Evolution and technological advances in ablation of complex atrial and ventricular arrhythmias

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EVOLUTION AND TECHNOLOGICAL ADVANCES IN ABLATION OF COMPLEX ATRIAL AND VENTRICULAR ARRHYTHMIAS

MICHAEL WOLF

Evolution and technological advances in ablation of
complex atrial and ventricular arrhythmias.

Michael Wolf

2020

Evolution and technological advances in ablation of complex atrial and ventricular arrhythmias.

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Maastricht, op gezag van de Rector Magnificus,
Prof. dr. Rianne M. Letschert,
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op vrijdag 2 oktober 2020 om 10:00 uur

door

Michael Wolf

geboren op 13 januari 1983 te Lier

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Prof. dr. P.G.A. Volders

To my incredible family

To all the extraordinary friends and colleagues I was lucky to meet all over the world

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1

Chapter 1

General introduction

Background

The interventional treatment of complex arrhythmias continues to grow in importance within our health care system.

ATRIAL FIBRILLATION AND ATRIAL TACHYCARDIA

Par excellence, atrial fibrillation (AF) is a serious public health problem because of its increasing incidence and prevalence in the aging population¹ and its association with elevated risks of cardiovascular events and death.²⁻⁷ Since the initial description of triggers in the pulmonary veins that initiate paroxysmal AF, catheter ablation of AF has become a common treatment to prevent recurrent AF. This is primarily achieved through isolation of the pulmonary veins, probably requiring complete isolation for full effectiveness.⁸ Over the past 20 years, the development of AF ablation technologies has been a constant effort to improve the pulmonary vein isolation (PVI) technique. The goal has been to improve patient outcomes, reducing the need for repeat procedures, to reduce procedure times and to increase the safety of the procedure. However, despite these advances and two decades of experience, long-term procedural success rates at curing AF are still suboptimal and may require repeat procedures or hybrid therapy with antiarrhythmic drugs to improve outcome. The reason for these suboptimal results is twofold; on one side the pathophysiological mechanism of AF is still not completely elucidated, and on the other side the ablation tools and techniques still fail to deliver durable and transmural ablation lesions. Even though fatal complications after AF ablation are rare, 2 – 3% will experience life threatening but usually manageable complications.⁹⁻¹¹

Pulmonary vein isolation

The cornerstone of ablation of AF is to achieve *durable* electrical isolation of the pulmonary veins.¹² Radiofrequency (RF) ablation, the most established ablation technique, aims to achieve PVI by applying circumferential contiguous and transmural point-by-point ablation lesions.¹³ Despite achieving nearly always acute procedural PVI, early and late PV reconnections are frequent and result in AF recurrences and the need for repeat ablation procedures. Indeed, with standard irrigated tip catheters only 65% of PV pairs remain isolated after adenosine-challenge during the index procedure¹⁴; only 72% of PV circles remain isolated at three months¹⁵ and the reported 1-year freedom of AF after a single procedure amounts 66%.¹⁶

Contact force-sensing catheters

Tip-tissue contact has shown to be an important factor in lesion creation and firm and stable contact force (CF) a prerequisite for durable, transmural RF lesions.¹⁷ As estimation of CF through tactile feedback or indirect measurements has been shown to be a poor predictor of actual tip-tissue contact, the utilization of catheters with embedded CF measuring sensors has led to improved outcomes and

fewer repeat procedures.¹⁸⁻²⁰ Both acute adenosine-proof PV isolation and one-year freedom of AF increased to 85%.^{14,21-22}

PART IA of this thesis investigated if the routine use of CF sensing catheters led to a better estimation of good catheter tip-tissue contact and improved PVI results when the experienced operator is blinded to the CF.

A protocol for pulmonary vein isolation with contiguous and optimized radiofrequency applications (PART IB)

In addition to CF, lesions depth and quality are determined by the ablation power and application time. The combination of these 3 factors in a logarithmic function (the Force-Power-Time Index or Ablation Index (AI)) was found to accurately describe the lesion depth.²³⁻²⁴ Therefore minimal AI targets would be more reliable in predicting lesion transmuralty and lesion durability. Other data showed that lesion contiguity was another important determinant in obtaining durable PVI.²⁵⁻²⁶

PART IB of this thesis consists of the development of a protocol aiming to improve the point-by-point RF PVI technique by combining strict criteria for both RF application contiguity and quality. In Chapter 3 we analysed optimal cut-off criteria for maximum distance between neighbouring RF applications and minimum AI targets associated with durable PV isolation.

