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**Invasive treatment of atrial arrhythmias,  
insight in mechanisms  
and outcome of different techniques**

**Rypko J. Beukema**

# Invasive treatment of atrial arrhythmias, insight in mechanisms and outcome of different techniques

## Proefschrift

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# 1

General introduction and outline of the thesis



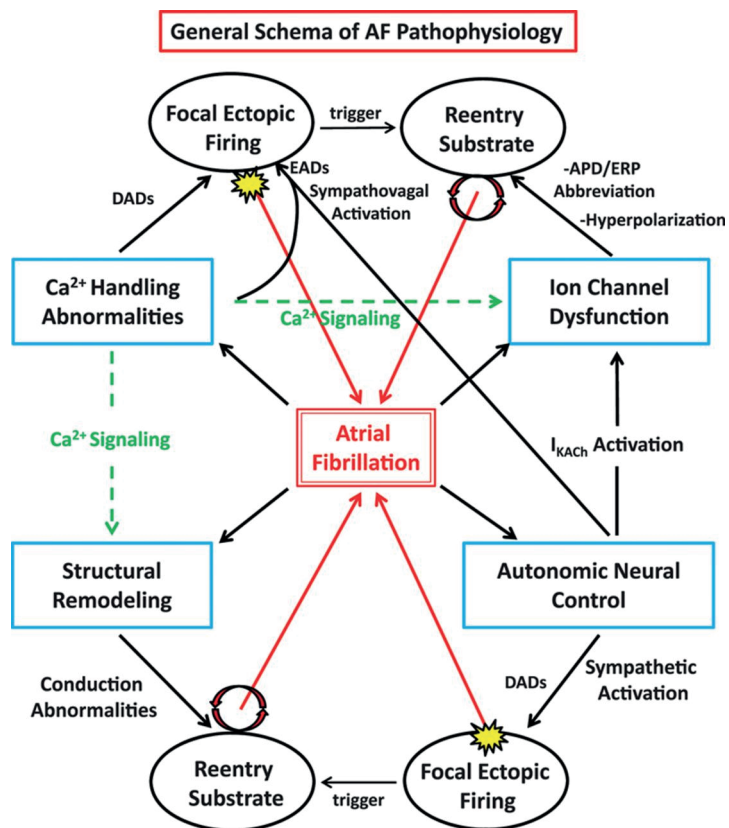
Since the 1980s, computerized multichannel systems for endocardial and epicardial mapping became available and gave insight into the mechanisms of arrhythmias and the opportunity to eliminate the source of arrhythmias with radiofrequency (RF) current. In the last decade the number of ablation procedures of complex atrial arrhythmias such as atrial fibrillation (AF), atypical atrial flutter and focal atrial tachycardia (AT) are increasing exponentially whereas the number of relatively simple ablation procedures such as atrioventricular (nodal) reentry tachycardia hardly increase over the last 10 years.<sup>1</sup> In addition with the rising number of AF/AT ablation procedures, the technique is rapidly changing and knowledge of pathological mechanisms of these conditions is increasing. Despite this progress, efficacy and efficiency of invasive treatment of complex atrial arrhythmias is still limited and AF is far from a curable disease.

### **Epidemiology and electrophysiological mechanism of AF**

AF is the most common arrhythmia, affecting 1-2% of the population and this number is expected to increase in the next decades due to enhanced detection, increases in attributable risk factors and improved survival in patients with cardiovascular conditions predisposing to AF.<sup>2</sup> The most feared complications of AF are thrombo-embolic stroke and heart failure due to rapid ventricular rate. Data from the Stockholm Cohort Study of Atrial Fibrillation showed that the increased mortality seen in patients with paroxysmal AF compared with the general population (HR 1.6; 95% CI, 1.4–1.8;  $P < 0.05$ ) was accounted for by deaths due to cardiovascular causes rather than stroke alone.<sup>3</sup> In addition long-term follow-up of the Framingham population demonstrated still a 1.5- to 1.9-fold increase in mortality in patients with AF after adjustment for preexisting cardiovascular (CV) conditions associated with AF.<sup>4</sup> Taking all this into account an increase in survival trend is seen over the last decades, presumably due to improvements in patient care such as oral anticoagulation to reduce risk of thrombo-embolic complications, together with better and more aggressive diagnosis and treatment of hypertension, ischemic heart disease, heart failure and hypercholesterolemia.<sup>1,5</sup>

It is well known that onset of AF requires triggers to induce the arrhythmia. Triggers increasing vulnerability to AF include alterations in sympathetic or parasympathetic tone resulting in a disturbance of sympathovagal balance. Increased sympathetic tone predisposes to AF by increasing automaticity and triggered activity including early and delayed afterdepolarizations. Enhanced vagal tone increases inducibility of AF by shortening of atrial effective refractory period, increasing dispersion of refractoriness, thereby increasing potential for re-entry. Electrical and structural remodeling may facilitate perpetuation of AF. Clinical, lifestyle and environmental factors play an important role in the genesis of AF. Complex interaction of these

factors result in changes creating an arrhythmogenic milieu favoring re-entry and perpetuation of this arrhythmia.<sup>6</sup> AF itself promotes a process of structural atrial remodeling by alterations in calcium handling, fibroblast activation, connective tissue deposition and fibrosis resulting in electrical dissociation of muscle bundles, which leads in turn to local conduction heterogeneity promoting re-entry and maintenance of the arrhythmia.<sup>6,7</sup> Figure 1 demonstrates a scheme representing the key mechanisms of AF. Most important etiological factors causing enhanced atrial remodeling are diabetes, heart failure, obesity, coronary artery disease, hypertension, aging and genetic predisposition.



**Figure 1** Principle mechanisms that produce and maintain AF, including focal ectopic firing and vulnerable substrates that can maintain re-entry.

APD = action potential duration; DAD = delayed afterdepolarization; EAD = early afterdepolarization; ERP = effective refractory period.

\* figure adapted from Andrade J, Khairy P, Dobrev D, Nattel S. *Circ res.*2014;114:1453-1468.

Many mechanisms have been proposed to explain how AF is commonly encountered in the setting of acute coronary syndrome (ACS). Although many theories exist, the pathophysiological mechanism of the onset of AF in the setting of ACS is still not fully delineated yet. Experimental models and clinical investigations have shown different factors accounting for new-onset AF in ACS. Myocardial infarction causing atrial ischemia or atrial stretch, enhanced inflammation and changes in autonomic nervous system activity. In addition to neurohormonal factors, changes in RAAS and other hormone activations are involved in the pathogenesis of AF development in this patient subset.<sup>8</sup> AF in the setting of ACS is associated with increased morbidity and mortality. Thus, proper understanding of the role of new onset AF complicating ACS will enable clinicians in tailoring treatment in these patients.

### New trends in the treatment of AF

Recent data overwhelmingly support an association between numerous modifiable cardiovascular risk factors and AF; hypertension, obesity, smoking, diabetes mellitus, obstructive sleep apnea and metabolic syndrome. The most recent European Society of Cardiology (ESC) guidelines emphasize the need for a multidisciplinary approach and targeting these risk factors in addition to conventional AF treatment including arrhythmia control and prevention of thromboembolic events.<sup>9</sup> A team of health care professionals, active patient involvement and education on lifestyle and risk factor management is required for the so called integrated AF management. A randomized study in 712 AF patients demonstrated that the nurse-led AF management (nurse-led care consisted of guidelines based, software supported integrated chronic care supervised by a cardiologist) compared to standard AF care resulted in increased use of evidence-based care and reduced by one third the composite outcome of cardiovascular hospitalization and cardiovascular death over a mean follow up of 22 months (14.3% vs. 20.8%, HR 0.65;95% CI 0.45-0.93;p=0.017).<sup>10</sup>

When confronted with the AF patient, a decision should be made as to which approach will be used for long-term management, rhythm control versus rate control. Rhythm control is established with antiarrhythmic drug therapy, cardioversion, radiofrequency (RF) catheter ablation, and/or a surgical procedure to maintain sinus rhythm. Rate control includes rate-slowing drugs or AV nodal ablation plus ventricular pacing. As a consequence many patients need to be reconsidered for the alternate strategy as the natural history of their disease progresses.

Based on the associated medical consequences seen in patients with AF, one would assume that maintenance of normal sinus rhythm would significantly reduce mortality, stroke, heart failure and decline in quality of life. However, the benefit of rhythm control compared with rate control only remains unclear and is an area of considerable debate.

Several prospective randomized trials and meta-analysis were conducted to compare the strategy of rate control with that of rhythm control.<sup>11</sup> The first major trials the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) and the Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) trial, including 4060 and 522 patients respectively, did not demonstrate a benefit of rhythm control on prognosis in terms of survival or combined end point of cardiovascular mortality, hospitalization for heart failure, thromboembolic complications, bleeding, pacemaker implantation, and severe adverse events.<sup>12,13</sup> Also trials conducted in the following years comparing rate- with rhythm control did not show a clear benefit of one approach over the other. In general, limitations of the trials are: a relatively short follow up period, the large cross over between the groups-mainly due to drug intolerance and toxicity-, discontinuation of anticoagulant therapy and a small number of patients actually achieving sinus rhythm (ranging from 26% to 63%).<sup>11</sup>

Moreover at the time the studies were performed, pulmonary vein isolation (PVI) was not yet a widespread method to treat patients with (especially paroxysmal) AF. It is therefore not clear what the effect of rhythm control, including PVI, would be on the prognosis. Ongoing studies such as the Early treatment of Atrial fibrillation for Stroke prevention Trial (EAST) will test whether an early, modern rhythm control therapy can reduce cardiovascular complications in AF.<sup>14</sup>

“Real world” data from European registries show that rate- and rhythm control is not a very strict division. The Euro Heart Survey demonstrates that among all rhythm control patients, 54% was also on typical rate control drugs (digitalis, beta-blocker, verapamil, or diltiazem) and 52% were on amiodarone or sotalol, which are known to also have rate control properties. Taken together, 84% of patients had some type of rate control besides the rhythm control treatment.<sup>15</sup> More recently, the PREFER in AF registry shows that rate control was given to nearly 80% of the entire AF population in Europe, but an isolated rate control strategy was used in only 40%. Rhythm control was the selected strategy in almost 60% of patients. Ablation was undertaken in 12% of those who received rhythm control management, and nearly one-quarter of those with recurrent forms of AF that were not associated with significant underlying heart disease. Thus in practice physicians mostly combine rhythm and rate control and offer ablation mainly in patients without structural heart disease.<sup>16</sup>

Rhythm control therapy is primarily designed to improve AF-related symptoms. Antiarrhythmic drugs, supplemented with cardioversion are recommended treatment options (I A/I B). The choice of antiarrhythmic drugs is based on safety considerations. Catheter ablation has evolved as a first therapeutic choice in AF management. Catheter ablation is the rhythm control therapy of choice in patients with symptomatic

recurrences of AF on antiarrhythmic drug therapy, which is classified as a I A indication for paroxysmal AF and I Ia, level of evidence C for persistent AF. Ablation therapy is even a valid first-line alternative to antiarrhythmic drugs in selected patients with symptomatic paroxysmal AF (I Ia B).<sup>9</sup>

### Catheterablation techniques of paroxysmal AF and “single shot” device techniques

Haïssaguerre and colleagues are the pioneers of techniques ablating ectopic triggers that arise from the pulmonary veins (PV) in paroxysmal AF.<sup>17</sup> Whereas initial reports describe segmental PVI, several randomized trials highlight the importance of complete isolation of the PVs in patients undergoing AF ablation (I Ia B).<sup>9,18</sup>

To reach such objectives it is essential to increase catheter stability, achieve predictable lesion formation, reduce procedure and X-ray exposure time, and make simple and automatic either different steps or the whole procedure by using an anatomically-based ablation approach.

The conventional technique for many years was ostial, lasso-guided, circumferential, point-by-point RF ablation of the PVs. These point-by point ablation procedures are relatively complex, lengthy procedures, requiring extensive left atrial (LA) mapping and the use of multiple catheters and often multiple transseptal punctures. This results in a slow learning curve, with success and safety dependent on operator experience. Spragg et al analyzed the complication rate in 641 AF ablations at the Johns Hopkins Hospital. Major complications occurred in 5% of the patients. Operator experience played a significant role; 9% occurred during the first 100 and 4.3% during the subsequent 541 procedures. The most recent consensus statement on AF ablation suggest that safety and efficacy results are better in centers performing more than 100 procedures annually.<sup>19,20</sup>

With the growing demand for AF ablation and relatively limited experienced operators, the use of a simpler, faster and less expensive technique for PVI was desirable. New technical developments aiming to simplify PVI and increase safety were developed in the last decade. The so called single-shot devices require a single trans-septal puncture and the simultaneous application of energy in order to perform easier, faster and safer procedures using circular catheters or balloon-like ablation devices. Four types of energy sources exist for single shot devices, i.e. RF, cryo-energy, ultrasound and laser energy.

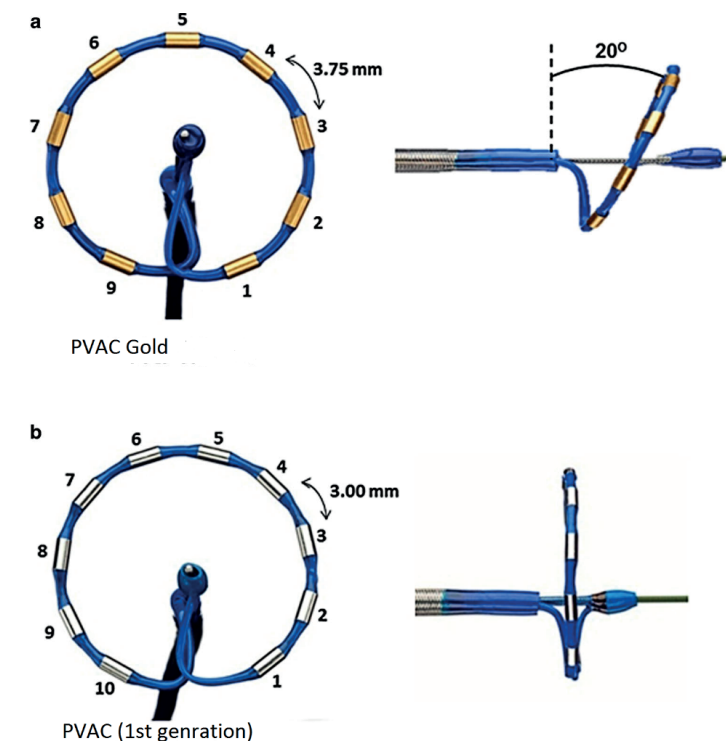
The 'single shot' multi-electrode circular ablation catheter, i.e. pulmonary vein ablation catheter (PVAC) consists of a 9 French (Fr), over-the-wire, decapolar circular mapping and ablation catheter (Medtronic Ablation Frontiers LLC, Carlsbad, CA, US). The system is designed to apply duty-cycled phased unipolar and bipolar RF energy over initially 10 and in the latest design 9 PVAC electrodes positioned at the antral part of the PV. The application of energy can shift from unipolar (deeper lesion) to bipolar (more contiguous lesion). Clinical success rates of PVI were similar to conventional point-by-point ablation using a three-dimensional (3D) navigation system. However, total procedural and fluoroscopic times were significantly shorter by using the PVAC.<sup>21,22</sup> Studies by Gaita et al. and Siklódy et al. raised a safety concern for the first generation PVAC catheter with platinum electrodes. This first generation PVAC was associated with a significantly higher rate of (asymptomatic) cerebral micro-embolisms occurring after PVAC ablation compared to irrigated RF ablation and cryoballoon.<sup>23,24</sup> The cause for embolism was electrode overheating, which was particularly found when electrodes 1 and 10 were in close proximity during ablation. In order to overcome this problem, a trial with specific procedural changes was carried out, the evaluation and Reduction of Asymptomatic Cerebral Embolism (ERACE) study. In this trial the ablation procedure was undertaken under therapeutic vitamin K antagonist and heparin for an activated clotting time > 350 seconds, the catheter was loaded into the introducer while submerged in saline solution to prevent air entrance, and the distal or proximal electrode of the circular catheter was shut off to prevent bipolar RF interaction. Using this strategy, the rate of subclinical cerebral embolism was reduced to a much lower 1.7%.<sup>2</sup>

Recently a new design of the PVAC catheter, PVAC-Gold was introduced which contains 9 gold electrodes instead of 10 electrode to overcome the overlapping, interaction issue (figure 2). Gold has more than 4 times better thermal conductivity than that of platinum, thereby providing faster cooling and more precise temperature control. Additionally, the array of the PVAC GOLD catheter is tilted forward by 20° relative to the catheter shaft in order to improve electrode to tissue contact.<sup>26</sup>

The first studies with the PVAC gold catheter demonstrate that the efficiency is comparable to the first generation device. Furthermore an improved biophysical efficiency and low incidence of asymptomatic cerebral embolism with the PVAC-Gold catheter is found.<sup>26,27</sup>

Another RF single shot device is the nMARQ (Biosense Webster) which is an irrigated circular multipolar catheter which allows for simultaneous mapping and ablation. The catheter is integrated into the CARTO electro-anatomic mapping system. Small series report efficacy and safety outcomes comparable to other techniques.<sup>2</sup>

Cryoballoon ablation (Artic Front®, Medtronic) is an ablation technique which relies on a nitrogen filled balloon capable of reaching temperatures of -50° -60° C leading to necrosis by freezing. The balloon is inserted into the ostium of the PV allowing a real one-shot energy delivery to the PV antrum, an additional multipolar wire distal to the balloon shows electrogram recordings and allows evaluation of PVI during the Cryo energy application. Recently the results of the FIRE AND ICE trial were published. This was a multicenter, randomized, noninferiority trial, with blinded end-point assessment, in which cryoballoon ablation was compared with RF ablation in 762 paroxysmal AF patients. The primary efficacy end point of time to first recurrence of



**Figure 2** PVAC catheter design.

- a) The newly designed PVAC Gold catheter  
 b) The 1<sup>st</sup> generation PVAC catheter. Several key improvements have been implemented: the ablation electrodes are made of Gold instead of Platinum; the new catheter consists of 9 electrodes; the inter-electrode spacing is increased to 3.75 mm to retain the effective arc length; the electrodes are at a 20° forward tilt.

\* figure adapted from . Gal P, Buist T, Smit JJJ et al. Neth Heart J. 2017 Jan; 25(1): 16–23.



AF (lasting >30 seconds), atrial flutter, or AT, use of antiarrhythmic drugs, or reablation occurred in 34.6% of the cryoablation group and 35.9% of radiofrequency ablated patients. The results met the noninferiority threshold (hazard ratio [HR] 0.96;  $P < 0.001$ ).<sup>29</sup> Moreover, regarding the secondary endpoints, cryoballoon ablation, as opposed to radiofrequency ablation, showed significantly fewer repeat ablations, direct-current cardioversions, all-cause rehospitalizations, and cardiovascular rehospitalizations during follow-up. Both patient groups improved in quality-of-life scores after AF ablation.<sup>30</sup>

High-intensity focused ultrasound (HIFU), applied via a balloon catheter, integrates a 9 megahertz ultrasound crystal which generates a ring of ultrasound energy at the base of the balloon. The third generation of HIFU-BC is steerable through a pull wire mechanism integrated in the handle of the catheter and is available in different balloon sizes from 20 mm to a maximum of 32 mm diameter (ProRhythm Inc, Ronkonkoma, New York, US). The catheter also has a lumen for insertion of a hexapolar spiral mapping catheter to record PV potentials. Initial reports using first and second generation HIFU balloon catheters describe long procedure times and limited efficacy (isolation of all PVs in 50 % of patients). Serious complications such as phrenic nerve palsy and deleterious atrial–oesophageal fistula were also reported. Later series with a technically improved third generation HIFU balloon demonstrated better outcome (acute PVI in 80% of all PV and 60% of veins after a single shot). No atrial–oesophageal fistula was reported and phrenic nerve palsy incidence was comparable to other balloon technologies. Despite of technical improvements, navigation and positioning were still challenging and this technique therefore has been abandoned for clinical use.<sup>31</sup>

The visually-guided ablation using a laser balloon (VGLB) technology (HeartLight, CardioFocus, Marlborough, Massachusetts) is a catheter with a variable-diameter, compliant balloon with a flexible tip that is delivered through a 12-Fr deflectable sheath. Within the central shaft of the balloon catheter is a 2-Fr endoscope that permits real-time visualization of the target tissue. The central shaft contains lumens for circulating deuterium oxide (D<sub>2</sub>O) to cool the balloon, a maneuverable optical fiber that generates a ~30° arc/spot of both nonablative visible light and near-infrared ablative light energy. This arc of light can be maneuvered to any location along the surface of the balloon to allow aiming and then ablation using diode laser energy (980 nm). The shaft of the catheter contains a radiopaque marker that can be visualized on fluoroscopy and allows correlation orientation between endoscopic and fluoroscopic images. In theory, this technology has distinct advantages over both point-by-point ablation and the cryoballoon catheter. It offers stable catheter position and contiguous lesions like other balloon-based technologies. Moreover it

has the ability to selectively titrate energy to each part of the circumferential lesion set like point-by-point RF ablation. In addition, the laser balloon diameter can be changed dynamically to suit each PV antrum. Furthermore it is the first ablation technology to allow the operator to directly visualize tissue changes during ablation.<sup>32</sup>

There is one randomized controlled study comparing the efficacy and safety of VGLB ablation with standard point-by-point RF ablation. A total of 353 patients (178 VGLB, 175 control) were randomized to either technique. A 12 months 61.1% in the VGLB group versus 61.7% in controls (absolute difference 0.6%; lower limit of 95% confidence interval [CI]: 9.3%;  $p < 0.003$  for noninferiority) were free of AF. Adverse events occurred in 11.8% of the VGLB group versus 14.5% in controls (absolute difference 2.8%; upper limit of 95% CI: 3.5;  $p < 0.002$  for noninferiority), and was mainly driven by cardioversions. The mean procedure time for VGLB was  $236.0 \pm 52.8$  minutes which is remarkably long for a single shot device. This may be in part be due to the relative inexperience of the operators.<sup>33</sup>

Single shot devices are nowadays routine ablation tools for paroxysmal AF in many electrophysiology laboratories worldwide. One has to acknowledge that more advanced substrate requires more than PVI alone. Therefore alternative ablation instruments are indispensable.

### Macro reentry- and focal atrial tachycardia

AT is defined as an organized atrial arrhythmia with a stable morphology and a stable activation sequence in both atria. The cycle length of an AT is usually stable, although there may be some variation depending on the underlying mechanism. The 2 following types of AT can be clearly differentiated based on their electrophysiologic mechanisms: macro re-entrant AT and focal AT (due to an automatic, triggered, or micro re-entrant mechanism)

Macro re-entrant AT comprises a heterogeneous group of right- or left atrial macro re-entrant circuits related to different anatomical and electrophysiological substrates. These arrhythmias are frequently associated with structural heart disease, congenital cardiac defects, previous cardiac surgical procedures, or surgical or catheter ablation procedures for AF. Often, these arrhythmias coexist with AF. Particularly extensive substrate modification generates focal areas of slow conduction and low voltage capable of sustaining localized reentry. The post-AF ablation macro reentry AT is a novel “iatrogenic” arrhythmia which is rapidly rising in number in a time where AF ablation procedures are expanding and the amount of tissue is not restricted to the PV antrum. The prevalence of left atrial AT after antral PVI is 4-11% and these arrhythmias typically occur within the first months of the initial ablation procedure.<sup>34,35</sup>

However after stepwise approach of persistent AF, including PVI and extended lesions in left and right atrium up to 40% of patients may develop post procedural ATs.<sup>36</sup>

The ECG has limited value in localizing the AT mechanism and circuit especially in the ablated atrium. The first step in the electrophysiology laboratory is the diagnosis of the mechanism underlying the AT. A simple distinction can be made by mean cycle length variation. If the variation of the mean cycle length during one minute is >15% a focal mechanism is the most likely diagnosis. On the other hand if the variation is <15% it does not rule out focal mechanism. Entrainment mapping is the next step; if the AT is entrained from three distinct atrial segments (e.g. septal, posterior or lateral LA for perimitral flutter) with post pacing intervals (PPI) < 30 msec at each of the sites, macro re-entry is confirmed. If this is not the case, macro re-entry is ruled out. Three dimensional electro-anatomic activation mapping displays the activation sequence of the AT within the atrial anatomy. Areas of constrained activation (usually scar or anatomic barrier) can be identified as a potential critical isthmus and is the target for ablation.<sup>37,38</sup>

Shah et al., demonstrated that 73% of ATs developing after AF ablation in paroxysmal and persistent AF were related to narrow, critical isthmuses usually involving the ridge between the left PVs and the LA appendage. When this isthmus was found, the AT usually could be terminated with 1 RF energy application; otherwise, long linear lesions (mitral isthmus or LA roof) lines had to be performed. RF ablation of these arrhythmias can be challenging and time consuming often due to tissue thickness, inability to create a transmural lesion or modification of the circuit resulting in new flutter circuits.<sup>39</sup>

True focal AT can have a variety of causes and mechanisms; (micro-)reentry, abnormal automaticity, and triggered activity.<sup>40</sup> Often focal AT occurs in patients without structural heart disease. The AT has a focal origin of activation that spreads centrifugally to both atria. Typically, activation is not continuous throughout the cardiac cycle length, which is the hallmark of re-entry. The origins are seen in both atria and are not randomly distributed. Kistler et al reported on 186 consecutive patients presenting for AT ablation and found that 63% of them were located in the right atrium (RA) and 37% in the LA.<sup>41</sup> In the LA, preferential AT sites include the PVs (upper veins are more common than the lower veins), mitral annulus, and coronary sinus musculature or atrial appendage. In the RA, preferential AT sites include the crista terminalis, tricuspid annulus, and perinodal area.<sup>42</sup> The perinodal origin may in fact arise from either side of the inter atrial septum or from the noncoronary aortic cusp. Tachycardias from this particular region are probably underestimated because

mapping of the noncoronary cusp is not a standard procedure for perinodal ATs.<sup>43,44</sup> Pharmacological treatment generally has limited efficacy and many patients experience side effects of antiarrhythmic drugs. Therefore, RF ablation is the preferred strategy for patients with significant symptoms. The major limitations to success is insufficient ectopy or tachycardia to allow the detailed activation mapping required to identify the site of origin (and provide an accurate end point to the procedure) and safe and stable catheter position. Multi-electrode three-dimensional electroanatomic mapping systems and image integration has enormously facilitated these procedures.

### Stand alone surgical AF therapy and hybrid ablation

Surgical therapy for AF is generally reserved for patients refractory to antiarrhythmic drugs and catheter ablation. The classic cut-and-sew maze procedure has been applied by relatively few surgeons. Although a 80-90% maintenance of sinus rhythm is described without antiarrhythmic medication on long term follow up, this procedure hasn't gained widespread acceptance due to its complexity and associated morbidity.<sup>45,46</sup> The Cox-maze IV procedure has replaced the "cut-and-sew" technique of the original Cox-maze operation with lines of ablation created by using bipolar RF and cryothermal energy devices.<sup>47</sup>

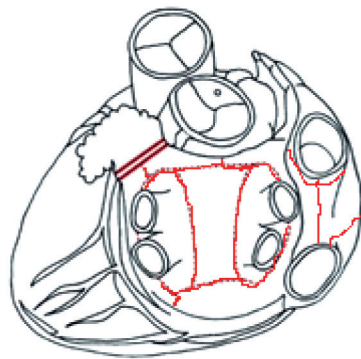
In 2005 a minimally invasive video-assisted thoracoscopic surgical (VATS) approach has been introduced. In contrast to the traditional Cox-maze procedures, the VATS technique is an epicardial stand-alone ablation on the beating heart using bipolar radiofrequency energy.<sup>48</sup>

Since its introduction there is a wide variety of approaches regarding access site (right, bilateral, subxyphoidal), lesion sets and energy sources to create lines of conduction block including RF, microwave, ultrasound, cryotherapy, and laser. RF, laser, ultrasound and microwave are heat-based energy sources that create lines of conduction block through thermal injury. Nowadays bipolar RF ablation is mostly used, it is performed by clamping atrial tissue and heating it between two electrodes until irreversible protein denaturation occurs. Its jaw-clamp structured device has the advantage of allowing real-time assessment of transmural lesions by measurement of impedance as atrial tissue is clamped and ablated.<sup>48</sup>

Three broad lesion sets in the surgical treatment of AF include (wide) PV isolation, LA lesion set and biatrial lesion set resembling a cox maze IV pattern (figure 3). Commonly performed lesions apart from the PV circles include a roofline connecting both superior PVs, a line from the roof line to the left trigone, a line from the superior PV to the LA appendix (LAA), a line from the RIPV to the coronary sinus, a superior vena cava and inferior vena cava circumferential lesion, and an intercaval line (line between



SVC and IVC). Additional lesions and different combinations of these lines varies between operators and generally depends on the amount of substrate and registered arrhythmias. Paroxysmal AF, which is mainly PV trigger related, can be treated by wide PVI. There is growing consensus that in patients with persistent or long-standing persistent AF a lesion set that incorporates more than PVI is more effective. In such patients, the lesion from the right PVs to the mitral annulus may be particularly important in prevention of post-procedure LA flutter.<sup>49</sup>



**Figure 3** Posterior view of the heart with common epicardial ablation lines (red) as applied in minimal invasive thoracoscopic AF ablation. See text for details.

A randomized controlled trial comparing minimally invasive surgical ablation vs catheter ablation (FAST trial). The surgical ablation consisted of the “Dallas” lesion set, which includes the use of bilateral PV antral isolation using a bipolar RF clamp with ganglionic plexi ablation. Subsequent linear ablation included a LA roof line, a line between the roof and the left fibrous trigone (anterior trigone line), and a line to the base of the resected LAA. This study demonstrates superior freedom from AF at 12 months with surgical ablation though at the cost of a higher rate of adverse events (23% vs. 3% in the catheter ablation group;  $P < 0.001$ ). Adverse events related to surgery include need for pacemakers (5%), hemothorax (3%), phrenic nerve injury (3%), transient ischemic attack (1%) and pulmonary embolism (1%).<sup>50</sup>

Outcomes from the Society of Thoracic Surgeons (STS) database from 2005 to 2010, comparing minimally invasive surgical ablation vs. sternotomy for lone AF, demonstrated a complication rate of 0.7% for mortality or stroke, 1% for need of pacemaker and a median length of hospital stay of 4 days.<sup>51</sup>

The hybrid thoracoscopic and transvenous approach combines an epicardial ablation with a percutaneous endocardial ablation in a single-step or sequential procedures. The combination of endocardial/epicardial lesions potentially improves transmuralty. The exact approaches, techniques, lesion sets, peri-procedural care, and endpoints differ substantially per center. However the fundamental principle is that the procedure starts with thoracoscopic epicardial ablation including antral PV isolation and a roofline. The right atrial lesions are less frequently used than the left atrial lesions. The endocardial procedure, either immediate or staged, is performed to ensure adequacy of PVI and bidirectional block across lines of ablation as well. The mitral isthmus and the tricuspid isthmus lines are particularly difficult to ablate from the epicardial surface of the heart and often require additional endocardial touch up.<sup>52,53</sup>

Data comparing immediate versus delayed endocardial procedure is limited. Each approach has advantages and disadvantages. The one step is time-consuming for both the surgeon and electrophysiologist and it requires careful peri-procedural anti-coagulation management with simultaneous transseptal and endoscope access. Furthermore a delayed endocardial procedure allows for healing from surgical wounds as well as epicardial lesion maturation. Advantages of a one step approach are that epicardial ablation can be guided by endocardial mapping and additional epicardial applications can be performed. Furthermore the surgeon is able to protect the phrenic nerve and esophagus from injury during endocardial ablation.<sup>52, 53</sup>

Mahapatra et al compared hybrid ablation in 15 patients with persistent and long-standing persistent AF to a matched control group of patients undergoing a repeat catheter ablation procedure. The surgical lesion set consisted of epicardial PVI, roof line, trigone line, superior vena cava isolation, LAA amputation, and ablation of the ganglionated plexi. After 3 to 5 days, all patients were brought to the electrophysiological lab for cavotricuspid isthmus and coronary sinus ablation. The authors reported a hybrid ablation success rate of 86.7% (13/15), off antiarrhythmic drugs, during a mean follow-up of  $20.7 \pm 4.5$  months whereas only 53% (16/30) of patients with extensive catheter ablation alone were free of AF without drugs.<sup>54</sup>

### Monitoring for AF recurrences

Assessment of clinical mid- and long term outcome after catheter- or surgical AF ablation remains a subject of discussion.

Success rates after AF ablation are currently based on symptoms, intermittent standard ECG recordings, and ambulatory long-term monitoring. However, asymptomatic AF is very common. Hindricks et al showed that >50% of patients with AF had a mixture

of symptomatic and asymptomatic AF prior to ablation, whereas only 38% of patients recognized all AF episodes accurately. After catheter ablation, the incidence of asymptomatic AF significantly increased: At 3, 6, and 12 months' follow-up, 38%, 37%, and 36% of patients with arrhythmia recurrence were completely asymptomatic.<sup>55</sup>

Several reasons may explain this phenomenon. First of all the placebo effect of an invasive procedure on the perception of AF. Another reason is a change in arrhythmia pattern after ablation therapy. Furthermore PVI creates partial autonomic denervation which may have an impact on the perception of AF.

Although symptomatic AF is the main indication for ablation, symptoms alone are an unreliable instrument for determination of success given the poor correlation between reported symptoms and AF. Also, from a scientific point of view and for comparing different ablation therapies an accurate number of recurrence of atrial arrhythmias is essential.

Implantable loop recorders have a sensitivity of > 95% and a negative predictive value which is even higher for identifying patients with any AF compared to Holter recordings, which makes it an attractive tool for detecting patients with AF recurrences.<sup>56</sup>

## Outline of this thesis

This dissertation comprises ten chapters grouped in three parts. The first part (Chapter 2 and 3) elaborates on clinical aspects and pathology of AF. **Chapter 2** addresses the prognostic predictive value of AF in the setting of an ST elevation acute coronary syndrome. **Chapter 3** describes the electrophysiological effects of acute left atrial dilatation and dedilatation in humans with long-standing persistent AF. The second part of the thesis (chapters 4, 5 and 6) focusses on percutaneous ablation of AF and AT. **Chapter 4 and 5** present the efficacy and efficiency of paroxysmal AF ablation with the multi-electrode duty-cycled RF ablation catheter. **Chapter 6** reviews the characteristics of focal AT originating from the aortic cusp. The third part (Chapter 7-9) discusses surgical management of AF and follow up methods. **Chapter 7** describes the results of a randomized, clinical trial comparing surgical ablation to catheter ablation for lone AF. **Chapter 8** demonstrates aspects and catheter ablation results of recurrent atrial arrhythmias after surgical AF ablation. **Chapter 9** evaluates AF burden monitoring techniques after AF surgery. **Chapter 10** contains the general discussion and summary of this thesis.

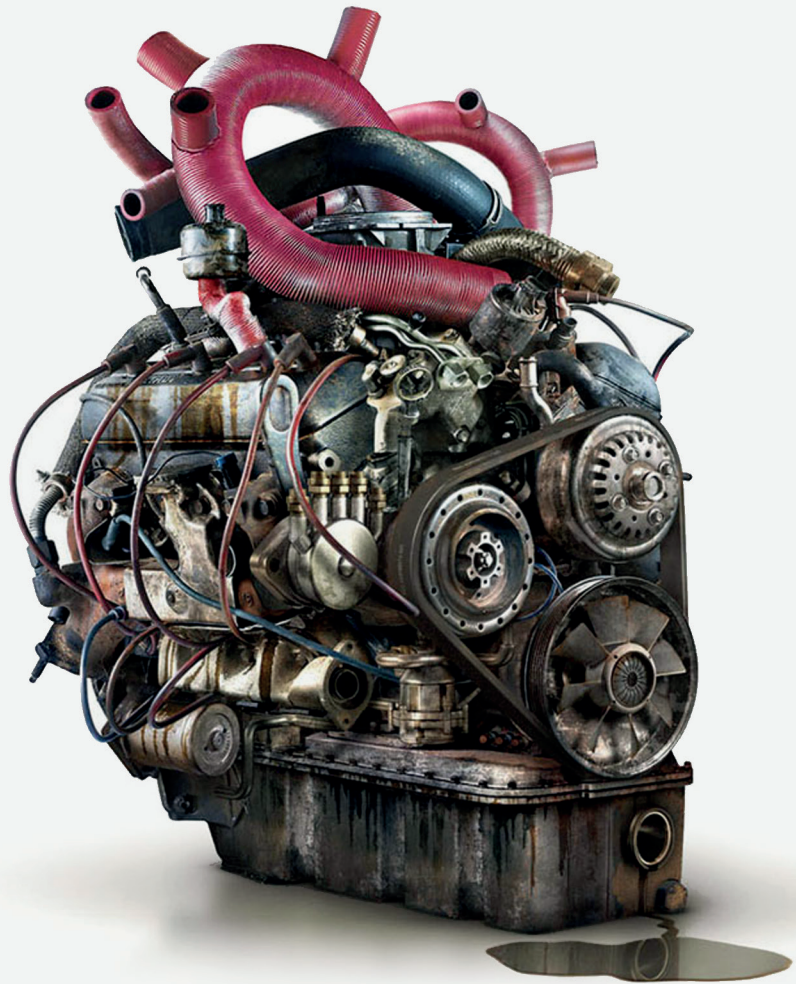
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# Part one

Clinical aspects and pathology of atrial fibrillation



# 2

## Atrial fibrillation after but not before primary angioplasty for ST-segment elevation myocardial infarction of prognostic importance

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## Abstract

### Aim

In patients with ST-segment elevation myocardial infarction (STEMI), it is uncertain whether atrial fibrillation has prognostic implications. There may be a difference between atrial fibrillation before and after reperfusion therapy.

### Methods and results

In patients with STEMI treated with primary percutaneous coronary intervention (PCI), ECGs were analysed before and after primary PCI. Of the 1623 patients with electrocardiographic data before primary PCI, 53 patients (3.3%) had atrial fibrillation. Patients with atrial fibrillation were older, were more often female, and less often had anterior MI location. Of the 1728 patients with electrocardiographic data after primary PCI, 52 patients (3.0%) had atrial fibrillation. Atrial fibrillation was more common in older patients and in those with Killip class >1. Also patients with occlusion of the right coronary artery or TIMI flow 0 before primary PCI more commonly had AF after the procedure. Not successful reperfusion was also associated with a higher incidence of AF after primary PCI. Although both atrial fibrillation before and after primary PCI were associated with increased mortality, multivariable analyses, adjusting for differences in age, gender and Killip class on admission, revealed that atrial fibrillation after PCI (OR 3.69, 95% CI 1.87–7.29) but not before PCI (OR 1.86, 95% CI 0.89–3.90) was independent and statistically significantly associated with long-term mortality.

### Conclusion

In patients with STEMI, atrial fibrillation after but not before primary PCI has independent prognostic implications. Possibly, atrial fibrillation after the PCI is a symptom of failed reperfusion and a sign of heart failure.

## Introduction

Atrial fibrillation (AF) is a commonly encountered arrhythmia in patients with acute myocardial infarction (AMI) with an overall incidence of 5–22%.<sup>1, 2, 3, 4, 5, 6, 7, 8, 9</sup> The predictive value of AF in diverse forms of ACS has been extensively studied. These observations stressed the importance of the time of the onset, the duration and the recurrence rate of AF to identify patients in increased risk of adverse events.<sup>4, 6, 10, 11</sup> The incremental predictive value of AF, however, has remained a matter of discussion given the large overlap between factors increasing the risk of developing AF and other cardiovascular adverse events. Furthermore, most of these results are provided by studies conducted in the thrombolysis or pre-thrombolysis era, and little is known about the impact of AF on cardiovascular risk in patients undergoing primary PCI for ST-segment elevation MI (STEMI).<sup>4</sup> Besides, the majority of studies on this subject are substudies of clinical trials and due to specific exclusion criteria, characteristics of the patient samples studied are different from the average patient hospitalised with a myocardial infarction. Our aim was to investigate the predictive value of AF with regard to its time of onset (i.e. before or after reperfusion therapy) in patients undergoing primary PCI for STEMI and to identify predictors for development of AF in STEMI patients.

## Methods

### Patients

Between April 1997 and December 2002, 2134 patients with symptoms consistent with acute MI of >30 min duration, presenting within 24 h after the onset of symptom and with a ST-segment elevation of more than 1 mm (0.1 mV) in two or more contiguous leads on the electrocardiogram, were admitted. All patients were treated with an invasive approach, with primary PCI performed with standard techniques if the coronary anatomy was suitable for PCI. Angiographically successful reperfusion was defined as TIMI flow grade 3, in combination with a myocardial blush grade 2 or 3. Additional treatment consisted of intravenous heparin, nitroglycerin and aspirin. After sheath removal, low-molecular-weight heparin was given for 1 to 3 days. Follow-up data were collected up to 18 months after randomisation via the registry office, the general practitioner, or via direct contact with the patient or his relatives by telephone. The research protocol was reviewed and approved by the medical ethics committee of our hospital, and patients were included after informed consent.

## Measurements

Electrocardiography (ECG) was performed at admission (first ECG), and at 3 h after PCI (second ECG), according to the protocol. All ECGs were analysed as pairs by an independent core laboratory (DIAGRAM BV, Zwolle, the Netherlands) and graded for ST-segment elevation resolution by two investigators who were unaware of the clinical data, angiographic findings, and outcome.

## Statistical analysis

Differences between group means at baseline were assessed with the two-tailed Student's t-test. Chi-square analysis or Fisher's exact test was used to test differences between proportions. Survival was calculated by the Kaplan-Meier product-limit method. The log-rank test was used to evaluate differences in survival curves. The Cox proportional-hazards regression model was used to calculate relative risks adjusted for differences in baseline characteristics. To predict the independent association between atrial fibrillation and clinical characteristics, multivariable logistic regression analysis was performed. Statistical significance was considered a two-tailed p value <0.05. The Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 10.1 was used for all statistical analysis.

## Results

Of the included 2134 patients, electrocardiographic data were available in 1623 patients (76%) before the primary PCI, and in 1728 patients (81%) after the primary PCI. Paired ECGs were available for 1472 patients. The mean age of the 2134 patients was 60.7 years (range 24–89) and there were 475 females (22%).

### Atrial fibrillation before primary PCI

Of the 1623 patients with electrocardiographic data before primary PCI, 53 patients (3.3%) had atrial fibrillation. Differences between patients with and without atrial fibrillation before primary PCI are summarised in Table 1. Patients with atrial fibrillation were older, were more often female and less often had anterior MI location. Independent predictors of AF before PCI were age (OR 1.04/years, 95% CI 1.03–1.07), Killip class >1 (OR 4.7, 95% CI 2.38–9.36), and inferior infarct location (OR 2.39, 95% CI 1.3–4.38).

