber devices currently include four elements into detection algorithms: RR onset, RR stability, VEGM and sustained rate duration. RR onset is based on the evidence of abrupt onset present in most VT, in contrast to the gradual onset of sinus tachycardia. It has high specificity for rejecting sinus tachycardia but may prevent detection of VT that originates during SVT and VT that starts abruptly with an initial rate below the VT detection rate.

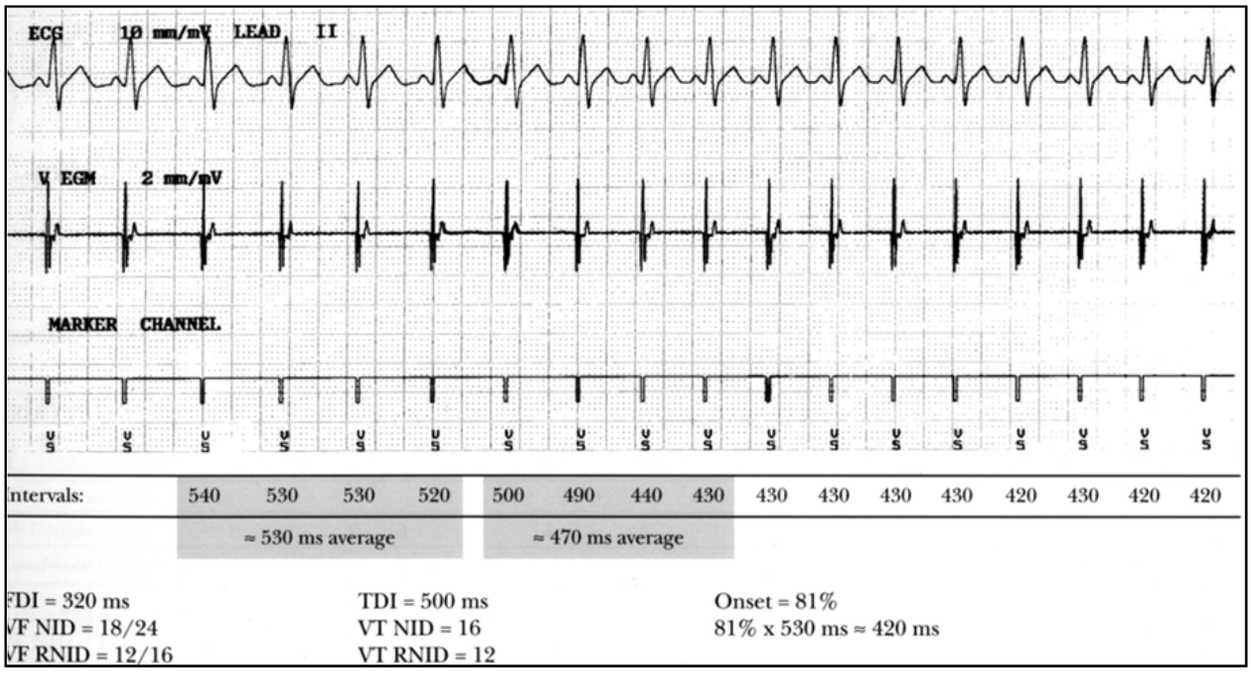

Figure 1. This particular RR onset algorithm analyses eight beats and compares mean ventricular rate of last four beats to mean ventricular rate of first four beats. If the ratio is over a pre-specified cut-off then the device recognises the tachycardia as VT.

RR stability discriminates monomorphic VT from AF based on regularity of the RR interval. The criterion depends on the analysis of cycle length variations and is continuously active during an episode; hence, when programmed "on", the stability algorithm withholds therapy despite ventricular rates in the tachycardia zone if the cycle length intervals are irregular. For most VT, the measured stability or the variation between RR intervals is<21 ms, as opposed to AF, where typically varies by 35–50 ms. Unlike onset, which is determined only once, stability algorithm continuously reevaluates the rhythm diagnosis during tachycardia. Nevertheless, it may misclassify a supraventricular arrhythmia with 2:1

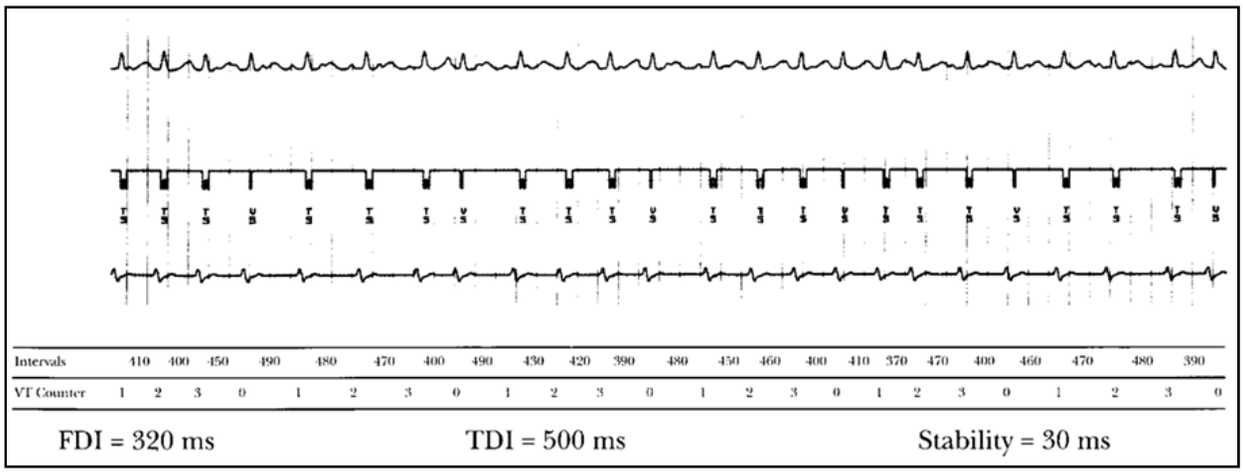

Figure 2. RR stability. Each RR interval is compared to the previous three. If the differences between the RR interval and each of the previous three are under a pre-specified stability cut-off then the arrhythmia is considered as VT.

conduction block, such as atrial flutter or a rapidly conducted AF with a pseudoregular ventricular pattern. Antiarrhythmic drugs may also affect the algorithm's performance. Use of amiodarone or Class IC antiarrhythmic drugs (e.g., flecainide or propafenone) may cause monomorphic VT to become irregular or polymorphic VT to slow down, leading to rhythm misclassification. For this reason, stability should not be programmed "on" unless AF with a rapid ventricular response has been documented.

Morphology discriminates VT from SVT on the basis of morphology-based algorithms that compare the differences between ventricular EGM in a previously stored template of a normally conducted beat with VT EGMs during a tachycardia episode. Common elements present in all morphology algorithms include: creation of a template by mathematically extracting electrocardiogram features and storing them; recording of electrocardiograms during an unknown tachycardia; time aligning templates and tachycardia electrocardiograms; classifying each tachycardia electrocardiogram as a match or non-match based on its comparison with the template; classifying the tachycardia as SVT or VT based on the number of electrocardiograms that match the template. Morphology analysis goes on until insufficient normal beats are recognized (and VT detection occurs) or until the heart rate slows out of the detection zone. Various morphology algorithms differ in their electrocardiogram source, methods of quantitative representation and alignment. In single-chamber ICDs, morphology algorithms are the only discriminators that distinguish regular SVT, such as atrial flutter or atrioventricular nodal reentrant tachycardia (AVNRT), from VT.