Acute PV isolation and freedom of atrial tachyarrhythmia outcome results in paroxysmal AF

The analysed criteria for inter-tag distance and AI were incorporated in a new PVI protocol, aiming at delivering stable, relatively high-power, short-duration RF applications relatively close to the left atrial-PV junction. The acute and mid-term clinical results of this ‘CLOSE’ (Contiguous Lesion Optimized pre-Specified Encircling) protocol were prospectively analysed in Chapter 4 and 5.

Safety evaluation of the ‘CLOSE’ protocol

Although rare, atrio-oesophageal fistula (AEF) is one of the most feared complications of PVI because of its high fatality rate. Whereas the incidence of AEF is low (0.02 to 0.11%),¹² there is a high (2 to 30%) incidence of subclinical oesophageal or peri-oesophageal injury on endoscopy performed early after PVI procedures.²⁷⁻³⁸ It was established that the only risk factor associated with the occurrence of oesophageal injury or ulcer is intra-oesophageal temperature rise (ITR)²⁷ and that an oesophageal ulcer is a necessary precursor for AEF.²⁷

In Chapter 6, we assessed the incidence of oesophageal injury (and potential risk of AEF) by performing echo-endoscopy in those patients revealing ITR during PVI according ‘CLOSE’ protocol.

Long-term efficacy outcomes of CLOSE-PVI for paroxysmal AF

Even though acute isolation of all PVs is generally always achieved by RF point-by-point PVI, the likelihood of finding four isolated veins at repeat procedures for AF recurrence has been very low

(varying from 41% to as low as 0%).³⁹⁻⁵³ In Chapter 7 we evaluated the durability of PV isolation in patients undergoing repeat ablation for AF recurrence after undergoing an index CLOSE-PVI procedure. AF burden is a new and clinically relevant endpoint shown to be related to symptoms, heart failure and stroke.⁵⁴⁻⁵⁸ In Chapter 8 we studied the impact of CLOSE-PVI on AF burden before and during the first two years after CLOSE-PVI using insertable cardiac monitors.

Mapping and ablation of the left atrial substrate

In more complex atrial arrhythmias, such as (long-standing) persistent atrial fibrillation and atrial tachycardia, the pathophysiological mechanism involves the left atrial substrate.

Linear ablation lesions are often applied in ablation of macro-re-entrant atrial tachycardia to interrupt the re-entrant circuit, but also in ablation of (long-standing) persistent AF in order to replicate various aspects of the surgical MAZE procedure because of the high recurrence rate observed in these patients when only PVI is performed.¹² However, performing linear ablation is challenging. Indeed, bidirectional block across LA lines should be the ablation endpoint (HRS/EHRA/ECAS recommendation¹²) but this is achieved in a limited amount of patients⁵⁹⁻⁶³ and incomplete electrical block can have pro-arrhythmic consequences and cause atrial tachycardia recurrence.³⁻⁴ On the other hand, increased success in completing linear block is often associated with an increased complication rate from higher ablation power and a higher risk of steam pop, perforation, and tamponade.⁶⁴ In Chapter 9 we focused on the optimization of left atrial linear ablation by applying the same elements of the *CLOSE protocol*, i.e. stable applications respecting strict criteria for maximal inter-application distance and minimal AI values.

During persistent AF, multiple atrial wavelets and localized (focal or re-entrant) sources have been reported to contribute to the maintenance of AF.⁶⁵⁻⁶⁷ In the last few years, there has been progress in mapping AF sources and mechanisms. Recently, AF propagation maps based on *direct contact mapping* using a multi-electrode basket catheter and dedicated software (CARTOFINDER™, Biosense Webster Inc) were able to reliably and reproducibly identify *repetitive atrial activation patterns* (RAAPS) in the majority of persistent AF patients.⁶⁸⁻⁷² Nevertheless, because the basket catheter has a long inter-electrode distance and therefore can't reach stable contact with whole atrial surface, some regions and therefore some repetitive activation patterns were probably missed. In Chapter 10 we sought to evaluate a new mapping method to identify and characterize these RAAPS during on-going AF based upon the automated annotation of unipolar electrograms (Cartofinder software) directly obtained by sequential recordings with a regional high-density contact mapping catheter (PentaRay™, Biosense Webster Inc) covering the entire bi-atrial endocardial surface.