### Atrial fibrillation after primary PCI

Of the 1728 patients with electrocardiographic data after primary PCI, 52 patients (3.0%) had atrial fibrillation. Differences between patients with and without atrial fibrillation after primary PCI are shown in Table 2. Atrial fibrillation was more common

**Table 1** Baseline characteristics of 1623 patients with data on atrial fibrillation before primary PCI.

Characteristic	Atrial Fibr. (N=53)	Sinus rhythm (N=1570)	p-value
Age, yrs (mean ± SD)	66 ± 11.2	60.5 ± 11.3	0.001
Men	66	78	0.03
Previous MI	9.4	9.7	0.95
Previous PCI	2	4.5	0.36
Previous CABG	0	2	0.30
History of stroke	2	3	0.67
Diabetes mellitus	8	11	0.45
Hypertension	25	28	0.60
Currently smoker	43	53	0.19
Hypercholesterolaemia	17	21	0.46
Killip class > 1	25	6	0.001
Family history	40	40	0.92
Anterior MI	30	49	0.009
Multi-vessel disease	60	53	0.28
Occlusion of LAD	30	45	0.04
Occlusion of RCA	47	34	0.06
TIMI 0 flow before PCI	57	60	0.59
Collaterals	6	9	0.38
Successful reperfusion*	79	88	0.06

Data are mean (standard deviation) or % unless otherwise indicated. MI = myocardial infarction. CABG = coronary artery bypass grafting. \* Successful reperfusion denotes TIMI 3 flow and blush grade 2 or 3

in older patients and in those with Killip class >1. Also patients with occlusion of the RCA or TIMI flow 0 before primary PCI more commonly had AF after the procedure. Unsuccessful reperfusion was associated with a higher incidence of AF.

Multivariable analyses revealed that statistically significant independent predictors of AF after PCI were age (OR 1.06/years, 95% CI 1.03–1.09), Killip class >1 (OR 2.6, 95% CI 1.2–5.7), and occluded RCA (OR 2.2, 95% CI 1.3–3.9). Failed reperfusion by primary PCI was not independently associated with post-procedure AF (OR 1.88, 95% CI 0.93–3.79).

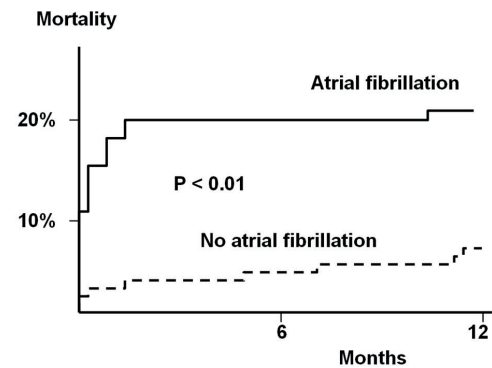
**Table 2** Baseline characteristics of 1728 patients with data on atrial fibrillation after primary PCI.

Characteristic	Atrial Fibr. (N=52)	Sinus rhythm (N=1676)	p-value
Age, yrs (mean $\pm$ SD)	67 $\pm$ 9.8	60.2 $\pm$ 11.3	0.001
Men	75	78	0.59
Previous MI	17	9.5	0.06
Previous PCI	5.8	4.1	0.56
Previous CABG	2	2	0.99
History of stroke	2	3	0.66
Diabetes mellitus	6	11	0.25
Hypertension	33	27	0.37
Currently smoker	40	54	0.05
Hypercholesterolaemia	25	21	0.53
Killip class > 1	17	6	0.001
Family history	33	42	0.20
Anterior MI	40	49	0.23
Multi-vessel disease	69	52	0.02
Occlusion of LAD	39	46	0.28
Occlusion of RCA	54	34	0.003
TIMI 0 flow before PCI	75	61	0.04
Collaterals	6	9	0.40
Successful reperfusion*	79	89	0.03

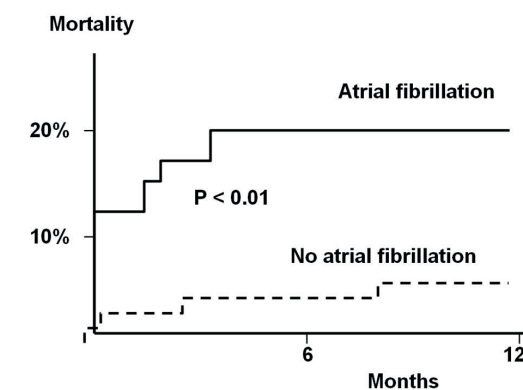
Data are mean (standard deviation) or % unless otherwise indicated. MI = myocardial infarction. CABG = coronary artery bypass grafting. \* Successful reperfusion denotes TIMI 3 flow and blush grade 2 or 3

### Mortality

Data on long-term survival were available in 1683 patients (79%) in the total study group, with a mean follow-up duration of 481 days (SD: 281). In this group, a total of 129 patients (7.7%) died during follow-up. In the 1623 patients with data on atrial fibrillation before PCI, follow-up data were available in 1198 patients; 72 patients (6.0%) died during long-term follow-up (Fig. 1). Among the 1728 patients with data on atrial fibrillation after PCI, follow-up was available of 1270 patients (71%). Of these patients, 71 (5.3%) died during the follow-up period (Fig. 2). Particularly in patients who died before the PCI, or shortly thereafter, no data on rhythm were available.



**Figure 1** Kaplan-Meier curves of patients with or without atrial fibrillation before primary PCI.



**Figure 2** Kaplan-Meier curves of patients with or without atrial fibrillation after primary PCI.

Both atrial fibrillation before and after primary PCI were associated with increased long-term mortality. Mortality in patients with pre-PCI AF was 21% while in those without AF only 5% ( $p < 0.01$ ). In patients with AF after primary PCI, mortality was 23% in contrast to 4.7% in those without AF after primary PCI ( $p = 0.001$ ).

After adjusting for differences in age, gender and Killip class on admission by means of multivariable analyses, however, atrial fibrillation after PCI (OR 3.69, 95% CI 1.87–7.29) but not before PCI (OR 1.86, 95% CI 0.89–3.90) remained statistically significantly associated with long-term mortality.



## Discussion

The current study underlines the importance of AF in identifying STEMI patients in increased risk, probably requiring more aggressive therapy and closer follow-up.

### Prevalence of AF

The overall prevalence of AF among AMI patients has been reported in a range of 5–22%. More recent studies show a slight decrease in incidence of AF in acute myocardial infarction compared with studies of the 1990s. This observed trend might be due to changing definitions of AF, size and characteristics of patient samples studied and differences in therapies that may decrease the risk of AF.<sup>1-8, 12</sup> This trend may be countered by the fact that patients involved in more recent studies (i.e. treated with thrombolysis or primary PCI) were older and in a worse cardiovascular condition than those involved in studies of the pre-thrombolytic era.<sup>1</sup> Advanced age and worse haemodynamic state (worse Killip class) have been uniformly associated with the development of AF in studies involving patients treated conservatively or with thrombolysis or, most recently, with primary, PCI.<sup>2, 3, 4</sup> Divergent results are available about the relation between the development of AF and the infarct-related artery (IRA), male or female gender, the presence of hypertension or diabetes.<sup>1-8</sup> In the present study, AF was diagnosed in 3.3% of patients on admission and was associated with advanced age, worse Killip class and inferior infarct location.

Post-PCI AF was diagnosed in 3% of our patients and was associated with advanced age, worse Killip class and the occlusion of RCA. Post-PCI AF, however, was assessed on ECGs obtained 3 h after the procedure, thus representing early AF occurrence. No additional data are available about AF occurrence during the preceding and the following period of hospitalisation. This offers an explanation for the lower post-PCI AF rate as compared with the findings of Kinjo et al.<sup>4</sup> In that study the rate of post-PCI AF was 7.7% representing AF occurrence rate during the entire hospitalisation. Similar in-hospital occurrence rates were reported by Pizzetti et al. (6%), Wong et al. (6.5%) and Crenshaw et al. (7.9%) among patients treated with thrombolysis.<sup>2, 6, 8</sup> Associated risk factors have been divergent among these studies regarding infarct-related artery, hypertension and diabetes, but worse Killip class and advanced age have been uniformly associated with the development of AF. The AF mechanism in acute coronary artery disease is multifactorial. Experimental studies in dogs revealed that atrial ischaemia promotes AF triggers and creates a substrate for AF maintenance by sustained reentry.<sup>13, 14</sup>

### Predictive value of AF

The prognostic value of AF in long-term and in-hospital mortality has been extensively studied previously in the thrombolytic and pre-thrombolytic era, and a recent meta-analysis revealed that AF in myocardial infarction was associated with at least a 40% increase in mortality compared with patients with sinus rhythm.<sup>15</sup> However, there is great variation among the different studies.<sup>9</sup>

In the pre-thrombolytic era, the prognostic importance of AF in patients suffering an AMI is not completely clear, but probably AF was an independent risk factor for long-term mortality.<sup>3, 5, 7, 9</sup>

In patients receiving thrombolysis the impact of AF on mortality seems to be reduced, also with controversial results.<sup>1</sup> In GUSTO-I late onset AF (onset during hospitalisation) was independently associated with increased 30-day mortality and in-hospital stroke but neither pre-admission nor late-onset AF had significant influence on 1-year mortality.<sup>2</sup> However, in GISSI-3 (319 pre-admission AF and 1069 late onset AF patients) AF was an independent predictor of both in-hospital and 4-year mortality.<sup>6</sup> In GUSTO-III both early (within 48 h after onset of AMI symptoms) and late (after 48 h) onset AF were independently associated with increased 30-day and 1-year mortality.<sup>8</sup> Asanin et al. found that late AF was an independent predictor for long-term (seven-year) mortality but not for in-hospital mortality.<sup>16</sup> Unfortunately, the definition of early and late onset AF varied between the different studies. In the GUSTO trials, late AF was defined as development of AF 48 h after onset of symptoms whereas Asanin et al. classified late AF as AF more than 24 h after symptom onset. Also the term 'new AF' may cause confusion. Some studies used 'new AF' to describe patients with AF on admission<sup>8, 17</sup> whereas other studies used this term exclusively to describe new-onset AF developed during admission.<sup>4, 6, 15</sup>

The prognostic value of AF in patients receiving primary PCI treatment for STEMI has been studied less extensively so far. Kinjo et al. proved the incremental value of late onset AF (AF during hospitalisation), but not baseline AF, in predicting long-term mortality in patients undergoing primary PCI for STEMI.<sup>4</sup> In-hospital mortality, however, was not independently predicted by either baseline or late-onset AF. In the APEX-AMI trial, new onset AF was independently associated with 90-day mortality.<sup>18</sup>

Our data confirmed the findings of Kinjo et al. The strength of the present study is, however, that all patients were included who were hospitalised with acute STEMI minimising selection bias. In our study, ECGs were obtained 3 h after PCI, and so AF with later onset or earlier termination was not taken into consideration. Therefore, our results suggest that early post-PCI AF may reflect less complete reperfusion or a

more compromised cardiac status, even though these potential confounders were included in our multivariate analyses. The possible causative role of AF also has to be taken into consideration, given its well-known detrimental effect on myocardial metabolism, blood supply and remodelling in such a highly vulnerable period.

The divergent way 'early' and 'late' onset AF and 'long-term follow-up' are defined in the above-mentioned studies makes the interpretation of the data harder and partially explains the controversial results. The establishment of a uniform classification may aid further evaluations and lead to a consensus regarding the incremental predictive value of AF in patients with acute STEMI.

### Study limitations

Evaluation of pre-PCI AF's prognostic value is always hindered by the absence of data on AF history, making it impossible to really distinguish between acute onset and persistent AF (i.e. not related to the acute ischaemic event). It is possible that pre-PCI AF could also have represented significant prognostic value if only patients with new onset AF had been taken into consideration.

Post-PCI AF was assessed routinely on ECGs obtained 3 h post-procedure. Therefore are conclusions about the prognostic value of post-PCI AF only applicable for patients with early AF occurrence, and not for the entire hospitalisation period? The results, however, are in agreement with the findings of Kinjo et al.<sup>4</sup> where any AF period during hospitalisation was taken into consideration. We had no data on medication during the follow-up period, such as aspirin, clopidogrel or coumarins.

### Conclusion

In patients treated with primary PCI for STEMI, atrial fibrillation after but not before the PCI has independent prognostic implications. It is unclear what the mechanism is of the worse prognosis, decreased LV function, less complete reperfusion or other medication during the follow-up period.

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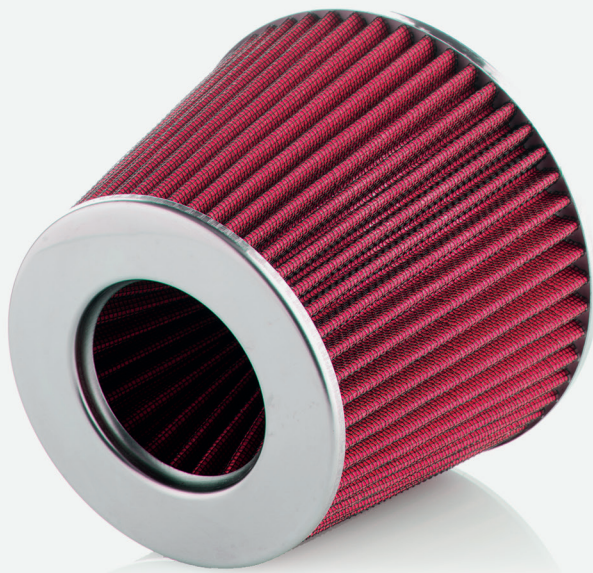
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# 3

## Electrophysiological effects of acute atrial stretch on persistent atrial fibrillation in patients undergoing open heart surgery

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## Abstract

### Background

The electrophysiologic effects of acute atrial dilatation and dedilatation in humans with chronic atrial fibrillation remains to be elucidated.

### Objective

To study the electrophysiological effects of acute atrial dedilatation and subsequent dilatation in patients with long-standing persistent atrial fibrillation (AF) with structural heart disease undergoing elective cardiac surgery.

### Methods

Nine patients were studied. Mean age was  $71 \pm 10$  years, and left ventricular ejection was  $46\% \pm 6\%$ . Patients had at least moderate mitral valve regurgitation and dilated atria. After sternotomy and during extracorporeal circulation, mapping was performed on the beating heart with 2 multielectrode arrays (60 electrodes each, interelectrode distance 1.5 mm) positioned on the lateral wall of the right atrium (RA) and left atrium (LA). Atrial pressure and size were altered by modifying extracorporeal circulation. AF electrograms were recorded at baseline after dedilatation and after dilatation of the atria afterward.

### Results

At baseline, the median AF cycle length (mAFCL) was  $184 \pm 27$  ms in the RA and  $180 \pm 17$  ms in the LA. After dedilatation, the mAFCL shortened significantly to  $168 \pm 13$  ms in the RA and to  $168 \pm 20$  ms in the LA. Dilatation lengthened mAFCL significantly to  $189 \pm 17$  ms in the RA and to  $185 \pm 23$  ms in the LA. Conduction block (CB) at baseline was  $14.3\% \pm 3.6\%$  in the RA and  $17.3\% \pm 5.5\%$  in the LA. CB decreased significantly with dedilatation to  $7.4\% \pm 2.9\%$  in the RA and to  $7.9\% \pm 6.3\%$  in the LA. CB increased significantly with dilatation afterward to  $15.0\% \pm 8.3\%$  in the RA and to  $18.5\% \pm 16.0\%$  in the LA.

### Conclusions

Acute dedilatation of the atria in patients with long-standing persistent AF causes a decrease in the mAFCL in both atria. Subsequent dilatation increased the mAFCL. The amount of CB decreased with dedilatation and increased with dilatation afterward in both atria.

## Introduction

Atrial fibrillation (AF) is the most frequently encountered cardiac arrhythmia in clinical practice and is likely to become even more common with the expected aging of the population. Atrial dilatation is a well-established risk factor for the development of AF.<sup>1</sup> On the other hand, AF is also a cause of atrial dilatation<sup>2</sup> and is accompanied by a decrease in atrial contractility and decrease in the compliance of fibrillating atria.<sup>3</sup> Acute atrial dilatation has been shown to cause an increase in local conduction delays.<sup>4</sup> In experimental studies, AF with concomitant congestive heart failure was associated with structural remodeling, including atrial fibrosis, causing an increase in anisotropy, and local conduction delays.<sup>5,6</sup> The increase in spatial heterogeneity of excitable properties by atrial dilatation raises the question whether acute dedilatation of chronically fibrillating atria would result in (partial) recovery of these atrial excitable properties. The hypothesis that electrical cardioversion of persistent AF was facilitated by lowering atrial pressure was supported by the impression of our thoracic surgeons performing surgical AF ablation. The objective of the present study was to evaluate whether acute dedilatation and dilatation of the atria in patients with long-standing persistent AF and structural heart disease could change the electrophysiological characteristics of AF. In particular, we hypothesized that acute dedilatation of fibrillating atria would diminish the amount of conduction block (CB) and reduce the degree of spatiotemporal dissociation during AF.

## Methods

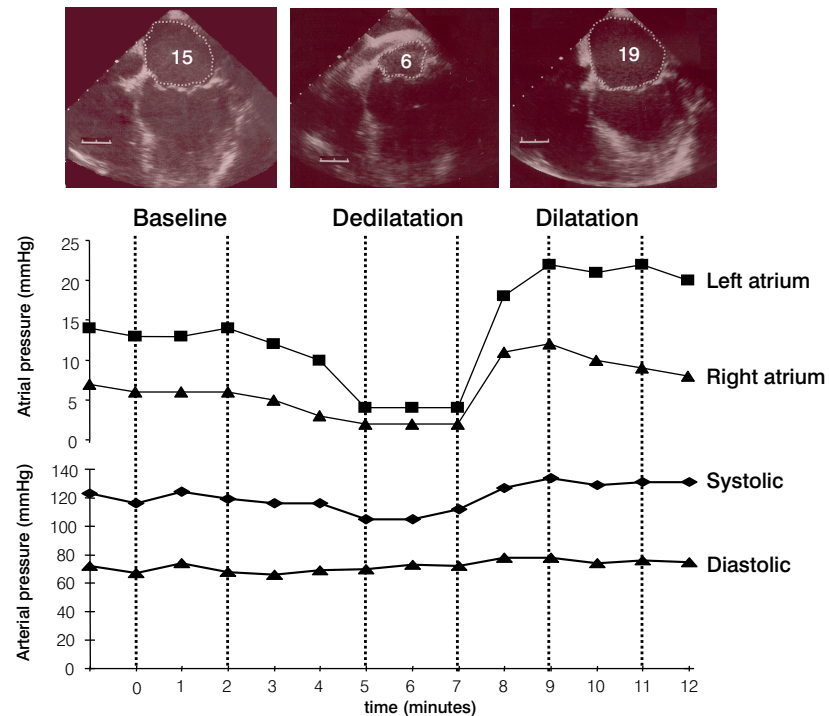
### Patient selection

Nine patients with long-standing persistent AF (>1 year) scheduled for elective cardiac surgery and concomitant radiofrequency-modified Maze surgery were included. All patients gave written informed consent. The intraoperative measurements were all performed in the Isala Klinieken, Zwolle, The Netherlands. The research protocol was approved by the hospital board and the medical ethics committee. Patients receiving class I or class III antiarrhythmic drugs were excluded from the study unless the drugs were stopped for more than 5 half-lives prior to surgery. Patients with prior cardiac surgery were also excluded. A 12-lead electrocardiogram, 24-hour cardiac rhythm monitoring, and transthoracic echocardiography were performed the day before surgery.

### Acute atrial dedilatation and dilatation

During general anesthesia, sternotomy was performed and the pericardium was opened to expose the heart. Cardiopulmonary bypass was accomplished by cannulation of

the superior and inferior caval veins and the aorta. A pressure catheter was inserted in the left atrial appendage to record left atrial pressure. Arterial blood pressure was recorded continuously in the femoral artery. Central venous pressure, pulmonary capillary wedge pressure, and cardiac output were measured with a Swan-Ganz catheter. The pulmonary capillary wedge pressure prior to sternotomy was taken as the baseline pressure in the left atrium (LA). Right and left atrial pressures were changed acutely by varying the amount of blood flow through the extracorporeal circulation. This was associated with a change in mean arterial pressure of  $5 \pm 3$  mm Hg. The amount of atrial dilatation and dedilatation was measured by transesophageal echocardiography. The size of the LA was measured by determining mediolateral and caudocranial size and also by tracing its circumference and calculating the surface area of the left atrial cavity as viewed in the 4-chamber mid-esophageal view (Figure 1).



**Figure 1** Overview of right and left atrial and arterial pressures at baseline, after dedilatation, and after dilatation in a patient. Corresponding transesophageal images with left atrial circumference are depicted. Acute atrial dedilatation and dilatation were successful, with similar arterial pressures.

The protocol for dilatation and dedilatation was as follows: First, left atrial pressure was adjusted to the baseline value measured prior to sternotomy. Then, after the atrial pressure had been stable for 2 minutes, it was lowered to 5 mm Hg. This caused a decrease in the circumference of the LA from  $15.2 \pm 3.4$  to  $12.2 \pm 3.8$  cm. This dedilatation was maintained for 2 minutes, and then atrial pressure was increased to twice the baseline pressure (with a maximum of 25 mm Hg). This resulted in dilatation of the LA to  $18.1 \pm 3.5$  cm. After 2 minutes the baseline pressure was restored.

### High-density epicardial atrial mapping

Intraoperative mapping during AF was performed at normothermia while on extracorporeal circulation. Right and left AF electrograms were recorded continuously with 2 mapping arrays of 64 electrodes (interelectrode distance 1.5 mm; surface area 1 cm<sup>2</sup>). In the online supplement (Figure S1), an example of the mapping catheter is provided. During dilatation and dedilatation of the atria, the position of the mapping electrodes was kept constant. The right atrial electrode was positioned directly ventral to the crista terminalis in the middle of the inferior and superior vena cava. The left atrial mapping electrode was positioned at the posterior base of the left atrial appendage. A silver plate was placed subcutaneously in the thoracic wall to serve as an indifferent electrode. The epicardial electrograms were recorded together with a surface electrocardiogram (lead II) and transferred to a computer by means of a custom-made 256-channel amplifier (0.75-Hz high-pass filter, 470-Hz low-pass filter; sampling rate 1000 Hz). Ten consecutive seconds of AF were analyzed during baseline and during dilatation and dedilatation of the atria. Local activation times at each electrode were determined from the steepest negative deflection in fibrillation potentials. In the case of double potentials or fractionated electrograms, the largest potential was taken. The median AF cycle length (mAFCL) was calculated from all fibrillation intervals recorded by the mapping arrays. The temporal variation in AFCL was measured as the beat-to-beat changes in AFCL at all electrodes. It was expressed as the standard deviation of the distribution of all beat-to-beat variations (p5-p50). The irregularity index was defined as the temporal variation of the time intervals between successive AF cycle lengths divided by the mAFCL for the total number of cycle lengths analyzed. The interelectrode conduction times were used to measure the amount of local conduction delays and intra-atrial block. The lower level of atrial conduction velocity is 25–30 cm/s,<sup>7</sup> and slower velocities are regarded as slow conducting areas. When conduction slows further to 10–15 cm/s, propagation of conduction fails. CB was therefore defined as a local conduction delay of  $\geq 15$  ms between 2 neighboring electrodes, corresponding to a conduction velocity of  $\leq 10$  cm/s. Since during atrial dilatation the same distance between the electrodes is covered by less myocardial cells, the conduction times were normalized for the degree of atrial stretch. The increase in the amount of atrial tissue between electrodes



was calculated from the change in left atrial size measured in the 4-chamber view. The factor by which the individual electrophysiological parameters were corrected was  $c$  after dilatation or dedilatation divided by  $c$  at baseline (where  $a$  is the mediolateral atrial size and  $b$  is the caudocranial atrial size, and  $c$  is calculated by using Pythagoras' principle  $a^2 + b^2 = c^2$ ).

### Statistical analysis

Data were expressed as mean $\pm$ SD, with the range of the data where appropriate. Fibrillation intervals were expressed as mAFCL. The statistical effects of acute atrial dedilatation and dilatation on mAFCL, temporal variability of AF, and amount of atrial CB were checked by a paired Student  $t$  test after testing whether variables were normally distributed. A  $P$  value of  $<.05$  was considered statistically significant.

## Results

### Baseline characteristics

Table 1 summarizes the clinical characteristics of the patients. Mean age was  $70.6\pm 10.2$  years. All patients were men and had an average AF duration of  $5.3\pm 5.0$  years. All patients had structural heart disease. Mean left ventricular ejection fraction was  $46.1\pm 6.0\%$  (range 35%–55%). Mean left atrial size was  $49.6\pm 4.5$  mm in the parasternal long-axis view and  $69.2\pm 4.7$  mm in the 4-chamber view. Mean right atrial size was  $62.6\pm 4.2$  mm.

### Simultaneous mapping of right and left atria

Figure 2 shows some simultaneously recorded fibrillation electrograms from the right atrium (RA) and the LA in a patient with mitral regurgitation. The electrograms and maps on the right side were recorded from the lateral wall of the RA and on the left side from the lateral wall of the LA. The 3 fibrillation maps of the LA show a more complex pattern of activation with multiple wavelets and areas of CB, whereas the 3 consecutive activation maps of the RA demonstrate a more uniform activation pattern with broad wave fronts and a limited number of wavelets. In this patient, there was a higher amount of CB in the LA (21.0% in the LA vs 14.7% in the RA). In all 9 patients with mitral valve disease, the mean percentage of left atrial CB tended to be higher than that of right atrial CB at baseline; however, this difference was not statistically significant.

### Changes in atrial pressures and size

Acute atrial dedilatation and dilatation were successfully performed in all patients. Mean left atrial pressure was  $14.4\pm 3.2$  mm Hg at baseline,  $5.0\pm 1.2$  mm Hg during

**Table 1** Baseline characteristics.

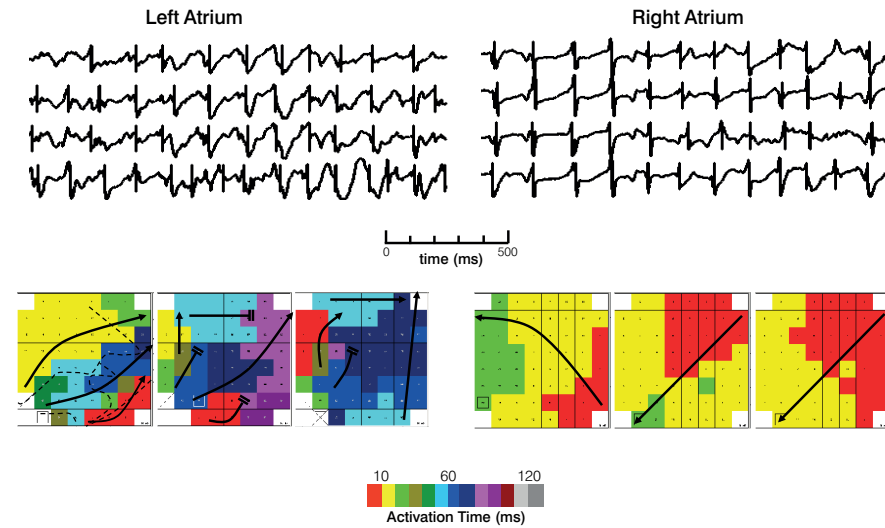
Number of patients	9
Age (years)	$70.6\pm 10.2$ (56-80)
Male (n)	9
AF duration (years)	$5.3\pm 5.0$ (1-15)
Atrial dimensions	
RA 4 chamber view (mm)	$62.6\pm 4.2$
LA parasternal long axis (mm)	$49.6\pm 4.5$
LA 4 chamber view (mm)	$69.2\pm 4.7$
Cardiac disease	
MR (n)	6
MR + CAD (n)	3
LVEF (%)	$46.1\pm 6.0$ (35-55)

Data are mentioned as frequencies, means  $\pm$ SD, and the range between parentheses where appropriate. AF: atrial fibrillation; CAD: coronary artery disease; LVEF: Left ventricular ejection fraction; LA: left atrium; MR: mitral valve regurgitation; RA right atrium

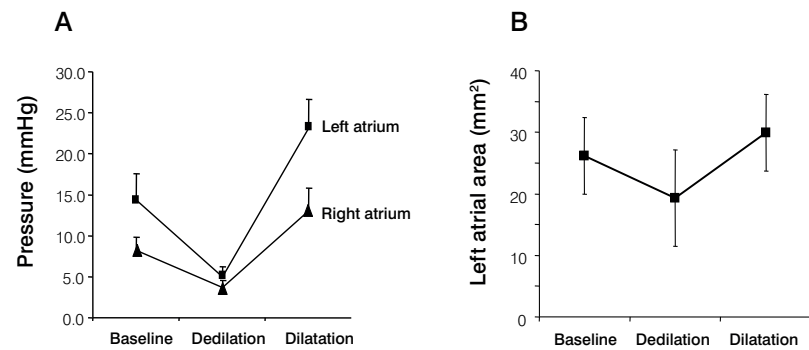
dedilatation, and  $23.1\pm 3.5$  mm Hg during dilatation (Figure 3). The corresponding central venous pressures were  $8.2\pm 1.6$ ,  $3.7\pm 0.9$ , and  $13.0\pm 2.8$  mm Hg, respectively. The left atrial size measured with transesophageal echo was  $26.2\pm 6.2$  mm<sup>2</sup> at baseline,  $19.3\pm 7.8$  mm<sup>2</sup> during dedilatation ( $P = .0005$ ), and  $29.9\pm 6.2$  mm<sup>2</sup> during dilatation ( $P = .001$ ).

### Effects on AFCL

Table 2 gives the average effects for all patients. In the RA, dedilatation shortened the mAFCL from  $184\pm 27$  to  $168\pm 13$  ms ( $P = .10$ ). Dilatation of the RA thereafter significantly prolonged the mAFCL to  $189\pm 17$  ms ( $P = .01$ ). The temporal irregularity interval (70% DI 60%) in the RA showed a nonsignificant reduction by dedilatation from  $50.4\pm 26.5$  to  $43.5\pm 17.1$  ms ( $P = .18$ ). Dilatation thereafter did not show changes. In the LA, dedilatation caused a statistically significant shortening of the mAFCL from  $180\pm 17$  to  $168\pm 20$  ms ( $P = .007$ ), whereas dilatation thereafter significantly increased the mAFCL to  $185\pm 23$  ms ( $P = .03$ ). The temporal irregularity interval (70% dominant intervals [DI] 60%) in the LA showed a nonsignificant reduction by dedilatation from  $38.3\pm 24.0$  to  $32.3\pm 18.3$  ms ( $P = .34$ ). Dilatation thereafter did not show changes (see Table 2). The AFCL between the RA and the LA did not differ during baseline, after dedilatation, and after dilatation ( $P\geq .66$ ). Figure 4 shows an example of the effects of atrial dedilatation and dilatation in a patient.



**Figure 2** Simultaneously recorded fibrillation electrograms from the lateral wall of the left and right atria. The 3 fibrillation maps of the left atrium show a more complex activation pattern with multiple wavelets and areas of conduction block compared to a more uniform activation pattern with broad wave fronts and a limited number of wavelets in the right atrium. In this patient, there was a higher amount of conduction block in the left atrium (21.0%) than in the right atrium (14.7%).

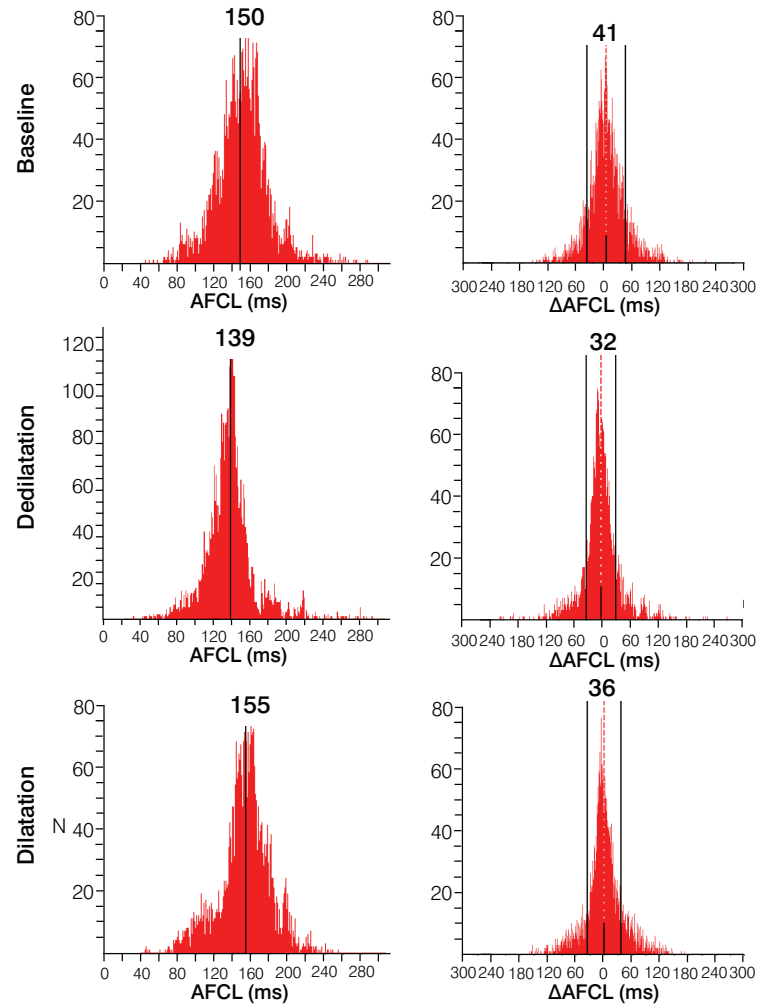


**Figure 3** **A:** Mean atrial pressures + SD at baseline, after acute dedilatation, and after dilatation. **B:** Mean left atrial area±SD at baseline, after acute dedilatation, and after dilatation.

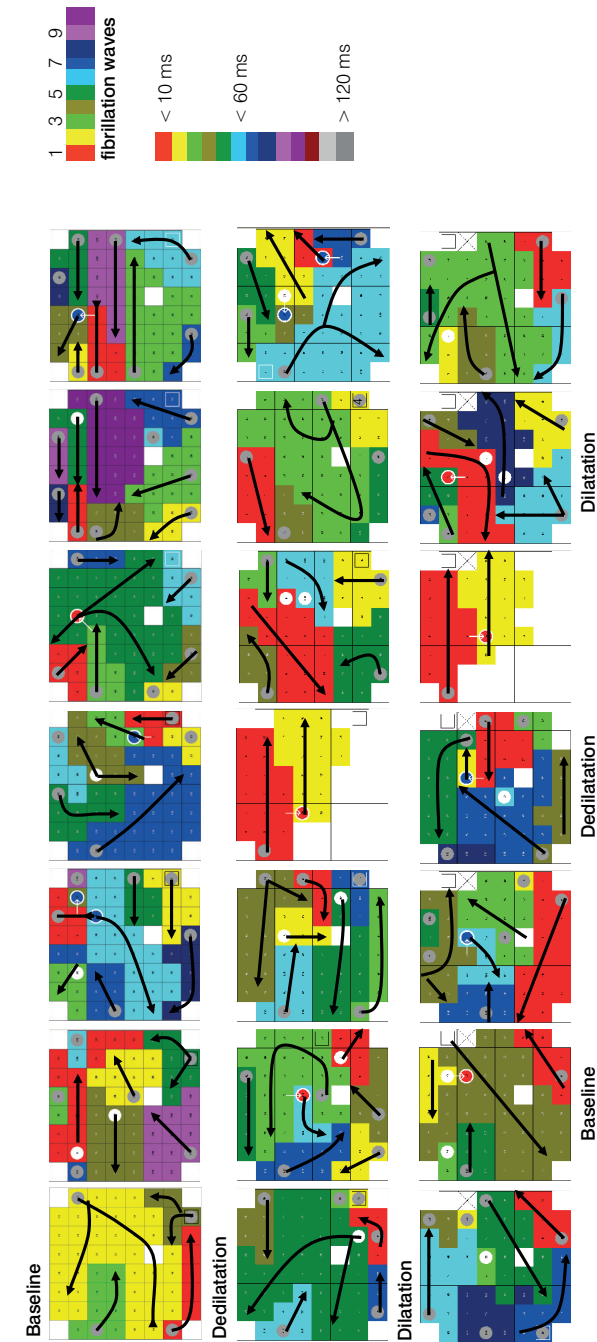
**Table 2** Electrophysiological effects of acute dedilatation and dilation afterward in the right and left atria.

Characteristic	Baseline		Dedilatation			Dilatation		
	LA	RA	LA	P BL vs dedil LA	RA	P dedil vs dil LA	LA	P dedil vs dil RA
mAFCL (ms)	179.8±16.8	183.6±27.0	168±20.4	0.007	168.1±13.0	0.03	189.4±16.9	0.01
Dominant velocity	65.0±2.5	61.9±4.6	69.2±11.9	0.49	62.3±4.7	0.79	56.9±10.8	0.16
TempΔ70%Dl60%	38.3±24.0	50.4±26.5	32.3±18.3	0.34	43.5±17.1	0.63	43.4±24.3	0.36
Non uniformity index	0.49±0.12	0.47±0.05	0.50±0.07	0.59	0.48±0.04	0.89	0.49±0.05	0.87
% ≥15 ms	14.7±9.9	10.3±3.5	7.9±6.3	0.026	7.4±2.9	0.058	15.0±8.3	0.028

Data are mentioned as means ±SD, except for the non-uniformity index, which is stated as median ±SD. Atrial cycle lengths and percentages of conduction were rounded to one decimal. P-values for differences between baseline and dilatation were not significant for all electrophysiological measures (all P-values > 0.14). mAFCL: median atrial fibrillation cycle length, ms; milliseconds, BL: baseline, vs: versus, dedil: dedilatation, dil: dilatation, LA: left atrium, RA: right atrium, TempΔ70%Dl60%: temporal beat to beat delta 70% of dominant intervals' 60<sup>th</sup> percentile.



**Figure 4** Example of the effects of atrial dedilatation and dilatation afterward on the atrial fibrillation cycle length (AFCL) and the irregularity index ( $\Delta$ AFCL) in the left atrium. In this patient, the median AFCL during baseline was 150 ms, with an irregularity index of 41 ms. Atrial dedilatation shortened the AFCL to 139 ms and reduced the irregularity index to 32 ms. Dilatation afterward lengthened the AFCL to 155 ms and increased the irregularity index to 36 ms.

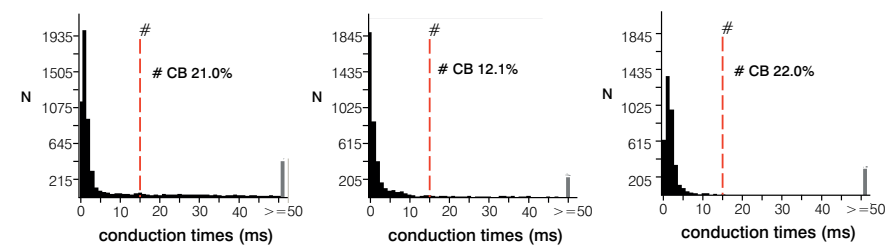


**Figure 5** Effects of atrial dedilatation and dilatation afterward on the amount of conduction block in the left lateral wall in a patient. The activation maps do not show a change in the number of fibrillation waves at different atrial pressure levels. Similar results were present for the study population.



## Effects on intra-atrial CB

Figure 5 illustrates the effects of atrial dilatation and dedilatation on the amount of CB in the left lateral wall. The activation maps do not show a change in the number of fibrillation waves at different atrial pressure levels. The mean amount of right atrial CB ( $\geq 15$  ms) in the study population at baseline ( $10.3\% \pm 3.5\%$ ) was similar to that after dedilatation ( $11.8\% \pm 4.9\%$ ) and dilatation ( $11.2\% \pm 6.1\%$ ; P value of differences  $\geq .25$ ). In the left atrial wall, these values were  $14.7\% \pm 9.9\%$  at baseline compared to  $13.9\% \pm 9.5\%$  after dedilatation and  $13.9\% \pm 10.6\%$  after dilatation (P values of differences  $\geq .57$ ). After correction for the amount of atrial tissue under the mapping electrode, dedilatation caused a decrease in right atrial CB during AF to  $7.4\% \pm 2.9\%$  ( $P = .047$  vs baseline). Dilatation afterward raised the percentage of CB to  $15.0\% \pm 8.3\%$  ( $P = .028$  vs dedilatation). After correction for the amount of atrial tissue under the mapping electrode, dedilatation caused a decrease in left atrial CB during AF to  $7.9\% \pm 6.3\%$  ( $P = .026$  vs baseline). Dilatation afterward raised the percentage of CB to  $18.5\% \pm 16.0\%$  ( $P = .058$  vs dedilatation). Figure 6 exhibits an example of a patient with a significant reduction of CB after dedilatation and an increase after dilatation.



**Figure 6** Example of a patient with 21.0% conduction block ( $\geq 15$  ms) at baseline, with a significant reduction to 12.1% after dedilatation and an increase to 22.0% after dilatation.

## Discussion

### Main findings

We tested the hypothesis that acute atrial dedilatation would decrease the amount of intra-atrial CB and diminish the number of fibrillation waves, thereby potentially increasing the likelihood of successful cardioversion. To our knowledge, this is the first study that reports the electrophysiological effects of acute dedilatation and dilation in patients with long-standing persistent AF with dilated atria and structural heart disease. We found that acute atrial dedilatation decreases the amount of CB in

the LA and RA significantly during persistent AF. This was associated with a shortening of the AFCL by 7% and 9% in the LA and RA, respectively. Spontaneous conversion to sinus rhythm as a result of atrial dedilatation was not observed. Increasing the atrial pressure above the baseline values significantly prolonged the AFCL compared to dedilated atria. Moreover, a significant increase in the amount of CB of fibrillation waves was observed in both the LA and the RA.

### Intra-atrial CB during AF

Direct measurements of the amount of CB during AF did not show a significant alteration after atrial dilatation or dedilatation. Only after correction for the amount of atrial tissue between the electrodes, the degree of CB was significantly altered. Atrial dedilatation caused a decrease in the amount of CB, whereas an increase in atrial pressure above the baseline led to an increase in the degree of atrial CB. The differences in CB were not significantly different between atria. In 1963, Penefsky and Hoffman<sup>8</sup> showed that mild atrial stretch did not affect the conduction velocity and transmembrane potentials in the atria. During excessive stretch, however, multiple deflections were observed as a sign of discontinuous conduction. More recently, experimental studies in rabbit and canine hearts<sup>4,9</sup> showed that acute atrial stretch clearly increased the amount of atrial CB. However, in these studies, structurally normal hearts were used without preexistent AF, whereas in our study population, the atria were chronically dilated owing to mitral regurgitation and long-standing persistent AF. We think that our study design more closely represents the clinical practice.