Nevertheless, morphology may detect VT inappropriately because of patient-related or algorithm-related factors. Patient-related factors include rate-dependent bundle branch block during SVT and exercise-induced myopotentials in sinus tachycardia [24]. Algorithm-related factors include misalignment of the sinus template with the tachycardia electrocardiogram, clipping of high-amplitude electrocardiograms, electrocardiogram changes during lead maturation, and shock-induced electrocardiogram changes [25]. In case of a possible sustained VT, a useful discriminator is the sustained-duration which overrides inhibition and starts therapy if the fast rate is persistent. It delivers therapy if a tachycardia

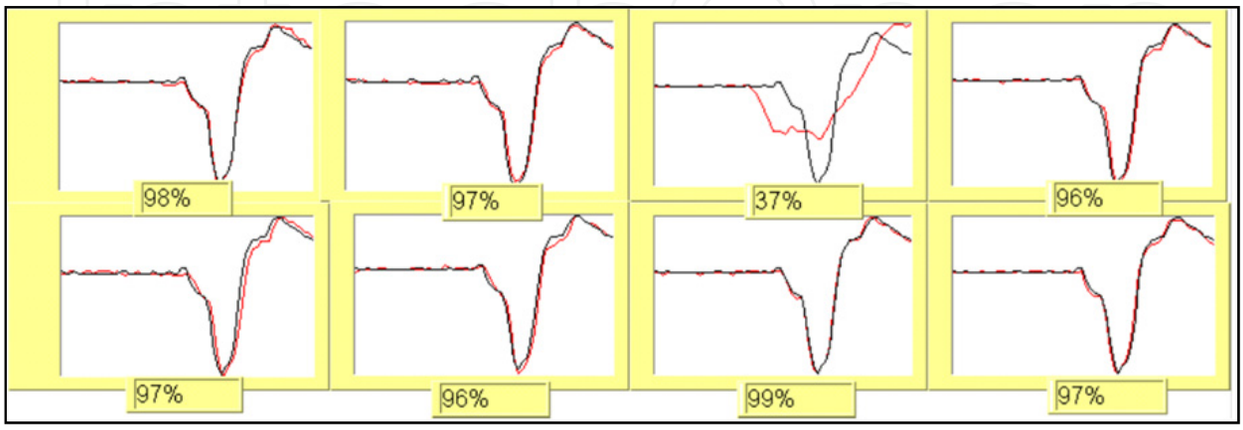

Figure 3. In this case morphology algorithm successfully discriminates a sinus tachycardia by matching tachycardia ventricular morphology with another morphology previously stored during sinus rhythm.

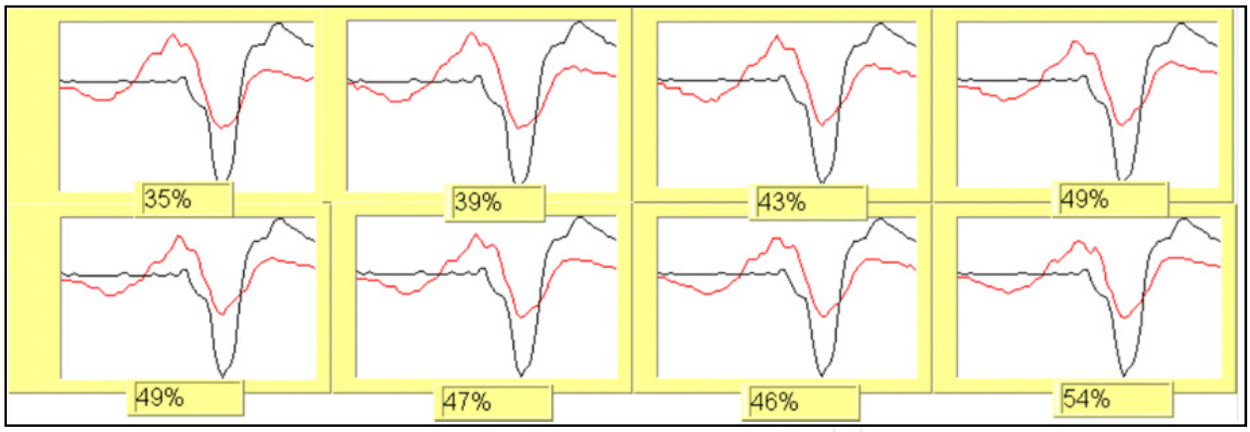

Figure 4. Ventricular morphology recorded during a tachycardia episode is recognized as different by morphology algohirthm, which in turn starts VT counter.

satisfies the VT rate criterion for a programmed duration, even if the discriminator indicates SVT. Since many cardiac patients are unable to maintain prolonged sinus tachycardia, the presumption is that sustained regular tachycardia lasting more than 3 min reflects VT. Thus, this feature ensures appropriate therapy of sustained VT at the price of decreased specificity for rejecting SVT. Indeed, inappropriate therapy is delivered for those SVT that remain above the rate boundary at the end of the programmed period.

3.3.2. Dual-Chamber SVT-VT Discriminators

Dual-chamber discriminators include analysis of atrial and ventricular rates and AV relationship, since dual chamber defibrillators acquire information simultaneously from the atrial and the ventricular leads. VT therapy is delivered immediately if ventricular rate is greater than atrial rate for a set number of beats. This occurs in more than 90% of detected arrhythmias which fall in the VT zone of dual-chamber ICD and in this case, no other data are necessary for therapy delivery. Therefore additional criteria for device diagnosis may be required only in less than 10% of VT. For instance, patients with AF may develop a slow VT, an atrial/ventricular counting algorithm would classify the situation as SVT because the atrial rate exceeds the ventricular rate, and other SVT discriminators may be necessary for a proper diagnosis. The best additional discriminator is morphology or stability.

Measures of AV association analyze the stability of the PR/RP interval and provide an implicit comparison of atrial and ventricular rates. Stable 2:1 AV association is what distinguishes atrial flutter from VT. Although 1:1 AV association does not discriminate between SVT and VT with 1:1 VA conduction, VT with 1:1 VA conduction begins often with transient AV dissociation.

P:R pattern identifies consistent timing relationships between atrial and ventricular electrocardiograms that occur during specific SVT, such as sinus tachycardia and atrial flutter. It identifies complex timing relationships, such as those present during variable AV block, and is insensitive to many transient perturbations. Yet, it is highly sensitive to sustained VT during SVT. The last discriminator, chamber of origin, is applied only to tachycardias with 1:1 AV

association. It discriminates sinus or atrial tachycardia with 1:1 AV conduction from VT with 1:1 VA conduction. Atrial tachycardia begins with a short PP interval, whereas VT begins with a short RR interval. Chamber of origin depends on accurate sensing of all atrial and ventricular events at the onset of tachycardia. Thus, it is susceptible to errors based on a single oversensed or undersensed event. In summary, data have demonstrated that dual-chamber discriminators are able to diagnose 60–95% of SVT episodes correctly without significantly missing true VTs. Above all, they may be useful in selected patients, as those with a VT zone with rates < 200 bpm and patients with no permanent AF and no AV block.

3.4. Remote monitoring of AF through implanted devices

Remote monitoring, especially wireless monitoring, offers multiple advantages over traditional office-based device follow-up. For instance it is useful for diagnosing technical issues such as lead fracture, device malfunction, early detection of tachyarrhythmias and heart failure progression, permitting a prompt clinical reaction [26]. The main potential advantage of remote control application in AF management is represented by early detection and early reaction to the arrhythmia occurrences. The current device diagnostics are very sophisticated and may give the physician full information about arrhythmia episodes, their number and duration, date and time of occurrence, onset mechanism, arrhythmia burden, effects of antitachycardia therapies and heart rate during the arrhythmia. The remote transmission of all these data allows a quicker identification of asymptomatic episodes, anticoagulation treatment and cardioversion decisions in a timely manner while the risk of thrombus formation is limited. Currently, the exact impact of the remote control as a clinical tool is still unknown. Moreover, it is still a matter of debate if device detection of AF with remote monitoring could be useful in selecting anticoagulation strategies, as well as the critical threshold of AF burden warranting anticoagulant therapy [27]. Despite the fact that anticoagulation has been shown to significantly improve the outcome in patients with AF, it is also associated with potentially life-threatening side effects and is therefore not well tolerated by patients. Automatic AF detection could make anticoagulation approach easier, allowing a swift therapeutic intervention. This technology seems particularly promising in patients with ICDs. Despite improvements in discrimination algorithms, SVTs continue to be the most common cause of inappropriate shocks. In these cases, the quick identification of the arrhythmia underlying an inappropriate shock may help physician in order to avoid further episodes. In table 1, advantages of remote monitoring in supraventricular tachycardia management are resumed.