VENTRICULAR TACHYCARDIA

The second part of this thesis focuses on the evolution and technical advances in ablation of ventricular tachycardia, more specifically in ischemic cardiomyopathy patients.

Catheter ablation for sustained monomorphic ventricular tachycardia (VT) after myocardial infarction (MI) has emerged as an effective tool for the control of VT recurrence.⁷² Recently few studies have reported long-term follow-up data of VT ablation in ischemic cardiomyopathy (ICMP) patients, guided predominantly by activation and entrainment mapping of inducible and hemodynamically tolerated VTs.⁷³⁻⁷⁴ However, alternative strategies predominantly based on substrate modification have gained prominence. These strategies not only have the advantage of identifying targets for ablation in patients in whom VT is not inducible or not tolerated, but they may also provide a more comprehensive treatment of the substrate for present but also future VT, as they are not limited to inducible or “clinical” types of VT. Long-term results of substrate modification strategies have not been reported.⁷⁵⁻⁷⁷

In Chapter 11 we reported long-term outcomes after single and multiple ablation procedures with elimination of local abnormal ventricular activities (LAVA) for VT ablation in post-MI patients. We also investigated the impact of strategy variants to perform and achieve LAVA elimination, more specifically the added value of multi-electrode mapping catheters and of real-time integration of pre-procedural imaging with delayed enhancement-magnetic resonance imaging or multi-detector computed tomography in post-MI VT ablation.

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I

Part I

ABLATION OF ATRIAL FIBRILLATION AND ATRIAL TACHYCARDIA

Part IA

Conventional contact force-guided pulmonary vein
isolation

2

Chapter 2

Prospective comparison between contact force vs. non-contact force guided pulmonary vein isolation after the learning period with contact force catheters

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Abstract

Purpose: Use of online contact force (CF) measurement during circumferential pulmonary vein (PV) isolation (CPVI) for atrial fibrillation (AF) has demonstrated improvements in procedural parameters and mid-term clinical outcome. However it is unknown if experience gained with CF measuring catheters improves the efficacy of subsequent CPVI procedures performed without CF measurement.

Methods & results: This prospective trial compared procedural results of CPVI performed without a CF measuring catheter to a control group performed with a CF measuring catheter, by an operator with prior experience with CF technology. Thirty-six eligible paroxysmal (n=27) or persistent (n=9) AF patients were consecutively enrolled. Twelve patients underwent CPVI with the non-CF catheter (CF- group) in a recall period and 24 with the CF catheter (CF+ group). After the first circumferential lesion set the number of PV pairs requiring additional touch-up lesions to achieve electrical isolation was significantly less in the CF+ group (2 of 48 (4.2%) vs. 7 of 24 (29.2%) in the CF+ and CF- group respectively, $p=0.005$). The procedure time was significantly lower in the CF+ group (117.9 ± 23.3 min vs. 134.1 ± 25.3 min, $p=0.033$). RF and fluoroscopy time did not differ between groups (31.5 ± 7.1 min vs. 31.8 ± 7.0 min and 11.8 ± 5.6 min vs. 11.0 ± 5.8 min in the CF+ and the CF- group, respectively).

Conclusion: With the use of online CF measurement PV isolation is more frequently complete following the first circumferential lesion set. A previous learning period with direct CF feedback is not a substitute for real-time direct CF measurement to maintain this advantage.

Introduction

The clinical efficacy of pulmonary vein isolation (PVI) is limited by arrhythmia recurrences thought to occur predominantly because of reconnections of the isolated pulmonary veins (PVs) [1]. The reconnections in PV conduction indicate a lack of durable transmural lesion formation during the ablation procedure. A firm contact between the tissue and the catheter tip during radiofrequency (RF) ablation has shown to be an important determinant of lesion size and quality [2-8]. Estimation of contact through tactile feedback or indirect measurements have been shown to be poor predictors of actual tip-tissue contact [9-10]. As a result, preliminary studies showed a high variability of applied contact force (CF) both between operators and within individual operator when blinded to CF measurements during the ablation [11-12]. Incorporation of a CF measuring sensor at the distal tip of the ablation catheter provides precise and real-time CF feedback. Six non-randomized and one randomized small clinical studies compared circumferential PVI (CPVI) performed with CF sensing catheters to standard open-irrigated-tip catheters. The use of CF sensing catheters was associated with improvement of procedural parameters and outcome. A significant reduction in procedure time [9, 13-17] and RF ablation time [13-15], as well as of fluoroscopy time [9, 14-15] and acute PV reconnection rate [14, 18] were observed. Furthermore a mid-term clinical benefit with a significant reduction of the AF recurrence rate at 12 months after PVI was recently demonstrated in 2 studies [15-16].