Kuijpers et al<sup>10</sup> showed that pacing-induced atrial stretch in new-onset AF caused increased dispersion of the atrial effective refractory period (AERP). Furthermore, conduction slowing and local CB were observed owing to the heterogeneous activation of a nonselective stretch-activated cation current. Ravelli et al<sup>11</sup> proved that pacing-induced atrial stretch (23% increase in atrial volume) resulted in a decrease in atrial conduction velocity. They objectified an increased incidence of slow conduction sites or local CBs and increased AF vulnerability, with as much as 6 of 10 patients developing AF episodes under stretch conditions. Kalifa et al<sup>12</sup> investigated the metabolic effects of acute atrial stretch-induced AF in rabbit hearts. Specific modifications of atrial myocytes energetics, such as lower the total adenine nucleotides' pool, could play a pivotal role in the perpetuation of the arrhythmia. Coronel et al<sup>13</sup> demonstrated in patients with mitral stenosis undergoing percutaneous transvenous mitral balloon valvotomy that this resulted in shortening of left atrial and right atrial activation times. The dispersion in activation times in the LA decreased significantly after than before the procedure. Fan et al<sup>14</sup> showed that the reduction of chronic atrial stretch in patients with mitral stenosis resulted in a homogeneous

increase in regional AERP in the group of patients without preexistent AF and a decrease in the dispersion of refractoriness in patients with long-standing persistent AF. Satoh and Zipes<sup>15</sup> studied the influence on electrophysiological properties caused by atrial stretch in open chest dogs. They observed significantly higher increases in AERP owing to stretch in thin parts of the atria. This pointed toward an increased dispersion of refractoriness caused by stretch to atrial tissue with different thickness and/or elasticity. An increase in AERP dispersion resulted in vulnerability to AF in all the 5 dogs studied, whereas at baseline, AF was not inducible. Thus, our results are in line with previous reports regarding the effects of atrial stretch on atrial conduction velocity and blocks.

### AF cycle length

In our study, acute dedilatation of the atria resulted in the shortening of the mAFCL by 7%–9%. Acute dilatation showed large increases in the mAFCL compared to dedilated atria (12.7% in the RA vs 10.1% in the LA). This is in contrast with the results of 2 animal studies that found an increase in dominant frequency (DF) by atrial dilatation.<sup>16,17</sup> In contrast to our study, the atria were not enlarged at baseline. Since AF was induced acutely, no electrical or structural remodeling was present in these atria.<sup>18</sup> Since DFs are measured by spectral analysis, they do not always correspond to the actual dominant AFCL.<sup>19</sup> DFs are especially affected by signal fractionation, which is an expression of underlying conduction disturbances.<sup>20</sup> Considering the increase in the amount of CB with acute atrial dilatation in the rabbit heart,<sup>4</sup> it is possible that the observed increase in DF by acute atrial dilatation reflects an increase in fractionation rather than an increase in the AFCL. Different electrophysiological mechanisms can explain the change in the AFCL with atrial stretch: a change in the amount of CB, an increase in the AERP, a change in conduction velocity, or a combination of the 3.

Our present report shows that lowering atrial pressures shortens the mAFCL slightly and lowers the amount of CB. Dilating the atria through raising the pressure from low to high lengthens AFCL, as well as increases the amount of CB. Our results are further supported by a report by Neuberger et al,<sup>21</sup> who observed that in dilated atria the excitable gap during AF is wider, probably caused by intra-atrial conduction defects and a higher contribution of anatomically defined reentrant circuits. A third explanation of the change in the AFCL with atrial dilatation is that atrial dilatation influences conduction velocity. Slowing of the conduction velocity lengthens the wavelets, and thus the number of wavelets decreases and AFCL lengthens. Slowing of conduction velocity by atrial dilatation is also directly or circumstantially supported by other studies.<sup>4</sup> To unravel the underlying mechanism of the change in the AFCL with atrial stretch, measurements of ERP should be performed during AF and at

different atrial pressures with slow fixed-rate atrial pacing.<sup>22</sup> Such measurements would take quite some time in the operating room, which was the reason for us to omit these measurements.

### Limitations

The present study has limitations and strengths. Unfortunately, the number of mapped patients is too small to calculate correlations between changes in pressure and atrial size and changes in electrophysiological parameters. The directions of electrophysiological changes were similar and significant, however. The protocol of first dedilatation and dilatation afterward was consequent and not varied. Variation of the protocol could have increased the reliability of the observations; however, at least double the patients would have been necessary to prove significance of changes. The amount of CB was, as in previous studies,<sup>7</sup> normalized for the degree of atrial stretch, and thus the amount of atrial tissue between electrodes. However, since the degree of stretch can vary at different sites, especially at sites with fibrosis, this normalization carries a certain inaccuracy. Further errors could be induced by an incomplete adaptation of the mapping catheter to changes in atrial size. However, the mapping catheter was small and was consequently placed in the same regions, probably with the similar tissue thicknesses and with similar degrees of fibrosis. Furthermore, proper signals were observed at all stages, pointing toward good contact of the electrodes to atrial tissue. Although the electroanatomic properties of the atria changed beneficially, the hypothesis that electrical cardioversion of AF was more successful at lower atrial pressures was not directly tested and is subject to further studies. We reduced atrial pressure, size, and stretch by reducing the flow of the cardiopulmonary bypass. It remains unknown how to achieve the reduction of atrial stretch in patients with nonoperated AF. One way to try this is (aggressive) diuretic therapy during antiarrhythmic therapy or before and after cardioversion. Other methods are “upstream therapeutic medicines,” such as angiotensin receptor blockers (“sartans”), because of their beneficial effect on the angiotensin II type 2 receptor, with positive remodeling of the myocardium and regression of hypertrophy and fibrosis.<sup>23</sup>

### Implications for clinical practice

Chronic atrial stretch induces activation of numerous pathways, leading to cellular hypertrophy, fibroblast proliferation, and tissue fibrosis.<sup>3</sup> The resulting substrate in dilated atria is characterized by increased electric alternans in atrial myocytes and slowing of conduction, promoting reentrant circuits in the atria and raising the vulnerability for persistent AF.<sup>24</sup> In our study, we acutely reduced atrial size and pressures, providing acute changes in some electrophysiological parameters. However, one should keep in mind that patients had chronic AF with chronically

dilated and remodeled atria. This could be the reason for the relatively modest, however significant, changes we have observed. Whether longer term reduction in atrial size and pressure could result in larger changes in electrophysiological properties, and possibly spontaneous cardioversion to sinus rhythm or higher success rates of active cardioversion, remains an issue for further research. These changes could facilitate beneficial atrial remodeling, easier conversion to sinus rhythm, and higher rates of long-term sinus rhythm.

### Conclusions

Acute dedilatation of the atria in patients with long-standing persistent AF causes a decrease in the mAFCL in both atria. Subsequent dilatation increased the mAFCL. The amount of CB decreased with dedilatation and increased with dilatation afterward in both atria. We did not observe changes in the temporal variation of the AFCL. These findings indicate beneficial electrophysiologic changes induced by dedilatation of the atria, which could possibly result into a higher chance of conversion to sinus rhythm.

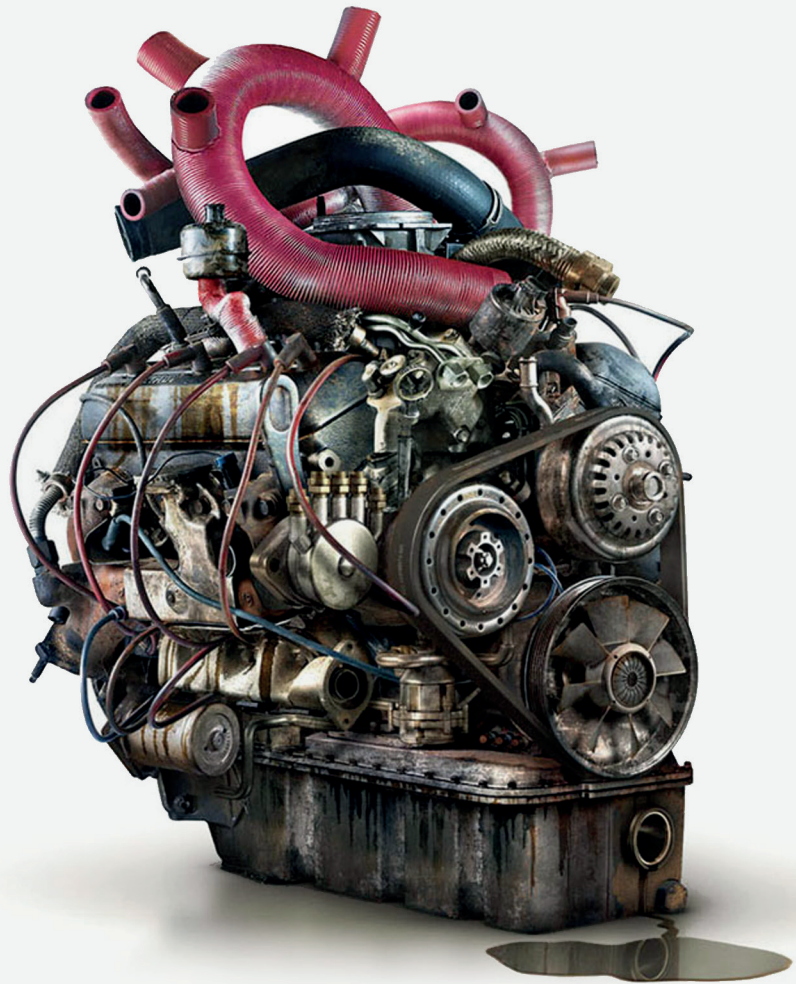
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# Part two

Percutaneous ablation of focal atrial tachycardia  
and atrial fibrillation



# 4

## **Efficacy of multi-electrode duty-cycled radiofrequency ablation for pulmonary vein disconnection in patients with paroxysmal and persistent atrial fibrillation**

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## Abstract

### Aim

A novel multi-electrode pulmonary vein ablation catheter (PVAC) combining circular mapping and duty-cycled multi-electrode radiofrequency (RF) energy delivery has been developed to map and isolate the pulmonary veins (PVs). The aim of this study was to assess the efficacy of multi-electrode RF ablation using the PVAC device.

### Methods and results

A total of 102 consecutive patients, age  $57.9 \pm 9.6$  years, with paroxysmal or persistent drug refractory atrial fibrillation (AF) were referred for ablation. All patients had documented AF episodes with an AF duration of  $9.3 \pm 7.5$  years (range 1.5–25). The mean total procedure time was  $139.30 \pm 37.72$  (median 135, range 115–172). The mean fluoroscopy time required for PVAC ablation was  $17 \pm 12$  min (median 16, range 12–33) and the total fluoroscopy time was  $32.1 \pm 11.3$  min (median 29, range 25–39). The mean multi-electrode RF ablation time required to achieve complete PV isolation was  $31 \pm 6.7$  min (range 16–51). In eight patients with persistent AF, additional ablations were performed to defragment septal and posterior part of the left atrium. In five patients additional RF ablations using conventional catheters were necessary. After multi-electrode duty-cycled RF ablation, 62 of 102 (60.8%) patients were in sustained sinus rhythm without anti-arrhythmic drugs. The mean follow-up duration was  $12.2 \pm 3.9$  months (range 6–15).

### Conclusion

This novel multi-electrode ablation technique can be used for PV isolation and left atrium ablation with a relatively low medium-term success rate after the first ablation of ~61%. Larger studies with longer follow-up are required to evaluate the efficacy and whether multi-electrode RF ablation is associated with a different complication rate compared with standard PV isolation.

## Introduction

Catheter ablation of atrial fibrillation (AF) is an acceptable option in patients whose quality of life is severely disturbed by AF and the arrhythmia has not responded to drug therapy or cardioversion.<sup>1</sup> Catheter ablation of AF requires expertise and remains a time-consuming procedure.<sup>2–7</sup> Newer catheter designs have been developed to reduce procedure time.<sup>8–13</sup> Radiofrequency (RF) ablation has become a successful therapeutic option for patients with symptomatic AF. Isolation of triggers within the pulmonary veins (PVs) is the main treatment strategy in these patients.<sup>2</sup> Conventional techniques use a ring-shaped mapping catheter and a second ablation catheter that applies RF energy in a unipolar fashion. Complete isolation of all electrical potentials at the PV ostium is a technically challenging procedure requiring a long learning curve and extensive fluoroscopy. In addition, serious complications have been reported including the creation of atrio-oesophageal fistulas by inadvertent high-power delivery.<sup>1–7</sup> New developments in catheter ablation of AF have attempted to address these challenges in a variety of methods. The pulmonary vein ablation catheter (PVAC) (Medtronic, Ablation Frontiers, Carlsbad, CA, USA) is a novel circular multi-electrode catheter that has been used to isolate PVs with duty-cycled radiofrequency energy. This multi-electrode over the wire device capable of circular mapping and RF energy delivery is intended to simplify the PV isolation procedure while reducing the risk of complications. Limited data are available on the safety and efficacy of this approach.<sup>8</sup> The objective of this study was to evaluate the efficacy of multi-electrode duty-cycled RF ablation with the use of PVAC.

## Methods

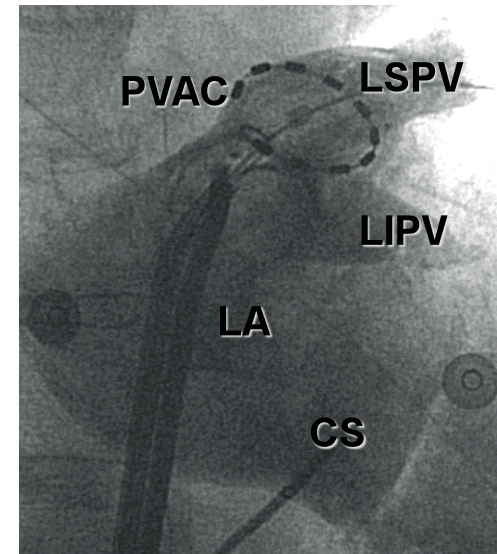
### Patients

A total of 102 patients with paroxysmal or persistent AF, who were scheduled to undergo elective PV disconnection and left atrial ablation, were included in a prospective registry. None of the patients had an ablation procedure before. All patients consented to their data being registered and used for publication as did the Board of Hospital Administrators. Patients were admitted 24 h prior to the ablation procedure. During hospitalization, cardiac rhythm in all patients was continuously monitored. Transthoracic echocardiography was performed routinely prior to ablation to determine right and left ventricular function, valvular abnormalities, and left and right atrial dimensions. Transoesophageal echocardiography was performed to assess inter-atrial septum and to rule out intra-cardiac thrombus. Multi-slice CT angiography was performed in all patients to assess the anatomy of the PVs, left atrium, and adjacent structures. Routine blood tests were performed, including electrolytes and cardiac enzymes.

### Ablation procedure

The ablation procedures were performed under conscious sedation or general anaesthesia. Two return electrode patches were placed between the scapulae. Two fixed-curve 8.5F SL-1 sheaths (St Jude Medical), and in selected cases a steerable sheath (Channel, Bard, Lowell, MA, USA), were introduced into the right femoral vein. A 6F deflectable quadripolar electrode catheter (Bard) was positioned into the coronary sinus. Transseptal puncture was performed with a modified Brockenbrough needle. An initial bolus of 10 000 units of heparin was given and 2 500–5 000 unit IV additional boluses to maintain an activated clotting time (ACT) between 300 and 350 s were given. ACT was determined every 30 min. Pulmonary vein angiography was performed for all PVs in anteroposterior, 30° left anterior oblique and 30° right anterior oblique positions to provide a geometric reference for catheter navigation. The PVAC (Medtronic, Ablation Frontiers) is a mapping and ablation catheter with a 25 mm diameter circular electrode array. This catheter has a bidirectional steering mechanism and an over-the-wire design. The details of this device have been described previously.<sup>8</sup> Experience with the PVAC in our centre was gained prior to this study in a pilot study of 15 patients.

The PVAC was introduced into the left atrium via the SL-1 sheath. Using a 0.032 in. guidewire placed in the vein, the catheter was positioned at the antrum of each PV to record local electrical activity at the veno-atrial junction prior to RF energy application. The PV ostia were visualized by selective contrast injection. Figure 1 is a representative example showing the fluoroscopic image of the position of the PVAC at the ostium of the left superior PV and the recorded electrograms at this position are shown in Figure 2. The positions of the PVAC catheter were documented using fluoroscopy. RF energy was applied using the RF generator with a target temperature of 60°C, 4:1 or 2:1 ratio between bipolar and unipolar energy, and 60 s duration. Multiple applications of RF were delivered using the available energy settings until isolation of the antrum of each vein was achieved. After extensive ablations were performed at all veno-atrial junctions, the PVAC was used to map all PV ostia. With the aid of the steerable channel sheath, the PVAC could be deployed in all right inferior pulmonary veins (RIPVs). If the PVs appeared to be incompletely isolated, additional RF applications were delivered using the PVAC until the PVs were completely disconnected based on PVAC signals. Thirty minutes post-ablation all PVs were mapped again with the PVAC and if necessary additional ablations were performed. In the case of failure to isolate the PVs with the PVAC, a conventional irrigated tip ablation catheter was used to isolate the PVs.



**Figure 1** Angiography (AP view) of the left atrium and the left sided pulmonary veins. In this representative example, the PVAC catheter is positioned in the LSPV. AP, anteroposterior; LA, left atrium; CS, coronary sinus; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; PVAC, pulmonary vein ablation catheter. See text for details.

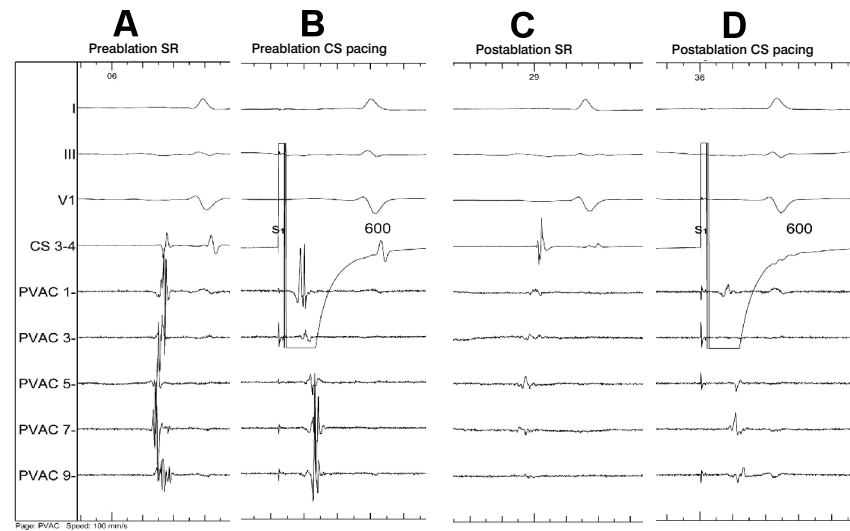
### Radiofrequency generator settings

The GENius™ generator (Medtronic, Ablation Frontiers) is a multi-channel RF generator capable of simultaneously delivering duty-cycled energy to up to 12 operator-selected electrodes. The generator has five preset energy settings: bipolar, unipolar, and three ratios of bipolar-to-unipolar energy: 4:1, 2:1, and 1:1. The energy was delivered in a temperature-controlled, power-limited manner with a maximum of 10 W per electrode. The generator displays in real-time the temperature and power for each electrode, as well as the number of seconds each electrode was within 5°C of target temperature during the application.

### Post-ablation management and follow-up

Post-ablation, patients were hospitalized for at least 24 h and monitored telemetrically. AF recurrence was defined as an atrial arrhythmia of >30 s. Low-molecular-weight heparin was given for 2–7 days and acenocoumarol for at least 3 months. Anti-arrhythmic drugs (Class I or III) were continued during the first 3 months and gradually tapered. About 24–48 h Holter monitoring was performed at 3, 6, and 12 months





**Figure 2** Tracings are surface ECG leads I, III, and V1 and intra-cardiac signals recorded from the proximal pair of a quadripolar catheter positioned in the coronary sinus and the pulmonary vein ablation catheter positioned in the left superior pulmonary vein. **(A)** The pre-ablation signals during sinus rhythm; **(B)** the pre-ablation signals during coronary sinus pacing; and **(C and D)** the signals post-ablation during sinus rhythm and coronary sinus pacing, respectively. See text for details

intervals. Furthermore, 1-week AF alarm monitoring was performed  $6 \pm 1.5$  (range 5–8) months after ablation. The AF alarm is a battery-powered electronic arrhythmia detection device with ECG recording capabilities. The device automatically detects arrhythmias and stores a digitalized ECG of arrhythmias. Furthermore, ECG storage can also be manually triggered to investigate if symptomatic episodes are actually related to an arrhythmia.<sup>14</sup> Oesophagoscopy was not performed routinely post-procedure. Transthoracic echocardiography was performed 1 day after the procedure in all patients. All patients visited our outpatient clinic at 1, 3, 6, and 12 months intervals. A standard 12-lead ECG was recorded at each outpatient visit. Transthoracic echocardiography and spiral CT or magnetic resonance imaging of the PVs were performed 3 months after RF ablation to document atrial size and PV ostial dimensions, respectively.

## Statistical analysis

Categorical variables are expressed as frequencies and percentages. Continuous data are presented as mean  $\pm$  SD. Comparison of continuous variables was performed with the Student's *t*-test. Comparison of proportions was performed with the  $\chi^2$  analysis or Fisher's exact test. All *P*-values are two-sided and *P*-value  $<0.05$  was considered statistically significant. A two-tailed *P* value of  $<0.05$  indicated statistical significance. Statistical analysis was performed using SPSS (SPSS Inc, Chicago, IL, USA).

## Results

### Clinical characteristics of the patients

A total of 102 consecutive patients, age  $57.9 \pm 9.6$  years, with paroxysmal ( $n = 90$ ) or persistent ( $n = 12$ ) drug refractory AF were referred for ablation. All patients had documented AF episodes with an AF duration of  $9.3 \pm 7.5$  years (range 1.5–25). Clinical characteristics of the patients are summarized in Table 1. Echocardiographic recordings demonstrated an average left atrial size of  $41.2 \pm 6.5$  mm in the parasternal long-axis view. Left ventricular ejection fraction was  $59 \pm 4.3$  (range 45–61).

**Table 1** Baseline patient characteristics.

	Number ( $\pm$ SD)	Range
No of Patients	102	
Gender (m/f)	87/15	
Age (years)	$53.4 \pm 8.9$	38-72
No. of cardioversions	43 (42%)	
No of ineffective AADs	$2.9 \pm 1.7$	1-4
Hypertension	21 (20.6%)	
Diabetes	4 (3.9%)	
History of TIA/stroke	6 (5.9%)	
Ischemic heart disease	5 (4.9%)	
Family history of AF	2 (2%)	
Left atrial size PSLAX (mm)	$41.2 \text{ mm} \pm 6.5$	31-44
LVEF (%)	$59 \pm 4.3$	45-61
Duration of AF (years)	$9.4 \pm 7.1$	1.5-25
Type of AF		
Paroxysmal	90	
Persistent	12	

### Procedural success

The mean total procedure time was  $139.30 \pm 37.72$  (median 135, range 115–172), including transseptal puncture and pre- and post-ablation mapping of the PVs. PV angiography was performed prior to ablation. Thirty patients had a left common trunk (Table 2). Deployment of the PVAC was successful in all the left-sided PVs and all right superior PVs. Deployment of the PVAC was not successful in 17 right inferior PVs. In these patients, a steerable channel sheath (Bard) was used. In 12 (11.8%) patients with persistent AF, the superior vena cava (SVC) was isolated using the PVAC. In 3 of these 12 patients, AF was converted to sinus rhythm during RF application around the SVC. The mean duty-cycled RF ablation time required to achieve complete PV isolation was  $31 \pm 7$  min (range 16–51). The RF duration for complete PV isolation tended to be greater for the common trunks in comparison with the other veins (P-value left common trunk vs. others,  $P < 0.01$ ). Table 2 summarizes the procedural data including PVAC ablation time per PV. There was no statistically significant difference in the PVAC ablation time between the right-sided and the left-sided PVs except for the left common trunks. The mean fluoroscopy time required for PVAC ablation was  $17 \pm 12$  min (median 16, range 12–33) and the total fluoroscopy time was  $32.1 \pm 11.3$  min (median 29, range 25–39).

**Table 2** Procedural data.

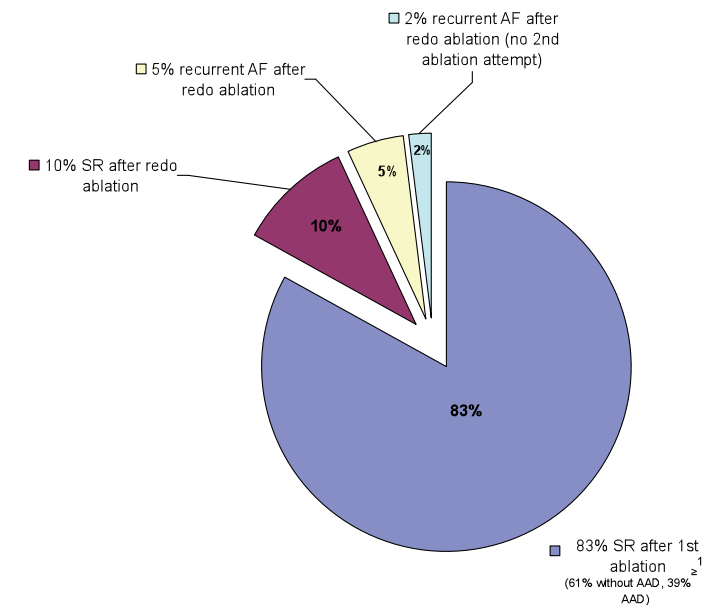
	Number of PVs	Diameter, mm	PVAC RF time, min	Additional ablations with irrigated tip catheter (n, pts)	Final confirmation of PV isolation (%)
LSPV	72	$20.9 \pm 6.3$	$6.7 \pm 1.6$	0	100
LIPV	72	$18.2 \pm 4.1$	$5.7 \pm 1.9$	0	100
RSPV	102	$20.6 \pm 4.3$	$5.6 \pm 1.6$	1	100
RIPV	102	$16.9 \pm 3.9$	$5.5 \pm 1.4$	2	100
LCPV	30	$28.7 \pm 4.0^*$	$10.5 \pm 2.1^\#$	2	100
Overall	378	$20.9 \pm 4.8$	$31 \pm 6.7$	5	100

\* $P < 0.01$  LCPV vs other PVs;  $^\#P < 0.01$  LCPV vs other PVs.

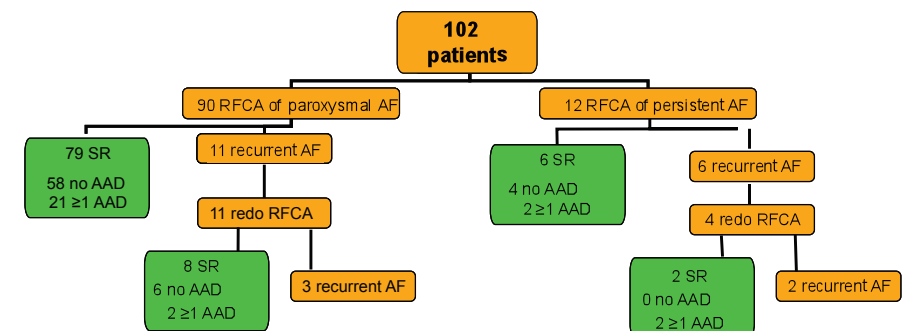
### Cardiac rhythm during follow-up

The mean follow-up duration was  $12.2 \pm 3.9$  months (range 6–15). In the total study population ( $n = 102$ ), 62 (60.8%) patients were in sustained SR without anti-arrhythmic drugs. In the paroxysmal AF group ( $n = 90$ ), after the PVAC ablation procedure,

**A** PVAC RF ablation results (N=102 paroxysmal and persistent AF)



**B**



**Figure 3** This diagram shows the radiofrequency ablation results. **(A)** Circle diagram showing pulmonary vein ablation catheter and re-ablation results for patients with paroxysmal and persistent AF. **(B)** Results for separate categories (persistent-, paroxysmal AF, with- and without anti-arrhythmic drugs). RFCA, radiofrequency ablation; AF, atrial fibrillation; SR, sinus rhythm; AAD, anti-arrhythmic drugs.

58 patients (64.4%) had sustained SR without anti-arrhythmic drugs. In the paroxysmal AF group, 11 (12.2%) patients with recurrent AF/AFI during follow-up underwent Lasso and Carto guided re-ablation using conventional irrigated tip catheters. In all the 11 patients, gaps in the ablation lines were identified and additional ablations were applied to create complete circumferential PV isolation. Three patients had a gap at the ridge between the left superior PV and the left atrial appendage. Three patients had a gap at the antero-inferior part of the right inferior PV antrum. Five patients had gaps at both right- and left-sided LA–PV junctions. Three patients had a drug refractory and highly symptomatic left atrial flutter after the PVAC procedure. Electro-anatomic propagation mapping and entrainment mapping were performed. These atrial flutters were due to incomplete ablation lines at the junction of the left superior PV and the left atrial appendage in two patients and an incomplete ablation at the anterior part of the RIPV antrum in one patient. All patients underwent successful flutter ablation. In the persistent AF group (n = 12), six patients (50%) had AF recurrences. Four of these six patients underwent re-ablation with isolation of PVs, defragmentation of the left atrium, and isolation of the SVC. For defragmentation, multi-array septal catheter and multi-array ablation catheter were used. Figure 3 shows the cardiac rhythm during the follow-up of the total study population. Oral anti-coagulation was taken by all patients.

### Complications

There were no procedural complications in this study. Specifically, there was no thrombus formation or charring detected on the electrodes of the PVAC catheter. Additionally, there were no phrenic nerve injuries and no oesophageal damage revealed by oesophagoscopy. CT angiography of the PVs performed 3 months post-ablation did not reveal PV stenosis.

## Discussion

### Main findings

The main findings are that duty-cycled multi-electrode ablation with the PVAC can be used for PV isolation with an acute success rate for PV isolation of 95% using the PVAC alone. In a minority of the patients (5%), PV isolation could not be achieved with the PVAC and additional ablations using conventional catheters were necessary. Furthermore, after a mean follow-up of 12 months, freedom from AF/AFI after multi-electrode duty-cycled RF ablation was ~61% (i.e. percentage of patients in SR without anti-arrhythmic drug therapy).

### Multi-electrode duty-cycled radiofrequency ablation

Boersma et al.<sup>8</sup> reported that duty-cycled bipolar/unipolar RF ablation is effective in isolating PVs using relatively low power (<10 W). The success rate, defined as freedom from AF without anti-arrhythmic drugs, was 83% with a follow-up duration of 6 months.<sup>8</sup> Unfortunately, there is no information regarding the distribution among both types of AF (persistent vs. paroxysmal) in this latter study. Our data indicate a lower success rate. The possible explanations in the different success rates may be the longer follow-up duration in our study and/or the intensity of rhythm monitoring post-ablation. Scharf et al.<sup>15</sup> investigated the efficacy and safety of duty-cycled RF ablation with multi-electrode ablation in 50 patients with long-standing persistent AF. The 6-month success rate was 80% and the 20-month success rate 66%. However, success was defined as a ≥80% reduction in AF burden on the 7-day ECG recording at 6 months, with or without anti-arrhythmic drug treatment. In fact, only 54% of patients were free of AF without anti-arrhythmic drugs after 6 months.

### Symptomatic vs. asymptomatic atrial fibrillation

Vasamreddy et al.<sup>16</sup> demonstrated that PV isolation resulted in 70% of patients remaining free of symptomatic AF recurrences over a 6-month time period, while only 50% remained free of episodes when asymptomatic AF recurrences were included in the outcome. Purerfellner et al.<sup>17</sup> demonstrated that many patients had many more asymptomatic AF episodes than formerly known or documented post-ablation. Long-term follow-up of the patients seems to be essential as success rates of the initial ablation procedure might vary over time. Freedom from AF after conventional ablation varies between 80 and 90%.<sup>3–5</sup>

### PVAC compared with other pulmonary vein isolation techniques

Multi-electrode duty-cycled RF ablation is a relatively novel ablation technique and was designed to make PV isolation procedures less complex and less time-consuming, since a single catheter can be used to produce contiguous lesions with each RF application. Our data indicate that freedom from AF after PVAC ablation is relatively low compared with published results of conventional ablation techniques.<sup>3–5</sup> Conventional techniques use a circular mapping catheter and a second ablation catheter to deliver RF energy in a unipolar fashion. Complete isolation of all electrical potentials at the PV ostium is a technically more challenging procedure requiring a longer learning curve and extensive fluoroscopy. New developments in catheter ablation of AF have attempted to address these challenges in a variety of methods. Arentz et al.<sup>18</sup> found that large circumferential periostial large area ablation around ipsilateral PVs with verification of conduction block is a more effective treatment of AF than isolation of each individual PV. Although the procedure and ablation times were significantly longer for isolation of large areas, the fluoroscopy time with a three-di-

mensional mapping system was significantly shorter. Recent technical advances in robotic and magnetic steering have facilitated catheter manipulation and demonstrated reduced radiation dosage for the physician, but are likely to increase procedural complexity, cost, and time. Variations on catheter design have also been proposed, with coiled electrodes implemented on helical and linear catheters demonstrating limited effectiveness and unsatisfactory complication rates. Alternative catheter shapes combined with novel energy sources have been proposed and are being evaluated in the clinical setting, including balloon catheters that deliver laser, cryoablation, and ultrasound energy.<sup>9–13</sup> However, these approaches are yet to demonstrate the ability to consistently isolate all veins without supplemental ablation catheters. Procedure or fluoroscopy times are not reduced, and reports have shown collateral damage complications such as phrenic nerve damage.

### Limitations and clinical implications

This study suggests that PVAC can be used for PV isolation. However, percentage of patients free from AF after ablation is relatively low (~58%). The follow-up duration is relatively short and longer follow-up is necessary to assess the long-term efficacy of this ablation technique. Although the PVAC has the potential advantage of being both a therapeutic and diagnostic tool, the current version of the PVAC is not ideal for larger veins. Therefore, CT or MR imaging of the PVs prior to ablation is needed to select patients. In the majority of the patients, this single catheter can be used to isolate the PVs and document isolation without switching to another mapping catheter. The ablations with the PVAC can be performed using a single transseptal puncture. The complication rate seems to be low, there were no adverse events in this study. However, only limited reports of experience with PVAC ablation have been published. Larger studies are required to evaluate whether the PVAC is associated with a different complication rate compared with standard PV isolation.

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# 5

## Pulmonary vein isolation to treat paroxysmal atrial fibrillation: conventional versus multi-electrode radiofrequency ablation



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## Abstract

### Purpose

For patients with symptomatic atrial fibrillation (AF), a curvilinear multi-electrode ablation (MEA) catheter has been reported to be successful to achieve pulmonary vein (PV) isolation. However, this approach has not been compared prospectively with conventional PV isolation (CPVI) using a standard circular mapping catheter and 3D electro-anatomic mapping. In this prospective non-randomized study, we compared the efficacy of these two techniques.

### Methods

Of 185 consecutive patients, age  $54.6 \pm 10.1$  years, with symptomatic paroxysmal AF (PAF), 96 patients underwent PV isolation by CPVI and 89 patients underwent MEA to isolate the PVs. CPVI was performed by encircling the left- and right-sided PVs. During MEA, the PV ablation catheter (Medtronic, USA) was used to isolate PVs with duty-cycled radiofrequency energy.

### Results

The mean procedure time was  $171.73 \pm 52.87$  min for CPVI and  $133.25 \pm 37.99$  min for MEA, respectively ( $P < 0.001$ ). The mean fluoroscopy time was  $31.07 \pm 14.97$  for CPVI and  $30.07 \pm 11.45$  min for MEA ( $P = 0.651$ ). At 12 months, 80% of patients who underwent CPVI and 82% of patients who underwent MEA were free of symptomatic PAF off antiarrhythmic drug therapy ( $P = 0.989$ ). Among the variables of age, gender, duration and frequency of PAF, left ventricular ejection fraction, left atrial size, structural heart disease, and the ablation technique, only an increased left atrial size was an independent predictor of recurrent PAF. Left atrial flutter occurred after CPVI in two patients and after MEA ablation in three patients.

### Conclusion

In patients undergoing catheter ablation for PAF, MEA and CPVI proved equally efficacious.

## Introduction

Haissaguerre et al. have demonstrated that arrhythmogenic activity that originates in the muscle sleeves of the pulmonary veins (PVs) may trigger or perpetuate atrial fibrillation (AF).<sup>1</sup> Circumferential peri-ostial ablation to electrically isolate the PVs from the left atrium has been performed to eliminate paroxysmal AF (PAF).<sup>2, 3, 4, 5</sup> Studies have shown that circumferential PV isolation guided by a circular mapping catheter and 3D electro-anatomic mapping technique is effective in eliminating PAF in patients. This “conventional” pulmonary vein isolation (CPVI) is an accepted technique for the treatment of patients with PAF.<sup>2, 3, 4, 5</sup> Another technique that has been used recently to treat PAF has been a single curvilinear catheter multi-electrode ablation with duty-cycled radiofrequency (RF) energy (MEA).<sup>6, 7, 8</sup> Studies investigating MEA approach are limited, generally small-sized, and have less than 1 year follow-up.<sup>9, 10, 11, 12, 13</sup> Therefore, the purpose of this prospective study was to compare the long-term efficacy and risk of conventional PV isolation with RF energy and a single catheter multi-electrode PV isolation ablation with duty-cycled RF energy in patients with PAF.

## Methods

### Patient characteristics

This prospective non-randomized study included 185 consecutive patients with symptomatic PAF referred for catheter ablation. The institutional review board approved this prospective registry. Exclusion criteria consisted of heart failure, a left ventricular ejection fraction  $< 45\%$ , a left atrial diameter  $> 45$  mm in the parasternal long axis view, and a previous ablation procedure for AF. In this study, multislice computed tomographic (CT) angiography was performed in all patients to assess the anatomy of the pulmonary veins, left atrium, and adjacent structures. Of 185 patients, 89 patients were treated with MEA and 96 patients were treated with CPVI. The clinical characteristics of the patients are described in Table 1.

### Electrophysiological study

All catheters were introduced through a femoral vein. A quadripolar electrode catheter (EPX, Bard, USA) was positioned in the coronary sinus. In the CPVI group, two 8.5F SL1 sheaths (St. Jude Medical, Inc) were advanced to the left atrium by a modified Brockenbrough technique. After transseptal catheterization, intravenous heparin was administered to maintain an activated clotting time of 300 to 350 s. Additionally, continuous infusions with heparinized saline were connected to the transseptal sheaths (flow rate of 1 mL/min) to avoid thrombus formation or air embolism.



**Table 1** Patient Characteristics.

	Total	CPVI	MEA	P value
No. of patients	185	96	89	
Age (mean±SD)	55.9±9.95	55.9±9.9	56.0±10.4	0.823
Male gender	142/185 (76.8%)	71/96 (74.0%)	74/89 (78.7%)	0.514
Diabetes	12/185 (6.5%)	9/98 (9.4%)	3/89 (4.5%)	0.086
Hypertension	32/185 (17.3%)	13/96 (13.5%)	19/89 (21.3%)	0.141
Pacemaker	8/185 (4.3%)	4/96 (4.2%)	4/89 (4.5%)	0.964
Reveal AF	20/185 (10.8%)	10/96 (10.4%)	10/89 (11.2%)	0.901
Familial AF	6/185 (3.2%)	4/96 (4.2%)	2/89 (2.2%)	0.683
COPD	3/185 (1.6%)	0/96	3/89 (3.4%)	0.115
Ischemic heart disease	9/185 (4.8%)	3/96 (3.1%)	6/89 (6.7%)	0.326
Non ischemic heart disease	6/185 (3.2%)	5/96 (5.2%)	1/89 (1.1%)	0.212
Left atrial diameter (mm)	40.59±5.37	40.02±5.74	42.50±3.40	0.047
LVEF	56±4.3	55±3.5	57±6.1	0.882

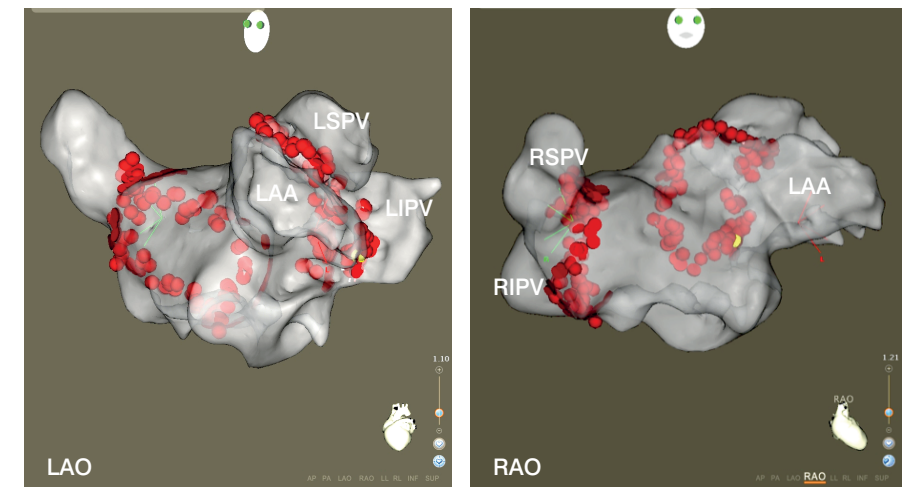
Data are shown as mean±SD. COPD indicates chronic obstructive pulmonary disease and LVEF indicates left ventricular ejection fraction

Angiograms of the PVs were performed in all patients. Bipolar and unipolar electrograms were filtered at band-pass settings of 30 to 500 and 0.05 to 200 Hz, respectively, and were recorded digitally (LabPro, Bard, USA). Pacing was performed from the coronary sinus or left atrial appendage with a stimulator (Bard, USA).

### 3D Electroanatomic mapping and irrigated tip radiofrequency ablation

Conventional PV isolation was performed in 96 patients. Mapping was performed with a steerable catheter with a 3.5-mm-tip electrode (ThermoCool Navistar, Biosense-Webster, USA) during coronary sinus pacing or sinus rhythm. In case of AF, sinus rhythm was restored by external cardioversion. In selected patients with recurrent AF after electrical cardioversion, flecainide 2 mg/kg IV with a maximal dose of 150 mg was administered. Flecainide administration was necessary in three patients in the MEA group and two patients in the CPVI group. After 3D reconstruction of the left atrial anatomy (Fig. 1), each PV ostium was identified by selective angiography and tagged on the electroanatomic map. A decapolar circular mapping catheter (Lasso, Biosense-Webster, USA) was positioned within the PVs during RF delivery as described previously by Ouyang et al.<sup>4</sup> Electrograms were recorded at the ostia of the PVs with a circular decapolar catheter (Lasso, Biosense-Webster). PV isolation was performed by applying radiofrequency energy at ostial sites at which

the earliest bipolar PV potentials and/or the unipolar electrograms with the most rapid intrinsic deflection were recorded. A 3D shell representing the left atrium was constructed by use of an electroanatomic mapping system (CARTO, Biosense-Webster, USA). Irrigated RF energy was delivered with a target temperature of 43°C, a maximal power limit of 40 W, and an infusion rate of 15–20 mL/min during RF energy delivery. RF ablation sites were tagged on the reconstructed 3D map of the left atrium. RF energy was applied for 20–60 s until the maximal local electrogram amplitude decreased by ≥70% or double potentials were documented. Irrigated RF ablation was performed away from the angiographically defined PV ostia—more than 1 cm away on the posterior wall, and more than 5 mm on the anterior wall. At the narrow border between the anterior aspect of the left PVs and the left atrial appendage (LAA), ablation was performed within approximately 5 mm of the ostium of the PVs, i.e., ablation was performed on the PV-side of the LAA ridge. The endpoint of the ablation procedure was defined as the absence or dissociation of PV potentials documented with a standard circular mapping catheter within the PVs ≥30 min



**Figure 1** Electro-anatomic 3D map of the left atrium and the pulmonary veins with the circumferential ablation lines around the ipsilateral pairs of pulmonary veins on the right and left side of the left atrium. This lesion pattern was applied in the CPVI (circumferential pulmonary vein isolation) group. LAO is left anterior oblique view. RAO is right anterior oblique view. LAA is left atrial appendage. LSPV is left superior pulmonary vein. LIPV is the left inferior pulmonary vein. RSPV is the right superior pulmonary vein. RIPV is the right inferior pulmonary vein. See text for details.