- Early detection of symptomatic and asymptomatic supraventricular tachycardia
- Electrical cardioversion within 48 hours of the onset of AF
- Evaluation of the effectiveness of antiarrhythmic therapy
- Modification of the previous antiarrhythmic therapy or anticoagulation
- Rapid reprogramming of ICD in case of inappropriate shocks
- Decrease of number of to traditional office-based device follow-up

Table 1. Main advantages of remote monitoring in SVT detection.

4. Cardioversion in patients with implanted pacemakers and defibrillators

Large-scale randomized trials have questioned the benefits of restoring normal sinus rhythm in patients with AF [17,28].However, the presence of AF in patients with implanted devices could lead to increased morbidity and mortality through adverse device-related complications, such as inappropriate shock deliveries or pacemaker mediated tachycardia with associated tachycardia induced cardiomyopathy. Therefore, AF termination could become necessary and, when appropriate precautions are taken, cardioversion becomes safe and effective in patients with implanted devices.

4.1. Internal cardioversion

Internal cardioversion (ICV) is a defibrillation technique performed through intracardiac electrodes which allows successful CV with very low energy levels. Low-energy ICV does not interfere with pacemaker function in patients with electrodes positioned in the RA, coronary sinus, or left pulmonary artery. ICV has been shown to be superior to conventional external cardioversion (ECV) in term of primary success rate, energy requirements and need of sedation instead of general anaesthesia [29]. However, there are some disadvantages related to the procedure such as the need for an electrophysiology laboratory and of specific technical competence for lead positioning that greatly hamper widespread use in clinical practice. Oesophageal cardioversion is another method to perform CV. This technique is quite simple, very fast and provides several advantages. The most important is a low energy requirement thanks to proximity of the oesophagus to the left atrium which warrants a lower energy dispersion and a lower defibrillation impedance. For this reason its safety has been demonstrated in patients with implantable devices [30]. In patients with ICDs, a programmed ventricular ICD discharge could be another option for a quick and safe cardioversion.

4.2. External cardioversion: how-to and precautions

ECV has long been a cause of concern regarding the potential adverse effects on the generator and on the leads induced by the electrical shocks. First of all, electricity conducted along an implanted electrode may cause endocardial injury and bring to a temporary or permanent increase in stimulation threshold, resulting in acute or chronic loss of ventricular capture. Moreover, other ECV related problems include physical dysfunction of the device, spurious programming or electrical reset induced by the shock and changes in sensing function or pacing impedance [31,32].

	Monophasic	Biphasic	p-value
AF duration before CV	18 (1–394) days	27 (1–1359) days	0.65
CV success	20/21 (95%)	22/23 (96%)	1.0
Success with initial shock	15/21 (71%)	17/23 (74%)	1.0
Cumulative shock energy	200 (200–1220) J	100 (100–650) J	0.001

Table 2. Comparison between AF cardioversion in patients with implanted rhythm devices treated with monophasic or biphasic shocks. For AF duration and cumulative shock energy, the median values and range are provided. Adapted from [31].

Devices assembled in last decades are considerably more sophisticated and better protected against sudden external discharges, even if data loss due to current surges is still possible. Voltage regulators protect the pacemaker circuitry by shunting the current away from the device through the lead to the electrode tip. However, this may result in concentration of the energy at the lead tip, causing burns and electrical trauma at the electrode-myocardial interface. This is the pathophysiological basis of the aforementioned pacing threshold and sensing changes.

Some precautions when performing ECV could be useful to ensure appropriate device function. First of all, the implanted device should be interrogated and, if necessary, reprogrammed before and after cardioversion. Prior to ECV, it is recommended to check pacemaker and leads function. Further precautions are necessary in pacemaker dependent patients such as programming higher voltage output in order to avoid loss of capture and switching to asynchronous mode (VOO or AOO). Current guidelines [33] do not set any interrogation timetable to follow after ECV. However, after the current discharge, it is safe to reassess device function immediately, at hospital discharge and 4-6 weeks later. Additional tests are needed in case of device malfunctioning.

Devices are typically implanted just under the collarbone, so the paddles used for ECV should be positioned as distantly as possible from the device. The positioning of paddles at least 8 cm away from pulse generator [31] did not produce changes in pacing thresholds or sensing measurements, preferably in the anterior-posterior configuration, as specified in AHA Guidelines [33]. The best paddles configuration is the anterior-posterior one. The antero-lateral orientation of cardioversion electrodes creates an electrical field parallel to the course of the leads thus maximizing current shunting through leads. The use of an antero-posterior orientation aims to prevent this 'antenna effect' since it creates an electrical field typically perpendicular to the main lead orientation. Furthermore, the anterior-posterior configuration needs, on average, lower energy requirements for termination of AF [31-33]. Different studies have demonstrated that biphasic shocks are superior to monophasic shocks for cardioversion because of the higher percentage of SR restoration, the fewer shocks needed and the lower energy delivered. However, few studies have focused the attention on patients with implanted devices. From the comparison of monophasic and biphasic shock energy application, it seems that there are no significant differences in terms of safety and efficacy. However, energy requirements are significantly lower for biphasic shocks when compared with monophasic shock waveforms.American and European guidelines do not specify the time between two consecutive shocks in patients with implanted devices. However, safe common practice might be a waiting time of at least 1 minute between shocks, as recommended for patients with AF without intracardiac devices [33].

5. Atrial pacing for AF prevention

Sustained AF depends on a complex electrophysiological substrate which has not been fully elucidated yet. Nonetheless, some animal models demonstrated that specific triggers, such as premature atrial beats, are needed for AF initiation and multiple atrial refractoriness

patterns facilitate AF persistency. Some device strategies have been developed in order to prevent AF onset.

5.1. Trigger suppression algorithms

Suppression of AF triggers strategy is mainly based on suppression of premature atrial beats, either by elevating the lower rate or by dynamic overdrive. Both these options, although cheap and easy to perform in an out-of-hospital setting, are not very effective. Re-programming a lower rate 10 bpm faster than 24 hours mean heart rate prevented AF recurrence in approximately 60% of patients over a 30-day follow up [34]. In another study, while atrial pacing vastly reduced total premature atrial beats from 3.8 per hour to 0.5 per hour, no difference was found in AF recurrence prevalence or time to first recurrence between paced and not paced patients [35]. At one year, 43% of all patients developed permanent AF, suggesting that atrial pacing does not prevent the natural progression of AF.

This strategy has also the drawback or requiring specific programming whenever mean heart rate changes, a quite common occurrence in AF patients. To address these issues, dynamic overdrive algorithms has been introduced. These algorithms work by increasing the paced rate upon detection of a premature atrial complex. The increased lower rate is then decreased again in steps until spontaneous atrial rate appears or a new premature atrial beat is detected. Premature beats can also increase dispersion of atrial refractoriness through the long-short cycle which is caused by the extrasystolic pause. In this setting, overdrive suppression algorithms are optimized to deliver either a series of paced beats or a higher pacing rate for a prespecified duration.

The advantage of these algorithms is to reduce atrial pauses following a premature beat while avoiding a fixed high heart rate, possibly leading to palpitations and tachycardiomyopathy. In general, mean heart rate is not significantly increased when these algorithms are working, and are well tolerated by the patients [36].