Following promising preliminary clinical results in early 2012, the Thermocool® SmartTouch™ catheter (Biosense Webster, Diamond Bar, CA, USA) became available for clinical use in European countries and quickly found its way into routine clinical practice. Up to the enrollment in the current prospective registry, the single operator involved in this study gained 18 months experience performing more than 100 CPVI procedures using online CF measurement with the Thermocool® SmartTouch™ catheter. In September 2013 the Thermocool® SmartTouch™ catheter was temporarily withdrawn worldwide from clinical use due to technical defaults leading to safety concerns in a small number of catheters. In this transient recall period, the operator involved in the current study returned to the use of the irrigated-tip ablation catheter without CF measurement technology (NaviStar® Thermocool® ablation catheter).

The prospective comparison of procedural parameters of consecutive CPVI procedures performed without CF measurements during the recall period to a control group undergoing CPVI with CF measurement technology might offer further unique insights for several reasons. First, the recall setting allows the comparison of CPVI with or without CF measurements beyond the learning curve period of the new technique. Second, it is unknown if operators' experience with routine use of CF sensing catheters leads to a better estimation of good catheter tip-tissue contact and improved CPVI results with ablation catheters without CF measurement. Additionally, a registry allows the assessment of benefit of CF measurement technology in a real world clinical setting.

Methods

Patient population and study design

Patients were enrolled in a prospective, non-randomized, single-center registry from September 2013 to June 2014. The registry protocol was approved by the ethical committee of the University Hospital of Antwerp. All consecutive patients with symptomatic paroxysmal or persistent AF refractory to at least one antiarrhythmic drug, who underwent a first ablation procedure during the recall period from September to the beginning of December 2013 were included. CPVI in these patients was performed without CF measuring technology (NaviStar® Thermocool® ablation catheter) (CF- group). Following the reintroduction of the SmartTouch™ catheter in early December 2013, all patients were consecutively included in the registry as the CF+ control group in a 1:2 ratio (patients were controlled for AF type and operator). Patients with long-standing persistent AF were excluded. Definitions of paroxysmal and persistent AF, success and failure and complications of the CPVI procedure are based on the HRS/EHRA/ECAS consensus statement on catheter and surgical ablation of AF [1].

Procedure

All ablation procedures were performed by a single, experienced operator (>300 CPVI procedures and >100 CPVI procedures with the Thermocool® SmartTouch™ catheter) (AS). All procedures were performed under general anesthesia and under uninterrupted warfarin or novel anticoagulants (last dose 24 hours before procedure). A decapolar coronary sinus catheter was introduced via the right femoral vein. Double transseptal puncture was performed with conventional long sheaths (St.-Jude Medical, SL0). Intravenous heparin was administered to achieve an activated clotting time of >300 seconds. A circular mapping catheter (LASSO®, Biosense Webster) was used to create an anatomical shell of the left atrium with fast anatomical mapping (FAM) guided by CT images acquired the day before the procedure. For ablation a 3.5 mm irrigated tip ablation catheter (Thermocool® NaviStar®) with and without CF sensing technology was used with power settings between 30-40 Watts with irrigation rates from 17 to 30 ml/min. After placing the LASSO® catheter in the ostium of the PVs contiguous circumferential antral ablations were performed around both the left and right sided veins in pairs ≥ 1 cm from the ostium of the pulmonary veins. In the anterior left PV - atrial appendage region RF was applied on the ridge. Along the posterior and inferior left atrial (LA) wall a power setting of 30 Watts and on the anterior wall a power setting of 35 Watts were used. At each application RF energy was delivered for 20 to 60 seconds. On the posterior wall 30 sec and on the anterior wall 60 seconds application duration was targeted with an impedance drop of 10 Ohms. The applications were stopped prematurely after 20 seconds on the posterior and after 40 seconds on the anterior wall in case of a > 80% local diminution of bipolar voltage or > 25 Ohms impedance drop or >10 Ohms impedance rise was observed. Attempts were made to make contiguous point-by-point applications during stable catheter position without jumps between the lesions. Without CF measurements, applications were only performed with stable near-field intracardiac signals, tactile feedback and 3D position suggesting