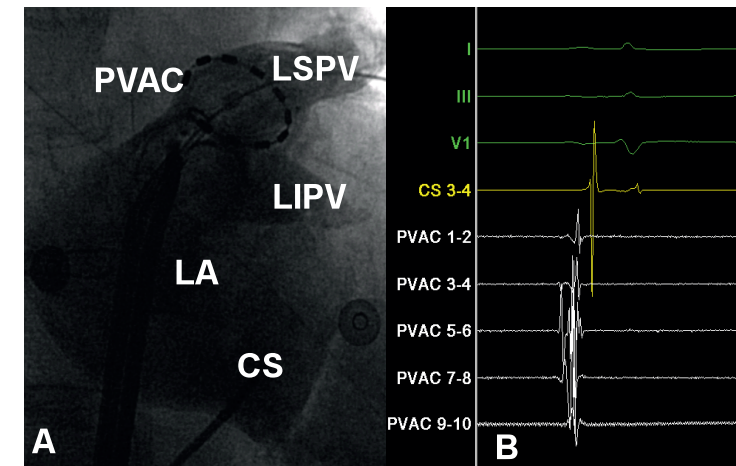
post-ablation.

### Multi-electrode ablation procedure

Multi-electrode ablation procedures were performed in 89 patients. Prior to the initiation of this study, we gained experience with the pulmonary vein ablation catheter (PVAC) catheter.<sup>6</sup> Two operators (AE and JJS) performed the ablation procedures in this study. Two return electrode patches were placed between the scapulae. One fixed-curve 10F SL-1 sheath (St Jude Medical, USA) and, in selected cases ( $n = 16$ , 18%), a steerable sheath (Channel, Bard, USA) were introduced into the right femoral vein. A 6F deflectable quadripolar electrode catheter (EPX, Bard, USA) was positioned into the coronary sinus. The PVAC (Medtronic, USA) is a mapping and ablation catheter with a 25 mm circular electrode array. This catheter has a bidirectional steering mechanism and an over-the-wire design. The details of this device have been described previously.<sup>6, 7, 8</sup> The PVAC was introduced into the left atrium via the SL-1 sheath. Using a 0.032 guidewire placed in the vein, the catheter was positioned at the antrum of each PV to record local electrical activity at the veno-atrial junction prior to RF energy application (Fig. 2). The pulmonary vein ostia were visualized by selective contrast injection. A pre-ablation template of electrical signals of all veno-atrial junctions was recorded using the PVAC. This enabled us to compare the pre-ablation PVAC signals with the signals recorded after every RF application. The GENius™ generator (Medtronic, USA) was used for RF energy delivery. This is a multi-channel RF generator capable of simultaneously delivering duty-cycled energy to up to 12 operator-selected electrodes. The generator has five preset energy settings: bipolar, unipolar, and three ratios of bipolar-to-unipolar energy—4:1, 2:1, and 1:1. The 4:1 modus was generally used. Only when the PV signals were not eliminated in a minority of cases was a 2:1 mode used, and sporadically, the 1:1 modus. Energy was delivered in a temperature-controlled, power-limited manner with a maximum of 10 W per electrode. The generator displays in real-time the temperature and power for each electrode, as well as the number of seconds each electrode was within 5°C of target temperature during the application. After ablations were performed at all veno-atrial junctions, the PVAC was used to map all PV ostia. If the PVs appeared to be incompletely isolated, additional RF applications were delivered using the PVAC until the PVs were completely disconnected based on PVAC signals (Fig. 3(a)–(c)). All PVs were mapped again 30 min post-ablation with the PVAC, and if necessary, additional ablations were performed. None of the patients who underwent MEA were converted to CPVI.

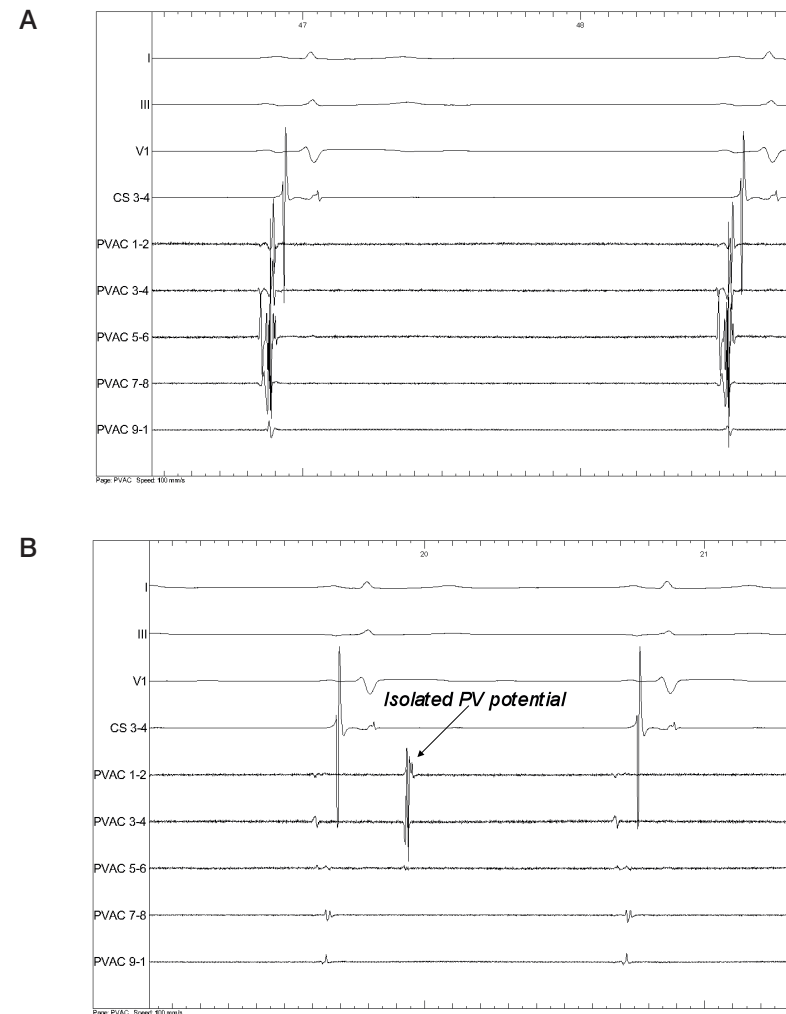
### Patient follow-up

Post-ablation, patients were hospitalized for at least 24 h and monitored telemetrically. AF recurrence was defined as an atrial arrhythmia of >30 s. Low-molecular-weight heparin was given for 2 to 7 days and acenocoumarol for at least 3 months. Anti-ar-



**Figure 2** Panel (A) shows angiography (AP view) of the left atrium and the left-sided pulmonary veins. The PVAC catheter is positioned in the LSPV. Panel (B) shows the surface ECG leads I, III, and V1. The intracardiac signals from proximal electrode pair of the quadripolar catheter positioned in the CS. Five bipolar PVAC signals from the ostium of the LSPV. LA = left atrium; CS = coronary sinus; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; PVAC = pulmonary vein ablation catheter. See text for details.

rhythmic drugs (class I or III) were continued during the first 3 months and gradually tapered. A 24–168 h Holter monitoring was performed at 3-, 6-, and 12-month intervals. Furthermore, 1 week AF alarm monitoring was performed  $6 \pm 1.5$  (range, 5–8) months after ablation. The AF alarm is a battery-powered electronic arrhythmia detection device with ECG recording capabilities. The device automatically detects arrhythmias and stores a digitalized ECG of arrhythmias. Furthermore, ECG storage can also be manually triggered to investigate if symptomatic episodes are actually related to an arrhythmia.<sup>14</sup> Patients were instructed to report symptoms suggestive of PAF and were provided with an event recorder to document the cause of their symptoms. During a mean follow-up period of  $363.98 \pm 138.65$  days (median, 380; interquartile range, 310–596 days), no patient was lost to follow-up. Transthoracic echocardiography and spiral CT or magnetic resonance imaging (MRA) of the PVs were performed 3 months after RF ablation to document atrial size and PV ostial dimensions, respectively. Esophagoscopy was not performed routinely post-procedure, but only if a complication was suspected. In the present study, no patients



**Figure 3** Tracings are ECG leads I, III, and V1 and bipolar intracardiac electrograms recorded from the proximal electrode pair of a catheter located in the coronary sinus and bipolar recordings from the pulmonary vein ablation catheter (PVAC). Panel (A) shows the right inferior pulmonary vein (RIPV) antrum signals during sinus rhythm pre-ablation. Panel (B) shows the signals from the RIPV post-ablation; note the dissociated PV spike in the PVAC recordings 1-2 and 3-4. In panel (C), note the irregular PV tachycardia with sinus rhythm recorded at the surface ECG leads and the recordings from the coronary sinus.



**Figure 3** Continued.

underwent esophagoscopy.

#### Study end point

The primary end point of the study was freedom from recurrent PAF after a single ablation procedure. Freedom from recurrent PAF was defined as the absence of symptomatic PAF off antiarrhythmic drug therapy. Previous studies have suggested that early recurrence of AF may be a transient phenomenon. Therefore, early recurrences of PAF within the first 3 months after PV isolation were excluded from the analysis.

#### Statistical analysis

Continuous variables are expressed as mean  $\pm$  SD and were compared with Mann-Whitney U test. Categorical variables were compared by  $\chi^2$  analysis or with Fisher's exact test. A Kaplan-Meier analysis with the log-rank test was used to determine the probability of freedom from recurrent PAF. A multivariate Cox regression analysis was performed to determine the independent predictors of recurrence of PAF. A value of  $P < 0.05$  was considered statistically significant.

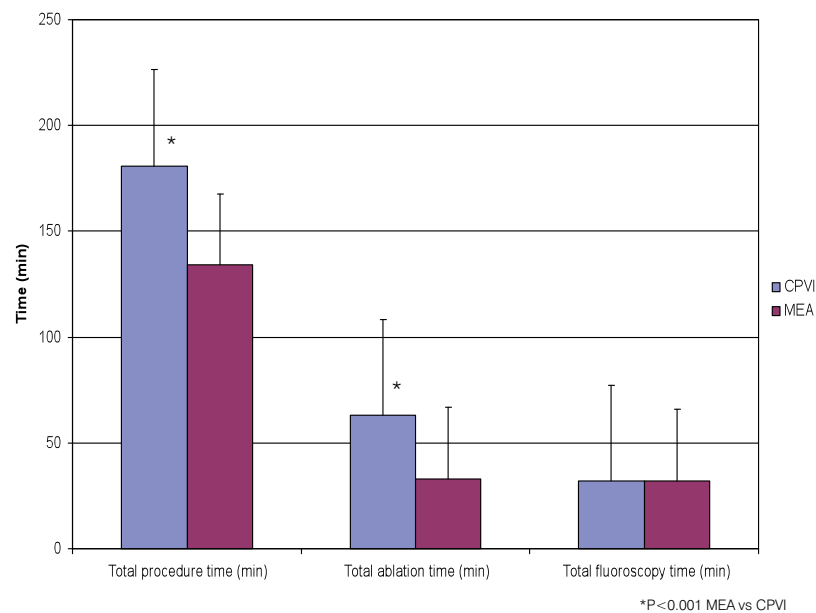
## Results

### Conventional versus multi-electrode ablation for PV isolation

Conventional 3D electro-anatomic mapping and Lasso-guided isolation of all PVs (CPVI) was performed successfully in all patients (N = 96). PV isolation using the multi-electrode ablation approach with the PVAC was successful in all patients (N = 89). In none of the patients in the MEA group was additional ablation using a conventional irrigated tip catheter necessary to achieve complete PV isolation. After the initial ablation to isolate the PVs, additional ablation after the 30 min waiting period was required in 11 of 96 patients in the CPVI group and 36 of 89 patients in the MEA group. In none of the patients was extra-PV ablation performed, so potential non-PV triggers were not targeted.

### Total procedure and fluoroscopy times

As shown in Fig. 4, the mean total duration of the procedure was  $175 \pm 56$  (median, 165; range, 140–210) min for the CPVI group, compared with  $138 \pm 35$  (median, 133; range, 115–163) min for MEA group ( $P < 0.001$ ). The mean duration of radiofrequency energy applications was  $52.69 \pm 34.91$  min in CPVI group and  $33.92 \pm 13.26$  min in



**Figure 4** Bar graph showing the total procedure time, total ablation time, and total fluoroscopy time for the MEA and CPVI groups. See text for details.

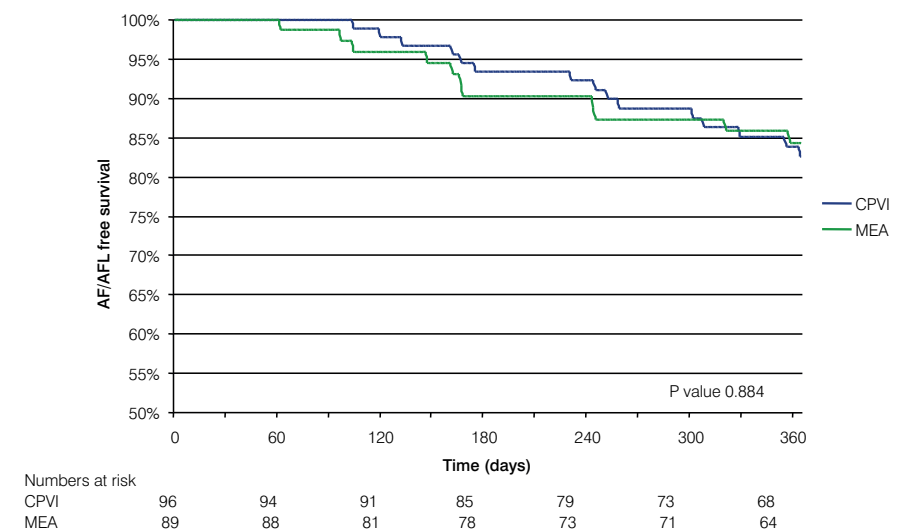
the MEA group ( $P < 0.001$ ). The mean total fluoroscopy times were  $32 \pm 11$  (median, 29; range, 25–40) min for the CPVI group, compared with  $31 \pm 13$  (median, 30; range, 23–38) min for MEA group ( $P = 0.278$ ).

### Freedom from recurrent AF

After the first ablation procedure, PAF recurred in 18 of the 96 patients (18.8%) who underwent CPVI and 15 of the 89 patients (16.9%) who underwent MEA ablation. At 12 months of follow-up, without any repeat ablation procedures, 83% of the patients who underwent conventional CPVI were free of symptomatic PAF, compared with 84% of patients who underwent MEA ablation ( $P = 0.989$ , log-rank test). A Kaplan–Meier curve of the arrhythmia-free survival after CPVI and MEA is shown in Fig. 5.

### Redo ablation procedures

A redo ablation procedure within 1 year after the initial procedure was performed in 28 patients (15.1%) in the total study group—15 (15.6%) of the patients who initially underwent CPVI and 13 (14.6%) of the patients who initially underwent MEA ablation. Three of the 89 (3.4%) patients in the MEA group and two of the 96 (2.1%) patients in the CPVI group had a drug refractory and highly symptomatic left atrial flutter. During



**Figure 5** Freedom from recurrent PAF after multi-electrode ablation (MEA, green line) and circumferential pulmonary vein isolation (CPVI, dark blue line). See text for details.

the redo procedures, recovery of conduction was found in  $\geq 1$  PV in all patients. In the CPVI group, 27 PVs in 15 patients were reconnected (average of  $1.80 \pm 0.41$  PVs per patient), and in the MEA group, 34 PVs in 13 patients were reconnected (average of  $2.61 \pm 0.65$  PVs per patient). The difference was statistically significant ( $P < 0.001$ ). During the redo ablation procedures, CPVI was performed in all patients. In patients with atrial flutter, electro-anatomic propagation mapping and entrainment mapping were performed. These atrial flutters were due to incomplete ablation lines at the junction of the left superior PV and the left atrial appendage in two patients and an incomplete ablation at the anterior part of the RIPV antrum in three patients; thus, even these LA flutters were the result of PV reconnections. All five patients underwent successful left atrial flutter ablation.

All patients who underwent a redo ablation procedure subsequently remained free of symptomatic PAF. In the final analysis, after a mean of 1.15 procedures per patient (213 procedures in 185 patients), the freedom from symptomatic PAF at 12 months of follow-up (after the most recent ablation) was 92% in patients who initially underwent CPVI, compared with 93% in patients who initially underwent MEA ablation ( $P = 0.708$ ). The mean duration of follow-up in the group of patients with repeat ablation was mean  $318 \pm 236$  days and median (Q1–Q3) was 355 (196–427) days.

## Discussion

### Main findings

In this prospective non-randomized study, symptomatic PAF was eliminated with electro-anatomic Lasso-guided circumferential peri-ostial encircling of the PVs (CPVI) and by multi-electrode duty-cycled RF ablation of the PVs (MEA) with equal efficacy. On the other hand, the total procedure time was significantly shorter with the multi-electrode ablation approach. Complications were rare with both catheter ablation techniques. The only complication in this study was left atrial flutter after CPVI in two patients and after multi-electrode ablation in three patients. PV stenosis was not observed in this study.

### Comparison of the two techniques

In our center, CPVI is performed with double transseptal puncture and the insertion of two catheters into the left atrium, whereas the multi-electrode ablation is performed with only a single catheter in the left atrium. We performed CPVI with the use of a 3D mapping system and a circular mapping catheter, which increases the cost of the procedure. The multi-electrode ablation obviates the need for 3D mapping and was associated with a shorter procedure time. On the other hand, the CPVI approach has

the greatest flexibility to accommodate multiple LA-PV anatomies such as common left PVs. We have to recognize that other groups are working with a single transseptal puncture that is used to introduce both the ablation catheter and the sheath supporting the Lasso catheter into the left atrium to perform CPVI. Furthermore, CPVI is also performed without the use of a 3D mapping system in several well-recognized centers. It is important to emphasize the fact that multi electrode ablation is associated with more ostial lesions as compared with more atrial lesions with conventional pulmonary vein isolation. Also, it is important to recognize that one difference in the acute procedural endpoint of the two arms relates to the fact that electrical PV isolation was defined using a standard circular mapping catheter in the CPVI arm, while only the MEA catheter was used to verify isolation in the MEA arm. Thus, one cannot rule out the possibility that the difference in procedure times was related in part to a potentially different endpoint. Indeed, the higher PV reconnection rate seen in those patients who initially underwent MEA ablation (as opposed to CPVI) may be related to this. But an important counterpoint is the similar overall 1-year clinical success rates in the two groups.

The fluoroscopy times were not different between the two ablation techniques. However, procedure and fluoroscopy times are operator-dependent. Our experience with CPVI has been more than ten times as large as with multi-electrode ablation. Previous studies reported a mean procedure time of  $148 \pm 26$  min using the conventional electro-anatomic approach.<sup>2, 3</sup> The impact of this ostial ablation approach for procedural efficacy and safety remains undetermined, and further studies are needed to compare the clinical outcome. The ostial ablation site is inherent to all multi-electrode ablation devices and all balloon technologies currently under investigation.

### Mechanism of arrhythmia recurrence after PV isolation

Both in the CPVI and the MEA group, we found during repeat procedure that the electrophysiological mechanism of the atrial arrhythmias was recovered PV conduction. In the current study, all patients with recurrent atrial tachycardia/flutter and all patients with recurrent AF had PV reconnection. This high PV reconnection rate in patients with clinical recurrences is consistent with prior data of AF recurrences after PV isolation. We eliminated atrial tachycardia/flutter and AF successfully by segmental RF applications in these patients. Satomi et al.<sup>15</sup> and Ouyang et al.<sup>16</sup> have elegantly demonstrated that when only the pulmonary veins are targeted for ablation during the initial ablation procedure, the incidence of non-PV atrial tachycardia/flutter is very low. In our study, none of the patients had a non-PV tachycardia.



It is important to recognize that we did not assess the incidence of PV reconnection in asymptomatic patients. However, the relatively high rate of PV reconnection in the symptomatic patients—1.8 PVs/patient in the CPVI group and 2.6 PVs/patient in the MEA group—suggests that even the asymptomatic patients will likely have PV reconnections. And how any such reconnections would affect the long-term clinical outcome is not known in these patients. However, there is increasing data that long-term outcome after AF ablation in patients without symptoms at the end of 1 year is not good; the long-term annualized AF recurrence rate has been reported to be linear at a rate as high as 10%/year (to 40% over the course of ~4 years).<sup>17</sup> The mechanism of these late recurrences is also thought to be a result of PV reconnection.<sup>18</sup> Thus, the data from our study suggest that, while the 1-year success rates are quite favorable as compared with the literature, it is quite possible that the long-term success rate will be lower as a result of PV reconnection.

### Safety

There were no complications in this study except for left atrial flutters, which are arguably more appropriately not considered as complications as much as proarrhythmic effect of left atrial ablation. None of the patients had PV stenosis after ablation.

A recent report on PVAC technique demonstrated a higher incidence of silent cerebral ischemic events compared with radiofrequency and cryoballoon ablation. In this study, 38.9% (14 of 36) of patients with paroxysmal AF, treated with MEA (PVAC) appeared to have new silent cerebral ischemic lesions at post procedural cerebral MRI. This number was significantly higher compared with irrigated RF ablation (8.3%) and cryoballoon (5.6%).<sup>19</sup> Although there are no studies demonstrating any clinical consequences of silent cerebral events after PVI, this high number of cerebral lesions with MEA is a concerning phenomenon. However, one should be careful interpreting the result of this study. The study is non-randomized, and ACT values were <300 a considerable amount of time.<sup>20</sup> The authors speculate that the fact that PVAC is a non-irrigated technique, using only cooling by local blood flow, and is insufficient in reducing thrombus formation. Another explanation is the fact that the non-simultaneous contact of the PVAC electrodes with the vein-atrium junction increases char formation on noncontact electrode tips. The rotations and pressing of the PVAC catheter to obtain better catheter-endothelium contact facilitates mobilization and embolization of char and thrombi. In our study, there were no symptomatic thromboembolic complications. However, we did not perform post-procedure cerebral MRI to evaluate possible silent cerebral lesions.

The most feared complication of left atrial ablation is atrio-esophageal fistula due to the thermal effect on the esophagus. Esophageal thermal alterations may be a precursor for potentially fatal atrio-esophageal fistula. As the PVAC-based ablation uses relatively low power (maximum 10 Watt), the risk of collateral damage is minimized compared with other techniques. Deneke et al. evaluated thermal effect of PVAC technique on the esophageal wall by using an esophageal temperature probe with metal thermocouple electrodes for continuous luminal esophageal temperature (LET) monitoring. Interestingly, endoscopy revealed only esophageal alteration in patients when LET monitoring was used and not in the control group of patients ablated with PVAC technique without LET monitoring.<sup>21</sup> Another study demonstrated no thermal esophageal lesions by endoscopy in 12 patients within 24 h of PVAC ablation.<sup>22</sup> We did not perform esophageal temperature monitoring neither routine endoscopy after the ablation procedure, but there were no symptoms suggesting collateral damage.

### Previous studies

Two randomized studies compared MEA to conventional point-by-point ablation. Bulava et al. included 102 patients (51 MEA versus 51 CARTO) and found significantly lower procedure and fluoroscopy times in the MEA group ( $171 \pm 40$  min vs  $224 \pm 27$  min,  $P < 0.001$ ;  $26 \pm 8$  min vs  $35 \pm 9$  min,  $P < 0.001$ ; respectively). Seventy-two percent of patients in the MEA group and 68% of the control group were free of AF during a mean follow-up of  $254 \pm 99$  days ( $P =$  not significant).<sup>10</sup> Bittner et al. found similar results. They randomized 80 patients with paroxysmal and persistent AF to either MEA ( $n = 40$ ) or CARTO ( $n = 40$ ) based ablation. During a mean follow-up of  $254 \pm 99$  days, 72% in the MEA group and 68% in the CARTO group were free of AF recurrences ( $P =$  not significant). The procedure and fluoroscopy times were significantly lower in the MEA group compared with the control group.<sup>9</sup> In contrast to these studies, the current study is non-randomized but shows a higher rate of freedom from AF after MEA during a longer follow-up (82% during mean follow-up of 12 months). Possibly, the fact that we excluded persistent AF patients contributed to this difference.

A recent non-randomized (case control) study describes efficacy of MEA in 209 patients with paroxysmal and persistent AF compared with a historical control group consisting of 211 patients treated with conventional PV isolation followed by anatomical lines at the roof and mitral isthmus. They reached success rates of 82% after 1.08 MEA procedures in the subgroup of patients with paroxysmal AF at a follow-up time of  $7.1 \pm 5$  months which was comparable the conventional treatment. Multivariate analysis revealed that independent predictors of success were smaller left atrial size, younger age, and absence of previous pacemaker implantation.<sup>23</sup>



## Limitations

This study is a non-randomized comparison of two approaches. In the future, a multicenter randomized comparison of the two techniques needs to be performed. The size of electrodes of the Lasso and the PVAC are different, and the mapping resolution is also different. We cannot exclude that the much higher pulmonary vein reconnection rate observed with multi electrode ablation could in fact be even higher. Another limitation is the relatively small left atrial size (mean LA size in MEA group  $42.50 \pm 3.40$ ). We realize that other studies included larger atrial sizes; this will influence the success rate. Another limitation of this study is that asymptomatic episodes of PAF may not have been recognized after the ablation procedures. The mean duration of follow-up in this study was 364 days. Long-term follow-up will be important to determine the long-term safety and efficacy of both ablation strategies. The complication rate seems to be low with both CPVI and MEA approaches, and there were no adverse events in this study. However, only limited reports of experience with PVAC ablation have been published. Larger studies are required to evaluate the whether the PVAC is associated with a different complication rate compared with standard PV isolation.

## Conclusions

Although several centers have reported the clinical results of multi-electrode ablation, this is the first study that directly compared this technique to CPVI in a prospective fashion. The results of the present study indicate that both electro-anatomic/Lasso-guided circumferential peri-ostial PV isolation and multi-electrode ablation eliminate PAF with equal efficacy. On the other hand, multi-electrode ablation was performed with a shorter procedure time. If the findings of this study are reproduced in a randomized study, it would be appropriate to use multi-electrode ablation as first-line therapy in patients with PAF who are appropriate candidates for catheter ablation. Lasso-guided 3D electroanatomic approach can be used as both first- and second-line therapy in patients referred for ablation of PAF.

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# 6

## Ablation of focal atrial tachycardia from the non-coronary aortic cusp: case series and review of the literature



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## Abstract

### Aims

Focal atrial tachycardia successfully ablated from the non-coronary cusp (NCC) is rare. Our aim was to describe the characteristics of mapping and ablation therapy of NCC focal atrial tachycardias and to provide a comprehensive review of the literature.

### Methods and results

Seven patients (age  $40 \pm 9$  years) with symptomatic, drug-refractory atrial tachycardia were referred for electrophysiological study. Extensive right and left atrial mapping revealed atrial tachycardia near His in all patients but either failed to identify a successful ablation site or radiofrequency applications only resulted in temporary termination of the tachycardia. Mapping and ablation of the NCC were performed retrogradely via the right femoral artery. Mapping of the NCC demonstrated earliest atrial activation during atrial tachycardia  $38 \pm 14$  ms (ranging 17–56 ms) before the onset of the P-wave. Earliest atrial activation in the NCC was earlier than earliest activation in the right atrium and left atrium in all patients. The P-wave morphology was predominantly negative in the inferior leads and biphasic in leads V1 and V2. The tachycardia was successfully terminated by radiofrequency application in  $10 \pm 6$  s (2–16 s), without complications. All patients were free of symptoms during a follow-up of  $19 \pm 9$  months. Literature search revealed 18 reports (91 patients) describing NCC focal atrial tachycardia, with 99% long-term ablation success with a 1% complication rate.

### Conclusion

Symptomatic focal atrial tachycardia near His may originate from the NCC and can be treated safely and effectively with radiofrequency ablation.

## Introduction

Focal atrial tachycardias (ATs) have a predilection for specific areas within the atrium, such as the crista terminalis,<sup>1</sup> pulmonary vein ostia,<sup>2</sup> near the tricuspid and mitral annulus,<sup>3,4</sup> the ostium of the coronary sinus (CS),<sup>5</sup> and para-Hisian regions.<sup>6,7</sup> In the last decade, a few reports were published on focal AT originating from the non-coronary cusp (NCC). The diagnosis of a NCC AT can be difficult and ablation therapy in the sinus of Valsalva can be challenging. In this report, we describe the electrophysiological (EP) characteristics of NCC AT and ablation techniques in seven patients with this arrhythmia. Secondly, we provide a comprehensive review of the available literature regarding NCC AT and its treatment.

## Methods

Our study population consisted of 7 patients (4 males; age  $40 \pm 9$  years, range 28–51 years) from a consecutive series of 112 patients undergoing EP study and radiofrequency (RF) ablation for focal AT, between June 2009 and June 2011, at the Isala Hospital in Zwolle, The Netherlands.

All patients had complaints of palpitations with a sudden onset and offset. None of the patients had an incessant tachycardia. The mean duration of symptoms was  $4.2 \pm 1.9$  years. Six patients had been ineffectively treated with beta-blockers and two patients with verapamil. One patient had a mitral valve prolapse with mild regurgitation. The remainder had structurally normal hearts. An EP study had previously been performed in three of seven patients. In one patient, an atrioventricular (AV) node reentrant tachycardia was confirmed and a successful ablation of the slow pathway had been performed 3 years prior to admission. Another patient had a prior history of lone atrial fibrillation for which a pulmonary vein isolation was performed 1 year prior to admission. Another patient had a past history of atrial fibrillation and supraventricular tachycardias due to a concealed bypass for which a pulmonary vein isolation and ablation of a para-Hisian concealed bypass was performed.

### Electrocardiogram analysis

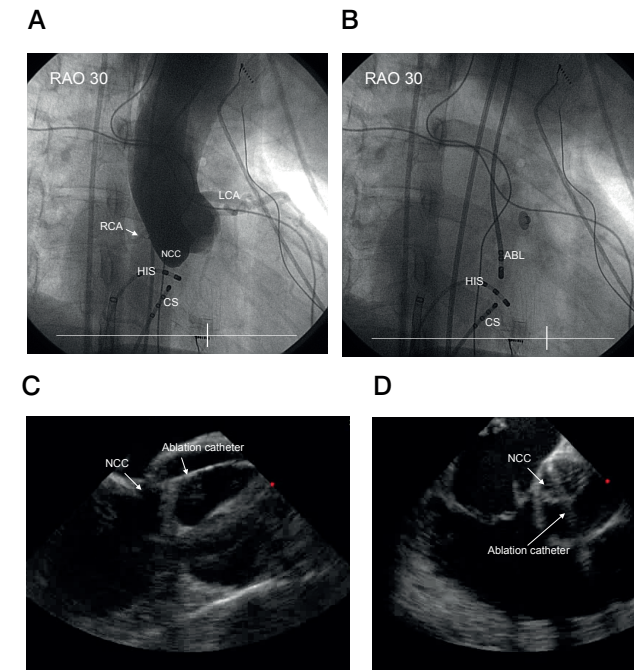
The P-wave morphology and duration were assessed on the surface electrocardiogram (ECG) during the tachycardia. The morphology was described as positive, negative, biphasic, or isoelectric depending on deviation from baseline. Criteria as described by Kistler et al.<sup>8</sup> were used to determine the likely site of origin.

### Electrophysiological study

After giving informed consent and withdrawal of antiarrhythmic medication for at least five half-lives, all patients underwent an EP study. The procedure was performed in a fasting state under light sedation. Catheters were introduced via the femoral veins to the right atrium (RA), right ventricular apex (RVA), CS, and at the His bundle (HB) region. After placement of the catheters, an intravenous heparin bolus of 5000 IE was administered. The stimulation protocol consisted of programmed stimulation at two basic cycle lengths (CLs) with up to two extrastimuli and burst pacing at the RA and RVA. If necessary, intravenous isoprenaline was administered to provoke the tachycardia. Focal AT was confirmed by the following criteria: (i) the atrial activation sequence during the tachycardia was different from that recorded during sinus rhythm; (ii) the atrial activation sequence during the tachycardia was different from that obtained during ventricular stimulation with retrograde ventriculoatrial conduction; (iii) VAAV response after discontinuation of ventricular pacing; (iv) induction of tachycardia independent of a critical prolongation of the A–H interval; (v) transient AV block during tachycardia; and (vi) inability to obtain concealed entrainment of the tachycardia using ventricular extrastimuli.<sup>9</sup>

### Mapping and ablation

Initially, mapping was performed in the RA in all patients using NaviStar ThermoCool, CARTO XP or CARTO 3 system (Biosense Webster, Johnson & Johnson). Activation time was measured from the onset of the local electrogram to a stable atrial electrogram recorded from the CS catheter. Whenever mapping in the RA and left atrium (LA) failed to identify a successful ablation site or the tachycardia was still inducible after focal ablation therapy, the aortic sinus (AS) was evaluated. The NCC was visualized retrogradely via the right femoral artery. Aortic root angiography and intracardiac echo (ICE) demonstrated the anatomical position of the NCC (Figure 1). After confirming the location of the coronary ostia, a 7Fr quadripolar catheter with 4 mm tip electrode (NaviStar ThermoCool, Biosense Webster) was introduced for mapping and ablation in the NCC.



**Figure 2** (A) Aortic root angiogram in right anterior oblique view showing the anatomy on the NCC and the coronary arteries. (B) Catheter position and successful ablation site in the NCC. (C, D) Intracardiac echocardiography confirming correct position of the ablation catheter in the NCC at the conjunction of the right coronary cusp in long axis (C).

### Results

In all patients, the RA and LA were extensively mapped before proceeding to investigate the sinus of Valsalva. The EP characteristics are demonstrated in Table 1. The AT was inducible with programmed stimulation in all patients. In one patient, the arrhythmia occurred spontaneously, in another patient isoprenaline was needed in conjunction with programmed stimulation to induce the AT. The earliest atrial activation was registered at the HB area in all patients. In four patients, RA unsuccessful RF applications were performed at the site of earliest activation at the right-sided para-septal AV nodal region. In five patients, LA unsuccessful RF applications were performed at the left-sided para-septal area. The atrial RF applications only resulted in temporary termination of the tachycardia.

**Table 1** Electrophysiological characteristics of AT.

	1	2	3	4	5	6	7
stimulation protocol (ms)	400+190, 400+280	spontaneous, 500+400, 600+400	500+340	400+340 + isoprel	400+290	600+280	burst CS, 300+280
site of earliest atrial activation	His	His	His	His	His	His	His
tachycardia cycle length (ms)	230-344	406-438-480	502	392-536	270-320	322-334	228-348
P wave duration (ms)							
Sinus rhythm tachycardia	132 80	108 42	130 60	120 48	100 44	114 44	150 66
activation time NCC preceding p wave (ms)	53	56	39	26	17	33	39
Energy source	RF	Irrigated tip, thermocool	Irrigated tip, thermocool	RF	Irrigated tip, thermo-cool	RF	Irrigated tip, thermo-cool
Energy settings	30W, 33grC	40W, 37grC	30W, 36grC	30W, 43C	40W, 32grC	30W, 46grC	30W, 32grC
RF application attempts left/right atrium	LA, RA	LA	RA, LA	RA, LA	RA	LA	-
Nr of RF applications NCC	4	7	3	1	7	2	2
Total RF time (sec.)	227	397	166	64	434	.	95
RF time to termination of tachycardia	12	16	spontaneous	16	2	6	8
AV conduction	2:1	1:1	1:1 and 2:1	1:1	1:1	1:1 and 2:1	1:1
AV ratio	2.6	4.2	4.7	3.7	3.4	1.7	5.6

Note: AV: atrio-ventricular; LA: left atrium; NCC: non coronary cusp; RA: right atrium; RF: radio-frequency.

Mapping of the NCC revealed that the activation occurred  $34 \pm 21$  ms earlier than atrial activation at the CS and preceded the onset of the P-wave by  $38 \pm 14$  ms (range 17–56 ms). The mean tachycardia CL was  $368 \pm 96$  ms (range 228–536 ms). The P-wave duration was  $122 \pm 17$  ms during sinus rhythm and shortened significantly to  $56 \pm 16$  ms during tachycardia ( $P < 0.001$ ). Atrial/ventricular (A/V) amplitude ratio at the site of successful ablation was  $>1$  in all patients ( $3.7 \pm 1.3$ ).

### P-wave morphology

P-wave morphology is provided in Figure 2. The P-wave morphology during tachycardia was clearly different from the P-wave morphology during sinus rhythm. The P-waves in the inferior leads were inverted in six of seven patients. P-wave morphology in leads I and AVL were mostly upright or isoelectric (six of seven patients). The leads V1 and V2 showed a biphasic morphology in six of seven patients with an initial negative deflection in four patients.

### Catheter ablation

In four patients, ablation was performed with an irrigated tip catheter and in the remaining three patients conventional RF ablation was performed. The choice of catheter and energy source was based on personal preference and experience of the operator. The AT was terminated with a mean number of RF applications of  $3.7 \pm 2.4$  (range 1–7) within 16 s (mean duration until termination of arrhythmia  $10 \pm 5$  s, range 2–16 s). Representative intracardiac electrograms and electroanatomical mapping are demonstrated in Figures 3 and 4.

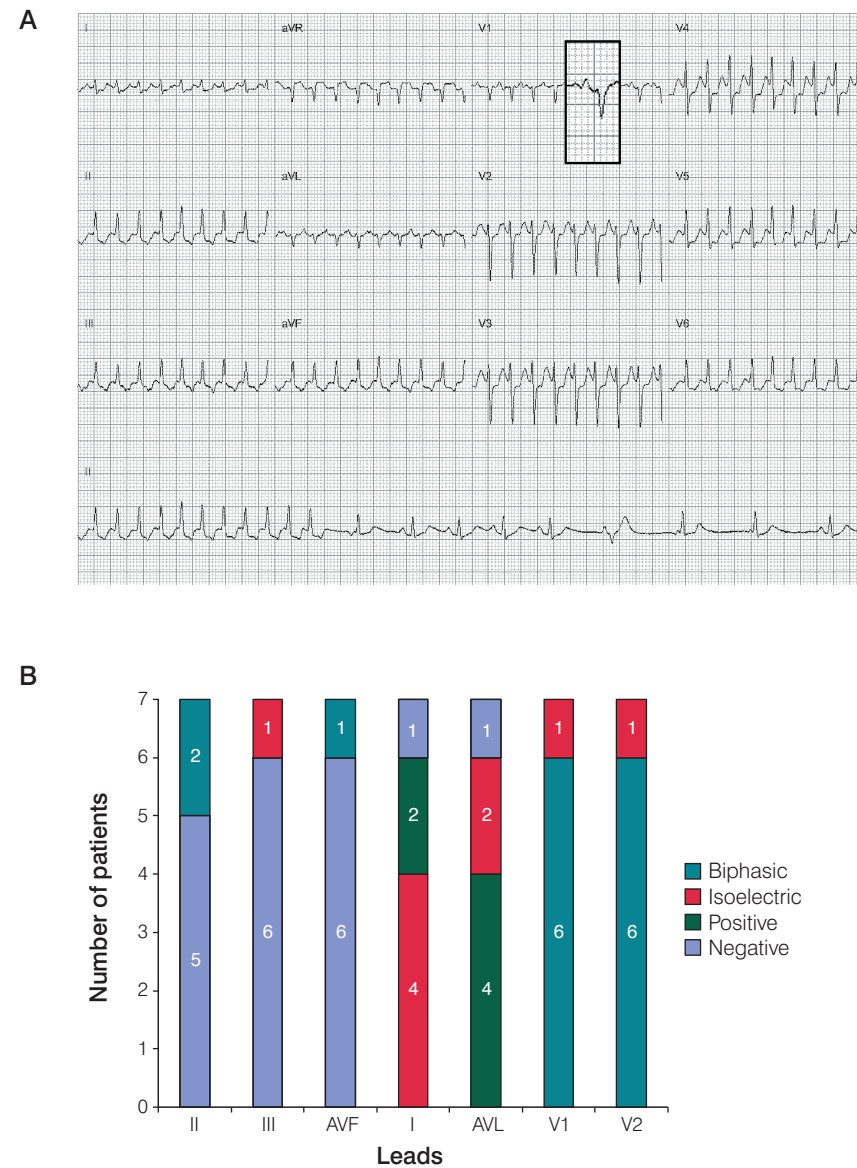
### Follow-up

There were no in-hospital or late complications. All patients were free of arrhythmias without antiarrhythmic drugs after a mean follow-up of  $19 \pm 9$  months.

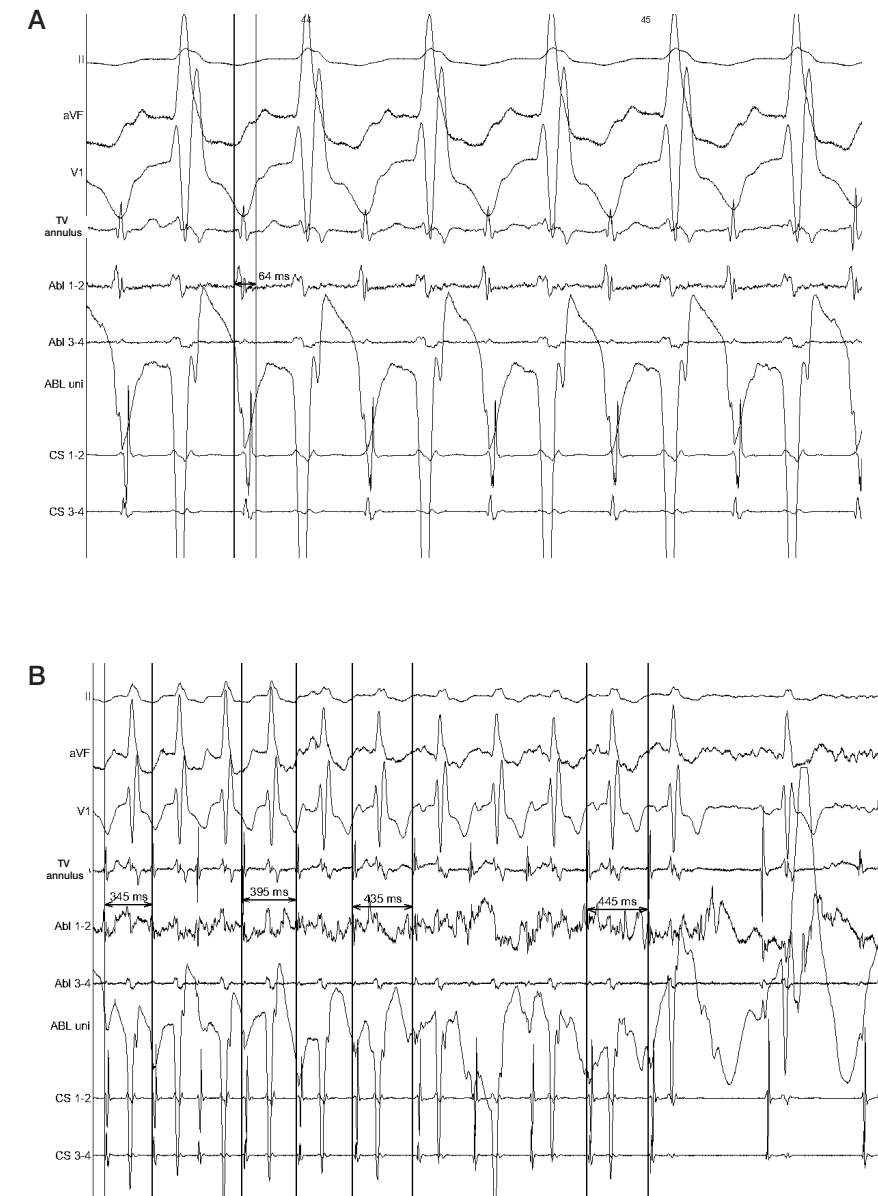
## Discussion and literature review

Experience with RF ablation of AT in the NCC is limited. A review of existing reports is presented in Table 2.10–27 The first report was published in 2004 by Tada et al.,<sup>10</sup> who described a 35-year-old patient with a symptomatic AT, which was successfully ablated from within the NCC. The authors emphasize the close anatomical relation of the NCC to the AV node transitional area and suggest that RF energy delivery through the NCC might even be safer than a right-sided approach for selected ATs near the AV node.