Efficacy of these algorithms in preventing AF is still a matter of debate. In one of the first prospective studies, AF suppression algorithm (St. Jude Medical, Sylmar, CA) was associated with a 35% reduction of AF burden in patients already implanted with a DDDR device [37]. Moreover, some effects on atrial remodeling, although little in magnitude, have been demonstrated. Other algorithms, such as the Atrial Preference Pacing algorithm (Medtronic, Minneapolis, MN) failed to show any reduction in the number of mode-switching episodes and symptomatic episodes despite a reduction of premature atrial beats [38].

Multicenter trials specifically designed to test efficacy and safety of these algorithms failed to demonstrate a net benefit over traditional pacing. The ATTEST trial evaluated three different algorithms for AF prevention (Atrial Preference Pacing, Atrial Rate Stabilization and Post Mode Switching Overdrive), and showed no difference in total number of AF episodes or median AF burden between patients with either the algorithms switched “on” or “off” [39]. The PIPAF trial had similar results, showing no difference in number of AF

paroxysms per week in a crossover population during a 3 months follow up [40]. Post Mode Switching Overdrive algorithm (Medtronic, Minneapolis, MN) provided no reduction of AF episodes at 120 bpm and was actually arrhythmogenic when programmed at 80 bpm.

5.2. Alternative site and multi-site pacing for AF prevention

Paroxysmal AF is usually related to an important inter-atrial and intra-atrial delay, which further increases atrial refractoriness dispersion and helps sustain AF. Unconventional atrial pacing techniques have been proposed in order to synchronize atrial activation and reduce dispersion of refractoriness. Alternative site pacing and dual-site pacing have been the most extensively studied strategies.

Alternative site atrial pacing attempts to reduce atrial activation time by selective pacing right atria at preferential conduction sites. The most common of these sites is probably the Bachmann's bundle, a band of fibrous tissue that travels from the superior part of the right atrium near the ostium of the vena cava superior to the upper part of the left atria appendage. Pacing at the Bachmann's bundle has been shown to reduce AF recurrence [41]. The incidence of AF recurrences at 1 year has been lowered with Bachmann's bundle pacing compared to traditional right atrial appendage pacing, and in those patients P-wave duration was actually shorter, providing an indirect evidence of a better inter-atrial and intra-atrial activation [42]. Another alternative site for atrial pacing is the low interatrial septum near the triangle of Koch, where most of the connections between right and left atria have been discovered. Pacing at the low interatrial septum has been associated with a reduced AF burden and again, with shorter P-wave duration [43]. These alternative pacing sites obviously require active-fixation leads, but appear to be as stable and safe as conventional, passive-fixation, atrial appendage leads.

Multi-site pacing is another promising strategy which has been quite successful in reducing atrial refractoriness dispersion. This approach is characterized by the use of two atrial leads. The first one is placed in the atrial appendage or actively fixated into the interatrial septum. The second one can be either placed into the distal coronary sinus or near its ostium. In the former case, specifically designed leads are necessary in order to avoid dislodgement whereas in the latter case an active-fixation lead is required.

Only a single multicenter trial has currently been performed in order to test feasibility and efficacy of multi-site pacing in AF prevention [44]. This study randomized 118 patients to multi-site pacing, overdrive atrial pacing or simple support pacing at a lower rate of 50 bpm. The study showed a reduction in AF recurrences and mean dose of antiarrhythmic drugs taken in both multi-site pacing and overdrive pacing, with no significant difference between these two groups.

To conclude, patients with paroxysmal AF and a P duration ≥90 ms may benefit from dual-site pacing as well as alternative site pacing. Hybrid therapy, using both alternative site pacing and suppression algorithms, could represent a future approach to AF prevention, though multicenter trials are still needed in order to gather enough evidence.

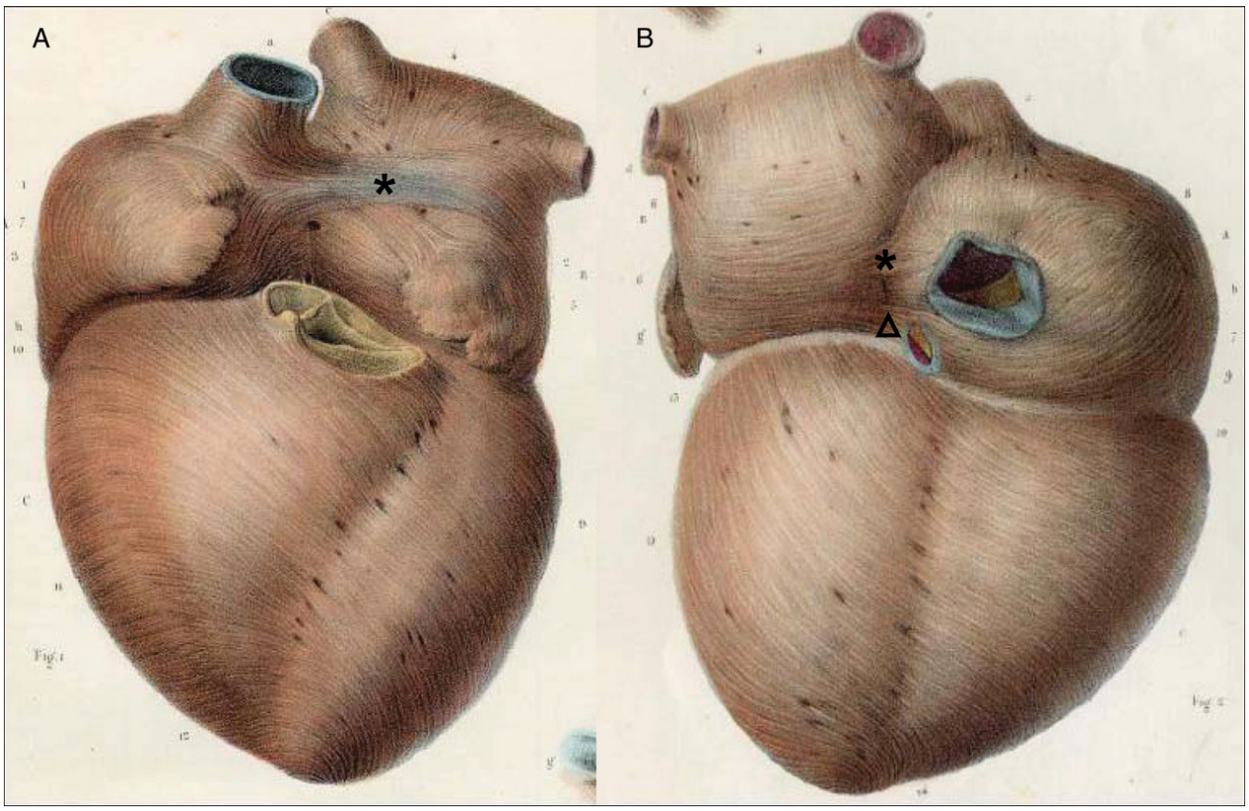

Figure 5. Superior (A) and inferior (B) view of the human heart. (A) Bachmann's bundle travels from the superior part of the right atrium near the ostium of the vena cava superior to the upper part of the left atrium (*). (B) components of the inferior interatrial route: asterisk denotes muscular bundles between the right atrium near the orifice of the vena cava inferior and the inferior surface of the left atrium; Arrowhead denotes interatrial bundles in the vicinity of the coronary sinus orifice (coronary sinus is removed). Reproduced from [41].