stable catheter position with observations of the baseline impedance value, in order to avoid edema due to initial low contact applications. Special attention for the confirmation of good contact was paid in the anterior LA appendage-PV ridge and posterior and inferior right PV antrum region. In these regions the threshold to prolong RF duration and sometimes to increase RF power was lower, in case in spite of catheter adjustments the contact was felt to be suboptimal. For these applications on the anterior wall a power increase up to 40 Watts or RF duration to maximum 65 seconds and on the posterior wall a power of 35 Watts or a maximum RF duration of 35 seconds was allowed. When utilizing the NaviStar[®] Thermocool[®] SmartTouch[™] catheter, applications were administered with a CF aimed between 10-30g and a stable CF curve throughout the application. No applications were made with a contact force < 5g, whereas power and RF time duration adjustment was allowed in the range between 5-10g following several attempts to increase CF above 10g. For safety outcome CF was aimed not to exceed 50g during application. Following circumferential ablation of a unilateral PV pair, entry and exit block of both PVs was assessed. If the PVs were not isolated, local bipolar voltage and pacing thresholds were mapped along the ablation line focusing at the region of the earliest PV potentials on the LASSO[®] catheter. Antral touch-up lesions were performed at sites of local bipolar voltage of >0.5 mV and/or if capture with 10 mA @ 2 ms bipolar pacing. If all attempts to antrally close the remaining gaps and isolate the PVs failed, more ostial applications were made. Following entry and exit block of one unilateral PV pair, the same protocol was repeated on the contralateral side. Following entry and exit block of all 4 PVs, after sequential reinsertion of the Lasso[®] catheter into each PV, adenosine was administered (with boli to induce atrioventricular block, with a minimum dose of 12 mg and maximum dose of 24 mg) in an attempt to unmask dormant conduction. In case of adenosine-induced PV reconnection, antral remapping of the previous lesion was performed as previously described. Adenosine injection was repeated in case of entry and exit block of the PV, absence of local bipolar voltage >0.5 mV and local non-capture with 10 mA @ 2 ms pacing at the suspected gap sites. Complete adenosine-proof electrical isolation of all PVs was considered the procedural endpoint.

Follow-up

The day following the procedure, all patients underwent a transthoracic echocardiography to assess the amount of pericardial effusion.

Primary and secondary endpoints

The primary endpoint was the incidence of touch-up lesions following the initial circumferential ablation lesion set for antral circumferential PV pair isolation with entry and exit block. Secondary endpoints were the incidence of adenosine-induced PV reconnection, the total procedure time (defined as the time from venous access to adenosine-proof PVI), the LA procedure time (defined as the time from completion of transseptal puncture to adenosine-proof PVI), the RF time and the fluoroscopy

time. The following procedural characteristics were also collected: mean and maximum power, mean and maximum temperature and mean contact force. The duration of hospitalization, the amount of pericardial effusion one day post-PVI, and procedural complications up to 6 weeks after the PVI procedure were also assessed.

Statistical analysis

Continuous variables were expressed as means $\pm$ standard deviation, and categorical values as frequencies (percentage). The two-sided unpaired Student's t-test was used to compare continuous variables when values were normally distributed or its non-parametric equivalent (Mann-Whitney U) when variables were not normally distributed. The Chi-square or Fisher's exact test was used to compare categorical variables. A p-value ≤ 0.05 was considered to be statistically significant. IBM SPSS Statistics version 20 (SPSS Inc, Chicago, IL, USA) was used for all statistical analysis.

Results

Study population

A total of 36 patients were enrolled in the registry from September 2013 to June 2014. During the recall period 12 patients were treated without the CF sensing technology (CF- group) and 24 patients were treated with the SmartTouchTM catheter (CF+ group). The baseline patient characteristics are detailed in Table 1. Overall no significant differences were observed between the CF- and the CF+ control group, except for a statistically higher percentage of patients treated with vitamin K antagonists in the CF- group.

Table 1. Patient characteristics.