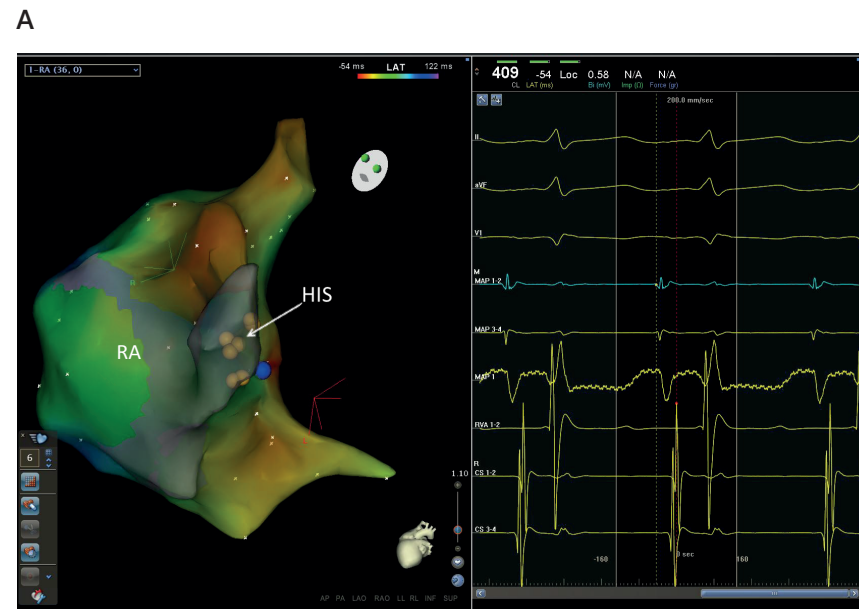




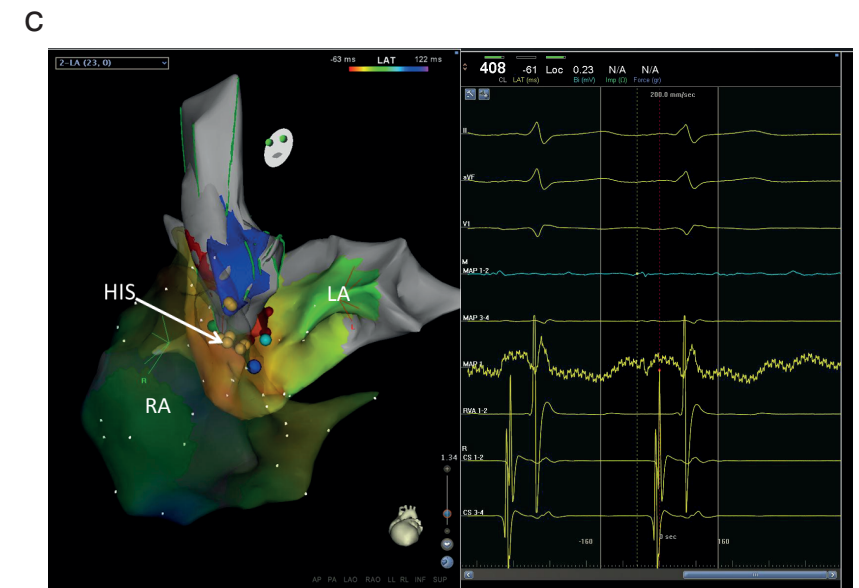
**Figure 2** (A) Twelve-lead ECG of a patient with AT from the NCC showing typical P-wave morphology with negative P-wave in the inferior leads and biphasic, negative-positive deflection in lead V1. (B) Characteristics of P-wave morphology in studied patients during AT on surface ECG.



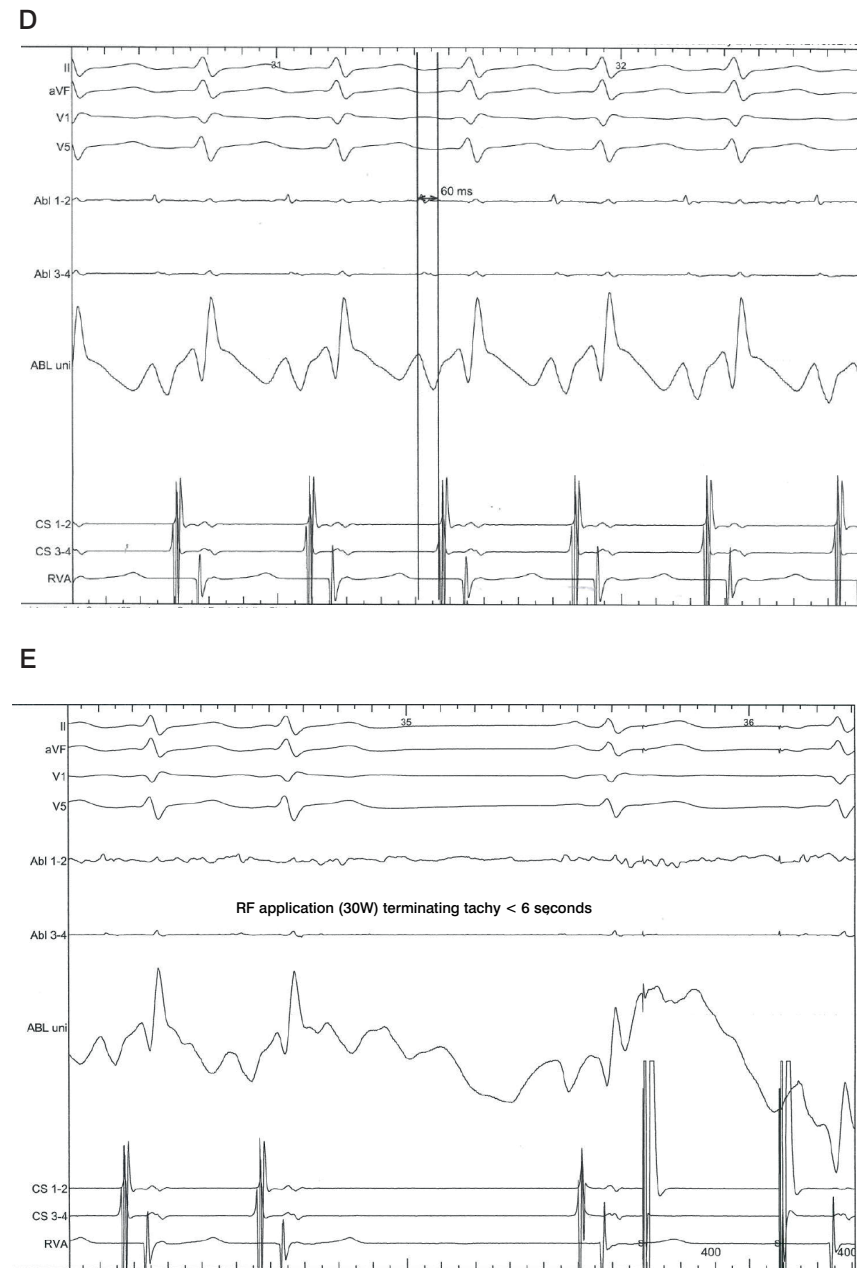
**Figure 3** Intracardiac electrogram at the successful ablation site within the NCC. (A) The earliest activation within the NCC preceded the P-wave by 64 ms. (B) Radiofrequency application at this site terminates the tachycardia after prolonging the CL.



**Figure 4** Three-dimensional electroanatomical mapping (CARTO) in a patient with AT originating from NCC. **(A)** Activation map of the RA. The activation spreads from the interatrial septum towards the free wall. The corresponding intracardiac electrogram showing earliest atrial activation during AT at the RA septum (indicated by the blue point) preceding the reference CS by 54 ms. **(B)** Further mapping of the LA showing centrifugal spread from the interatrial septum. The green point indicates the earliest activation in the LA septum preceding the reference CS by 54 ms as well. **(C)** CARTO map displays the spatial relationship between the NCC, the interatrial septum, and HB. The light blue point indicates the earliest activation, deep within the NCC. **(D)** Intracardiac electrogram showing earliest atrial activation during AT in the NCC preceding the reference CS by 60 ms, no his potential was recorded at this site. **(E)** RF ablation at this site terminates the tachycardia in 6 s. AO, aorta; AT, atrial tachycardia; CS, coronary sinus; LA, left atrium; NCC, non-coronary cusp; RA, right atrium; RF, radiofrequency ablation.



**Figure 4** Continued.



**Figure 4** Continued.

### Epidemiology

The prevalence of AT originating from NCC is unknown. Ouyang et al.<sup>11</sup> found the prevalence of NCC AT in all patients with focal AT to be 4.1%. In the current study the prevalence was 6.3%. Park et al.<sup>25</sup> found even a higher prevalence of 8.8%. These numbers might be overestimated in specialized centres, due to a referral bias. On the other hand, previously diagnosed para-Hisian ATs probably contain ATs originating from the NCC. Because mapping of the NCC is not a standard procedure for para-Hisian ATs, the published cases might underestimate the prevalence of NCC-related ATs.

### Anatomy of non-coronary aortic sinus

The aortic root occupies a central position in the heart, all chambers of the heart are directly related to the aortic valve and its leaflets are incorporated directly into the cardiac skeleton. Whereas the right and left coronary cusps make direct contact with the ventricular myocardium, the NCC is located closer to the superior AV junction and is immediately adjacent to the atrial myocardium of the interatrial septum. Gami et al. examined 603 autopsy hearts and found myocardial sleeves in the aortic root, either above the semilunar cusps or intercuspally in 57% of examined hearts. However, myocardial extensions above the NCC were rare (0.66%) and extensions into the valve cusp even more exceptional.<sup>28</sup> The NCC is exclusively composed of fibrous walls. Some suggest that this dispersed tissue might be a potential arrhythmogenic substrate as well.<sup>29,30</sup> It remains unclear whether the arrhythmogenic substrate for NCC AT is actually a myocardial sleeve within the cusp, atrial tissue adjacent to the NCC, or fibrous tissue (microreentry).

### Characteristics of atrial tachycardia from non-coronary cusp

As the NCC AT is sensitive to adenosine and the tachycardia is reproducibly inducible and terminated by atrial stimulation, the mechanism of NCC AT is due to either reentry or triggered activity.<sup>11</sup> The atrial activation pattern of NCC AT is extensively described by Liu et al.: Initially, the tachycardia activates the RA para-Hisian area followed immediately by activation of the LA anteroseptal area. Rather than propagation of the impulse from the RA to the LA, the authors state that both atria become activated from the NCC. Furthermore, they found that the initial activation area in the first 20 ms is diffuse.<sup>20</sup> This phenomenon is in line with our findings of a significantly shorter P-wave duration during tachycardia than during sinus rhythm, which clearly suggests a septal origin of the focal tachycardia. However, the P-wave duration on itself cannot distinguish between an AT with a left septal origin, which typically have a short P-wave duration, and a NCC AT.<sup>31</sup>

**Table 2** Literature review of AT originating from the non-CS.

Investigator	Number of patients	Type of arrhythmia	Structural heart disease	Previous unsuccessful ablation	Tachycardia cycle length (msec)	Activation time NCC preceding p wave (msec)	Follow up Time + method, efficacy	complications
Tada, 2004 <sup>10</sup>	1	AT	normal LV, dilated aortic root	no	504	38	10 months successful	None
Ouyang, 2006 <sup>11</sup>	9	AT	none	6 patients (67%) previously misdiagnosed as RA AT, AVNRT	358±63	32.4±4.6	9±3 months, 100% success TTE+holter 3,6,9 month	None
Yamada, 2006 <sup>12</sup>	1	AT	not reported	not reported	400	70	Not reported	None
Raatikainen, 2007 <sup>13</sup>	1	AT	no	no	390	40	7 months successful	None
Rillig, 2008 <sup>14</sup>	6	AT/VT/PVC (6 AT and 15 VT)	not reported	no	386	-	6 months, 100% success 6 mth holter, TEE, cardiac MRI (cerebral MRI in 6 pts)	None
Das, 2008 <sup>15</sup>	10	AT	2 poor LV	1 previous EP study	-	-	41±12 months, 7/10 successful	None
Joung, 2008 <sup>16</sup>	1	AT	no	no	480	55	10 months	None
Kriatselis, 2008 <sup>17</sup>	7	AT near His, (5 mitral annulus AT, 7 NCC AT)	1 tachycardiomyopathy	not reported	435±62	55±15	14±8, holter (10/12 patients)	none
Gil-Ortega, 2009 <sup>18</sup>	1	AT	poor LV, EF 25%	no	460	12	5 months holter+TTE successful (LV function improved, EF 65%)	None
Weber, 2009 <sup>19</sup>	1	AT	not reported	no	544	51	not reported	none
Liu, 2010 <sup>20</sup>	13	AT		3 pt's (23%) previous unsuccessful ablation	391±79	37±3	13±3 months	None
Zou, 2010 <sup>21</sup>	5	AT	none	not reported	363±44	-	>3 months, 100% success	None
Chen, 2010 <sup>22</sup>	1	AT	no	1 week prior RA and LA ablation attempts	380	52	2 years	None
Yamashita, 2010 <sup>23</sup>	1	AT	no	no	400	30	6 months	none
Wang, 2011 <sup>24</sup>	16	AT (16 NCC AT, 6 LCAS AT)	1 valvular disease, 1 tachycardiomyopathy	no	341±60	21±9	30±13 months	none
Park, 2012 <sup>25</sup>	10	AT (10 NCC AT, 1 LCC AT, 1 RCC AT, 7 aortic sinus AVRT)	Not reported	Not reported	349±19	40±10	20±10 months, 1 recurrence	Complete heart block in patient with AVRT from RCC
Miřochová, 2010 <sup>26</sup>	2	AT	Not reported	Not reported	387	36	14 months	none
Ju, 2012 <sup>27</sup>	5	AT (5 NCC AT, 15 RA para-Hisian AT)	None	Not reported	366±39	35±7	19±12 months	none

AT, atrial tachycardia; AVNRT, atrioventricular node reentrant tachycardia; EF, ejection fraction; EP, electrophysiological; LA, left atrium; LCAS, left coronary aortic sinus; LV, left ventricle; MRI, magnetic resonance imaging; NCC, non-coronary cusp; PVC, premature ventricular complex; RA, right atrium; TEE, transoesophageal echocardiography; TTE, trans thoracic echocardiography; VT, ventricular tachycardia.

### P-wave morphology

ATs might originate from different locations within the AS, mostly from the NCC but sporadically ATs arise from the left coronary cusp, only a single report described a case of AT originating from the right coronary cusp.<sup>32</sup> The most useful tool to differentiate between the cusps, according to the authors, are the P-wave morphology in leads I and AVL on the surface ECG and the local A/V ratio at successful ablation sites. Non-coronary cusp AT typically shows a positive P-wave in leads I and AVL and a local A/V ratio of  $>1$  (as opposed to a negative–positive P-wave deflection in left coronary cusp AT with a local A/V ratio  $\leq 1$ ).<sup>24</sup> The P-wave morphology of the NCC AT in the different reports is not consistent. Some studies describe a typical P-wave morphology for this arrhythmia: predominantly negative P-waves in the inferior leads, positive or isoelectric in leads I and AVL, and biphasic in right precordial leads V1 and V2 (mostly negative–positive)—whereas other studies describe a wide variety of morphologies. Das et al.<sup>15</sup> found a wide variation in P-wave morphologies in their patients and conclude that the NCC AT reflects a more heterogeneous origin. Although the present study shows a typical P-wave morphology pattern similar to Ouyang et al., one should be careful to use the P-wave morphology as a diagnostic instrument for NCC AT because para-Hisian AT, particularly anteroseptal AT, present with a similar P-wave morphology.<sup>11,33</sup> Furthermore, variation in P-wave morphology can be explained by cardiac rotation, body habitus, and atrial tissue mass distribution.

### Mapping and ablation

In the present study, the decision to evaluate the NCC was made after extensive LA and RA mapping revealed focal AT with earliest atrial activation near the HB. In most patients, attempts were made to ablate foci in the RA and LA before considering to proceed to NCC mapping. Because the focal atrial ablations only resulted in temporary termination of the arrhythmia, mapping of the NCC was performed. The majority of other reports describe a similar strategy.<sup>11,14,20</sup> However, Das et al.<sup>15</sup> suggest to proceed to NCC mapping after RA mapping reveals earliest activation in the RA peri-AV nodal septum. The authors suggest to apply RF energy once in the NCC at the site of earliest activation. If the tachycardia terminates within 10 s, the procedure is successful. If the tachycardia persists after 10 s of RF application, one should consider to map the LA.<sup>15</sup> We feel that the most reasonable strategy for selecting appropriate ablation site for focal ATs in the vicinity of the AV node should be to start with extensive activation mapping on both sides of the interatrial septum, followed by NCC mapping. To minimize the risk of inadvertent damage to the AV conduction system, these three compartments should be meticulously mapped to localize the exact origin of the tachycardia before considering ablation.

### Safety of ablation in non-coronary cusp

Ablation in the NCC seems a safe procedure, as no complications were reported in the studies. However, the number of reports on this subject is very limited and possibly complications are underreported due to a publication bias. Rillig et al. describe safety issues of ablation in the NCC, particularly the potential risk for cerebral embolism. One of their patients showed transient thickening of the aortic valve. It was speculated that valve leaflet oedema was responsible for this phenomenon due to RF application on the valve surface. Another patient in their series showed silent cerebral ischaemia on the magnetic resonance imaging (MRI) scan 1 day after the ablation procedure, which was not identifiable on the MRI at 6-month follow-up. In this patient the transoesophageal echo showed plaque in the aortic wall in close proximity to the ablation site.<sup>14</sup> Manipulation in the sinus of Valsalva is a potential risk for cerebral or peripheral thromboembolism. The NCC is even more prone to calcification compared with the other cusps due to the absence of diastolic coronary flow, which increases the shear stress.<sup>34</sup> Therefore, a thorough assessment of the aortic root preferably by ICE is recommended as a standard peri-operative procedure or before ablation. Intracardiac echo can accurately guide the ablation catheter, identify endocardial details of the ASs, and the distance to the coronary ostia. Moreover, ICE is a tool to confirm stable contact and verify continuous stability during RF delivery.<sup>35</sup>

A variety of energy sources are currently available for ablation procedures. An in vitro study compared standard RF energy, cooled-tip RF energy, or cryothermal energy for coronary cusp ablation.<sup>36</sup> Although none of the modalities caused acute damage to the coronary cusps, cryothermal ablation appeared to be the least thrombogenic and least traumatic technique. D'Avila et al. suggest cryoablation as the first choice technique for safety reasons. However, this technique was associated with lesser lesion depth and, particularly with NCC ablation, this might result in recurrence of the arrhythmia.<sup>36</sup> Irrigated tip catheters are preferable as an alternative to cryoablation, as it causes larger lesions and is associated with less thrombo-embolic risk as compared with conventional RF. The risks and management of other potential complications such as AV block, aortic valve, or coronary arterial damage should be evaluated in further clinical research, as well as the optimal choice of energy sources and settings.

### Conclusion

Symptomatic focal AT near the HB region may originate from the NCC. This arrhythmia can be treated effectively with RF ablation in the NCC. Further research is warranted to evaluate mapping strategy, ablation techniques, and safety issues.



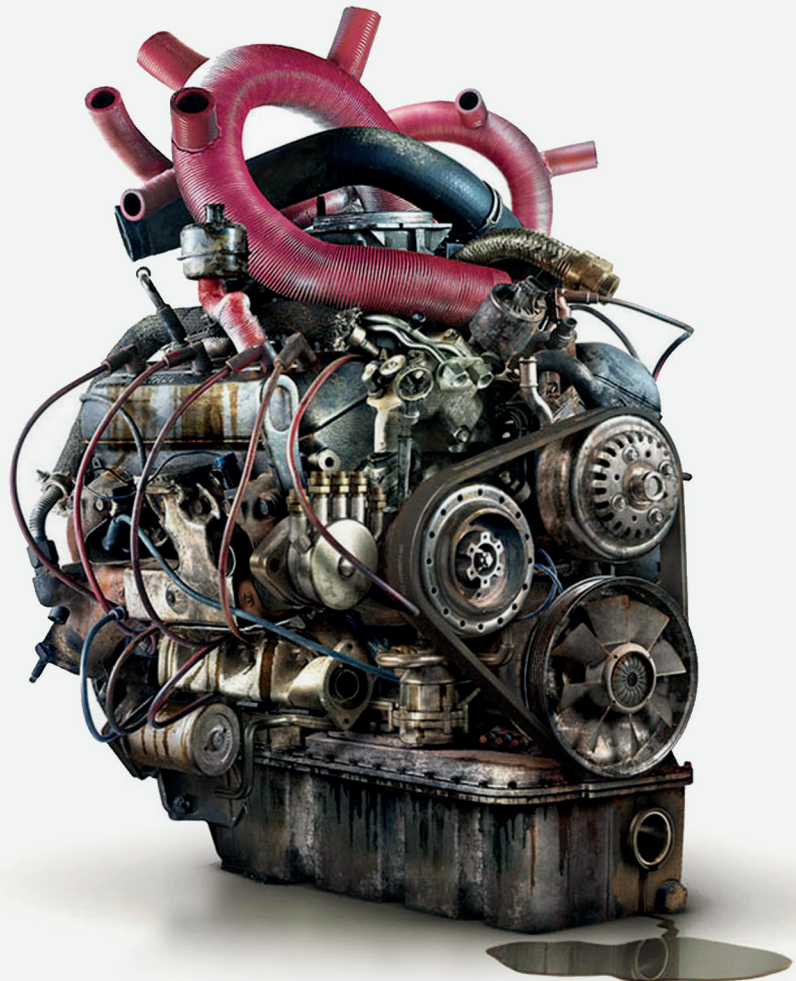
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# Part three

Surgical management of atrial fibrillation  
and follow up methods



# 7

## Randomized controlled trial of Surgical versus Catheter Ablation for Lone Atrial Fibrillation



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## Abstract

### Objectives

Current guidelines recommend both percutaneous catheter ablation and surgical ablation in the treatment of atrial fibrillation (AF), with different levels of evidence. No direct comparison has been made between surgical and percutaneous ablation as primary treatment of AF. We therefore conducted a randomized controlled trial comparing the safety and efficacy of these 2 treatment modalities.

### Methods

Fifty patients, with symptomatic paroxysmal or persistent AF, and without structural heart disease, were randomized to either minimally invasive thoracoscopic pulmonary vein isolation and left atrial appendage ligation (MIPI) or percutaneous pulmonary vein isolation with point by point RF energy (CA). All patients received an implantable continuous looprecorder. The primary endpoint was defined as freedom of atrial tachyarrhythmias after 6 months of follow-up, without the use of anti-arrhythmic drugs (AAD). Secondary endpoints were AF burden <0.5% and reduction of AF burden after 6 months, whereas the safety endpoint was the absence of procedure related complications.

### Results

Median age was 57 (37-75) and 78% was male. Paroxysmal AF was present in 74%. The primary endpoint was 59% versus 39% in favor of CA ( $P=0.156$ ). The decrease in AF burden, six months after ablation, was 15.5% (95% CI 9.7%-43.1%) in MIPI compared to 26.1% (95% CI 11.2%-59.6%) in CA ( $P=0.375$ ). A similar proportion of patients had AF burden <0.5% (63 versus 65%,  $P=0.87$ ). More complications occurred after MIPI than CA (34.8% versus 11.1%;  $P=0.046$ ).

### Conclusions

The short-term efficacy of preventing AF is similar for CA and MIPI. CA results in significantly less complications than MIPI.

## Introduction

Electrical isolation of the pulmonary veins (PV) by catheter ablation has emerged as a well established treatment for symptomatic, drug refractory AF. Multiple studies and meta-analyses have demonstrated the superiority of catheter ablation over AAD in patients with paroxysmal AF without structural abnormalities.<sup>1</sup>

Single procedure success rates however are limited and patients who require a second procedure almost universally demonstrate recurrence of PV conduction. The surgical Cox-Maze-III procedure is recognized as a very effective treatment of AF but due to its invasiveness and complexity it is not widely used as a stand-alone procedure nowadays. As an alternative, MIPI was introduced in 1999 by Wolf et al, which allows an epicardial approach for pulmonary vein isolation on a beating heart through less invasive incisions.<sup>2</sup> Although stand-alone surgical AF ablation is not common, ESC/AHA/ACC guidelines state that it can be considered (class IIb, level C) for either patients who failed catheter ablation in the past or when the patient prefers a surgical approach.<sup>3,4,5</sup> Previous studies and recent meta-analysis even suggested that MIPI would have a better efficacy compared with endocardial CA.<sup>6</sup>

At present, no direct comparison has been made between surgical and CA as a first invasive procedure in patients with AF. The aim of the present study therefore was to perform a randomized controlled trial to compare the efficacy and safety of CA versus MIPI in the treatment of AF patients without structural heart disease.

## Methods

### Purpose

The purpose of this prospective randomized clinical study was to compare the success rate of surgical versus percutaneous AF ablation, in order to prevent recurrences of AF, in patients without structural heart disease. Furthermore, we assessed the safety of both invasive treatment strategies. The study was approved by the Internal Review Board and registered (ClinicalTrials.gov Identifier: NCT00703157).

### Study population

Patients in the Isala Heart Center (Zwolle, the Netherlands) with symptomatic "lone" paroxysmal or early persistent AF (continuous AF duration < 3 months) with failure of at least one class 1 or 3 AAD were eligible. Patients should be aged  $\geq 18$  years. At least one symptomatic episode of AF was required within 6 months prior to inclusion. Structural heart disease, like coronary ischemia, cardiomyopathy and/or

more than mild valvular heart disease, should have been excluded by appropriate tests. Patients were excluded when they had permanent or persistent AF >3 months, ejection fraction <40%, left atrial size >50mm (parasternal long axis), use of amiodarone (no use within 6 months prior to study entry), history of cerebrovascular disease, pregnancy, life expectancy of less than one year and previous left atrial ablation.

### Enrollment

After written informed consent had been obtained, consecutive patients were implanted a continuous looprecorder (Reveal® XT, Medtronic, USA). This implantable loop recorder (ILR) is a single lead electrocardiographic (ECG) subcutaneous monitoring device able to monitor atrial tachyarrhythmia burden. Patients were followed for a minimum of one week after ILR implantation and a maximum of 6 months in order to establish the required AF burden.

If a patient had demonstrated a minimum of 10% AF burden after one week ILR monitoring and had complaints associated with AF, this patient was randomized to one of the treatment arms. Because many patients were highly symptomatic also with a burden <10%, or did not reach 10% burden because of early electrical cardioversion, we observed that many patients could not be randomized. A protocol amendment was initiated therefore, after approval in October 2012, allowing an AF burden of 2% in one week as a threshold for randomization. Moreover patients were followed for a maximum of 2 months instead of 6 months to establish the required AF burden. The majority (75 of 80) of patients were included in the study before the amendment was effectuated. Patients were randomized electronically at a 1:1 ratio to catheter ablation or surgical ablation.

### Ablation techniques

#### Catheter ablation

The ablation procedure was performed under general anesthesia. Vitamin K antagonists were discontinued for 3-5 days prior to ablation and bridged with low-molecular-weight heparin. Transesophageal echocardiography was performed directly pre-ablation procedure to assess interatrial septum and to exclude left atrial thrombus or other significant structural heart disease. Venous access was obtained through the femoral vein. A 6F deflectable quadripolar catheter (Bard, Lowell, Massachusetts, USA) was positioned into the coronary sinus. Transseptal access to the left atrium was achieved guided by fluoroscopy and pressure with a Brockenbrough needle, transseptal sheath (SL1, St Jude) and a guidewire. An initial bolus of 10.000 units of heparin was given and additional administration to achieve an activated clotting time between 300 and 350 seconds. All sheaths were continuously flushed with saline containing 2500 IU heparin per 500 mL saline. Pulmonary vein angiography was

performed for ipsilateral PVs to provide a geometric reference for catheter navigation and localization of the antrum. A 3-dimensional electroanatomic map of the left atrium (LA) was constructed (CARTO, Biosense-Webster). Isolation of all PVs was performed using circumferential periostial applications of radiofrequency energy, with a power limit of 40 Watt on the anterior LA and 30 Watt on the posterior LA, and verified with a decapolar circular mapping catheter (Lasso, Biosense Webster). The ablation was performed with a 3.5mm irrigated tip catheter (Thermocool, Biosense Webster). RF energy was applied for 20-60 seconds until the local electrogram amplitude was eliminated. The endpoint of the ablation procedure was defined as the absence or dissociation of PV potentials documented with a circular decapolar mapping catheter within the PVs  $\geq$ 30 minutes post-ablation.

#### Surgical ablation

In supine position under general anesthesia, a double lumen tube was introduced. In the right hemithorax, a 5-10 cm incision in the fourth intercostal space in the anterior axillary line was placed. A soft tissue retractor was used to introduce the scope through the sixth intercostal space (submammary). The pericardium was opened anterior to the phrenic nerve. Two stay sutures were placed in the pericardium. Blunt dissection of Waterstone's Groove was performed followed by a blunt dissection and opening of the oblique sinus (OS) caudal of the right inferior pulmonary vein (RIPV). Then, blunt dissection and opening of the OS cranial of the right superior pulmonary vein (RSPV) between RSPV and right pulmonary artery was performed. Hereafter a silastic tape can be placed around the RPV's in order to facilitate proper positioning of the device.

An irrigated bipolar clamp device (Cardioblate, Medtronic, USA) was introduced for PV isolation. This device has a self-regulating ablation protocol based on an impedance feedback system. Transmurality feedback is indicated based on a steady-state plateau in tissue impedance. After introduction of the device, antral tissue around the right sided PVs was clamped after gentle traction of the tape and RF energy was applied to ablate the left atrial wall adjacent to the junction with the right sided PVs. After RF energy application the clamp was repositioned approaching the antrum of the vein pair from 180°, then additional applications were performed. Isolation was confirmed with pacing manoeuvres at the left atrium-PV junction. After 30 minutes pacing manoeuvres were repeated to check for electrical reconnection. The left hemithorax was opened similar to the right hemithorax, except for the incision of the pericardium, that was incised posterior of the phrenic nerve. Additional left atrial appendage (LAA) ablation or removal or exclusion with stapler or preferably with endoloop was performed. The LAA exclusion was verified on transesophageal echocardiography. Ganglionated plexi ablation and additional ablation lines were not performed.

### End points

The primary endpoint was defined as freedom from atrial tachyarrhythmias with a duration of  $\geq 30$  seconds after 6 months of follow-up, without the use of anti-arrhythmic drugs. A 3 months blanking period was initiated. Secondary endpoints were AF burden  $< 0.5\%$  and reduction of absolute AF burden after 6 months. AF burden postablation was calculated per month. The absolute decrease in average AF burden in month 4 to month 6 post ablation was determined as compared to the average AF burden up to 3 months before the procedure. The safety endpoint was the absence of procedure related complications. Complications were regarded as major if it resulted in death, irreversible damage to structures, stroke, atrio-esophageal fistula, conversion to sternotomy or need for re-operation. Pericardial effusion not needing intervention and managed conservatively, small groin hematoma not requiring blood transfusion and without significant drop in haemoglobin, and procedure related mild infection (such as urinary tract infection or respiratory tract infection) were regarded as minor complications.

### Post procedural care

Anticoagulation was re-initiated as soon as possible, after control of bleeding, and was continued at least 3 months after the procedure. When CHADS score was  $\geq 1$ , patients were kept on anticoagulation. During the blanking period of three months the AAD were tapered off.

### Follow-up

During follow up, patients were seen at 3 and 6 months after the ablation procedure at the outpatient clinic or at other occasions when patients had symptoms. At each visit, a 12-channel ECG and ILR device download was performed to assess any recurrences of arrhythmias.

### Statistical analysis

All statistical analyses were performed using the Statistical package for the social sciences (SPSS) version 22 (IBM Nederland B.V., Amsterdam, The Netherlands). A two sided P-value of  $< 0.05$  was considered significant. Because of small sample size we performed as-treated patient analysis. Descriptive statistics were used to describe patient population and procedure characteristics. Categorical variables were reported as frequencies and percentages. Quantitative/continuous variables were described using the mean and standard deviation when normally distributed or using the median with the interquartile range when not normally distributed. To determine if the data was normally distributed the Shapiro-Wilk and Kolmogorov-Smirnov tests were used in combination with Q-Q plots and histograms. Data was not normally distributed and therefore t-test could not be used. The Mann-Whitney U test was used for the continuous variables. The Chi-square test or Fisher's exact test was used for the comparison of

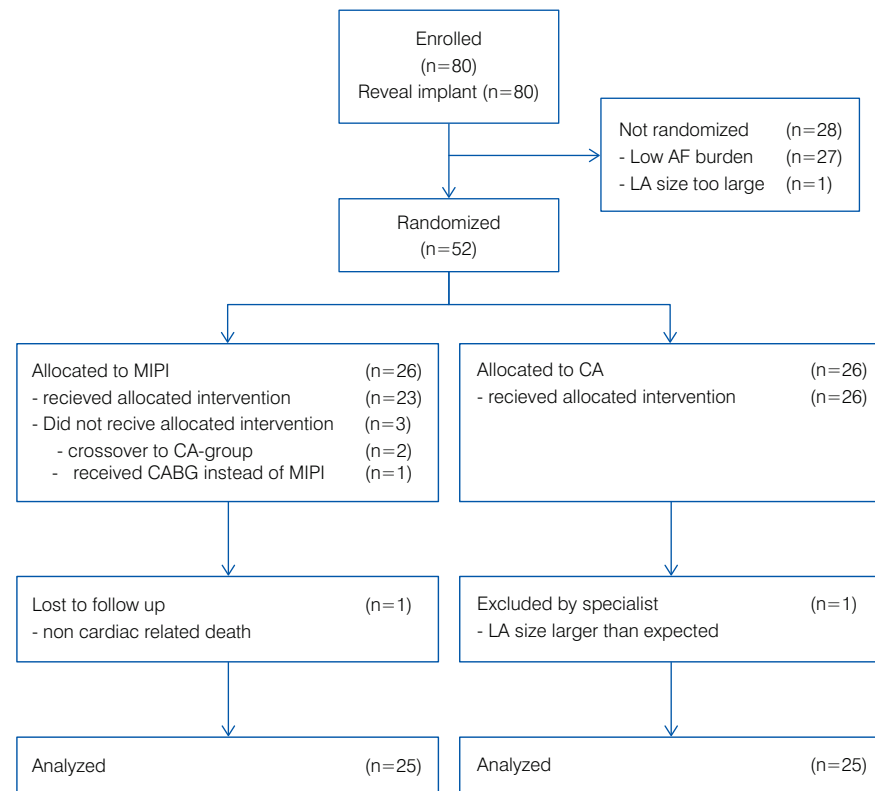
categorical variables. We performed Cox survival analysis with log rank test for efficacy of both treatment strategies. Time to first documented recurrence was analysed by de log-rank statistic and plotted using Kaplan-Meier survival curve. We assessed the proportion of patients with AF burden  $< 0.1\%$ ,  $< 0.5\%$ ,  $< 1.0\%$  during follow-up with a chi-squared test for differences. We additionally tested for differences in absolute AF burden reduction. Because the age was significantly higher in the CA group, logistic regression was used to determine if age influenced the outcome of the variables that were significantly different between both groups. Age did not have a significant interaction with the main endpoints and therefore no correction was performed in the analysis.

## Results

Eighty patients were enrolled in the study and underwent ILR implantation. Twenty eight patients did not reach randomization criteria. Twenty seven patients did not reach the required AF burden and one patient was excluded because of a LA size larger than 50 mm. A total of 52 patients were randomized, 26 to catheter ablation and 26 to surgical ablation. Figure 1 shows the patient distribution. All patients in the catheter group received catheter ablation. In the surgical group 23 patients underwent MIPI and 2 patients received CA because after randomization these patients refused surgical ablation. One patient in the surgical group was excluded because of significant coronary artery disease necessitating coronary artery bypass surgery combined with PVI. In the CA group one patient was excluded from analyses after ablation because on the pre-procedural TEE a much larger left atrium was seen than expected ( $> 50$  mm antero-posterior diameter, with LA volume  $> 50$  cc/m<sup>2</sup>). Baseline characteristics are demonstrated in Table 1.

### Procedural characteristics

Table 2 demonstrates the procedural characteristics. The total median procedure time was not significantly different ( $P=0.14$ ) between CA (168 min ranging 124-195) and MIPI (176 min, 155-221). In the CA group complete electrical isolation was achieved in all pulmonary veins (100%). In one patient with AF which could not be converted to sinus rhythm using electrical cardioversion after PV isolation, an additional roof line and fractionation guided ablation was performed. Afterwards, the patient was converted to sinus rhythm. In the MIPI group, PV isolation and LAA ligation was successful in all patients. In one patient, the ligament of Marshall was cut in addition to PV isolation, again because of recurrent AF after electrical cardioversions. This patient could subsequently not be converted to sinus rhythm. Hospitalization duration was significantly longer ( $P<0.001$ ) in MIPI with a median of 9 days (range 8-10) versus a median of 3 days (2-3) after CA.



**Figure 1** Patient distribution.

Study design and patient distribution. AF: atrial fibrillation; CA: catheter ablation; CABG: coronary artery bypass grafting; LA: left atrium; MIPI: minimal invasive thoracoscopic pulmonary vein isolation

### Efficacy

The primary endpoint, freedom from all atrial tachyarrhythmias without AAD after 6 months, occurred more often after CA than after MIPI (59 versus 39%) but this difference was not significant ( $P=0.16$ ). Kaplan-Meier plot with log rank test showed a difference with  $P=0.142$  (Figure 2). The decrease in AF burden, six months after ablation, was 15.5% (95% CI 9.7%-43.1%) in MIPI compared to 26.1% (95% CI 11.2%-59.6%) in CA ( $P=0.38$ ). A similar proportion of patients had AF burden  $<0.5\%$  (63% in CA versus 65% in MIPI,  $P=0.87$ ). AF burden  $<1.0\%$  was more often present in CA (63%) than MIPI (65%), without reaching statistical significance ( $P=0.87$ ). Table 3 demonstrates the AF burden during the 6 months follow up.

**Table 1** Baseline characteristics.

	Catheter ablation (N=27)	MIPI (N=23)	P value
Age	59 (54-66)	55 (48-61)	0.017
Male	20 (74.1%)	19 (82.6%)	0.486
AF duration (years)	3.9 (1.5-8.0)	3.6 (1.6-8.7)	0.977
LVEF (%)	55 (50-60)	55 (50-60)	0.942
LA size, PLAX(mm)	40 (38-44)	39 (37-42)	0.604
Failed AAD prior to randomization			
Flecainide	18 (66.7%)	16 (69.6%)	
Propafenone	0	2 (8.7%)	
Sotalol	14 (51.9%)	14 (60.9%)	
Amiodarone	3 (11.1%)	2 (8.7%)	
Beta-blocker	14 (51.8%)	16(69.5%)	
Verapamil/diltiazem	6 (22.2%)	1 (4,3%)	
Digoxine	4(14.8%)	2 (8.7%)	
CHA <sub>2</sub> DS <sub>2</sub> VASC-score			0.338
0	9 (36%)	9 (36%)	
1	8 (32%)	11 (44%)	
2	5 (20%)	4 (16%)	
3	3 (12%)	1 (4%)	
AF burden pre-ablation (%)	29.2 (13.0-79.2)	26.3 (15.0-74.7)	0.861
Diabetes mellitus	2 (7.4%)	2 (8.7%)	1.000
Hypertension	11 (40.7%)	11 (47.8%)	0.615

AAD: anti arrhythmic drugs; AF: atrial fibrillation; CHA<sub>2</sub>DS<sub>2</sub>VASC-score

CHF, 1. HTN, 1. Age > 75, 2. Diabetes, 1. Stroke/TIA/systemic embolism, 2. Vascular disease (CAD, MI, PAD, aortic plaque); LA: left atrium; LVEF: left ventricular ejection fraction; PLAX: parasternal long axis

### Safety

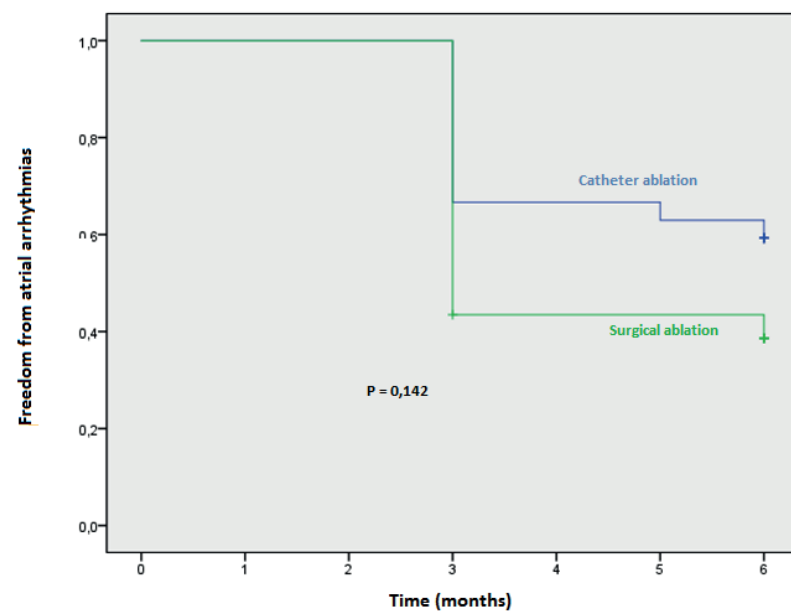
Procedural related adverse events occurred significantly more often in MIPI than CA (34.8% versus 11.1%,  $P=0.046$ ). This was mainly due to a difference in major complications (21.7% in MIPI versus 0% in CA,  $P=0.016$ ). Table 4 shows procedural and non-procedural adverse events. All complications in the CA group were minor complications, whereas in the MIPI group there were 5 major complications. In the MIPI group one patient required an acute conversion to median sternotomy because of bleeding from a laceration of the left upper PV at the LA junction. One patient required pericardiocentesis for pericardial effusion with tamponade. Another patient in the MIPI group developed post-operative lung herniation through one of the right



**Table 2** Procedural characteristics.

	Catheter ablation (n=27)	Surgical ablation (n=23)	P-value
Total procedure time (min)	168 (124-195)	176 (155-221)	0.143
Fluoroscopy time (min)	23 (17-31)	-	
Total ablation time (min)	31 (24-41)		
RF energy (sec)		200 (177-278)	
Additional ablation			
roofline	1	0	
Marshall's ligament	0	1	
Left atrial appendage ligation	..	23/23 (100%)	
Hospitalization (days)	3 (2-3)	9 (8-10)	<0.001

RF: radio frequency



No. at risk

Catheter ablation 27

17

17

16

16

Surgical ablation 23

9

9

9

9

**Figure 2** Kaplan–Meier curves displaying time to first atrial tachyarrhythmia with 3-month blanking period. (log-rank:  $p = 0.142$ ).**Table 3** Atrial fibrillation burden during follow up.