6. Atrial pacing for AF termination

Antitachycardia pacing (ATP) is a reliable method of suppressing ventricular arrhythmias, and is currently widespread as a standard ICDs therapy. More recently, its usefulness has been demonstrated also in terminating atrial tachyarrhythmias with a wide excitable gap such as atrial tachycardia or atrial flutter. Unfortunately, AF lacks a wide excitable gap, and its multiple reentrant wavelets do account for its resistance to ATP termination. Atrial ATP is now available in all modern implantable devices. Many different types of atrial ATP are available, as they differ from each producing company. The most common are: atrial burst (steady rate pacing), atrial ramp (auto-decremental pacing), atrial burst plus (steady rate pacing followed by two extrastimuli) and 50-Hz burst pacing for 3 seconds, none of which proved to be more effective than the others in terminating AF.

Efficacy of atrial ATP is low, mainly because of the aforementioned mechanisms, and it varies from 30 to 54% [39]. However, several variables must be taken into account. First of all, ATP success in terminating AF greatly depends on the cycle length of the arrhythmia:

being as low as 29% if the cycle length is ≤ 190 ms and as high as 65% when the cycle length is > 320 ms [45]. Also, atrial ATP is more effective if delivered in recent-onset AF paroxysms. Another possible use of atrial ATP depends on the common pathophysiology between AF and atrial flutter. In patients in whom those two arrhythmias coexist, ATP delivery while the patient is in atrial flutter may prevent further degeneration of atrial flutter into AF.

7. Ablate and pace

7.1. Rationale and indications for ablate and pace

Atrioventricular junction (AVJ) ablation and subsequent pacing, also called "ablate and pace" may be considered whenever it is not possible to achieve adequate rate control despite optimal pharmacological therapy or after unsuccessful AF ablation. Complete AV block is achieved by selective catheter-mediated destruction of the AV node or His bundle, with radiofrequency current serving as the predominant source energy. AVJ ablation is usually performed by a right-sided approach, which offers lower prevalence of complications and is related to shorter hospitalizations. When the right-sided approach fails, left-sided ablation can be performed during the same session or at another session. Left-sided ablation is usually faster, as requires fewer radiofrequency applications, but is associated with a significantly higher risk of bleeding [46,47]. An expert electrophysiologist can usually produce an effective AV block in more than 98% of cases. Regression of AV block late after ablation is rare, and occurs in less than 5% of total procedures [48].

Current European [1] and American [33] guidelines list ablate and pace as a palliative treatment. Indeed, in contrast to other ablative procedures in which the ablation erases the electrophysiologic substrate of the disease, ablate and pace only works indirectly, changing an irregular and fast ventricular rate into a regular, pacemaker-dependent, normofrequent rate. It could also be said that ablate and pace replaces one disease (uncontrolled AF) with another (iatrogenic complete AV block) [49]. Moreover, the procedure is completed by a pacemaker implant, with all the short- and long-term complications associated with a device implant procedure.

Nonetheless, ablate and pace improves symptoms and quality of life compared to medical therapy, and improves survival making it similar to survival rates in the general population [1,33]. Usually, patients who benefit the most of ablate and pace strategy are those patients with tachycardia-mediated cardiomyopathy, as symptoms are usually related to a fast ventricular response.

A meta-analysis, including less than 1200 patients affected by symptomatic permanent AF, demonstrated that AVJ ablation and pacemaker implantation significantly improved quality of life, reducing symptoms and hospitalizations [10]. Similar results have been shown for patients with paroxysmal or persistent AF refractory to any form of pharmacological rate control [50]. Ablate and pace seems also beneficial in restoring an adequate cardiac function: in the Ablate and Pace Trial (APT) 156 patients undergoing AV node ablation and pacemaker implant experienced an improvement of cardiac systolic function along with

clinical status and quality of life [51]. Moreover, in a small study recruiting 56 patients with EF less than 40%, ablate and pace strategy was associated with an improvement of mean EF from 0.26 to 0.34, with one fourth of the patients actually achieving the goal of a normal (≥55%) EF.

The outcome of an ablate and pace strategy could be further improved by alternative sites pacing, such as the right ventricular outflow tract, the interventricular septum and the His bundle, although no clear evidence is currently available.

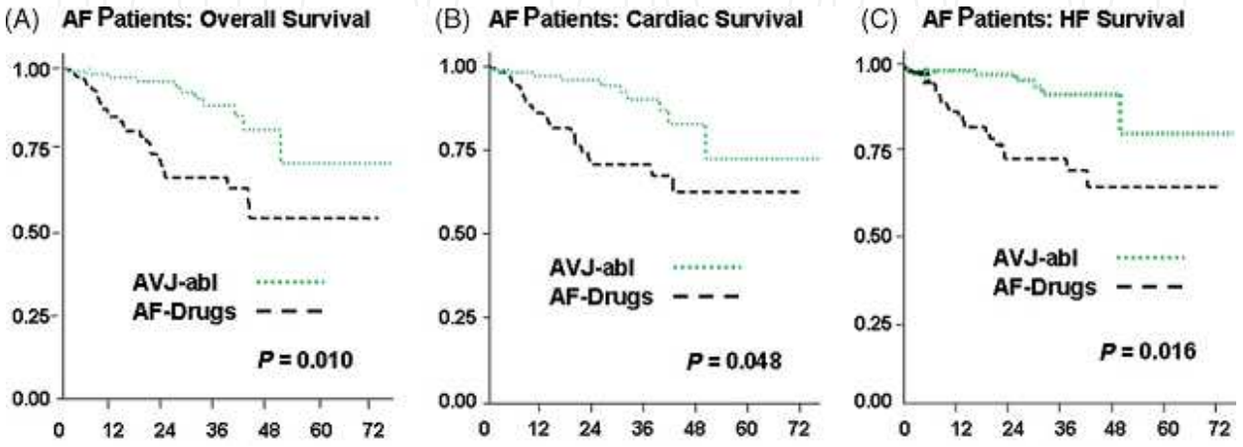

Figure 6. Comparison of Kaplan–Meier estimates of overall (A), cardiac (B), and heart failure (C) survival between AF patients who underwent AVJ ablation and AF patients treated only with anti-arrhythmic drugs. The p-values presented derive from the adjusted hazards ratio analysis stratified according to the corresponding cause of death. Reproduced from [51].

7.2. Which device in which patient? Recommendations for different types of devices in "ablate-and-pace" strategy

Selection of the appropriate device (pacemaker or ICD) and the optimal stimulation modality (VVI, DDD, or CRT) must be based on a number of clinical variables. First of all, type of AF (paroxysmal, persistent or permanent) is of the utmost importance to determine the correct strategy. In patients with paroxysmal AF, dual-chamber pacemakers are obviously preferred in an effort to maintain AV synchrony during sinus rhythm following ablation. Automatic mode switching capability of modern dual-chamber devices prevents rapid ventricular rate when AF occurs and, as already said, provides a major diagnostic tool in detecting AF episodes. The device can be easily reprogrammed to VVIR modality when AF becomes persistent or permanent.

Associated ischemic or valvular heart disease, systolic and diastolic function and the presence and severity of heart failure symptoms should also be taken into account. Current recommendations for cardiac resynchronization are still valid in this subtype of patients. In fact, it has been demonstrated that AF patients undergoing AVJ ablation before CRT implant have a better survival rate when compared with AF patients under a pharmacological rate control strategy [52]. Upgrading to a biventricular device should be considered for patients with HF and a right ventricular pacing system when AV node

ablation is performed. It is not currently established whether biventricular pacing could be useful in patients without left ventricular dysfunction, although some recent evidences are in favor of a possible role in reducing AF-related symptoms [53]. In severely symptomatic patients with permanent AF, CRT significantly prevents hospitalization and worsening of clinical conditions during a 2-years follow-up [53].

7.3. Safety of ablate and pace therapy

As said before, ablation of the AV node produces a new illness (the iatrogenic AV complete block) out of an old one. Complications related to ablate and pace strategy include those commonly associated with device implant, thromboembolism associated with anticoagulation withhold and progression from paroxysmal to permanent AF. AVJ ablation procedure creates a temporary proarrhythmic state, which in turn can rarely lead to polymorphic VT and cardiac arrest. In fact, the 1-year mortality rate after ablate and pace is approximately 6.3%, which include a 2% risk of sudden cardiac death [54]. Although this issue has raised some criticisms, programming a higher lower rate of about 80-90 beats per minute for the first 1-2 months seems a viable option for reducing the risk of sudden death [55]. Nonetheless, mortality associated with ablate and pace is still low, reaching 10.5% in 5 years [56], with no significant difference in mortality between ablation and pharmacological control rate.

8. Two birds with one stone: Usefulness of implanted devices in AF associated with other cardiac diseases

8.1. Bradycardia and syncope: Recommended type of devices and optimal settings in low-response AF

VVIR is the mode of choice for patients with permanent AF and a slow ventricular response, in whom pacing is necessary. On the contrary, for most patients with brady–tachy syndrome, a dual chamber pacemaker is indicated. As most patients with symptomatic bradycardia often have associated chronotropic incompetence or at least the potential for this to occur, a dual-chamber pacemaker with rate-adaptive capabilities (DDDR) is recommended. In patients with frequent AF relapses associated with slow ventricular rates, DDDR becomes essential. Rate responsiveness in patients with chronic AF depends on autonomic regulation of the AV node, which is usually poorly regulated in this population. the DDDR pacemaker could be reprogrammed to VVIR afterwards if AF degenerates over time into permanent type. A DDD pacemaker, which has no rate-adaptive capability, could be reprogrammed only to VVI, which could not be optimal for the patient.

8.2. Heart failure: Cardiac resynchronization therapy in AF

Latest ESC [12] and AHA/ACC/HRS Guidelines [57] have considered atrial fibrillation patients, who constitute an important subgroup of HF patients, as eligible to receive CRT.

Both ventricular conduction delay and AF are associated with poor prognosis in HF and CRT may be therefore indicated in these patients. Few randomized trials have been done in order to assess the efficacy of CRT in AF patients [58-60]. The MUSTIC trial showed good one-year results of biventricular pacing in patients with severe HF and major intraventricular conduction disturbances with either SR or AF [58]. Because of the high drop-out rate, the impact of these results were limited even though the results underlined the importance of an high percentage of biventricular pacing to achieve real CRT-related benefits in patients with AF. The PAVE study demonstrated that in patients undergoing AV node ablation for AF, biventricular pacing provided a significant improvement in the 6-minute walk test and ejection fraction compared to right ventricular pacing [59]. These beneficial effects of CRT were greater in patients with impaired systolic function or symptomatic HF [59]. An intrinsic, intermediate-to-high, irregularly spontaneous AF rhythm reduces the percentage of effectively biventricular paced captured beats. Even in a patient who has normofrequent AF, phases of effective biventricular capture alternate with phases of competing AF rhythm which translates into spontaneous, fusion, or pseudo-fusion beats. The presence of fusion and pseudo-fusion leads to inaccuracy and overestimation of the effective pacing capture. Furthermore, the global effective 'CRT-dose' may be markedly reduced compared with atrial synchronous rhythm with a short AV interval achieved during SR, since the number of effective biventricular captured beats are reduced. Moreover, in AF patients, spontaneous ventricular rate tends to overdrive biventricular pacing rates during exertion, determining a further reduction of paced beats precisely when patients are most in need of biventricular capture, and thus greatly limiting functional capacity [60,61]. Another problem is the possible negative impact on prognosis of negative chronotropic therapy in achieving adequate rate control. In fact, the SCD-HeFT study has shown that amiodarone therapy provided no benefit in patients in NYHA class II and decreased survival among patients in NYHA class III, as compared with those who received placebo [62].

To achieve a ventricular rate control delivery, devices-derived features have been developed in order to maximize ventricular pacing during potentially disruptive events. These features are ventricular rate regularization and in ventricular sense response pacing. The former consist in performing biventricular pacing, which 'overrides' intrinsic rhythm, through faster ventricular-paced depolarization, allowing to reduce short cycles through retrograde concealed penetration of the AV node. The other feature is characterized by the activation of LV pacing soon after a premature RV sensed event is detected. Another mechanism in the management of AF is the combination between CRT and atrial tachyarrhythmia prevention pacing algorithm. The ADOPT trial [37] has demonstrated the efficacy and safety of the AF suppression algorithm in reducing symptomatic AF burden in patients with permanent pacemaker with prior history of AF and with normal EF. A subsequent study, the MASCOT trial, has been designed to determine whether the addition of atrial overdrive pacing to CRT could reduce the incidence of permanent AF. The overall incidence of permanent AF was low and was similar for the two treatment groups underlying that probably the advanced atrial remodelling in the setting of HF and AF may preclude benefit from atrial algorithms in this altered milieu [63].

AVJ ablation and placement of a permanent pacemaker has been used in patients with fast, symptomatic and drug-refractory AF to confer symptomatic relief and improve exercise tolerance. In the setting of CRT and AF, the AVJ ablation is emerging as a useful tool to optimize CRT delivery because it allows a complete heart rate control through a constant biventricular pacing.

From the current evidences it emerges that the real benefits of CRT in AF population seem to be confined only to AF patients treated with AVJ ablation. The magnitude of reverse remodelling, of improving of the systolic function and of the decrease in NYHA functional class, the percentage of responders seems to be higher in AF patients treated with CRT and AVJ ablation [51,52]. AVJ ablation in addition to CRT appears also to improve long-term overall mortality and hospitalization compared with CRT alone, primarily by reducing HF death [53].

The outcomes of AF with AVJ ablation patients are similar to the outcomes of patients in SR. Several trials have concluded that AF patients display similar survival as sinus rhythm patients provided that AVJ ablation is performed. However, data from larger randomized clinical trials will be needed before utilizing this as a standard practice since this would create a large number of pacemaker- dependent HF patients with all stimulation dependency-related problems.

In patients with permanent AF who undergo CRT without AVJ ablation, a few studies have suggested that cardioversion and aggressive rhythm control result in better clinical outcomes [64]. Limited data showed that in patients with severely depressed left ventricular EF, left bundle branch block and permanent AF a more vigorous approach to restoring SR is justified prior to implantation of a CRT device or after, in case of recurrences conferring clinical and instrumental improvement. However, currently available antiarrhythmic drugs are only partially effective in maintaining sinus rhythm, and this is achieved at the cost of potential risk [17]. In contrast, catheter ablation may offer another approach for achieving sinus rhythm in these patients. Several clinical trials have demonstrated catheter ablation as a promising alternative compared to pharmacologic therapy, that significantly improved LV function, NYHA class and exercise capacity in patients with AF and symptomatic LV dysfunction [65-68]. The results of these nonrandomized series provide a potent rationale for a randomized clinical trial comparing ablation to pharmacologic therapy.

Author details

Federico Guerra*, Michela Brambatti, Maria Vittoria Matassini and Alessandro Capucci
Cardiology Clinic, Marche Polytechnic University, Ancona, Italy

9. References

[1] Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et al. (2010) Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). European Heart Journal. 31:2369-2422.