	Catheter ablation (N=27)	Surgical ablation (N=23)	p value
<b>Absolute AF burden (%)</b>			
0 months			
3 months	29.2 (13.0-79.2)	26.3 (15.0-74.7)	0.861
6 months	0.09 (0.0-10.3)	0.4 (0.09-13.5)	0.118
	0.09 (0.0-0.1)	0.1 (0.0-3.7)	0.164
<b>Difference AF burden(%)</b>			
3 months			
6 months	24.1 (6.8-63.6)	17.9 (9.5-43.2)	0.830
	26.1 (11.2-59.6)	15.5 (9.7-43.1)	0.375
<b>AF burden &lt;0.1%</b>			
3 months	16/27 (59%)	8/23 (35%)	0.084
6 months	16/27 (59%)	9/23 (39%)	0.156
<b>AF burden &lt;0.5%</b>			
3 months	18/27 (66.7%)	12/23 (52.2%)	0.297
6 months	17/27 (63%)	15/23 (65%)	0.869
<b>AF burden &lt;1.0%</b>			
3 months	18/27 (67%)	14/23 (61%)	0.670
6 months	17/27 (63%)	15/23 (65%)	0.869

Values for as treated population.

Values are given in frequencies/total number of patients and percentages.

sided surgical incisions for which reconstruction with a patch of marlex mesh was performed. One MIPI procedure was complicated by left phrenic nerve paralysis and another patient developed a unilateral recurrent laryngeal nerve paralysis related to endotracheal intubation. One patient in the CA developed a ventilator associated pneumonia, treated with antibiotics. One patient in the CA group developed a urosepsis due to an indwelling urinary catheter. Pericarditis without significant effusion was successfully treated with ibuprofen in both groups.

**Table 4** Procedural and non procedural related adverse events.

	Catheter ablation (n=27)	Surgical ablation (n=23)	P value
Pericarditis	1	2	
Pleuropericarditis with blood clot	0	1	
Pericardial effusion	0	1	
Conversion to sternotomy	0	1	
TIA/stroke	0	0	
Pneumothorax	0	0	
Phrenic nerve paralysis	0	1	
Upper respiratory tract infection	1	0	
Pacemaker implant	0	0	
Death	0	0	
other	1 (urosepsis)	2 (lung herniation requiring surgical correction, laryngeal nerve palsy)	
Total	3 (11.1%)	8 (34.8%)	0.046
Minor	3	3	1.00
major	0	5	0.016

TIA: Transient ischemic attack

## Discussion

This is the first randomized controlled trial that randomized patients without structural heart disease with symptomatic AF to surgical or percutaneous ablation as a first invasive procedure to prevent recurrences of AF. After short-term follow-up with ILR, no significant differences could be observed in efficacy, although there was a trend towards higher success after CA. Both strategies reduced AF burden significantly and similarly. Procedure related complications occurred significantly more often in MIPI than in CA, mainly because of a difference in major complications.

Endocardial, as well as epicardial PVI ablation approaches have demonstrated to be successful. Whereas CA is most popular as a first line therapy in paroxysmal and early persistent AF, surgical epicardial ablation is mostly restricted to patients with (multiple) unsuccessful CA procedures or evidence of advanced substrate.<sup>7,8</sup> Both European and American guidelines however recommend both surgical and

percutaneous first-line treatment of AF, although with differences in class and level of evidence (class 1, A class 2a, A for CA in paroxysmal and persistent AF, and class 2b, B for surgical ablation).<sup>2,3</sup> Review studies of minimally invasive surgery for lone AF show a 12 months AAD-free, success rate of 65-92%.<sup>9,10</sup> However the individual studies, are generally small sized, single centre and describe a variety of surgical techniques and follow up methods. For this reason a reliable meta-analysis cannot be carried out. Moreover, in most studies, patients after unsuccessful CA are included, which is an importantly different group of patients than patients without previous ablation.

Head-to-head randomized comparison of surgical and catheter ablation was performed before, although always in populations comprising a large proportion of patients with unsuccessful previous CA.<sup>11, 12</sup> The FAST trial was a prospective, randomized trial in 124 patients who had failed a previous CA procedure or had hypertension and an enlarged LA.<sup>11</sup> Patients were randomized in a 1:1 ratio to either CA or MIPI. Importantly, 2/3 of patients had unsuccessful CA before randomization. The 12 months success rate, defined as freedom from atrial tachyarrhythmias >30 seconds in duration, measured by 7 day holter monitoring, was significantly higher for the surgical group than the CA group (65.6% versus 36.5%,  $p= 0.0022$ ). The authors explained the relatively poor efficacy in the catheter group by the fact that patients were in an advanced stage of AF and might have required additional substrate ablation. Moreover, performing epicardial ablation lines after previous endocardial ablation, increases the probability of creating transmural lesions without gaps in lines, and thus isolation of the PVs and elimination of triggers. In vivo as well as in vitro studies demonstrate a large heterogeneity in thickness and composition of the atrial epicardium and myocardium. Aging and associated disease promote development of elastic fibres, collagen, fat content and smooth muscle cell hyperplasia. This process has a hindering effect on RF electrical current in the tissue and limits the creation of a transmural lesion.<sup>13</sup> Traditionally, surgical epicardial approach is performed in patients with one or more endocardial ablation attempts. In these patients it is more likely to create electrical PV disconnection with additional epicardial ablation than in patients without a previous endocardial ablation.

Importantly, follow-up method in the FAST trial did not consist of continuous monitoring, and shorter episodes of AF can be easily missed in this way. When assessing AF burden <0.5% in our study, which is only 0.8 hours per week, success rates would be 63-65% for MIPI and CA. Although efficacy was superior for surgical ablation in the FAST trial, the major early complication rate was significantly higher for the surgical group (23.0% versus 3.2%), which is in accordance with our present study. The same phenomenon of higher efficacy rates in patients with previous

unsuccessful CA was described by Pokushalov et al. They randomized 64 patient with paroxysmal and persistent AF after a failed initial pulmonary vein ablation to repeat CA (n=32) or MIPI (n= 32).<sup>12</sup> The follow-up method consisted of continuous monitoring with an ILR. The surgical procedure consisted of PV isolation, lines to create a box lesion and ablation of ganglionic plexi. At 12 months follow-up 81% of surgical patients were free of atrial arrhythmias without AAD versus 47% in the CA group (p=0.004). Again, in this study, major complication rate was much higher in surgical procedures than after CA (22 versus 3.2%, P=0.02). Surgical and catheter AF ablation are highly complex procedures. The most recent worldwide survey of CA reported a 4.5% complication rate.<sup>14</sup> It has to be recognized that the data were from voluntary surveys and likely underestimate the true complication rates. In our present study, most complications were general surgery related complications, like bleeding and damage to organs or the nervous system. The high complication rate of ablation surgery is observed in many studies involving highly experienced surgeons, possible highlighting the need for cardiac electrophysiological surgery as a subspecialty in order to reduce complication rates.

Our study has some unique aspects. We randomized patients to MIPI or CA only in patients undergoing a first invasive treatment for AF. Further, we used continuous rhythm monitoring to assess arrhythmia outcome. It has been shown that monitoring of symptoms in AF patients is unreliable in that respect. Only 52% of symptoms correlate with documented AF and nearly half of AF episodes are asymptomatic.<sup>15</sup> The HRS task force recommends 24-hour holter monitoring as an acceptable monitoring strategy for patients enrolled in a clinical trial. Hanke et al demonstrated that intermittent monitoring dramatically overestimates the success rate of ablation procedures. Fortyfive patients were monitored after AF surgery with ILR as well as quarterly 24-hour holter monitoring. The sensitivity of detecting AF with holter monitoring was only 0.60.<sup>16</sup> Another study in 647 AF patients with a mean AF burden of 0.12% showed that even with intensive intermittent monitoring at least 30 days of holter monitoring would be required to reach a sensitivity of 82% in detection of AF.<sup>17</sup> For scientific as well as for AF patient management decisions continuous monitoring after ablation procedures is strongly recommended. Apart from the AF burden, the objective evaluation of the characteristics of various atrial arrhythmias after ablation will guide the best strategy and best time of re-intervention.

The main limitation of our study is the small sample size. A larger than expected proportion of patient did not meet the requirement of AF burden >10%. Highly symptomatic episodes of AF required electrical cardioversion before patients could reach the 10% within one week looprecorder monitoring criterion. Later, nearly at the end of the study, we changed this inclusion criterium to 2% AF burden. Secondly, this

trial was conducted in a single center. Pooling of randomized data from different centers and new larger multi-center randomized data are mandatory. The present follow-up duration of 6 months is relatively short, but was pre-defined as the primary endpoint. Furthermore, most recurrences occur between 3 and 6 months of follow-up. In conclusion, in patients without structural heart disease and with symptomatic paroxysmal or persistent AF, first line invasive treatment by minimal invasive surgical PV isolation seems equally effective as CA on the short term. CA however, has much lower complication rates.

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# 8

**Catheter ablation of symptomatic postoperative atrial arrhythmias after epicardial surgical disconnection of the pulmonary veins and left atrial appendage ligation in patients with atrial fibrillation**

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## Abstract

### Objectives

Minimally invasive thoracoscopic epicardial pulmonary vein isolation (MIPI) has an important role in the surgical treatment of atrial fibrillation (AF). However, the management of recurrent atrial arrhythmias after MIPI and long-term success rate of catheter ablation have not been well studied.

### Methods

Electrophysiological study was performed in 23 patients,  $378 \pm 282$  days after MIPI surgery, because of recurrent symptomatic atrial arrhythmias.

### Results

A total of 20 patients presented with paroxysmal and persistent AF, 2 patients had a combination of AF and atrial tachycardia (AT) and 1 patient had a combination of AF and atrial flutter. All patients showed pulmonary vein (PV) reconnection. ATs were micro-re-entry PV-related ATs and atrial flutter was cavotricuspid isthmus dependent. Eighteen of 23 patients (78.3%) were free of atrial arrhythmias after one catheter ablation procedure at a mean follow-up of  $50 \pm 16$  months. Three patients underwent a second ablation procedure for recurrent AF and macro-re-entry left atrial flutter. Eventually 20 of 23 patients (87%) remained free of atrial arrhythmias after a mean of  $1.1 \pm 0.3$  ablation procedures.

### Conclusions

Catheter ablation of recurrent atrial arrhythmias following MIPI for paroxysmal and persistent AF is a feasible and effective treatment with a good long-term success rate. Reconnection of PVs accounts for most recurrences.

## Introduction

Surgical treatment of atrial fibrillation (AF) using the Cox maze technique is highly successful but is a complex procedure requiring cardiopulmonary bypass and cardioplegic arrest, and is associated with significant morbidity.<sup>1</sup>

Since the first report by Wolf *et al.*,<sup>2</sup> minimally invasive thoracoscopic radiofrequency ablation has been an accepted technique for surgical AF treatment. Principle of this epicardial ablation method is to isolate the pulmonary veins (PVs) in order to prevent the initiation of AF. One-year success rates of this ablation technique range from 51 to 85%.<sup>3</sup> Reports regarding the mechanism, electrophysiological findings and treatment of recurrent atrial arrhythmias are very limited. In the present study, we assessed the clinical and electrophysiological characteristics of recurrent symptomatic atrial arrhythmias after minimally invasive surgical PV isolation (MIPI) and left atrial appendage ligation and the long-term outcome of catheter ablation for these arrhythmias.

## Methods

From May 2006 to February 2012, 41 patients underwent MIPI at the Isala Hospital. The indication for MIPI in all patients was symptomatic paroxysmal or persistent lone-AF, refractory to at least one class 1 or class 3 antiarrhythmic medication. All patients preferred a surgical approach as an alternative to catheter ablation. Patients with previous left atrial ablation procedures were excluded from this study. In 23 patients, electrophysiological study was performed because of recurrent symptomatic atrial arrhythmias. All patients consented to their data being registered and used for publication as did the Board of Hospital Administrators.

### Statistical analysis

Continuous data were reported as mean  $\pm$  standard deviation in case of normal distribution or median  $\pm$  interquartile range when variables were not normally distributed, and unpaired *t*-tests were used for group comparisons. Nominal data were expressed as percentages and numbers. A probability value of  $<0.05$  identified a statistically significant result. Kaplan–Meier analysis was used to assess freedom from reintervention after surgery.

### Surgical procedure

PVs were isolated using an irrigated bipolar RF ablation clamp (Cardioblate, Medtronic, USA). All lesions were made with this bipolar RF ablation device, which



has a self-regulating ablation protocol based on an impedance feedback system. Transmurality feedback is indicated based on a steady-state plateau in tissue impedance. This minimally invasive PV isolation procedure was performed on a beating heart.

In supine position under general anaesthesia, double lumen tube was introduced. Defibrillator pads were placed on the thoracic wall. In the right hemithorax, a 10 cm incision in the fourth intercostal space in the anterior axillary line was placed. A soft tissue retractor was used to introduce the scope through the sixth intercostal space (submammary). The pericardium was opened anterior to the phrenic nerve. Two stay sutures were placed in the pericardium. Blunt dissection of Waterstone's Groove was performed followed by a blunt dissection and opening of the oblique sinus (OS) caudal of the right inferior pulmonary vein (RIPV). Then, blunt dissection and opening of the OS cranial of the right superior pulmonary vein (RSPV) between RSPV and right pulmonary artery was performed. After introduction of the bipolar ablation device, antral tissue around the right-sided PVs was clamped after gentle traction of the tape and RF energy was applied to ablate the left atrial wall adjacent to the junction with the right-sided PVs. After RF energy application, the clamp was repositioned approaching the vein pair from 180°, then a second RF application was performed. Isolation was confirmed with pacing manoeuvres at the left atrium (LA)-PV junction. After 30 min, pacing manoeuvres were repeated to check for electrical reconnection. The left hemithorax was opened similar to the right hemithorax, except for the incision of the pericardium, that was incised posterior to the phrenic nerve. Additional left atrial appendage (LAA) ablation or removal or exclusion with stapler or preferably with endoloop was performed. Ganglionated plexi ablation and additional ablation lines were not performed. Complications of surgical ablation were temporary phrenic nerve palsy in 2 patients, 1 patient with pleuropericarditis, 1 patient with tamponade requiring pericardial drainage and 1 patient with TIA 5 days after surgery.

### Postoperative care and cardiac rhythm monitoring

All patients were treated with oral anticoagulant for at least 3 months, and continued based on the patient's stroke risk scheme CHA<sub>2</sub>DS<sub>2</sub>-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74 years, sex category). Antiarrhythmic drugs were tapered off 3 months after surgery in the presence of stable sinus rhythm. After discharge, patients were seen at the outpatient clinic 1 week, 3, 6 and 12 months after surgery. The rhythm follow-up was either 24-h Holter monitoring at 3, 6 and 12 months or continuous rhythm monitoring with implantable loop recorder (Reveal XT; Medtronic, Inc.).

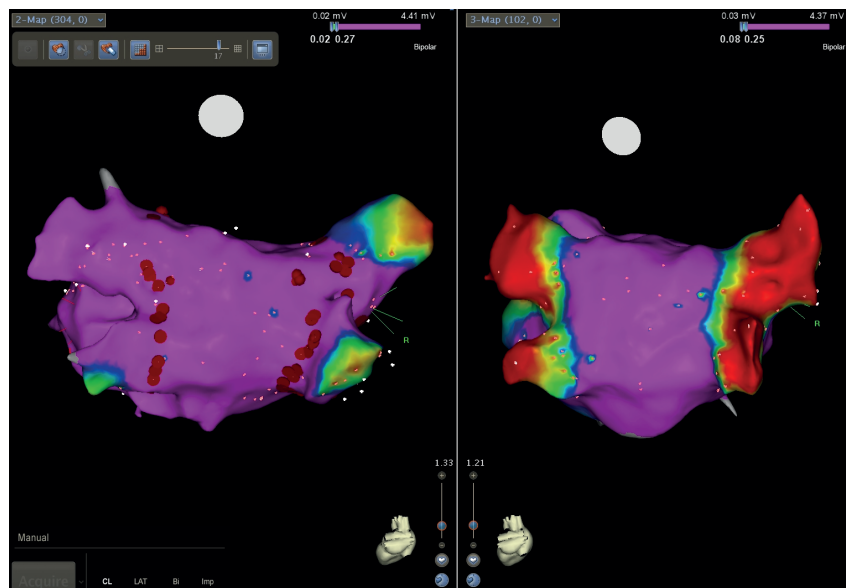
### Electrophysiological study and ablation after surgical pulmonary vein isolation

Patients with symptomatic atrial arrhythmias after surgery were referred to our cardiac electrophysiology division, and underwent electrophysiological study.

Transoesophageal echocardiography was performed before each procedure. Oral anticoagulants were substituted to low molecular weight heparin 4 days prior to the procedure. Patients were transferred to the cardiac catheterization laboratory in a fasting state, and conscious sedation was administered. All catheters were introduced through the femoral vein. Using fluoroscopic guidance, a quadripolar electrode catheter (EPX, Bard, USA) was positioned in the coronary sinus. In all patients, a double trans-septal puncture was performed using fluoroscopic guidance. Two 8.5-Fr SL1 sheaths (St Jude Medical, Inc.) were advanced to the LA by a modified Brockenbrough technique. After trans-septal catheterization, intravenous heparin was administered to maintain an activated clotting time of 300–350 s. Additionally, continuous infusion with heparinized saline was connected to the trans-septal sheaths (flow rate of 1 ml/min) to avoid thrombus formation or air embolism. Atriovenography of the LA and PVs was performed in all patients to define the ostium of the PVs. For circular mapping of PV ostia, a decapolar adjustable circular mapping catheter (Lasso, Biosense-Webster, USA) was placed trans-septally at the ostium of the target PVs. Bipolar and unipolar electrograms were filtered at band-pass settings of 30–500 and 0.05–200 Hz, respectively, and were recorded digitally (LabSystem pro, Bard, USA). Pacing was performed from the coronary sinus or LAA with a stimulator (Bard, USA) at twice the diastolic threshold with a pulse width of 2 ms. RF energy was applied with a Stockert (Cordis Webster) generator delivering a 500–550-kHz sine wave output.

After double trans-septal puncture, a decapolar circular mapping catheter (Lasso, Biosense-Webster, USA) and mapping catheter (Navistar, Biosense-Webster) was introduced into the LA. A three-dimensional (3D) shell representing the LA was constructed by use of an electroanatomical mapping system (Carto, Biosense-Webster, USA). First, all the PVs were mapped to assess gaps in the ablation lines at the LA-PV junction. In patients with gaps at the LA-PV junction, a circular mapping catheter was positioned within the PV ostia during RF delivery. PV isolation was performed by applying RF energy at ostial sites at which the earliest bipolar PV potentials and/or the earliest unipolar electrograms with the most rapid intrinsic deflection were recorded. Irrigated RF energy was delivered with a target temperature of 43°C, a maximal power limit of 40 W and an infusion rate of 8–15 ml/min during RF energy application. RF ablation sites were tagged on the reconstructed 3D map of the LA. RF energy was applied for ≥20 s until the maximal local electrogram amplitude

decreased by  $\geq 70\%$  or double potentials or disappearance of PV potentials was noted. Depending on the location of the gaps in the surgical RF ablation lines, endocardial irrigated RF ablation was performed in the posterior wall  $>1$  cm and in the anterior wall  $>5$  mm from the angiographically defined PV ostia. At the narrow border between the anterior aspect of the left PVs and the LA appendage, ablation was performed within  $\sim 5$  mm of the ostium of the PVs. The circular mapping technique in conjunction with the 3D electroanatomical map substantially facilitated identification of gaps (Fig. 1). The end point of the ablation procedure was defined as absence or dissociation of PV potentials documented with the circular mapping catheter within the PVs  $\geq 30$  min postablation. In patients with AT/AFL, activation mapping and/or entrainment mapping was performed to identify the arrhythmogenic substrate. In case of re-entrant atrial flutter, entrainment mapping was used to identify the critical isthmus of the flutter circuit, and RF energy was applied until block across the isthmus was achieved.



**Figure 1** Carto bipolar electroanatomical voltage map of the LA from the posterior view of a representative patient with reconnection in all four pulmonary veins after MIPI procedure. The left and right panels show the situation before ablation and after ostial endocardial pulmonary vein ablation, respectively. Note extensive scarring with voltages  $<0.05$  mV after electrical isolation.

## Results

Of 41 patients who underwent MIPI, 23 patients (56.1%) aged  $58 \pm 10$  years (range: 37–75) had electrophysiological (EP) study and ablation because of recurrent atrial arrhythmias. Five other patients had recurrent atrial arrhythmias after surgery but did not undergo EP study either because they were asymptomatic, responded well to antiarrhythmic drugs or for personal reasons refused EP study. Patients who underwent EP study had AF with a duration of  $6.0 \pm 4.5$  years prior to MIPI. AF episodes lasted for 4 h to  $>24$  h and 16 patients (69.6%) had paroxysmal AF and 7 patients (30.4%) had persistent AF. Clinical characteristics are provided in Table 1. All patients underwent AF surgery as described. The actual surgical bipolar radiofrequency ablation time was  $180 \pm 66$  s. Procedure-related complications of catheter ablation were cerebrovascular accident (with minimal function loss of right hand) in 1 patient, groin haematoma in 1 patient, another patient with a femoral arterio-venous fistula requiring thrombin injection and 1 patient with a cardiac perforation with open pericardium managed conservatively.

**Table 1** Clinical preoperative patient characteristics (mean).

No of patients	23
Age (years)	$58 \pm 10$
Gender male/female	17/6
BMI (kg/m <sup>2</sup> )	$29.2 \pm 3.7$
CHADS-VASC (range)	1.4 (0-5)
Type of AF	
Paroxysmal	16
persistent	7
Duration of AF (years)	$6.0 \pm 4.5$
Hypertension	8 (34%)
Diabetes mellitus	3 (13%)
Preoperative flutter ablation	3 (13%)
No of antiarrhythmic drugs for AF	$3.4 \pm 0.9$
Structural/congenital heart disease	1 (situs inversus)
History of stroke/TIA	2
Left atrial dimension (mm)	$43 \pm 3.3$

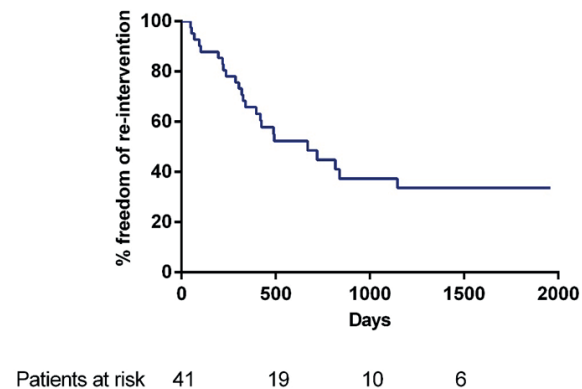
Demographics and clinical characteristics of all patients who underwent electrophysiological study for recurrent atrial arrhythmias after minimal invasive surgical ablation for atrial fibrillation.

AF = atrial fibrillation; BMI = body mass index; TIA = transient ischemic attack

<sup>a</sup> Statistically significant compared with preoperative AF burden  $P$ ,  $<0.05$ .

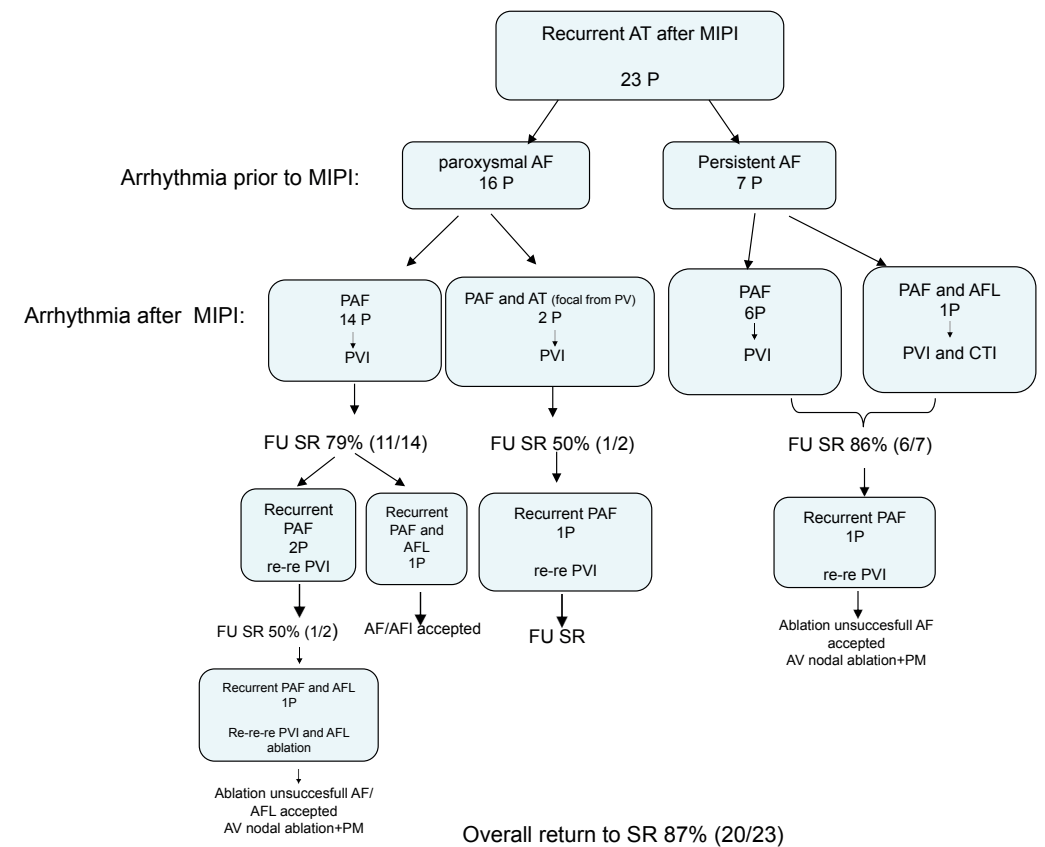
### Electrophysiological study and catheter ablation after surgery

Electrophysiological study was performed  $378 \pm 282$  days after surgery (Fig. 2). All patients had symptomatic postoperative atrial arrhythmias resistant to antiarrhythmic drug therapy. The arrhythmias in 20 patients were recurrent paroxysmal AF, 2 patients presented with the combination of paroxysmal AF and PV-related (micro-re-entry) atrial tachycardia (AT) and 1 patient had a combination of paroxysmal AF and cavotricuspid isthmus-dependent atrial flutter (Fig. 3). In all 23 patients, there was PV reconnection. Two patients had reconnection of a single PV (8.7%). Six patients (26.1%) had reconnection in two PVs, 5 of these patients showed reconnection in a PV pair (3 left-sided PV pair and 2 right-sided PV pair). Six patients (26.1%) had reconnection of 3 PVs and 9 patients (39.1%) presented with reconnection of all PVs. The reconnected PVs showed conduction delay between the LA and PV.



**Figure 2** Kaplan–Meier curve demonstrating freedom from re-intervention following MIPI.

The most common site for reconnection on the left was the ridge between left-sided PVs and LAA and the intervenous ridge between the left-sided PVs, whereas on the right side most gaps were found at the inferior side of the right lower PV. The right upper PV did not show a specific pattern of reconnection site. The residual LA-PV conduction gaps were eliminated with additional RF deliveries. Electrical disconnection of all targeted PVs was achieved in all patients. In the patient who presented with AF and atrial flutter, entrainment mapping confirmed cavotricuspid isthmus-dependent atrial flutter and an ablation of the cavotricuspid isthmus was performed in addition to PV reconnection.



**Figure 3** Treatment and outcome of recurrent atrial arrhythmias after MIPI.

AF: atrial fibrillation; AFL: atrial flutter; AT: atrial tachycardia; CTI: cavotricuspid isthmus ablation; FU: follow-up; MIPI: minimally invasive pulmonary vein isolation and left atrial appendage ligation; P: patients; PAF: paroxysmal atrial fibrillation; PV: pulmonary vein; PVI: pulmonary vein isolation; SR: sinus rhythm

Eighteen of 23 patients (78.3%) were free of atrial arrhythmias after percutaneous catheter ablation with a follow-up duration of  $48.1 \pm 16.0$  months (range: 15.6–78.6). Five patients had symptomatic recurrence of atrial arrhythmias after catheter ablation. Three of these patients, all presenting with recurrent paroxysmal AF, underwent a second electrophysiological procedure 8–23 months after the first catheter ablation procedure. Two patients showed reconnection at the same site as during the previous procedure. Again reconnection was performed. After a follow-up of 42 and 52 months, both patients remained free of arrhythmias. The third patient subsequently required a third ablation procedure for symptomatic paroxysmal atrial flutter and AF, which he

developed soon after reablation. The LIPV appeared to be reconnected, and was reisolated. Entrainment and propagation mapping revealed a macro-re-entry left atrial flutter around the occlusive LAA. RF ablation at the ridge between LAA and LSPV terminated the arrhythmia. Unfortunately, the patient developed recurrent AF and flutter, and was eventually treated with AV nodal ablation and pacing. There were 2 patients with recurrent arrhythmias, respiratory paroxysmal AF and combination of paroxysmal AF and atrial flutter after one catheter ablation procedure who refused another invasive procedure. These patients were treated with AV nodal ablation and pacing, respiratory antiarrhythmic drugs and pacemaker therapy. Thus eventually, 20 of 23 patients (87.0%) were free of atrial arrhythmias after one MIPI and a mean of  $1.1 \pm 0.3$  percutaneous ablation procedures.

## Discussion

The results of the present study demonstrate that symptomatic atrial arrhythmias after minimally invasive epicardial PV isolation are predominantly due to reconnection of epicardial ablation lines. To the best of our knowledge, this is the first report that describes the long-term success rate of percutaneous catheter reablation in this population. At a mean follow-up of  $48.1 \pm 16.0$  months, 78.3% of patients were free of arrhythmias after catheter ablation and 87.0% of patients after a second ablation procedure after MIPI. The adverse event rate was 10%, which is slightly higher when compared with prior reports.<sup>4</sup>


Since the first report of epicardial ablation by Wolf *et al.*,<sup>1</sup> the procedure gained popularity. The studies published in the last decade describing results of minimally invasive surgery for lone AF are small sized, and observational in nature. The 1-year success rate, defined as freedom from AF off antiarrhythmic drugs, ranges from 51 to 86%.<sup>3, 5</sup> Furthermore, there is a wide variety in patient selection, follow-up method, lesion pattern, surgical technique and energy source among different reports and this might be responsible for differences in outcome. The current study shows a relatively high rate of postoperative recurrent atrial arrhythmias. However, data from the subgroup patients with continuous monitoring, implanted with a loop recorder, demonstrate that the mean AF burden significantly reduced after surgery from  $42.7 \pm 40.0\%$  preoperatively to  $7.6 \pm 15.1\%$  at 3 months post-surgery ( $P = 0.003$ ). Although such a significant reduction in AF burden does not fulfil the definition of procedural success, it might still be judged as a successful procedure from a patient's perspective. EP study revealed that recurrent arrhythmias were predominantly related to PV reconnection. This suggests that initial lesions were often not transmural. Possibly, additional RF applications or more extensive testing for isolation could have resulted in better outcome.

## Previous studies

Kron *et al.* found recurrent atrial arrhythmias in 20 of 50 patients (40%) after minimally invasive thoracoscopic AF surgery. PV reconnection was the predominant finding by EP study. The authors speculate on reasons for reconnection. Particularly, reconnection on the left-sided PVs has a preference site at the intervenous ridge and the PV-LAA ridge. This might be related to atrial folds and ridges that increase myocardial thickness, which affect both endocardial and epicardial techniques.<sup>6, 7</sup> These results are in line with the findings of the current study. However, Zeng *et al.* investigated sites of reconduction after minimally invasive PV isolation, and found that recurrent atrial arrhythmias are related to gaps at the roof and the bottom of the PV. The main reason for reconduction at this site would be that the electrodes of the ablation clamp could only sufficiently achieve transmural lesion when myocardial tissue is 'squeezed' inside the clamp and ablating perpendicular to the target tissue. At the roof and bottom of the PV rings, this effect is not reached.<sup>8</sup> In the current study, at least two RF applications with two different clamp positions were performed on both sides. After the first RF application, the clamp was repositioned approaching the vein pairs from a different angle to overcome this effect.

Liu *et al.*<sup>9</sup> studied 8 patients with recurrence of atrial arrhythmias after minimally invasive thoracoscopic PV isolation. They found, like Zeng *et al.*,<sup>8</sup> that PV gaps are distributed exclusively in the roof or the bottom of the PV antrum. However, the mechanism maintaining the clinical or induced atrial arrhythmia in the majority of their patients was not the reconnected PV but macro-re-entry or non-PV focal activity. In 2 patients, complex fractionated atrial electrogram (CFAE) ablation converted AF into AT, perimitral re-entry was found in 4 patients and 3 patients had focal left atrial ATs. The authors emphasize the potential proarrhythmic effect of the left atrial appendix excision lesion. This lesion in the lateral LA creates an isthmus between LAA and mitral annulus and an isthmus between LAA and anterior wall of the left PV, facilitating development of perimitral macro re-entrant ATs. Patients who develop perimitral atrial flutter often have more severe and drug-refractory symptoms than they had from AF and this arrhythmia is relatively difficult to treat with catheter ablation, often requiring ablation within the coronary sinus.<sup>10</sup> The findings in our study are clearly different from those of Liu *et al.* Although all the patients included in our study had LAA ligation, only 1 patient developed macroreentrant LAA-related left atrial flutter. In fact, 20 patients (87%) who presented with recurrent atrial arrhythmias had PV reconnection-related arrhythmias. Whether the surgical technique of LAA ligation, lesion size or patient characteristics predict the development of postoperative macroreentrant left atrial arrhythmias remains to be investigated.

### Pulmonary vein isolation only versus substrate ablation

The concept described by Haïssaguerre *et al.*<sup>11</sup> that initiation of paroxysmal AF is due to PV-related triggers, and can be successfully eliminated by PV isolation is well accepted. However, in non-paroxysmal AF, PV triggers are less dominant, and the arrhythmogenic substrate involves a larger portion of the LA. Although the type of AF, paroxysmal versus persistent, is a definition by duration and not by pathophysiological substrate, it is appreciated that in the majority of persistent AF patients a mechanically and electrically remodelled atrial substrate is responsible for AF perpetuation. Previous data suggested that in these cases, additional substrate ablation with linear left atrial lesions or ablating areas with CFAEs was necessary to achieve more satisfying arrhythmia-free outcome.<sup>12, 13</sup> 

However, recently the randomized STAR AF 2 trial was presented. This trial was designed to explore the optimal method and outcomes of ablation in persistent AF. A total of 589 persistent AF patients received either PV isolation alone, PV isolation plus CFAE ablation or PV isolation plus additional LA lines. At 18 months, freedom with or without antiarrhythmic drugs was not significantly different between the three strategies.<sup>14</sup> It is uncertain if these results of endocardial catheter ablation studies apply for surgical epicardial ablation. There are no randomized data in minimally invasive surgical studies regarding the approach in persistent AF patients. During minimally invasive epicardial ablation, a wider antral area is ablated when compared with endocardial catheter ablation. Thus, a larger left atrial volume and relatively more substrate is treated. Wolf *et al.* described minimally invasive thoracoscopic PV isolation in his series of 27 patients. Nine out of the 27 patients had persistent and permanent AF and success was achieved in all these non-paroxysmal AF patients.<sup>2</sup> Our findings are in line with Wolf *et al.* All 7 patients with persistent AF who had recurrent atrial arrhythmias appeared to have PV reconnection, suggesting non-transmural lesion rather than lack of substrate treatment. The results can be partially explained by the fact that the current study did not include long-standing persistent and permanent AF patients and patients did not have greatly enlarged left atria, which is known to represent advanced substrate.

A review paper by La Meir *et al.* demonstrated that minimally invasive epicardial AF surgery yields a 12-month success rate of 67–80%, off antiarrhythmic drugs, in persistent AF patients. Studies performing additional lines were relatively more successful than studies describing PV box lesion only.<sup>3</sup> One has to realize that creating additional lines is challenging. Incomplete ablations can cause non-transmural gaps that are potentially proarrhythmic. Furthermore, extensive ablation can have a deleterious effect on left atrial mechanical function, and is associated with postoperative bradyarrhythmia requiring permanent pacemaker in 6–10% of




patients.<sup>15, 16</sup> Further research is warranted to determine the best approach for (long-standing) persistent AF patients and identifying the patient characteristics benefitting most from additional ablation procedures.

### Role of epicardial fat

Epicardial fat is a form of visceral adipose tissue and the volume of epicardial fat has been correlated to visceral adiposity. Enhanced local inflammation due to increased adipocytokines and proinflammatory cytokines by adipocyte secretion may generate myocardial remodelling, and contribute to the development of AF.<sup>17</sup> Furthermore, epicardial fat hampers epicardial ablation techniques. An *in vivo* study in sheep has shown that epicardial fat has a detrimental effect on lesion formation. Fat absorbs part of the RF energy, and creates a barrier to the transmission of energy to the myocardium during epicardial ablation.<sup>18</sup> The current study presents a population of patients presenting with recurrent atrial arrhythmias after epicardial ablation. The population is remarkably obese with a body mass index of >25 in 83% of patients. Epicardial fat may have contributed to the lack of transmural epicardial lesion formations in the patients. Whereas the amount of epicardial fat and thickness of the epicardium undoubtedly limits lesion depth, one should realize that the histological composition, particularly fibrosis is another factor influencing lesion formation.

### Hybrid techniques

Recently the hybrid technique has been introduced, which combines transvenous endocardial and thoracoscopic epicardial ablation procedure either as a concomitant or staged procedure.<sup>19–21</sup> Generally, surgical epicardial PV isolation is followed by additional endocardial substrate ablation. A major advantage is the verification of epicardial PV isolation by endocardial entrance- and  block and endocardial gap closure if conduction is still present. La Meir *et al.*<sup>19</sup> found that in 5 of 35 patients (14%), who underwent a hybrid ablation approach, endocardial PV conduction was still present after epicardial confirmation of bidirectional block. In another study, 23% of patients required additional endocardial ablation to complete PV isolation.<sup>20</sup> A recent study by Eckstein *et al.* gives important insight into atrial transmural conduction of fibrillation waves. Simultaneous endo-epicardial mapping in goats revealed that the degree of endo-epicardial dissociation of electric activations resulting in transmural conduction of fibrillation waves is correlated with increasing AF substrate.<sup>22</sup> Whereas focal ectopic discharge in patients with little substrate can be targeted by either epicardial or endocardial ablation, the endo-epicardial dissociation concept supports a dual treatment with hybrid approach for patients with advanced remodelling.



### Follow-up method

The majority of studies describing epicardial surgical PV isolation estimate the efficiency of ablation by 24- or 48-h Holter monitoring at different intervals.<sup>3</sup> The current consensus regarding rhythm monitoring post-AF ablation recommends at least two 24-h Holter monitoring examinations annually.<sup>4</sup> Previous studies in minimally invasive AF surgical patients have demonstrated that more intensive monitoring significantly increases detection of recurrent arrhythmias and that up to 19% of patients have asymptomatic recurrent AF episodes.<sup>23, 24</sup> Charitos *et al.* investigated the sensitivity of intermittent rhythm monitoring after intervention in 647 AF patients with implantable continuous monitoring devices. The study demonstrated that the random follow-up with four 24 h Holter monitoring tests would have a sensitivity of only 54% in detecting recurrent AF, and a single 30-day Holter a sensitivity of 63%.<sup>25</sup> It is clear that intermittent monitoring overestimates procedural success. Furthermore, as the nature of these postoperative arrhythmias is intermittent and symptoms are often lacking, the preferred follow-up method is continuous monitoring, particularly for anticoagulant decision-making.

### Limitations

The current study has limitations due to its observational, non-randomized design and the limited number of patients enrolled. Furthermore, the population consists of patients with paroxysmal and persistent AF with limited substrate. The electrophysiological properties and long-term success rate of patients with long-standing persistent and advanced atrial remodelling were beyond the scope of this study.

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## Monitoring of atrial fibrillation burden after surgical ablation: relevancy of end-point criteria after radiofrequency ablation treatment of patients with lone atrial fibrillation

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## Abstract

Studies have shown that continuous rhythm monitoring enables the detection of significantly more atrial fibrillation (AF) episodes than routine follow-up of patients, i.e. based on perception of symptoms or on 24–48 h Holter monitoring. The positive outcome of radiofrequency ablation (RFA) may be easily overestimated, especially in patients with paroxysmal AF. Thirty-three consecutive patients, aged  $59.4 \pm 8.9$  years (range 38–75 years) participated in this study. All patients had documented AF episodes with an AF duration of  $9.4 \pm 7.1$  years (range 1.5–25 years). A new monitoring device, the AF-Alarm was used to more accurately assess the outcome after surgical isolation of pulmonary veins. The AF-Alarm was applied for a duration of  $128 \pm 42.5$  h (range 49–191 h) during a period of 8–15 days. The success rate was 87% based on serial electrocardiograms (ECGs) and 24–48 h Holter monitoring during regular outpatient visits. Combination of ECG, Holter and AF-Alarm data yielded a significantly lower success rate, i.e. at the latest follow-up 69% of the patients were free from AF after surgical ablation ( $P < 0.05$ ). Furthermore, the AF-Alarm device demonstrated a dissociation between symptoms and atrial arrhythmic events and confirmed the occurrence of asymptomatic AF episodes. The most important limitation of the AF-Alarm device was noise detection with oversensing and inappropriate detection of non-existing AF episodes in 9% of patients. Long-term follow-up of the patients seems to be essential as success rates of the initial ablation procedure might vary over time. External recorders like the AF-Alarm may be used as an additional tool to document symptomatic and asymptomatic episodes of atrial arrhythmias in the outpatient setting.

## Introduction

In general, atrial fibrillation (AF) is associated with a doubling of cardiovascular mortality, an increased risk of systemic emboli and stroke (4- to 5-fold increase in non-rheumatic patients and 18-fold increase in patients with rheumatic valve disease), and a deterioration in cardiac function due to a combination of loss of atrial transport, irregular or rapid ventricular rates, and progressive cardiomyopathy. The increased mortality associated with AF is independent to the underlying cardiovascular condition.