* Corresponding Author

[2] De Sisti A, Attuel P, Manot S, Fiorello P, Halimi F, Leclercq JF. (2000) Electrophysiological determinants of atrial fibrillation in sinus node dysfunction despite atrial pacing. Europace. 2:304-311.
[3] Lamas GA, Lee KL, Sweeney MO, Silverman R, Leon A, Yee R, et al. (2002) Ventricular pacing or dual-chamber pacing for sinus node dysfunction. New England Journal of Medicine. 346:1854-1862.
[4] Veasey RA, Arya A, Silberbauer J, Sharma V, Lloyd GW, Patel NR, Sulke AN. (2011) The relationship between right ventricular pacing and atrial fibrillation burden and disease progression in patients with paroxysmal atrial fibrillation: the long-MinVPACE study. Europace. 13:815-820.
[5] Sweeney MO, Bank AJ, Nsah E, Koullick M, Zeng QC, Hettrick D, et al. (2007) Minimizing Ventricular Pacing to Reduce Atrial Fibrillation in Sinus-Node Disease. New England Journal of Medicine. 357:1000-1008.
[6] Silberbauer J, Veasey RA, Freemantle N, Arya A, Boodhoo L, Sulke N. (2009) The relationship between high-frequency right ventricular pacing and paroxysmal atrial fibrillation burden. Europace. 11:1456–1461.
[7] Savelieva I, Camm J. (2003) Atrial fibrillation and heart failure: natural history and pharmacological treatment. Europace. 5: S5-S19.
[8] Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L, for the Cardiac Resynchronization—Heart Failure (CARE-HF) Study Investigators. (2005) The effect of cardiac resynchronization on morbidity and mortality in heart failure. New England Journal of Medicine. 352:1539–1549.
[9] Dickstein K, Bogale N, Priori S, Auricchio A, Cleland JG, Gitt A, et al. (2009) The European cardiac resynchronization therapy survey. European Heart Journal. 30:2450 –2460.
[10] Wood MA, Brown-Mahoney C, Kay GN, Ellenbogen KA. (2000) Clinical outcomes after ablation and pacing therapy for atrial fibrillation: a meta-analysis. Circulation. 101:1138–1144.
[11] Vardas PE, Auricchio A, Blanc JJ, Daubert JC, Drexler H, Ector H, et al. (2007) Guidelines for cardiac pacing and cardiac resynchronization therapy. European Heart Journal. 28:2256–2295.
[12] Dickstein K, Vardas PE, Auricchio A, Daubert JC, Linde C, McMurray J, et al. (2010) Focused update of the European Society of Cardiology guidelines on device therapy in heart failure. An update of the 2008 European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 European Society of Cardiology guidelines for cardiac and resynchronization therapy. European Heart Journal. 31:2677-2687.
[13] Brignole M, Vardas P, Hoffman E, Huikuri H, Moya A, Ricci R, et al. (2009) Indications for the use of diagnostic implantable and external ECG loop recorders. Europace. 11:671–687.
[14] Nieuwlaat R, Capucci A, Camm AJ, Olsson SB, Andresen D, Davies DW, et al. (2005) Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. European Heart Journal. 26:2422-2434.
[15] Israel CW, Grönefeld G, Ehrlich JR, Li YG, Hohnloser SH. (2004) Long-term risk of recurrent atrial fibrillation as documented by an implantable monitoring device: implications for optimal patient care. Journal of the American College of Cardiology. 43:47-52.

[16] Orlov MV, Ghali JK, Araghi-Niknam M, Sherfesee L, Sahr D, Hettrick DA. (2007) Asymptomatic atrial fibrillation in pacemaker recipients: incidence, progression, and determinants based on the atrial high rate trial. Pacing and Clinical Electrophysiology. 30:404-411.

[17] Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, et al. (2002). A comparison of rate control and rhythm control in patients with AF. New England Journal of Medicine. 347:1825–1833.

[18] Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, et al. (2012) Subclinical AF and the Risk of Stroke. New England Journal of Medicine. 366: 120-129.

[19] Ricci RP, Morichelli L, Santini M. (2009) Remote control of implanted devices through Home Monitoring™ technology improves detection and clinical management of AF. Europace. 11:54-61.

[20] Hindricks G, Pokushalov E, Urban L, Taborsky M, Kuck KH, Lebedev D, et al. (2010) Performance of a new leadless implantable cardiac monitor in detecting and quantifying AF: Results of the XPECT trial. Circulation: Arrhythmias and Electrophysiology 3:141-147.

[21] Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. (1999) A randomized study of the prevention of sudden death in patients with coronary artery disease. New England Journal of Medicine. 341:1882-1890.

[22] Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. (2005) Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. New England Journal of Medicine. 352:225-237.

[23] Daubert JP, Zareba W, Cannom DS, McNitt S, Rosero SZ, Wang P, et al. (2008) Inappropriate ICD Shocks in MADIT II. Journal of the American College of Cardiology. 51:1357-1365.

[24] Swerdlow CD, Ahern T, Chen PS, Hwang C, Gang E, Mandel W, et al. (1994) Underdetection of ventricular tachycardia by algorithms to enhance specificity in a tiered therapy cardioverter-defi brillator. Journal of the American College of Cardiology. 24:416–424.

[25] Duru F, Bauersfeld U, Rahn-Schonbeck M, Candinas R. (2000) Morphology discriminator feature for enhanced ventricular tachycardia discrimination in implantable cardioverter defibrillators. Pacing and Clinical Electrophysiology. 23:1365-1374.

[26] Brugada P (2006) What evidence do we have to replace in-hospital implantable cardioverter defibrillator follow-up? Clinical Research in Cardiology. 95(Supplement 3):iii3-iii9.

[27] Ip J, Waldo AL, Lip GY, Rothwell PM, Martin DT, Bersohn MM, et al. (2009) Multicenter randomized study of anticoagulation guided by remote rhythm monitoring in patients with implantable cardioverter-defibrillator and CRT-D devices: Rationale, design, and clinical characteristics of the initially enrolled cohort. The IMPACT study. American Heart Journal. 158:364-370.

[28] Carlsson J, Miketic S, Windeler J, Cuneo A, Haun S, Micus S, et al. (2003) Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. Journal of American College of Cardiology. 41(10):1690-6.

[29] Lévy S. (2005) Internal defibrillation: where we have been and where we should be going? Journal of Interventional Cardiac Electrophysiology. 13:61-66.
[30] Santini L, Forleo GB, Romeo F. (2011) Esophageal electrical cardioversion of atrial fibrillation: when esophagus gives a help to cardiologists. Cardiology Research and Practice. 2011:983937.
[31] Manegold JC, Israel CW, Ehrlich JR, Duray G, Pajitnev D, Wegener FT, Hohnloser SH. (2007) External cardioversion of atrial fibrillation in patients with implanted pacemaker or cardioverter-defibrillator systems: a randomized comparison of monophasic and biphasic shock energy application. European Heart Journal. 28:1731–1738.
[32] Gammage MD. (2007) External cardioversion in patients with implanted cardiac devices: is there a problem? European Heart Journal 28 :1668–1669
[33] Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. (2011) 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Journal of American College of Cardiology. 57:101-198.
[34] Garrigue S, Barold SS, Cazequ S, Gencel L, Jaïs P, Haissaguerre M, Clémenty J. (1998) Prevention of atrial arrhythmias during DDD pacing by atrial overdrive. Pacing and Clinical Electrophysiology. 21:250–255.
[35] Gillis AM, Wyse G, Connolly SJ, Dubuc M, Philippon F, Yee R, et al. (1999) Atrial pacing periablation for prevention of paroxysmal atrial fibrillation. Circulation. 99:2553–2558.
[36] Lam CTF, Lau CP, Leung SK, Tse HF, Lee KLF, Tang MO, et al. (2000) Efficacy and tolerability of continuous overdrive atrial pacing in atrial fibrillation. Europace 2:286–291.
[37] Carlson MD, Ip J, Messenger J, Beau S, Kalbfleisch S, Gervais P, et al. (2003) A new pacemaker algorithm for the treatment of atrial fibrillation: results of the Atrial Dynamic Overdrive Pacing Trial (ADOPT). Journal of the American College of Cardiology. 20:627–633.
[38] Murgatroyd FD, Nitzsche R, Slade AK, Limousin M, Rosset N, Camm AJ, et al. (1994) A new pacing algorithm for overdrive suppression of atrial fibrillation. Pacing and Clinical Electrophysiology. 17:1966–1973.
[39] Lee MA, Weachter R, Pollak S, Kremers MS, Naik AM, Silverman R, et al. (2003) The effect of atrial pacing therapies on atrial tachyarrhythmia burden and frequency. Journal of the American College of Cardiology. 41:1926–1932.
[40] Adler S, Ziegler P, Koehler J, Holbrook R, Hettrick DA. (2001) Post mode switch overdrive pacing algorithm reduces atrial tachyarrhythmia recurrence in patients with bradycardia and atrial tachyarrhythmias. Circulation. 104:II-624.
[41] Platonov PG. (2007) Interatrial conduction in the mechanisms of atrial fibrillation: from anatomy to cardiac signals and new treatment modalities. Europace 9:vi10-vi16.
[42] Bailin SJ, Adler S, Giudici M. (2001) Prevention of chronic atrial fibrillation by pacing in the region of Bachmann's bundle: results of a multicenter randomized trial. Journal of Cardiovascular Electrophysiology 12:912–917.