Martinek et al.<sup>1</sup> demonstrated in a series of 14 patients with a pacemaker device and treated with pulmonary vein radiofrequency ablation (RFA) for their drug-refractory and highly symptomatic AF, that continuous monitoring enables the detection of significantly more AF episodes than routine follow-up of patients, i.e. based on perception of symptoms or on 24–48 h Holter monitoring. The outcome of RFA in patients with AF is likely easily overestimated, especially in patients with paroxysmal AF.<sup>1–10</sup> Recurrences of atrial arrhythmias might increase the risk for stroke, therefore, adjustment of anticoagulant drug regimen should be based on appropriate monitoring. In this respect, the definition of an 'atrial arrhythmic episode' can be questioned as some guidelines refer to a minimum time period of 30 s, increasing the likelihood of erroneous diagnosis of sinus rhythm.<sup>1–3</sup> In this study, we evaluated the additional value of a new external cardiac rhythm monitoring device, i.e. the AF-Alarm device in patients with paroxysmal AF who underwent surgical RFA.

## Methods

From January 2006 to January 2008, 33 patients were included in the minimal invasive surgical pulmonary vein isolation registry. We evaluated the medium-term results of a novel ablation technique to eliminate AF by means of an irrigated bipolar RF ablation device. All patients consented to their data being registered and used for publication as did the Board of Hospital Administrators. All patients underwent a minimal invasive pulmonary vein isolation and left atrial appendage ligation (MIPi) procedure. Patients were followed in the outpatient clinic or follow-up data were obtained from attending or referring physicians.

## Surgical procedure

In a supine position under general anesthesia, a double lumen tube was introduced. Defibrillator pads were placed on the thoracic wall. In the right hemithorax, a 10-cm incision in the fourth intercostal space in the anterior axillary line was placed. The

pericardium was opened anterior to the phrenic nerve. Two stay sutures were placed in the pericardium. Blunt dissection of Waterston's Groove was performed followed by a blunt dissection and opening of the oblique sinus (OS) caudal of the right inferior pulmonary vein (RIPV). Then, blunt dissection and opening of the OS cranial of the right superior pulmonary vein (RSPV) between RSPV and the right pulmonary artery was performed. The Navigator was used to pass a tape around the RSPV and RIPV in one or separately, or the Navigator was used to apply the bipolar ablation device directly.

Introduction and application of the bipolar device around the pulmonary veins after gentle traction of the tape and ablating the left atrial wall adjacent to the junction with the pulmonary veins. RF energy was applied twice per pulmonary vein pair. Isolation was confirmed with pacing maneuvers at the LA-PV junction. The left hemithorax was opened similar to the right hemithorax, except for the incision of the pericardium, that was incised posterior of the phrenic nerve. Additional left atrial appendage ablation or removal or exclusion with stapler or preferably with endoloop was performed.

### Cardiac rhythm monitoring

Early postoperative care, including anticoagulant management, was similar as for routine cardiac surgery. Cardiac rhythm was continuously monitored after surgery until stable rhythm returned. Temporary epicardial wires attached to the right ventricle as well as to the right atrium were used to pace the patient, to monitor the rhythm, or to overdrive the atrium. Postoperative atrial arrhythmias were treated with sotalol 80–160 mg or amiodarone 200 mg and combined with direct-current cardioversion if necessary. After discharge, patients were seen in the outpatient clinic within four weeks, at three months, at six months and at 12 months after operation, or earlier when necessary. Antiarrhythmic drugs were tapered gradually after cardiac rhythm was considered stable. The presence of atrial contraction as documented by transthoracic and transesophageal Doppler echocardiography was performed at three and six months after surgery and related to the presence of electrical activity in the surface electrocardiogram (ECG). In all patients at variable time points, but minimally three months after the surgical procedure, the external loop recorder was applied for a duration of  $128 \pm 42.5$  h (range 49–191 h) during a period of 8–15 days. The ECG was recorded in this time period by means of the AF-Alarm including a patient cable and using three skin-electrodes. The patient was requested to manually activate the marking of symptomatic episodes. The documented episodes (either resulting from automatic detection or from manual triggers) were analyzed for appropriate detection and for AF-burden assessment. The next section describes the AF-Alarm device in detail.

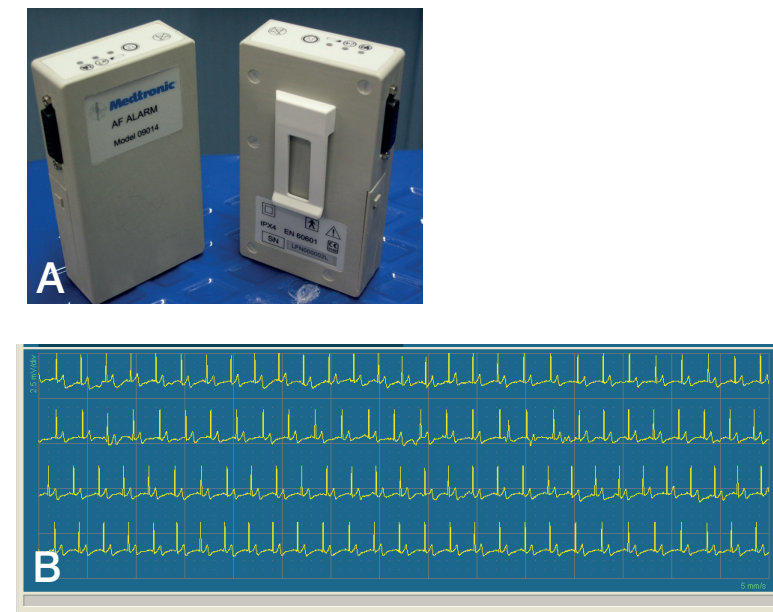
### AF-Alarm device

The AF-Alarm is a battery powered electronic arrhythmia detection device with ECG recording capabilities. The AF-Alarm provides the patient with an audible and visual signal upon detection of AF and provides storage of ECG strips and RR intervals at AF onset and termination.

The AF-Alarm device (Fig. 1) provides extra buttons that can be used to program the device but also to mark symptomatic episodes. Automatic detection as well as manual triggers result in the storage of the digitized ECG. For automatically detected episodes, the ECG during the 2-min 'onset' time window is stored, as well as the 2-min time window within which 'sinus rhythm' is detected; for manually triggered episodes the time window from 2 min before until 2 min after the trigger is stored in the device memory.

### Statistical analysis

Categorical variables are expressed as frequencies and percentages. Continuous data are presented as mean  $\pm$  S.D. Comparison of continuous variables was performed with the Student *t*-test. Comparison of proportions was performed with  $\chi^2$



**Figure 1** AF-Alarm device (A) and an example of ECG signals registered with this device (B).

analysis or Fisher's exact test. All *P*-values are two-sided and *P*<0.05 was considered statistically significant. A two-tailed *P*<0.05 indicated statistical significance. Statistical analysis was performed using SPSS (SPSS Inc, Chicago, IL, USA).

## Results

### Patient characteristics

Thirty-three patients, aged 59.4±8.9 years (range 38–75 years) participated in the RF MIPI registry. All patients had documented AF episodes with an AF duration of 9.4±7.1 years (range 1.5–25 years). Each AF episode lasted 4–24 h. Thirteen patients (39%) had paroxysmal AF and 20 patients (61%) had persistent AF. Clinical characteristics of the patients are summarized in Table 1.

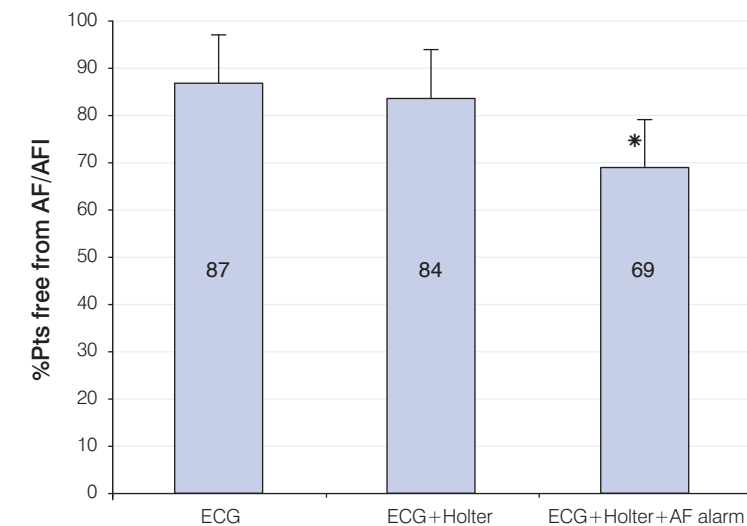
**Table 1** Baseline patient characteristics

	Number (±SD)	Range
No of Patients	33	
Gender (m/f)	20/13	
Age (years)	59.4 ± 8.9	38-75
Hypertension	11 (33%)	
History of TIA/stroke	2 (6%)	
Family history of AF	6 (18%)	
Left atrial size PSLAX (mm)	41.2 mm ± 6.5	31-47
Dextrocardia	2 (6%)	
LVEF (%)	54±4.3	25-61
Duration of AF (years)	9.4 ± 7.1	1.5-25
No of ineffective AADs	2.9±1.7	2-6
Type of AF		
Paroxysmal	13	
Persistent	20	
Permanent	0	

S.D., standard deviation; AF, atrial fibrillation; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack; PSLAX, left parasternal long axis view; AADs, antiarrhythmic drugs.

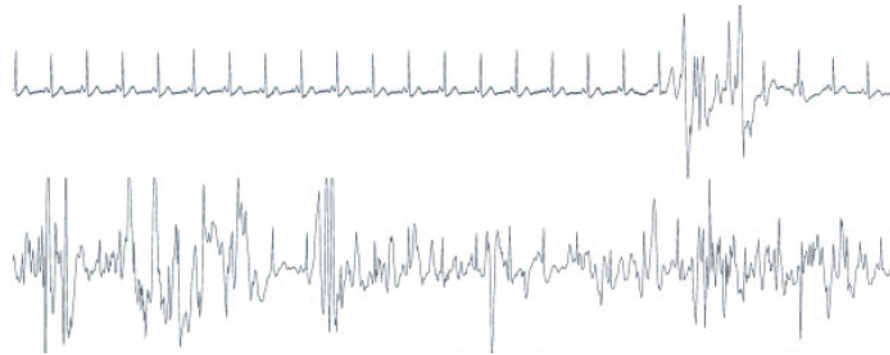
### Cardiac rhythm after surgical PV isolation and LAA ligation

The mean follow-up duration was 15±5.3 months (range 3–30 months). Fig. 2 shows cardiac rhythm at the latest follow-up based on ECG, combination of ECG and Holter and combination of ECG, Holter and AF-Alarm recordings. During follow-up, sustained sinus rhythm, including atrial rhythm (AR) or an atrial-based paced rhythm (ABPR) was present in 87% of patients based on ECG only, 84% based on ECG plus Holter and the success decreased to 69% after combining the ECG, Holter and AF-Alarm data (*P*<0.05). Antiarrhythmic drugs were used in 64% of survivors who were free of AF. Oral anticoagulation was taken by 97% of patients. In the postoperative period when the AF-Alarm registrations were made, 19 patients were free from antiarrhythmic medication and three were not treated with anti-coagulant medication. The AF-Alarm device confirmed successful ablation in 69% of patients as indicated by 0% AF burden (time spent in AF). One patient demonstrated the presence of persistent AF, as revealed by an AF-burden of 99%. In three patients (9%) automatic



**Figure 2** Bar graph demonstrating cardiac rhythm at the latest follow-up based on ECG, combination of ECG and Holter and combination of ECG, Holter and AF-Alarm recordings. During follow-up sustained sinus rhythm, including atrial rhythm (AR) or an atrial-based paced rhythm (ABPR) was present in 87% of patients based on ECG only, 84% based on ECG plus Holter and the success decreased to 69% after combining the ECG, Holter and AF-Alarm data (*P*<0.05). See text for details.

recordings were documented by the AF-Alarm which appeared inappropriately detected either as a result of noise registration (muscle potentials and/or poor connection/contact of ECG-electrodes with skin, Fig. 3 ) or to frequent premature atrial contractions jeopardizing and misleading the detection algorithm (Fig. 4 ). In five patients, manually triggered ECG registrations during presence of symptoms correlated with sinus rhythm; in a sixth patient the symptoms correlated with the presence of a non-sustained ventricular tachycardia.



**Figure 3** False positive detections: noise registration (loose electrodes, muscle potentials).



**Figure 4** False positive detections: occurrence of premature atrial contractions.

## Discussion

Conversion to and maintenance of sinus rhythm is often chosen as the primary end-point in studies looking at the success rate of AF ablation, however, many controversies exist in the determination of the success rate of the ablation procedure. The success rates also vary with the treatment of persistent or paroxysmal AF, the applied ablation procedures and evidence for potential underlying substrates.

As nicely indicated by previous studies,<sup>6–10</sup> the success rate varies if one looks at freedom from AF recurrences with or without associated symptoms. Vasamreddy et al.<sup>6</sup> demonstrated that studies requiring an intensive monitoring of the recurrences of episodes lack from a sufficiently high patient compliance since they lack the consistency to accurately register every occurrence of symptomatic episodes, even when using a special wireless monitoring system that was applied in every patient on several occasions for five consecutive days.

The use of long-term ECG-observational devices to document presence or recurrence of arrhythmic episodes have been frequently proposed but rarely implemented. Several devices are commercially available to allow out-of-hospital monitoring of the analogue ECG-signal for up to 96 continuous hours. Subsequent analysis to identify arrhythmic episodes as short as 30 s requires adequate attention and resources. Continuous recording might help to better detect asymptomatic episodes as compared to discontinued recordings – e.g. triggered by occurrences of symptoms or at fixed time points during the day – which methodology often suffers from low patient compliance adhering to the protocol. Implantable devices assure 100% patient compliance, yet available devices are rather expensive. External devices, such as the AF-Alarm, allow for easy application and fast diagnosis of relevant ECG information while offering a good cost/effectiveness balance and assuring high patient compliance.

The outcome of this observational study confirms that continuous observations is a good tool to document the absence/presence of asymptomatic episodes which will trigger subsequent medication adjustments. In this particular study, one patient was even diagnosed to have a non-sustained ventricular tachycardia during the extended period of ECG registration.

## Limitations and shortcomings

It has been suggested to take a blanking or stabilization period into account of some three months post-ablation prior to assessing the recurrence of arrhythmias. In this stabilization period, the rate of recurrences might gradually decay and is not



representative for the final clinical outcome, yet documentation of recurrences might help to better understand the remodeling process that is ongoing. Unfortunately today, too limited observations allow for such an adequate understanding.

If patients would have been monitored in the current study for longer time periods, there is a likelihood that more patients would have demonstrated recurrences. Longer registration periods merely depend on the tolerance of the patient to wear the sticky electrodes longer. This study was applied in only 33 patients, representing only a small sample of the current population presenting itself in the outpatient clinic. Therefore, observed ablation success rates are only indicative.

### Conclusion

This study demonstrates that the longer the observational period the lower the success rate post-surgical ablation for AF. Furthermore, the current observed results demonstrate that the use of an external cardiac rhythm monitoring device like AF-Alarm is feasible to support the diagnosis of atrial arrhythmic recurrences in a better way than current standard practice. AF-burden is a continuous measure and a better parameter to assess success of the ablation therapy. Assessment of the AF-burden at regular time intervals allows optimal titration of the anti-arrhythmic and anti-coagulant therapies. In the future, implantable loop recorders may offer an objective mean to document occurrences of atrial episodes while the patient is out of the hospital and no longer under direct control of the treating physician. Thus, demonstration of long-term absence of recurrences seems to be the most solid end-point to determine success of the initial ablation procedure.

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# 10

General discussion and summary  
Algemene discussie en samenvatting  
Dankwoord  
Curriculum vitae  
List of publications



## General discussion and summary

This thesis highlights novel insights regarding several aspects of the pathophysiology and invasive treatment of a spectrum of complex atrial arrhythmias, particularly atrial fibrillation (AF) in different settings and discusses the value of different treatment modalities and follow up methods of invasive AF ablation procedures. AF is an electrocardiographic diagnosis with a wide spectrum of underlying diseases. The variety of underlying triggers, substrates and modulating factors result in wide variation in interindividual clinical presentation and unpredictable response to therapies. Particularly in last decade an enormous progress has been made in identifying mechanisms of complex atrial arrhythmias, identification of triggers, its localization and amount of substrate, attempting to tailor ablation techniques and monitoring of ablation result. Although great progress has been made in the treatment of this arrhythmia, the incomplete understanding of the underlying pathophysiological mechanisms has been one of the reasons for the lack of fully tailoring therapy to the individual patient's underlying heart disease and limited long term success of the currently available drug and ablation therapies.

### Mechanism of atrial fibrillation

Paroxysmal AF usually begins with ectopic electrical activity in the pulmonary veins (PVs). Rapidly firing atrial activity in the muscular sleeves at the PV ostia or inside the PVs have been described as potential underlying mechanism for AF.<sup>1</sup> These muscle sleeves have distinct electrophysiological (EP) properties, e.g. shorter action potential duration, shorter effective refractory period and enhanced autonomic sensitivity. In experimental studies, high frequency electrical stimulation of autonomic neurons in the vicinity of the PVs resulted in early afterdepolarizations and ectopic firing in the PVs. Atropine prevented action potential shortening and triggered firing of myocytes in the PVs. Furthermore, atenolol allowed action potential shortening and prevented triggered firing in the PVs.<sup>2, 3</sup>

The interaction between the two limbs of the autonomic nervous system, ectopic triggers and the development of structural and electrical atrial changes, known as remodeling, leads to progression of AF. The major stressors promoting atrial remodeling are high rate of atrial cell depolarizations and excessive volume and pressure load. The remodeling process includes myocyte growth, hypertrophy, necrosis and apoptosis, alterations in the composition of extracellular matrix, recalibration of energy production and expenditure, changes in the expression of cellular ionic channels and atrial hormones. These changes result in a cascade of reactions leading to structural, functional, electrical, metabolic, and neurohormonal consequences.<sup>4</sup> Mechanisms underlying the progression of paroxysmal AF with

short duration of arrhythmic episodes to more frequent episodes with longer duration of AF and eventually persistent and longstanding persistent AF is not fully delineated yet.<sup>5,6</sup> It is likely that structural atrial remodeling leading to atrial pathology enables the development of cardiovascular events, which might explain the relatively high stroke rate among the patients with AF progression. In addition, Glotzer et al showed that patients with a higher AF burden, which is the case in patients demonstrating AF progression, are more prone to have a stroke.<sup>7</sup>

**Chapter 3** describes the results of high density intra-operative mapping of longstanding persistent AF. This study explored the effects of acute stretch on intra atrial conduction properties (cycle length, conduction velocity and pattern, amount of conduction block) in patients with longstanding persistent AF undergoing open heart surgery. In nine patients who were scheduled for cardiac surgery and concomitant radiofrequency (RF) modified maze surgery were studied intraoperatively with bi-atrial high density mapping using epicardial multielectrode arrays. Atrial pressure and size were altered by modifying extracorporeal circulation settings. Atrial dedilatation resulted in a significant decrease of the mean cycle length (7% and 9% for the left atrium and right atrium, respectively) and amount of conduction block and subsequent dilatation increased the mean cycle length and percentage of conduction block significantly. This is the first study in humans with longstanding persistent AF that demonstrates the amount of intra-atrial conduction block decreases with acute dedilatation. Several animal studies show a similar effect of stretch on prolongation of the atrial effective refractory period.<sup>8,9</sup>

In contrast, Solti et al reported that atrial dilatation resulted in a decrease of atrial effective refractory period along with an increase of atrial conduction times in a dog study. In this latter study, atrial stretch was induced with balloon inflation.<sup>10</sup> The vulnerability of the atrium to arrhythmias significantly increased on balloon dilatation (either spontaneous arrhythmias or induced by extrastimulus or burst pacing). Although the mechanism for these differences is not clear, our patients had longstanding persistent AF whereas in the latter study, AF and atrial flutter was artificially induced in healthy dogs. Therefore, it is not possible to compare our clinical study with the canine data. Several factors, including different atrial tissue characteristics or unequal atrial stretch may play a role in the discrepancy between these experimental results and our patient data. A resembling conclusion among the studies is the enhanced susceptibility to AF during an acute rise in atrial pressure.

An unanswered question remains to which extent electrical reverse remodeling can be achieved with long term reduction in atrial size and pressure, especially in patients with longstanding persistent AF. From a therapeutic point of view, there is increasing

interest in modifiable modulating factors such as hypertension, obstructive sleep apnea, obesity, valvular heart disease, congestive heart failure, ischemia, endocrine abnormalities and inflammation.<sup>11,12</sup> It is known that modification of important risk factors and treatment of underlying diseases is very important and significantly enhances outcome of surgical and catheter ablation for AF.

### AF and acute coronary syndrome

AF is a common complication of acute myocardial infarction (MI) with an overall incidence of 5–22%. Not surprisingly, the development of new onset AF is more likely in patients of older age, extensive myocardial damage, higher Killip class, and signs of cardiogenic shock.<sup>13,14</sup>

The prognostic impact of AF that occurs in the setting of acute MI is controversial. Some studies describe an independent adverse effect on mortality and others failed to detect this association.<sup>15</sup> New AF may lead to adverse outcomes in patients with MI through adverse haemodynamic effects such as loss of atrial contraction, high ventricular rates, loss of atrioventricular synchrony and an irregular ventricular intervals leading to a decrease in cardiac output.<sup>16</sup>

A recent systematic review and meta-analysis, including 43 studies and 278 854 patients, showed that AF carries an excess risk of in-hospital, short-term (30 days to 1 year), and long-term (>1 year) mortality among patients with acute MI, with at least a 40% increase, regardless of the type of AF (pre-existing or new-onset). Increased risk included both sudden and non-sudden cardiac death. This worse prognosis persisted, in patients with new-onset AF, even after adjustment for confounding factors such as age, diabetes mellitus, hypertension, prior MI, heart failure, and coronary revascularization.<sup>17</sup>

In **Chapter 2** we describe the association of timing of AF with regard to mortality in primary percutaneous coronary intervention (PCI) patients presenting with a ST elevation MI. In this substudy of a multicenter randomized trial, electrocardiographic data before primary PCI from a total of 1623 ST elevation MI patients were available and 53 (3.3%) of these patients had documented AF. In addition, of the 1728 patients with electrocardiographic data available after primary PCI, 52 patients (3.0%) had AF. Factors associated with AF were older age, Killip class >1, TIMI 0 flow prior to PCI, unsuccessful reperfusion and occlusion of the right coronary artery. Multivariate analyses revealed that mortality was significantly higher in patients with AF after PCI and not in patients with AF prior to PCI.

AF complicating acute MI is multi-factorial in its pathogenesis. A variety of factors have been proposed to initiate AF in the setting of acute MI such as haemodynamic disturbance, atrial ischaemia, excess catecholamine release, electrolyte imbalance, heart failure, ventricular remodelling, acute hypoxia, pericarditis and inflammation – either on their own or in varying combinations.<sup>18</sup>

Although incidence and prevalence of AF is reduced to some extent by improved reperfusion strategies, occurrence of AF in the setting of acute MI and its prognostic significance is still dependent on the associated co-morbidities as well as the magnitude and consequences of MI.

### Single shot ablation for AF, The PVAC catheter

Catheter ablation for AF has emerged as an alternative to antiarrhythmic drug (AAD) therapy in patients who remain symptomatic despite AAD or even as a first line treatment in selected patients.<sup>19,20</sup> Although a wide variety of ablation techniques have been used to treat AF, it is generally agreed that the electrical disconnection of all PVs is still the cornerstone of the treatment. Novel methods aiming at simpler and faster pulmonary vein isolation (PVI) by use of the so-called “single shot” devices have therefore been developed in recent years. The introduction, Chapter 1, gives a detailed overview of the current techniques available. In chapter 4 and 5 the results of the circular multi-electrode PV ablation catheter (PVAC; Medtronic Inc, Minneapolis, MN, USA) are described.

In **Chapter 4** we present the 12 months follow-up data including efficacy and safety outcome of the first generation PVAC. The study included 102 consecutive patients (90 paroxysmal AF and 12 persistent AF) with AF for a mean duration of 9.3±7.5 years (range 1.5–25) of time since first diagnosis of AF. The mean fluoroscopy time required for PVAC ablation was 17±12 min (median 16, range 12–33) and the mean total procedure time was 139.30±37.72 min (median 135, range 115–172). In eight patients with persistent AF, additional ablations were performed to defragment septal and posterior part of the left atrium and in 5 patients additional ablation with a conventional catheter was required. After a mean follow-up duration of 12.2±3.9 months 62 of 102 (60.8%) patients were in sustained sinus rhythm without anti-arrhythmic drugs. There were no procedural complications in this study.

The efficacy outcome in our study with the first generation PVAC devices is slightly lower when compared to other reports. This might be related to the fact that this was an unselected group of patients (“real life data”) including paroxysmal and persistent AF patients with a relatively extensive substrate for AF. Furthermore the learning curve might have played a role in this early PVAC study.<sup>21,22,23,24</sup>

**Chapter 5** compares the outcome of PVAC catheter ablation to conventional point by point ablation to isolate the PVs. In this prospective, non-randomized observational study the efficacy of first generation PVAC ablation in 89 patients was compared to conventional circumferential RF point by point ablation in 96 patients with paroxysmal AF. At 12 months follow up 82% of PVAC patients and 80% of conventional PVI patients were free of AF off AAD (P=0.989). Furthermore the mean procedure time was significantly shorter for PVAC ablation (133.25±37.99 min versus 171.73±2.87, P<0.001). No major adverse events occurred in either group.

Other studies describe a similar 12 months outcome of PVAC ablation in paroxysmal AF.<sup>24,25</sup> The long term outcome of PVAC ablation shows similar result compared to conventional PVI.<sup>26,27</sup> As mentioned in Chapter 1 of this thesis major concerns about the safety of the PVAC catheter arose in 2011 when an increased incidence of silent cerebral embolisms was reported with the phased RF technique in comparison with irrigated tip RF ablation.<sup>28,29</sup> For this reason several improvements in the design of the original PVAC catheter were made which resulted in the development of the PVAC Gold catheter (Medtronic Inc, Minneapolis, MN, USA). This newer generation catheter contains 9 instead of 10 electrodes to eliminate the potential bipolar short circuit between overlapping electrodes 1 and 10 which was assumed to be the major reason for micro embolisms. In addition, platinum electrodes were replaced by gold which has a better thermal conductivity, thereby providing faster cooling and more precise temperature control, preventing of tissue overheating. Furthermore a 20-degree forward tilt was added to the distal segment of the catheter for a more uniform electrode-tissue contact with the PV antrum.<sup>30,31</sup>

Initial experiences with the PVAC Gold catheter were promising with similar one year success rate compared to the first generation PVAC but shorter RF application time and less fluoroscopy.<sup>32,33</sup>

In 2016 the PRECISION GOLD trial reported the results of cerebral magnetic resonance imaging in 51 patients within 48 hours pre- and 24 hours post-ablation. The results were a low incidence of asymptomatic cerebral embolism (2.1%) when using the PVAC gold catheter in combination with uninterrupted oral anticoagulant therapy and heparinization with ACT levels ≥ 350 seconds.<sup>34</sup> However the rate of micro-embolic signals with PVAC gold is still significantly higher as compared to conventional irrigated tip catheter ablation as demonstrated by a recent randomized study.<sup>35</sup>

In view of the increasing number of AF patients requiring invasive therapy and the results of the STAR-AF trial, which emphasizes the relevance of PVI even in patients with persistent AF, the significance of technologies aiming at PVI exclusively will probably increase further.<sup>36</sup>

The most widespread “single shot” device for PVI at this moment is the cryoballoon. Both, the cryoballoon and the PVAC are effective in reducing procedure time and require less operator experience compared to point by point ablation. The main shortcoming of the PVAC system is that mapping possibilities are limited. For example, during RF delivery EGMs recorded with the PVAC cannot be displayed and therefore disappearance of PV potentials cannot be followed in real time. On the other hand, ablation procedure with the PVAC Gold catheter seems to require less fluoroscopy time and procedure time compared to cryoballoon ablation.<sup>32,33</sup>

In conclusion, the increasing demand of ablation therapy for AF patients requires faster, safer and more cost-effective techniques. There are concerns regarding increasing incidence of asymptomatic cerebral embolization with the PVAC Gold. These safety issues should be settled before widespread use of this device. The results of ongoing prospective, randomized trials should be awaited. If proven safe, phased multi-electrode radiofrequency ablation is a potentially promising technology providing a time efficient method of pulmonary vein isolation in paroxysmal AF patients.

### Focal atrial tachycardia

Focal atrial tachycardia (AT) was previously considered an arrhythmia due to enhanced automaticity. Nowadays, it is known that triggered activity and micro re-entrant etiologies are even more common in the arrhythmogenesis of the so-called “focal” ATs. By definition focal AT is an atrial arrhythmia originating from an area (focus smaller than 2 cm) with an excitation wave spreading centrifugally to the rest of the atria.<sup>37,38</sup>

Focal AT may occur in conditions leading to enhanced atrial stretch such as hypertension or cardiomyopathy or in response to toxic agents or hypoxemia. A specific incessant form of focal AT is seen in post AF ablation patients. Particularly linear ablation and ablation of complex fractionated activity may lead to these very symptomatic and drug-refractory “focal” ATs.

In the absence of structural heart disease or previous ablation, focal AT has a good prognosis and is amenable to ablation therapy. Of note, mapping and ablation of ATs can be very challenging, particularly ATs arising from the interatrial septal area, including non coronary aortic cusp (NCC) due to its anatomical relationship with

important structures in the paraseptal region such as the, His bundle and arrhythmogenic tissue in the aortic sinus.

**Chapter 6** presents a case series, our experience in mapping and ablation of ATs originating from the aortic sinus and the NCC and extensive literature review of focal AT arising from this area. EP study was performed in 7 patients (4 males; age  $40 \pm 9$  years, range 28–51 years) with drug-refractory AT. A parahisian origin was confirmed in all patients after initial right atrial mapping. The second step was left atrial mapping and subsequently mapping of the aortic sinus including the NCC either if left and right atrial mapping failed to identify a successful ablation site or RF applications were not successful in terminating the tachycardia. Mapping of the NCC demonstrated earliest atrial activation during AT  $38 \pm 14$  ms (ranging 17–56 ms) before the onset of the P-wave. Earliest atrial activation in the NCC was earlier than earliest activation in the right atrium and left atrium in all patients. The tachycardia was successfully terminated by RF application in  $10 \pm 6$  s (2–16 s), without complications. All patients were free of symptoms during a follow-up of  $19 \pm 9$  months.

NCC related AT is difficult to recognize on the surface ECG. The specific morphology among different reports is not consistent. The most typical morphology is predominantly negative P-waves in the inferior leads, positive or isoelectric in leads I and AVL, and biphasic in right precordial leads V1 and V2 (mostly negative–positive). NCC AT typically shows a positive P-wave in leads I and AVL and a local A/V ratio of  $>1$  (as opposed to a negative–positive P-wave deflection in left coronary cusp AT with a local A/V ratio  $\leq 1$ ).<sup>39,40</sup>

A couple of algorithms have been reported to determine the site of origin of focal AT.<sup>41,42</sup> However the diagnostic accuracy is very limited for foci located close to the interatrial septum and NCC. Because of the central position of this area in the heart slight cardiac rotation and variation in body habitus and atrial tissue mass distribution can dramatically influence the P wave morphology polarity. Ablation of focal AT requires 3D mapping systems. The current 3D mapping systems combined with dedicated multi-electrode diagnostic catheters, enable operators to map during AT and automatically create high-density 3-dimensional electroanatomic maps. The techniques provide detailed insight into AT mechanisms and facilitates rapid mapping and ablation of these ATs. However, the currently available multipolar mapping catheters are not suitable for mapping in the sinus of Valsalva, which still requires conventional mapping with conventional ablation catheters. Although no randomized studies are available, based on our experience and published reports, novel technologies such as image integration and intracardiac echocardiography contribute to safety and efficacy of mapping and ablation in this area.



### Atrial fibrillation - Surgical approach

The maze procedure was introduced in 1987 by Dr Cox for the surgical treatment of AF. This procedure with a set of multiple specific biatrial lesions was designed to interrupt atrial macro re-entrant circuits, thereby creating a “maze” and reducing the ability of the atrium to fibrillate. Although freedom of AF and even freedom from late stroke were high, the procedure was technically challenging requiring sternotomy, cardiopulmonary bypass and extensive suture lines.<sup>43,44</sup>

In 2002 the Cox-maze IV procedure was introduced which replaced the bilateral incisions of the traditional cut-and-sew procedure with epicardial linear lines of ablation created with bipolar RF devices (or less often cryotherapy or microwave energy). During the procedure the left atrial appendage (LAA) is generally excised. Although the Cox-maze IV can be performed through a small right-sided intercostal thoracotomy, it still requires cardiopulmonary bypass.<sup>45,46</sup>

Since 2005 AF surgery made a major step with the introduction of minimally invasive thoroscopic technique providing access to the entire atrial epicardium of a beating heart. A variety of ablation strategies exist involving isolating the PVs either as a box or separately with or without ablation of the ganglionated plexi and with or without additional ablation lines.<sup>47</sup>

The bidirectional bipolar RF ablation devices are often used for surgical treatment of AF and consist of a clamp with two jaws, which are applied on opposite sides of the atrial tissue. The energy passes through the tissue between the two jaws. When conductance falls, transmuralty is inferred. Because RF energy is delivered between two closely approximated electrodes embedded in the jaw of a clamp device, the energy is focused and results in discrete lesions. The energy is confined to between the jaws of the clamp, reducing the possibility of collateral cardiac or extracardiac damage. The limitation of these devices is that they can only ablate tissue that can be clamped within the jaws of the device. This shortcoming has limited the potential lesion sets, particularly in the beating heart. Moreover, in the clinical situation, multiple ablations are often required to achieve entrance and exit block. These devices have been incapable of fully ablating the right and left atrial isthmus and have required adjunctive ablation with cryotherapy, or unipolar or unidirectional bipolar RF ablation to perform a complete Cox-maze III lesion set.<sup>48</sup>

La Meir et al describe in their meta analysis a success rate of stand alone thoroscopic AF surgery, defined as freedom from any AF episode longer than 30 seconds off AAD at 12 months, of 65-92% for paroxysmal AF patients and 67% to 80 % in persistent AF patients.<sup>49</sup>

It should be mentioned that they included small sized studies (ranging from 14 to 114 patients) and rhythm follow up varied with only intermittent ECG or Holter monitoring.

Studies comparing stand alone surgical AF ablation with catheter ablation are very limited. A recent meta-analysis of comparative studies investigating minimally invasive thoroscopic AF surgery versus catheter ablation for AF suggests a superior efficacy of surgery (freedom from recurrent atrial arrhythmias 78% vs 53%).<sup>50</sup> Major complications however were significantly higher in surgical treated patients (28% vs 8%). Although surgical PV ablation may be more likely to result in transmural lesions the differences in efficacy in these studies may also be driven by patient selection. Most patients included in these studies had failed prior invasive AF ablation procedures. Furthermore follow up in the included studies was performed with intermittent monitoring.

**Chapter 7** of this thesis describes the results of a randomized controlled trial comparing surgical AF ablation with catheter ablation, with the use of continuous rhythm monitoring (ILR). A total of 50 patients (57 years, 39 male), with “lone” symptomatic paroxysmal or persistent AF, were randomized to either minimally invasive thoroscopic PVI with LAA ligation or point by point radiofrequency PVI. The ILR was implanted prior to treatment to record a pre-ablation AF burden. At 6 months the decrease in AF burden was 15.5% (95% CI 9.7%-43.1%) in the surgical group compared to 26.1% (95% CI 11.2%-59.6%) in the catheter ablation group ( $P=0.375$ ). Freedom from AF, defined as an AF burden of  $<0.5\%$ , at 6 months was 63% in the surgical group versus 65% in the catheter group ( $P=0.87$ ). Complications occurred significantly more often in the surgical patients 34.8% versus 11.1% in the catheter group ( $P=0.046$ ). In conclusion, the short term outcome, in terms of preventing AF, is similar for catheter ablation and surgical ablation but surgery is associated with significantly more complications.

Although the sample size of the trial is small, the strength of this study is the fact that these patients did not have a previous ablation procedure. Therefore this population can be regarded as a “real life” unselected, lone AF cohort. We realize that superiority of surgical technique, as previous reports suggest, might be related to the patient selection; patients with several unsuccessful endocardial ablations are more likely to benefit from an epicardial approach.<sup>49</sup>

Furthermore, in light of frequent episodes of silent AF after ablation, continuous monitoring with ILR follow up is the only method that can provide reliable results when a trial endpoint is defined as “freedom of AF”.<sup>51</sup> A major advantage of a preoperative implanted ILR is that symptomatic AF can be definitively confirmed and pre-operative

AF burden provides necessary data to make a reliable comparison with the post-operative situation.

### Recurrent atrial arrhythmias after AF surgery

With the improvement of techniques for minimal invasive AF surgery, this treatment is becoming more effective and safe and therefore available for use on a larger scale. Nevertheless early and late ablation failures is still a major clinical concern.

**Chapter 8** examined the electrophysiological characteristics of recurrent atrial arrhythmias after surgical AF ablation and the long term outcome of catheter ablation of these arrhythmias. The study included 23 patients who underwent an EP study, 378 ± 282 days after AF surgery, because of recurrent symptomatic atrial arrhythmias. Surgical ablation consisted of minimally invasive thoracoscopic PVI with an irrigated bipolar RF ablation clamp (Cardioblate, Medtronic, USA) and ligation of the LAA. Intraoperatively the PVs were tested for entrance block and retested for reconnection after 30 minutes. The recurrent arrhythmias consisted of paroxysmal and persistent AF in 20 patients, 2 patients had a combination of AF and AT and 1 patient had a combination of AF and atrial flutter. All patients showed PV reconnection. ATs appeared to be micro-reentry, PV-related ATs and atrial flutter was cavotricuspid isthmus dependent. Eighteen of 23 patients (78.3%) were free of atrial arrhythmias after one catheter ablation procedure at a mean follow-up of 50 ± 16 months. Three patients underwent a second ablation procedure for recurrent AF and macro-reentry left atrial flutter. Eventually 20 of 23 patients (87%) remained free of atrial arrhythmias after a mean of 1.1 ± 0.3 ablation procedures. This study demonstrates that recurrences of atrial arrhythmias after surgical ablation are predominantly due to reconnection of surgical ablation lines and that touch up ablation, in a staged manner, with catheter ablation is very effective.

Despite achieving exit and entrance block post ablation with bipolar epicardial RF, PV reconnection seems to be the most common finding in patients with recurrent AF. Previous reports demonstrate a similar finding.<sup>52,53,54</sup> PV reconnection likely develops during the healing process. Prolonged atrial-to-PV conduction times is seen often during EP studies, consistent with damaged myocardial tissue that is still able to conduct.

On the other hand we have to acknowledge that the study population consisted of patients with limited AF substrate and therefore macro reentrant tachycardias outside the PVs is less likely. Trumello et al emphasize the need for appropriate lesion set in the initial surgical procedure.<sup>55</sup> The study analysed 36 patients with recurrent atrial arrhythmias after surgical ablation with various energy sources and lesion sets.

Particularly patients with advanced substrate and persistent AF who were treated with PV isolation only were likely to develop perimitral macro-reentry circuits. The authors conclude that a simplified maze procedure albeit curative for AF may nevertheless, predispose to macro-reentry tachycardias. On the one hand these patients may be undertreated, on the other hand it is well known that mitral isthmus ablation can be cumbersome in thoracoscopic epicardial procedures. A staged endocardial or hybrid approach may be a good alternative.

### Rhythm Follow up after AF ablation

Although catheter ablation and surgical ablation for AF is an effective treatment and there is currently an explosive number of AF ablation trials, there is no consensus of the definition of success or follow-up strategies. Symptoms are the main motivation for undergoing catheter or stand alone surgical ablation in patients with AF, however it is well known that reliance on perception of AF by patients after AF ablation results in an underestimation of recurrence of the arrhythmia. Even in patients with highly symptomatic AF, as many as half of all episodes can occur without any associated symptoms.<sup>56</sup>

Verma et al demonstrated with ILR monitoring that the ratio of asymptomatic to symptomatic episodes increases from 1.1 before to 3.7 after ablation. Possible mechanisms for this effect are the shorter durations of arrhythmic episodes after ablation, slower rates, or autonomic modulation.<sup>51</sup>

Symptoms alone underestimated post ablation AF burden, with 12% of patients having asymptomatic recurrences only. Other studies report rates of post ablation asymptomatic AF episodes as high as 44%.<sup>57</sup>

In **Chapter 9** we describe the evaluation of an external cardiac rhythm monitoring device *the AF-Alarm* in patients who underwent surgical AF ablation. Thirty-three patients, aged 59.4 ± 8.9 years (range 38–75 yrs) with paroxysmal or persistent AF with a duration of 9.4 ± 7.1 years since AF diagnosis, underwent minimal invasive thoracoscopic PVI and LAA ligation. The AF-Alarm was applied for a duration of 128 ± 42.5 h (range 49–191 h) during a period of 8–15 days. Apart from the AF alarm serial ECGs and 24-48 hour Holter monitoring was performed. Patients were requested to manually activate when they experienced symptomatic episodes. The AF Alarm provides an audible and visual signal upon detection of AF and provides storage of ECG strips and RR intervals at AF onset and termination. Automatic detection as well as manual triggers resulted in the storage of the digitized ECGs. After a mean follow-up duration of 15 ± 5.3 months, the combination of ECG, Holter and AF-Alarm data yielded a success rate of 69%, defined as sustained sinus rhythm.

The combination of only ECG and Holter resulted in success rate of 84% ( $p < 0.05$ ). Five patients (15%) had several manual activated episodes which appeared to be sinus rhythm. Oversensing of the AF alarm occurred in 9% of patients. In conclusion, external rhythm monitoring with the AF Alarm after AF surgery is feasible and results in better detection of recurrent arrhythmias than standard practice.

In the absence of continuous monitoring post ablation, great caution should be exercised when AF is judged “suppressed” or “cured.” As mentioned before, the freedom from symptoms related to AF has been used as a surrogate endpoint of freedom from AF episodes and ablation success. It is clear that also external event recorder monitoring is not capable of detecting 100% of arrhythmias and the main drawback of these systems is that they are only tolerated by highly motivated patients over a short period of time. Post procedure arrhythmia monitoring is also relevant because of the significant number of patients experiencing palpitations in the absence of an arrhythmia. Israel et al describe in their study population that included 40% of pacemaker patients, reporting symptoms suggestive of AF that were not confirmed by ECG, neither by pacemaker interrogation.<sup>58</sup>

The ILR is a subcutaneous device that allow for continuous monitoring of arrhythmias for up to 3 years, which overcome the limitations described above. Originally in the AF algorithms, AF detection is performed using incoherence of R-R intervals over a 2 minute period as the PP intervals couldn't be sensed reliably. As assessed in the XPECT study, the Reveal XT ICMs have an overall accuracy for AF detection of 98.5%.<sup>59</sup>

However false positive AF detection was a concern. The majority of inappropriate AF detections in ILRs are caused by runs of atrial ectopy with irregular coupling intervals, sick sinus, and sinus arrhythmia. The latest generation of a loop recorder (Reveal LINQ, Medtronic) utilizes an advanced algorithm involving identification of a P wave between 2 RR complexes to reduce inappropriate detections. Recent studies demonstrated a significant reduction in the false positive detection rate compared to the previous device generations and showed an even higher overall accuracy for AF detection of 99.4%, with sensitivity, specificity, positive predictive value, and negative predictive value for identification of AF of 98.4%, 99.5%, 97.2%, and 99.7%, respectively.<sup>60</sup>

The use of ILRs opens exciting new possibilities for monitoring the ablation result, for scientific reasons, as well as for selection of patients for an ablation procedure. However, future research is needed to assess the value of ILR in AF treatment before official recommendations can be given,

## Conclusion

The results of this thesis provide novel insights into the pathophysiological mechanisms and invasive treatment and follow up patients with complex atrial arrhythmias and AF in particular. AF represents a spectrum of arrhythmias with a wide variation in underlying diseases. Knowledge about the underlying mechanisms in each individual patient with AF is essential for determining the most appropriate treatment options. The outcome of catheter ablation for the large group of patients with paroxysmal AF and limited amount of substrate using the so called “single-shot” percutaneous ablation techniques is very promising whereas patients with advanced substrate require a tailored approach in which surgeons and electrophysiologists collaborate. Moreover, integrated AF care models result in improved freedom from AF and patient survival.