[43] Padeletti L, Pieragnoli P, Ciapetti C, Colella A, Musilli N, Porciani MC, et al. (2001) Randomized crossover comparison of right atrial appendage pacing versus interatrial septum pacing for prevention of paroxysmal atrial fibrillation in patients with sinus bradycardia. American Heart Journal, 142:1047–1055.

[44] Saksena S, Prakash A, Ziegler P, Hummel JD, Friedman P, Plumb VJ, et al. (2002) Improved suppression of recurrent atrial fibrillation with dual-site right atrial pacing and antiarrhythmic drug therapy. Journal of the American College of Cardiology. 40:1140–1150.

[45] Adler SW, Wolpert C, Warman EN, Musley SK, Koehler JL, Euler DE. (2001) Efficacy of pacing therapies for treating atrial tachyarrhythmias in patients with ventricular arrhythmias receiving a dual-chamber implantable cardioverter defibrillator. Circulation. 104:887–892.

[46] O Souza, S Gursoy, F Simonis, G Steurer, E Andries, P Brugada (1992) Right-sided versus left-sided radio frequency ablation of the His bundle. Pacing and Clinical Electrophysiologhy. 15:1454–1459.

[47] Kalbfleisch SJ, Williamson B, Man KC, Vorperian V, Hummel JD, Calkins H, et al. (1993) A randomized comparison of the right- and left-sided approaches to ablation of the atrioventricular junction American Journal of Cardiology. 72:1406–1410.

[48] Brignole M. (2000) Ablate and pace: palliating the symptoms? American Journal of Cardiology. 86:4K-8K.

[49] Brignole M, Gianfranchi L, Menozzi C, Alboni P, Musso G, Bongiorni MG, et al. (1997) Assessment of atrioventricular junction ablation and DDDR mode-switching pacemaker versus pharmacological treatment in patients with severely symptomatic paroxysmal atrial fibrillation: a randomized controlled study. Circulation. 96:2617–2624.

[50] Kay GN, Ellenbogen KA, Giudici M, Redfield MM, Jenkins LS, Mianulli M, Wilkoff B. (1998) The Ablate and Pace Trial: a prospective study of catheter ablation of the AV conduction system and permanent pacemaker implantation for treatment of atrial fibrillation. Journal of Interventional Cardiac Electrophysiology. 2:121–135.

[51] Gasparini M, Auricchio A, Metra M, Regoli F, Fantoni C, Lamp B, et al. (2008) Long-term survival in patients undergoing cardiac resynchronization therapy: the importance of performing atrio-ventricular junction ablation in patients with permanent atrial fibrillation. European Heart Journal. 29:1644–1652.

[52] Leon AR, Greenberg JM, Kanuru N, Baker CM, Mera FV, Smith AL, et al. (2002) Cardiac resynchronization in patients with congestive heart failure and chronic atrial fibrillation: effect of upgrading to biventricular pacing after chronic right ventricular pacing. Journal of the American College of Cardiology. 39:1258–1263.

[53] Brignole M, Botto GL, Mont L, Oddone D, Iacopino S, De Marchi G, et al. (2012) Predictors of clinical efficacy of 'Ablate and Pace' therapy in patients with permanent atrial fibrillation. Heart. 98:297-302.

[54] Nowinski K, Gadler F, Jensen-Urstad M, Bergfeldt L. (2002) Transient proarrhythmic state following atrioventricular junction radiofrequency ablation: pathophysiologic mechanisms and recommendations for management. American Journal of Medicine. 113:596–602.

[55] Evans GT, Scheinman MM, Bardy G, Borggrefe M, Brugada P, Fisher J, et al. (1991) Predictors of in-hospital mortality after DC catheter ablation of atrioventricular junction. Results of a prospective, international, multicenter study. Circulation. 84:1924–1937.

[56] Ozcan C, Jahangir A, Friedman PA, Patel PJ, Munger TM, Rea RF, et al. (2001) Long-term survival after ablation of the atrioventricular node and implantation of a permanent pacemaker in patients with atrial fibrillation. New England Journal of Medicine. 344:1043–1051.

[57] Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA, Freedman RA, Gettes LS, et al. (2008) ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of American College of Cardiology. 51:e1-62.

[58] Linde C, Leclercq C, Rex S, Garrigue S, Lavergne T, Cazeau Set al. (2002). Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation in cardiomyopathy (MUSTIC) study. Journal of the American College of Cardiology. 40:111-118.

[59] Doshi RN, Daoud EG, Fellows C, Turk K, Duran A, Hamdan MH, Pires LA. (2005) Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). Journal of Cardiovascular Electrophysiology. 16:1160-1165.

[60] Brignole M, Gammage M, Puggioni E, Alboni P, Raviele A, Sutton R, et al. (2005) Comparative assessment of right, left, and biventricular pacing in patients with permanent atrial fibrillation. European Heart Journal. 26:712-722.

[61] Leclercq C, Mabo P. (2008) Cardiac resynchronization therapy and atrial fibrillation. Do we have a final answer? European Heart Journal. 29:1597–1599.

[62] Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. (2005) Amiodarone or an implantable cardioverterdefibrillator for congestive heart failure. New England Journal of Medicine. 352:225–237.

[63] Padeletti L, Muto C, Maounis T, Schuchert A, Bongiorni MG, Frank R, et al. (2008) Atrial fibrillation in recipients of cardiac resynchronization therapy device: 1-year results of the randomized MASCOT trial. American Heart Journal. 156:520-526.

[64] Azpitarte J, Baún O, Moreno E, García-Orta R, Sánchez-Ramos J, Tercedor L. (2001) In patients with chronic atrial fibrillation and left ventricular systolic dysfunction, restoration of sinus rhythm confers substantial benefit. Chest. 120:132-8.

[65] Butter C, Winbeck G, Schlegl M et al.(2004) Management of atrial fibrillation in cardiac resynchronization therapy clinical practice of CRT: How to improve the success rate. European Heart Journal. 6: D106–D111.

[66] Chen MS, Marrouche NF, Khaykin Y, Gillinov AM, Wazni O, Martin DO, et al.(2004) Pulmonary vein isolation for the treatment of atrial fibrillation in patients with impaired systolic function. Journal of the American College of Cardiology. 43:1004–1009.

[67] Hsu LF, Jaïs P, Sanders P, Garrigue S, Hocini M, Sacher F, et al. (2004) Catheter ablation for atrial fibrillation in congestive heart failure. New England Journal of Medicine. 351:2373–2383.

[68] Gentlesk PJ, Sauer WH, Gerstenfeld EP, Lin D, Dixit S, Zado E, et al. (2007) Reversal of left ventricular dysfunction following ablation of atrial fibrillation. Journal of Cardiovascular Electrophysiology. 18: 9–14.