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## Algemene discussie en samenvatting

In dit proefschrift worden diverse aspecten belicht van de pathofysiologie en invasieve behandelingen van verschillende atriale aritmieën, voornamelijk atriumfibrilleren (AF), in verschillende omstandigheden. Daarnaast worden verschillende behandelingsmodaliteiten beschreven evenals de waarde van follow-up methodes na een invasieve AF ablatie procedure. AF is een electrocardiografische diagnose met een breed spectrum aan onderliggende aandoeningen. De variëteit aan onderliggende triggers, substraat en modulerende factoren resulteert in enorme verschillen in interindividuele klinische presentatie en een onvoorspelbare respons op behandeling. De laatste tien jaar zijn grote stappen gemaakt in het ontdekken van mechanismen van complexe boezemritmestoornissen, het identificeren van triggers, de oorsprong van deze triggers en de hoeveelheid substraat. Ook is tegenwoordig meer aandacht voor het monitoren van het ablatieresultaat. Ondanks deze vooruitgang is de nog immer incomplete kennis van de pathofysiologie één van de redenen waarom tegenwoordig nog geen toegespitste behandeling bestaat, gericht op de onderliggende oorzaak van de boezemritmestoornis en is het lange termijn succes van ablatieve en medicamenteuze therapieën beperkt.

### Mechanismen van atriumfibrilleren

Paroxysmaal AF begint met ectopische, elektrische activiteit in de pulmonaal venen (PVs). Het onderliggende mechanisme van AF berust op snel vurende atriale activiteit vanuit de zogeheten *muscular sleeves* rond de PV ostia of in de PVs.<sup>1</sup> De muscular sleeves hebben markante electrofysiologische (EP) eigenschappen. Zo is de duur en effectieve refractaire periode van de actiepotentiaal korter in vergelijking met het overige atriale weefsel en is er sprake van een versterkte autonome sensitiviteit. In experimentele studies konden vroege na-depolarisaties en ectopische elektrische activiteit worden geprovoceerd door middel van hoogfrequente elektrische stimulatie van de autonome neuronen in de nabijheid van de pulmonaal venen. Atropine verhindert actiepotentiaal verkorting en stimuleert spontane triggers van PV myocyten. Atenolol geeft daarentegen wel actiepotentiaal verkorting en remt de spontaan vurende triggers in de PVs.<sup>2,3</sup>

Progressie van AF wordt veroorzaakt door de interactie tussen de beide takken van het autonome zenuwstelsel, ectopische triggers en de ontwikkeling van structurele en elektrische atriale veranderingen, ook wel *atriale remodeling* genoemd. De belangrijkste factoren die atriale remodeling bevorderen zijn de hoge frequentie van atriale depolarisaties en overmatige volume en drukbelasting. Het proces van remodeling bestaat uit myocytontwikkeling, hypertrofie, necrose en apoptose, verandering van de samenstelling van de extracellulaire matrix, recalibratie van ener-



gieproductie en verbruik, verandering van de expressie van cellulaire ionkanalen en atriale hormonen. Deze processen leiden op hun beurt weer tot een cascade van reacties die resulteren in structurele, functionele, elektrische, metabole en neuro-hormonale veranderingen.<sup>4</sup> Het is niet volledig bekend welke mechanismen verantwoordelijk zijn voor de progressie van paroxysmaal AF met korte aritmische episoden naar persistent en uiteindelijk langdurig persistent atriumfibrilleren.<sup>5,6</sup> Het is aannemelijk dat structurele atriale remodeling die leidt tot atriale pathologie medeverantwoordelijk is voor het ontstaan van cardiovasculaire events. Dit verklaart de relatie tussen het risico op cerebrovasculaire aandoeningen (CVA) en AF progressie. Zo hebben Glotzer e.a. aangetoond dat patiënten met een relatief hogere AF burden, zoals wordt gezien bij AF progressie, meer risico hebben op een CVA.<sup>7</sup>

**Hoofdstuk 3** beschrijft de resultaten van peroperatief atriale high-density mapping bij patiënten met persistent AF. De studie onderzoekt het effect van acute verandering van atriale druk, ofwel *stretch* op de intra-atriale geleidingseigenschappen (cycluslengte, geleidingssnelheid en patroon, mate van conductie blok) bij patiënten met langdurig, persistent AF die een openhartoperatie ondergaan. In totaal werden 9 patiënten, die gepland waren voor een openhartoperatie met concomitante radiofrequente (RF) gemodificeerde maze-chirurgie, peroperatief onderzocht met bi-atriale high density mapping met behulp van epicardiale multielectrode arrays. Verandering van atriale druk en omvang werd gestuurd door de instelling van extracorporele circulatie te wijzigen. Afname van de atriale omvang (dedilatatie) resulteerde in een significante afname van de gemiddelde cycluslengte (7% en 9% van linker- respectievelijk rechter atrium) en afname van conductieblok. Het effect van dilatatie was een significante toename van gemiddelde cycluslengte en percentage conductieblok. Dit is de eerste studie bij mensen met langdurig, persistent AF die aantoont dat de mate van intra-atriale conductieblok afneemt bij acute dedilatatie. Verschillende experimentele dierstudies laten een vergelijkbaar effect zien van stretch op de atriale effectieve refractaire periode.<sup>8,9</sup> Solti et al. daarentegen beschrijven in een onderzoek bij honden dat atriale dilatatie een afname van atriale effectieve refractaire periode veroorzaakt en juist een toename van de atriale geleidingstijden. Deze studie heeft gebruik gemaakt van balloninflatie om atriale stretch te genereren.<sup>10</sup> De gevoeligheid van het atrium voor aritmieën werd significant groter na ballondilatatie (zowel spontane aritmieën als geïnduceerde aritmieën bij extrastimulus testen of burst pacing). Alhoewel er geen verklarend mechanisme is voor deze verschillende bevindingen moet worden opgemerkt dat onze patiënten bekend waren met langdurig persistent AF terwijl de laatst beschreven studie kunstmatig AF en atriale flutters hebben geïnduceerd bij gezonde honden. Diverse factoren, waaronder verschil in weefselkarakteristieken van de atriale wand en ongelijke verdeling van atriale stretch kunnen een rol spelen bij de discrepantie tussen de

experimentele studies en patiëntendata. Een overeenkomstige conclusie is de verhoogde gevoeligheid voor AF tijdens acute toename van atriale druk.

Het blijft onduidelijk in welke mate herstel van atriale elektrische remodeling, het zogenaamde *reverse remodeling*, kan worden bereikt met afname van atriale druk en omvang, in het bijzonder bij patiënten met langdurig persistent AF. Vanuit therapeutisch oogpunt groeit de interesse in modificeerbare modulerende factoren zoals hypertensie, obstructieve slaapapnoe, obesitas, hartklep-aandoeningen, hartfalen, ischemie, endocriene afwijkingen en inflammatie.<sup>11,12</sup> Het is alom bekend dat modificatie van deze risicofactoren en behandeling van onderliggende ziektes een significant verschil kunnen maken in uitkomst van chirurgische- en catheterablatie van AF.

### AF en acuut coronair syndroom

AF is een veel voorkomende complicatie van een acuut myocard infarct (MI) met een incidentie van 5-22%. New onset AF komt zoals verwacht meer voor bij hogere leeftijd, uitgebreide myocardiale schade, hogere Killip-klasse en cardiogene shock.<sup>13,14</sup>

De prognostische impact van AF ten tijde van een acuut myocard infarct is controversieel. Er zijn studies die een onafhankelijk negatief voorspellend effect op mortaliteit beschrijven terwijl andere studies deze associatie niet kunnen bevestigen.<sup>15</sup> New onset AF heeft een negatieve invloed op de klinische uitkomst van MI-patiënten vanwege onder meer de negatieve hemodynamische effecten zoals verlies van atriale contractiliteit, hoge ventriculaire volgfrequentie, verlies van atrioventriculaire synchroniteit en irregulaire ventriculaire intervallen die leiden tot een afname van de cardiac output.<sup>16</sup>

Recente meta-analyses en systematic review, in totaal 43 studies en 278 854 patiënten, laten zien dat de mortaliteit, zowel korte termijn (30 dagen tot 1 jaar) als lange termijn (> 1 jaar), van een acuut MI met ten minste 40% is verhoogd wanneer er sprake is van AF, ongeacht het type AF (pre existent of new onset). Het verhoogde risico geldt zowel voor plotse dood als niet plotse, cardiale sterfte. Zelfs na correctie voor confounders zoals leeftijd, diabetes mellitus, hypertensie, eerder MI, hartfalen en coronaire revascularisatie, is er sprake van een slechtere prognose bij patiënten met new onset AF.<sup>17</sup>

In **Hoofdstuk 2** wordt de associatie beschreven tussen mortaliteit en het moment dat AF optreedt bij patiënten met een ST elevatie MI die een primaire percutane coronaire interventie (PCI) ondergaan. In deze substudie van een multicenter, gerandomiseerde trial waren de electrocardiografische gegevens voorhanden van 1623 ST-elevatie

MI-patiënten voorafgaand aan primaire PCI. In deze groep hadden 53 (3.3%) patiënten AF. Voorts waren de elektrocardiografische gegevens aanwezig van 1728 patiënten na primaire PCI. In deze groep hadden 52 (3.0%) patiënten AF. De volgende factoren waren geassocieerd met AF: hogere leeftijd, Killip klasse >1, TIMI 0 flow voorafgaand aan PCI, onsuccesvolle reperfusie en occlusie van de rechter coronair arterie. Multivariate analyse toonde aan dat de mortaliteit significant hoger was bij patiënten met AF ná PCI en niet bij patiënten met AF voorafgaand aan PCI.

De pathogenese van AF als complicatie van het acute MI is multifactorieel. Verschillende factoren worden verantwoordelijk geacht voor de initiatie van AF in de setting van een MI waaronder hemodynamische instabiliteit, atriale ischemie, overvloedige catecholamine uitstoot, elektrolyt stoornis, hartfalen, ventriculaire remodeling, acute hypoxie, pericarditis en inflammatie. Zowel een combinatie van factoren als afzonderlijk kunnen AF initiëren.<sup>18</sup>

Ondanks de afname van incidentie en prevalentie van AF door verbeterde reperfusie technieken wordt het ontstaan van AF in de setting van een acuut MI en de prognostische impact nog steeds bepaald door zowel de co morbiditeit als de omvang en het beloop van het MI.

### Single shot ablatie voor AF, de PVAC catheter

Catheterablatie voor AF is uitgegroeid tot een goed alternatief voor antiaritmische medicatie (AAD) voor patiënten die symptomatisch blijven ondanks AAD en zelfs als eerstelijns therapie voor bepaalde AF-patiënten.<sup>19,20</sup> Hoewel er tegenwoordig een veelheid bestaat aan ablatietechnieken om AF te behandelen blijft de hoeksteen van de behandeling de elektrische disconnectie van alle PVs. De laatste jaren zijn nieuwe ablatiemethoden ontwikkeld, waaronder de zogenaamde "single shot devices", met als doel pulmonaal vene isolatie (PVI) eenvoudiger en sneller te laten verlopen. In hoofdstuk 1, de introductie, wordt een gedetailleerd overzicht gegeven van de technieken die tegenwoordig beschikbaar zijn. In hoofdstuk 4 en 5 worden de resultaten beschreven van de circulaire multi-electrode PV-ablatie catheter (PVAC; Medtronic Inc, Minneapolis, MN, USA).

In **Hoofdstuk 4** presenteren we de 12 maanden follow-up, waaronder effectiviteit en veiligheids uitkomsten, van de eerste generatie PVAC catheter. Er werden 102 patiënten geïncludeerd (90 paroxysmaal AF en 12 persisterend AF) met een historie van AF gedurende gemiddeld 9.3±7.5 jaar (range 1.5-25). De gemiddelde fluoroscopie tijd voor de PVAC procedure bedroeg 17±12 min (mediaan 16, range 12-33) en de gemiddelde totale proceduretijd was 139±38 (mediaan 135, 115-172). Bij 8 patiënten met persisterend AF werd additionele ablatie verricht, om

defragmentatie van septum en linker atrium posteriorwand te verkrijgen en bij 5 patiënten werd additionele ablatie met een conventionele RF ablatie-catheter verricht. Na een gemiddelde follow-up duur van 12.2 ± 3.9 maanden waren 62 van de 102 (60.8%) patiënten blijvend in sinusritme, zonder AAD. Er waren geen procedurele complicaties in deze studie.

De effectiviteit van de eerste generatie PVAC catheter in onze studie is enigszins lager in vergelijking met andere studies. Dit zou gerelateerd kunnen zijn aan het feit dat de studiepoupopatie een ongeselecteerde groep patiënten betrof ('real life data') waaronder paroxysmaal en persisterend AF patiënten met relatief uitgebreid substraat voor AF. Daarnaast kan de leercurve een rol gespeeld hebben aangezien dit een van de eerste PVAC-studies betreft.<sup>21,22,23,24</sup>

**Hoofdstuk 5** vergelijkt de uitkomst van pulmonaal vene isolatie door middel van PVAC-ablatie met conventionele point-by-point ablatie. In deze prospectieve, niet-gerandomiseerde observationele studie werd de effectiviteit van de eerste generatie PVAC ablatie bij 89 patiënten vergeleken met 96 patiënten met paroxysmaal AF die een conventionele ablatieprocedure ondergingen. Na een follow-up duur van 12 maanden was 82% van de PVAC-patiënten en 80% van de conventioneel behandelde patiënten vrij van AF zonder anti-aritmica (p=0.989). De gemiddelde proceduretijd was significant korter voor de PVAC-ablatie procedures (133.25 ± 37.99 min versus 171.73 ± 2.87, p<0.001). Er waren geen belangrijke ongewenste effecten in één van de groepen.

Andere studies beschrijven een vergelijkbaar 12-maanden-uitkomst van PVAC ablatie bij paroxysmaal AF.<sup>24,25</sup> De langetermijnuitkomst van PVAC ablatie laat een soortgelijk resultaat zien als conventionele PVI.<sup>26,27</sup> Zoals in hoofdstuk 1 van dit proefschrift staat beschreven ontstond in 2011 reden tot zorg toen een verhoogde incidentie van asymptomatische cerebrale microembolieën werd gerapporteerd bij gebruik van phased RF in vergelijking met geïrrigeerde tip catheter RF ablatie.<sup>28,29</sup> Dit is de reden dat diverse verbeteringen werden aangebracht in het design van de originele PVAC catheter die hebben geresulteerd in de PVAC gold catheter (PVAC; Medtronic Inc, Minneapolis, MN, USA). Deze nieuwe generatie catheter bevat 9 in plaats van 10 elektroden om de mogelijkheid van een elektrische kortsluiting tussen overlappende elektroden 1 en 10 te verhinderen die de vermoedelijke hoofdoorzaak was van de micro-embolieën. Tevens werden de platinum elektroden vervangen door gouden elektroden waarvan de thermische geleidingseigenschappen beter zijn dan die van platinum. Hierdoor kan snellere koeling worden verkregen, betere temperatuurregulatie en kan weefsel oververhitting worden voorkomen. Daarnaast werd een 20 graden-voorwaardse kanteling aangebracht aan het distale segment van de

catheter om optimaal, uniforme electrode-weefsel contact te verkrijgen met het PV antrum.<sup>30,31</sup>

De eerste ervaringen met de PVAC gold zijn veelbelovend waarbij een vergelijkbaar 12 maanden succes wordt beschreven in vergelijking met de eerste generatie PVAC catheter maar kortere RF-applicatietijd en kortere fluoroscopietijd.<sup>32,33</sup>

In 2016 kwam de PRECISION GOLD trial met resultaten van cerebrale magnetische resonantie (MRI) onderzoek bij 51 patiënten die 48 uur voorafgaand en 24 uur na de ablatie ingreep werd verricht. Het resultaat was een lage incidentie van asymptomatische cerebrale embolieën (2.1%) bij ablatie met de PVAC gold catheter in combinatie met ononderbroken orale anticoagulantia en heparinisatie met *activating clotting time* (ACT)  $\geq$  350 seconden.<sup>34</sup> Echter, recent gerandomiseerd onderzoek heeft aangetoond dat de incidentie van microembolieën nog steeds hoger is bij PVAC Gold dan bij conventionele geïrrigeerde tip catheterablatie.<sup>35</sup>

Met het oog op het stijgende aantal AF-patiënten die voor invasieve therapie in aanmerking komen en het resultaat van de STAR AF trial, die het belang aangeeft van isolatie van PVs zelfs bij patiënten met persisterend AF, zal de vraag naar technieken die zich primair richten op PV isolatie steeds verder stijgen.<sup>36</sup>

Het “single shot” device dat momenteel het meest wordt gebruikt is de cryoballoon. Zowel de cryo ablatie als de PVAC-ablatie hebben hun dienst bewezen waar het gaat om reductie van proceduretijd. Ze vereisen minder ervaring van de operateur in vergelijking met point-by-point ablatie. De belangrijkste tekortkoming van het PVAC-systeem is de beperkte mappingsmogelijkheden. Zo kan bijvoorbeeld tijdens RF-applicatie geen EGM-registratie worden weergegeven, waardoor het verdwijnen van PV-potentialen niet *real time* kan worden weergegeven. Anderzijds zijn er aanwijzingen dat ablatieprocedures met de PVAC Gold catheter lagere fluoroscopie- en proceduretijden hebben, vergeleken met cryo ablatie.<sup>32,33</sup>

Concluderend kan men zeggen dat de immer groeiende vraag naar AF ablatietherapie vereist dat de technieken sneller, veiliger en meer kosteneffectief worden. Er zijn zorgen omtrent de verhoogde incidentie van asymptomatische cerebrale micro-embolieën van de PVAC Gold catheter waarvoor gepaste oplossingen dienen te komen alvorens op grote schaal gebruik gemaakt gaat worden van dit device. De resultaten van lopende, prospectieve, gerandomiseerde trials moeten worden afgewacht. Mits het een veilige techniek blijkt is phased multielectrode RF-ablatie een potentieel veelbelovende technologie, die voor paroxysmaal AF-patiënten een tijd-efficiënte methode van PVI betekent.

## Focale atriale tachycardie

Vroeger dacht men dat het mechanisme van focale atriale tachycardie (AT) uitsluitend berustte op versterkte automatie. Later werd duidelijk dat met name de mechanismen *triggered activity* en *micro re-entry* verantwoordelijk zijn voor de aritmogenese van focale AT. Focale AT wordt gedefinieerd als een atriale aritmie, afkomstig uit één gebied (focus kleiner dan 2 cm<sup>2</sup>) met een activatiegolf die zich centrifugaal verspreidt over de rest van de atria.<sup>37,38</sup>

Focale AT kan worden uitgelokt door situaties waarbij er sprake is versterkte atriale stretch zoals hypertensie of cardiomyopathie, als reactie op toxische stoffen of bijvoorbeeld hypoxemie. Een specifieke onophoudelijke vorm van focale AT wordt gezien bij post AF ablatiepatiënten. Met name lineaire ablatie en ablatie van complex gefragmenteerde atriale activiteit zijn geassocieerd met deze vorm van sterk symptomatische focale AT die vaak medicatie resistent is.

Wanneer er geen sprake is van structureel hartlijden of eerdere ablatiebehandeling heeft focale AT een goede prognose en is toegankelijk voor ablatietherapie. Elektroanatomisch mappen en ableren van ATs kan echter erg complex zijn. Zo zijn ATs uit de interatriale septum regio, waaronder de non coronary cusp van de aorta (NCC) vaak een uitdaging om te ableren vanwege de anatomische relatie met belangrijke structuren in de paraseptale regio waaronder de bundel van his.

In **Hoofdstuk 6** wordt de ervaring beschreven van het mappen en ableren van AT met een oorsprong in de sinus aorta en NCC en een uitgebreid literatuuroverzicht gegeven van focale AT uit dit gebied. Elektrofysiologisch onderzoek werd verricht bij 7 patiënten (4 mannen; leeftijd  $40 \pm 9$  jaar, range 28-51 jaar) met medicamenteus resistente AT. Een oorsprong nabij de bundel van his, parahisian, werd bevestigd bij alle patiënten na initieel mappen van het rechter atrium. De tweede stap was het mappen van het linker atrium en vervolgens de sinus aorta en NCC wanneer linker- en rechter atrium mapping niet de succesvolle ablatie localisatie kon identificeren of wanneer RF-applicaties niet resulteerden in het termineren van de ritmestoornis. Mappen van de NCC liet zien dat de vroegste atriale activatie tijdens tachycardie  $38 \pm 14$  msec (range 17-56 msec) voor de onset van de P-top werd gevonden. De vroegste activatie in de NCC was vroeger dan de vroegste activatie in het rechter en linker atrium bij alle patiënten. De tachycardie werd succesvol beëindigd middels RF binnen  $10 \pm 6$  sec (range 2-16 sec) zonder complicaties. Alle patiënten waren vrij van symptomen gedurende een follow up van  $16 \pm 9$  maanden.

NCC gerelateerde AT is moeilijk te herkennen op het oppervlakte ECG. De beschrijving van de p top morfologie is niet consistent in de verschillende artikelen. De meest

typische morfologie is een voornamelijk negatieve p top in de inferior afleidingen, bifasisch in de rechts precordiale afleidingen V1 en V2 (met name negatief-positief). NCC AT heeft typisch een positieve p top in afleidingen I en AVL met een locale A/V ratio van  $>1$  (in tegenstelling tot de linker coronary cusp welke een negatief-positieve P top deflectie vertoont met een locale A/V ratio  $\leq 1$ ).<sup>39,40</sup>

Diverse algoritmes zijn beschreven die de origine van de focale AT bepalen.<sup>41,42</sup> De diagnostische betrouwbaarheid is echter beperkt voor foci nabij het interatriale septum en NCC. De P-top morfologie en polariteit kan sterk beïnvloed worden door onder meer de centrale positie van dit gebied in het hart, cardiale rotatie en variatie in habitus. Ablatie van focale AT vereist een 3D mappingsysteem. De huidige 3D mapping systemen, gecombineerd met diagnostische multi-elektrode catheters, maken het mogelijk gedurende AT automatisch een hoge densiteit 3-dimensionele elektro-anatomische map te creëren. De technieken geven een gedetailleerd inzicht in het AT mechanisme en faciliteert het spoedig mappen en ableren van deze ATs. Desondanks kunnen de huidige multipolaire mapping catheters niet gebruikt worden voor het mappen in de sinus van Valsalva en dienen conventionele mapping en ablatiecatheters hiervoor te worden gebruikt. Alhoewel er geen gerandomiseerde studies bestaan, kunnen we op basis van onze ervaring en de aanwezige literatuur stellen dat nieuwe technieken zoals image integration en intracardiale echocardiografie bijdragen aan veiligheid en effectiviteit van mappen en ableren in deze regio.

### Atriumfibrilleren- chirurgische benadering

De maze-procedure, als chirurgische behandeling van AF, werd in 1987 door Dr Cox geïntroduceerd. Deze procedure, waarbij een patroon van multipole bi-atriale laesies wordt gemaakt, heeft als doel het onderbreken van atriale macro-re-entry circuits waarbij een soort elektrisch 'doolhof'(engels: 'maze') wordt gecreëerd waardoor het atrium niet meer in staat is te fibrilleren. Alhoewel de ingreep zeer succesvol is in de zin van uitblijven van AF en zelfs het voorkomen van herseninfarct op de lange termijn, is het technisch gezien een moeilijke ingreep die een thoracotomie vereist, hartlong-machine en een patroon van uitgebreide atriale incisies en hechtingen.<sup>43,44</sup>

In 2002 werd de Cox-maze IV procedure geïntroduceerd, waarbij de traditionele bi-atriale incisies, het zogenaamde snijden en hechten ("cut-and-sew"), werd vervangen door epicardiale lineaire ablatielijnen. Deze ablatielijnen werden verricht met bipolaire RF devices (of minder gebruikelijk cryothermie of microgolf energie). Doorgaans wordt tijdens dezelfde ingreep excisie van het linker hartoor (LAA) verricht. Alhoewel de Cox-maze IV kan worden verricht via een beperkte rechtzijdige intercostale thoracotomie, is nog steeds een hartlongmachine vereist.<sup>45,46</sup>

In 2005 werd een belangrijke stap gezet op het gebied van AF chirurgie met de introductie van de minimaal invasieve thoroscopische techniek waarbij toegang wordt verkregen tot het gehele atriale epicard bij een kloppend hart. Er bestaat een variëteit aan ablatiestrategieën waaronder isolatie van alle PVs als één blok, de zgn 'box lesion' danwel separaat. Daarnaast kan ablatie worden verricht van ganglion plexi met of zonder additionele ablatie lijnen.<sup>47</sup>

Het veel gebruikte bi-directionele bipolaire RF-ablatie device voor chirurgische AF ablatie bestaat uit een tang, die RF energie afgeeft en wordt aangebracht op twee tegenoverliggende delen van atriaal weefsel. De energie verloopt door het weefsel tussen de twee poten van de tang. Transmuraliteit is bereikt, wanneer een daling van de geleiding zichtbaar is. Doordat de RF-energie wordt afgegeven tussen twee dicht bij elkaar gelegen elektroden, die zijn ingebed in de bek van de tang, is de energie geconcentreerd en resulteert in discrete laesies. Juist doordat deze energie gebundeld is tussen de bek van de tang, is het risico op bijkomende cardiale of extracardiale schade beperkt. Het nadeel van deze devices is dat uitsluitend atriaal weefsel kan worden ge-ableerd dat door de tang geklemd kan worden. Hierdoor is het aantal potentiële laesies beperkt, met name bij een procedure zonder hartlong-machine. Er zijn vaak multipole applicaties nodig om *entrance* en *exit* block te verkrijgen. De klemdevices blijken niet capabel te zijn in het compleet ableren van rechter- en linker atrium isthmus, waardoor het noodzakelijk is om additionele ablatie met cryothermie of unipolaire of unidirectionele bipolaire RF-device te verrichten, om een complete Cox-maze III laesie set te verkrijgen.<sup>48</sup>

La Meir et al. beschrijven in een meta-analyse een succeskans van standalone thoroscopische AF chirurgie van 65-92% voor paroxysmaal AF en 67% tot 80% voor persisterend AF. Succes in dit kader is gedefinieerd als afwezigheid van AF episodes langer dan 30 seconden, zonder AAD na 12 maanden.<sup>49</sup> Er moet worden opgemerkt dat de geïnccludeerde studies niet omvangrijk waren (variërend van 14 tot 114 patiënten) en ritme follow-up bestond slechts uit intermitterend ECG of holter-monitoring.

Studies die standalone AF chirurgie vergelijken met catheterablatie zijn schaars. Een recente meta-analyse welke minimaal invasieve chirurgische AF chirurgie versus catheter ablatie voor AF beschrijft, suggereert dat chirurgie superieur is qua effectiviteit (vrij van recidief atriale aritmieën 78% vs 53%).<sup>50</sup> Daarentegen treden majeure complicaties significant vaker op bij chirurgisch behandelde patiënten (28% vs 8%). Hoewel de chirurgische PV-ablatie waarschijnlijk resulteert in meer transmuraliteit van de laesies, kan het verschil in effectiviteit in deze studies ook vooral gedreven zijn door patiëntselectie. De meeste patiënten die in deze studies waren

geïnccludeerd hadden een voorgeschiedenis van niet-geslaagde catheterablatie. Bovendien bestond de follow-up in de geïnccludeerde studies uit intermitterend monitoring.

**Hoofdstuk 7** van dit proefschrift beschrijft de resultaten van een gerandomiseerde studie die chirurgische AF ablatie vergelijkt met catheterablatie, waarbij gebruikt wordt gemaakt van continue hartritme monitoring (ILR). Er werden 50 patiënten gerandomiseerd (gemiddeld 57 jaar, 39 mannen) met symptomatisch paroxysmaal of persisterend AF naar hetzij minimaal invasieve thoroscopische PVI met LAA ligatie, hetzij punt bij punt radiofrequente PVI (catheterablatie). Een ILR werd geïmplanteerd voorafgaand aan de behandeling, om de pre-ablatie AF burden te bepalen. Na 6 maanden was de AF burden afgenomen met 15.5% (95% CI 9.7%-43.1%) in de chirurgische groep en 26.1% (95% CI 11.2%-59.6%) in de catheterablatie groep ( $p=0.375$ ). Vrijheid van AF, gedefinieerd als AF burden  $<0.5\%$ , na 6 maanden was 63% in de chirurgische groep versus 65% in de catheter groep ( $p=0.87$ ). Complicaties traden significant vaker op bij chirurgische patiënten 34.8% versus 11.1% in de catheterarm ( $p=0.046$ ). Concluderend kan gezegd worden dat de korte termijn uitkomst van catheterablatie en chirurgische AF ablatie vergelijkbaar is wat betreft effectiviteit, maar chirurgie is geassocieerd met significant meer complicaties.

Hoewel de omvang van de studie klein is, is de kracht van de studie onder meer het feit dat de patiënten geen eerdere ablatie hebben ondergaan. De populatie kan worden gezien als een 'real life' AF cohort. Wij realiseren ons dat de superioriteit van de chirurgische techniek, zoals voorgaande artikelen suggereren, gerelateerd kan zijn aan patiëntselectie; patiënten met diverse niet succesvolle endocardiale ablatie ingrepen in de voorgeschiedenis zijn wellicht meer gebaat bij een epicardiale poging.<sup>49</sup>

In het kader van de vaak voorkomende episodes van "silent AF" na een AF ablatie ingreep is follow-up met ILR de enige methode die een betrouwbaar resultaat kan geven wanneer men het studie eindpunt definieert als "vrijheid van AF".<sup>51</sup> Een belangrijk voordeel van een preoperatief geïmplanteerde ILR is dat symptomatische AF definitief kan worden bevestigd. Pre-operatieve AF burden is noodzakelijk om een vergelijking te maken met de postoperatieve situatie.

### Recidief atriale aritmieën na AF chirurgie

Met de verbeterde technieken van minimaal invasieve AF chirurgie is deze behandeling effectiever en veiliger geworden en daarmee geschikt voor gebruik op grotere schaal. Desalniettemin zijn de vroege en late recidieven van aritmieën een reden tot zorg.

**Hoofdstuk 8** bestudeert de elektrofysiologische karakteristieken van recidief atriale aritmieën na chirurgische AF ablatie en de langetermijn uitkomst na catheterablatie van deze aritmieën. Er werden 23 patiënten geïnccludeerd die een EP studie ondergingen,  $378 \pm 282$  dagen na AF chirurgie, vanwege recidief symptomatische atriale aritmieën. Chirurgische ablatie bestond uit minimaal invasieve thoroscopische PVI met een geïrrigeerde bipolaire RF-ablatie klemdevice (Cardioblade, Medtronic, USA) en LAA ligatie. Peroperatief werden de PVs gecontroleerd op entrance block en opnieuw getest op reconnectie na 30 minuten. De recidieven van aritmieën bestonden uit paroxysmaal en persisterend AF bij 20 patiënten, 2 patiënten hadden een combinatie van AF en AT en 1 patiënt had een combinatie van AF en atriale flutter. Alle patiënten vertoonden PV reconnectie. ATs bleken te berusten op micro re-entry, PV gerelateerde AT en atriale flutter bleek een cavotricuspidale isthmus afhankelijke flutter. Achttien van de 23 patiënten (78.3 %) waren vrij van atriale aritmieën na één catheterablatie procedure na een gemiddelde follow up periode van  $50 \pm 16$  maanden. Drie patiënten ondergingen een tweede catheter ablatie behandeling, vanwege recidief AF en macro re-entry linker atrium flutter. Uiteindelijk waren 20 van de 23 patiënten (87%) vrij van atriale aritmieën na gemiddeld  $1.1 \pm 0.3$  catheterablatie procedures. Deze studie toont aan dat recidief atriale aritmieën na chirurgische AF ablatie voornamelijk berusten op reconnectie van chirurgische ablatielijnen en dat complementeren van deze hiaten met catheter ablatie, op een gefaseerde wijze, zeer effectief is.

Ondanks het bereiken van acuut exit block en entrance block na ablatie met een bipolair epicardiaal RF-device blijkt PV reconnectie toch de meest voorkomende bevinding bij patiënten met recidief AF. Eerdere studies beschrijven een vergelijkbare uitkomst.<sup>52,53,54</sup> PV reconnectie ontstaat vermoedelijk tijdens het rijpingsproces. Vaak ziet men bij EP studies verlengde atrium-PV geleidingstijden, hetgeen past bij beschadigd myocardweefsel dat nog wel in staat is te geleiden. Daartegenover moeten we bekennen dat de studiepopulatie bestaat uit patiënten met beperkt AF substraat en derhalve het risico op macro re-entry tachycardieën buiten de PVs lager is. Tumello et al benadrukken de noodzaak voor een adequate laesie set bij de initiële chirurgische procedure.<sup>55</sup> De studie analyseerde 36 patiënten met recidief atriale aritmieën na chirurgische ablatie met verschillende energiebronnen en laesie sets. Voornamelijk de patiënten met uitgebreid substraat en persisterend AF die waren behandeld met uitsluitend PV isolatie liepen het risico op het ontwikkelen van perimitraal annulus gerelateerde macro re-entry tachycardieën. De auteurs concluderen dat het uiterst onwenselijk is wanneer een gesimplificeerde maze ingreep, ofschoon deze curatief voor AF kan zijn, patiënten vatbaar maakt voor macror-entry tachycardieën. Enerzijds moet men waken voor onderbehandeling bij deze patiëntencategorie, anderzijds is het alom bekend dat mitraal isthmus ablatie



zeer lastig kan zijn bij thoracoscopische epicardiale procedures. Een gefaseerde endocardiale of hybride benadering kan een goed alternatief zijn.

### Ritme follow-up na AF ablatie

Ondanks het feit dat zowel catheterablatie als chirurgische ablatie effectieve therapieën zijn gebleken voor AF en er momenteel een enorme hoeveelheid aan AF studies bestaan, is er geen consensus over de definitie van succes of follow-up strategieën. Symptomen zijn nog altijd de belangrijkste reden om catheter- of chirurgische ablatie te verrichten. Daarentegen wordt het aantal recidief aritmieën sterk onderschat, wanneer men uitsluitend vertrouwt op de perceptie van AF aangegeven door patiënten. Zelfs bij patiënten met sterk symptomatisch AF blijkt dat minstens de helft van alle AF episodes symptomeloos verloopt.<sup>56</sup> Verma et al. hebben laten zien middels ILR monitoring dat de ratio asymptomatische/symptomatische AF episodes toeneemt van 1.1 voorafgaand tot 3.7 ná ablatie. Mogelijke verklaring voor dit effect kan zijn de kortere duur van aritmische periodes na ablatie, lagere hartfrequentie of autonome modulatie.<sup>51</sup> Louter vertrouwen op symptomen geeft een onderschatting van de werkelijke AF burden aangezien 12% van de patiënten alleen asymptomatische recidieven heeft. Een andere studie beschrijft dat zelfs 44% van de post ablatie AF episodes asymptomatisch verloopt.<sup>57</sup>

In **hoofdstuk 9** beschrijven we de evaluatie van een extern hartritme monitoring device, het *AF alarm*, bij patiënten die een chirurgische AF ablatie hebben ondergaan. Drieëndertig patiënten, leeftijd  $59.4 \pm 8.9$  jaar (range 38-75 jaar) met paroxysmaal of persisterend AF met een gemiddelde duur van  $9.4 \pm 7.1$  jaar sinds de diagnose AF, ondergingen minimaal invasieve thoracoscopische PVI en LAA ligatie. Het AF-alarm werd aangebracht gedurende  $128 \pm 42.5$  uur (range 49-191 uur) tijdens een periode van 8-15 dagen. Behoudens het AF-alarm werd tevens een serie ECGs en 24-48 uur holtermonitoring verricht. Patiënten werden verzocht het device manueel te activeren wanneer ze een symptomatische episode ervoeren. Het alarm geeft een visueel en auditief teken wanneer detectie van AF plaatsvindt en legt ECG strips vast op het moment van AF begin en einde. Zowel automatische als manuele triggers resulteren in digitale opslag van de ECGs. Na een gemiddelde follow-up duur van  $15 \pm 5.3$  maanden geeft de combinatie van ECG, holter en AF-alarm aan dat het succespercentage van de ingreep 69% bedraagt (gedefinieerd als sustained sinusritme). De combinatie van uitsluitend holter en ECG resulteert in een succespercentage van 84% ( $p < 0.05$ ). Vijf patiënten (15%) hadden diverse manueel geactiveerde episodes, waarbij sprake bleek van sinusritme. Oversensing van het AF-alarm trad op bij 9% van de patiënten. We kunnen concluderen dat externe ritmemonitoring met het AF-alarm na AF-chirurgie goed toepasbaar is en resulteert in adequatere detectie van recidief aritmieën vergeleken met standaard follow-up.

Zonder gebruik van continue monitoring na ablatie, dient men uiterst voorzichtig te zijn met opmerkingen als “AF is verdwenen”, “afwezig” of “genezen”. Zoals eerder vermeld, de vrijheid van AF gerelateerde symptomen wordt gebruikt als surrogaat eindpunt van vrijheid van AF en als ablatie succes. Vanzelfsprekend is ook een externe eventrecorder niet in staat om 100% van de aritmieën te detecteren. De voornaamste beperking van het systeem is dat deze devices alleen getolereerd worden door zeer gemotiveerde patiënten gedurende een relatief korte periode. Naast het detecteren van postoperatieve aritmieën is monitoring ook zeer relevant voor het vastleggen van palpatatieklachten welke niet berusten op aritmieën. Israel et al. beschrijven in hun studie met pacemakerpatiënten dat 40% van de patiënten symptomen van AF rapporteert die niet in overeenstemming zijn met het ECG of pacemaker interrogatie gegevens.<sup>58</sup>

De ILR is een subcutaan device die continue monitoring van aritmieën uitvoert tot 3 jaar na implantatie. AF-detectie door het device berust op registreren van incoherentie van RR-intervallen gedurende 2 minuten periode, omdat pp intervallen niet betrouwbaar gesensed kunnen worden. De XPECT studie evalueerde de Reveal XT intracardiale monitor, waaruit blijkt dat AF episodes in 98.5% adequaat werden beoordeeld.<sup>59</sup> Niettemin is de foutpositieve AF detectie een zorgelijk gegeven. Het leeuwendeel van de onterechte AF detectie episodes in de ILRs worden veroorzaakt door runs van atriale ectopieën met irregulair koppelingsinterval, sick sinus en sinus aritmieën. De laatste generatie loop recorder (Reveal Linq, Medtronic) maakt gebruik van een geavanceerd algoritme waarin ook de registratie van een p top tussen 2 RR complexen wordt meegenomen om het aantal incorrecte AF registraties te reduceren. Recente studies bevestigen dat het percentage foutpositieve AF-detectie episodes significant lager is vergeleken met oudere versies van het device. De sensitiviteit, specificiteit, positie voorspellende waarde en negatief voorspellende waarde voor identificeren van AF bedragen respectievelijk 98.4%, 99.5%, 97.2% en 99.7%.<sup>60</sup>

Het gebruik van ILRs biedt nieuwe mogelijkheden voor het monitoren van AF-ablatie-resultaat, voor wetenschappelijke doeleinden en niettemin voor het selecteren van patiënten voor een ablatie ingreep. Evenwel is verder onderzoek noodzakelijk om de exacte waarde van ILR voor AF behandeling te bepalen voordat officiële aanbevelingen kunnen worden gegeven.

### Conclusie

De resultaten van dit onderzoek geven een nieuw inzicht in het pathofysiologische mechanisme, invasieve behandeling en follow-up methoden van patiënten met complexe atriale aritmieën, in het bijzonder van AF. AF representeert een spectrum van aritmieën met een grote variatie aan onderliggende ziektes. Kennis over het



onderliggende mechanisme bij iedere individuele patiënt met AF is essentieel voor het bepalen van de meest passende behandeling. De uitkomst van catheterablatie - voor de grote groep patiënten met paroxysmaal AF en beperkt substraat - middels een zogenaamde 'single shot' percutane ablatietechniek is een veelbelovende behandeling. Daarentegen vereist de behandeling van patiënten met uitgebreid substraat een aanpak op maat waarbij elektrofysiologen en chirurgen samenwerken. Daarnaast resulteren geïntegreerde AF-zorgmodellen in een verbetering van AF-behandeling en overleving van AF-patiënten.

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## Curriculum Vitae

Rypko Joost Beukema is op 17 juni 1975 geboren in Groningen. In 1993 behaalde hij zijn VWO diploma aan het Hogeland College te Warffum. Vervolgens heeft hij een jaar *English Literature and Culture* gestudeerd in Bournemouth (GB) waarna hij aan de studie geneeskunde aan de Rijks Universiteit van Groningen is begonnen. Na het behalen van zijn artsdiploma is hij gedurende anderhalf jaar gaan werken als junior- en later senior house officer General Medicine in The Princess Royal Hospital, Telford (GB). Tijdens het werken op de hartbewaking onder leiding van Dr M. Heber werd Rypko gegrepen door het vak cardiologie. Na het engelse avontuur werd hij in 2004 aangenomen als arts-assistent cardiologie in de Isala klinieken, Zwolle. Voorts werd hij in 2006 aangenomen voor de opleiding tot cardioloog in de Isala klinieken (Dr J.C.A. Hoorntje, Dr A.W.J. van 't Hof, Dr A.R. Ramdat Misier). Al vroeg in de opleiding is Rypko betrokken bij wetenschappelijk onderzoek in de klinische elektrofysiologie onder supervisie van Dr A. Elvan. Na het B-jaar cardiologie in het Deventer ziekenhuis (Dr J. van Wijngaarden) werd naast de opleiding tot cardioloog de start gemaakt met dit promotieonderzoek. In 2012 rondde hij de opleiding tot cardioloog af en werd aansluitend aangenomen voor een fellowship elektrofysiologie in de Isala klinieken. Sinds 2014 is hij werkzaam als cardioloog elektrofysioloog in het Radboudumc te Nijmegen en is in 2016 toegetreden tot de staf. Rypko is tevens nauw betrokken bij het onderwijs als docent voor geneeskunde studenten van de Radboud Universiteit Nijmegen.

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*Under review*