	CF- group (n=12)	CF+ group (n=24)	P-value
Demographics			
Age (years)	62.2 ± 8.5	58.6 ± 11.3	0.341
Range	48 – 76	29 – 76	
Men, n (%)	11 (91.7)	19 (79.2)	0.640
Medical history, n (%)			
Arterial hypertension	6 (50.0)	8 (33.3)	0.471
Coronary artery disease	1 (8.3)	5 (20.8)	0.640
History of myocardial infarction	0 (0)	3 (12.5)	0.536
Valvular heart disease	0 (0)	3 (12.5)	0.536
Dyslipidemia	2 (16.7)	3 (12.5)	1.000
Diabetes mellitus	0 (0)	2 (8.3)	0.543
Ejection fraction			
%	58.1 ± 8.0	56.0 ± 7.9	0.471
Range	45 – 68	37 – 68	
Mild to moderate LV dysfunction (LVEF ≤ 45%), n (%)	1 (8.3)	1 (4.2)	1.000
Atrial fibrillation, n (%)			
Paroxysmal AF	9 (75.0)	18 (75.0)	1.000
Persistent AF	3 (25.0)	6 (75.0)	
CHADSVASc score	1.5 ± 0.9	1.6 ± 1.6	0.824
Left atrium configuration			
Diameter (mm)*	43.0 ± 4.3	42.0 ± 3.6	0.448
Range	34 – 48	36 – 50	
Volume FAM map (ml)**	164.3 ± 24.8	157.9 ± 28,3	0.506
Range	127 – 204	117 – 221	
Classic 4 PV configuration, n (%)	11 (91.7)	24 (100)	0.333
Accessory right middle PV	1 (8.3)	0 (0)	
Antiarrhythmic drugs, n (%)			
Number of drugs tried	1.5 ± 0.9	1.4 ± 0.9	0.728
Class I AAD	8 (66.7)	12 (50.0)	0.481
Sotalol	7 (58.3)	12 (50.0)	0.732
Amiodarone	3 (25.0)	7 (29.2)	1.000
Anticoagulative drugs, n (%)			
Vitamin K antagonist	11 (91.7)	13 (54.2)	0.031
Novel oral anticoagulant	1 (8.3)	5 (20.8)	0.640
Aspirin derivative	0 (0)	2 (8.3)	0.543

Data are presented as mean ± standard deviation or absolute number (n) + percentage (%)
 AAD: antiarrhythmic drugs; AF: atrial fibrillation; CF-: group in which CPVI is performed with the NaviStar® Thermocool® ablation catheter; CF+: control group in which CPVI is performed with the Thermocool® SmartTouch™ catheter; FAM: fast anatomical map; LV: left ventricle; PV: pulmonary vein.

* Left atrial diameter on transthoracic echocardiography posterior long axis view.

** Left atrial volume of fast anatomical map with Carto® system.

*** Antiarrhythmic and anticoagulant drug treatment prior to the ablation procedure.

Procedural results

The procedural endpoint (complete bidirectional electrical adenosine-proof isolation of all PVs with entry and exit block) was reached in 100% of performed procedures. The mean total lesion set length, as well as the mean lesion set length of left and right-sided PV circles were similar between both groups (Table 2).

The number of PV pairs requiring touch-up to achieve electrical isolation after the first circumferential lesion set was significantly less in the CF+ group (2 of 48 PV pairs (4.2%) compared to 7 of 24 PV pairs (29.2%) in the CF- group ($p= 0.005$) (Table 2). Adenosine-induced acute PV reconnection occurred only in 1 patient (CF- group), who had also required touch-up applications after the first circumferential lesion set. If touch-ups were required, bidirectional electrical PV isolation was achieved with additional antral RF applications; no ostial touch-up applications were necessary.

Table 2. Procedural parameters.

	CF- group (n=12)	CF+ group (n=24)	P-value
Number of PV pairs requiring touch-up (n, %)	7/24 (29.2)	2/48 (4.2)	0.005
Number of patients requiring touch-up (n,%)	7/12 (58.3)	2/24 (8.3)	0.002
Number of adenosine-induced reconnected PV pairs (n, %)	1/24 (4.2)	0/48 (0)	0.333
Total procedure time (min)	167.8 ± 26.0	151.8 ± 24.8	0.075
Total left atrial time (min)	134.1 ± 25.3	117.9 ± 23.3	0.033
RF time (min)	31.8 ± 7.0	31.5 ± 7.1	0.919
Fluoroscopy time (min)	11.0 ± 5.8	11.8 ± 5.6	0.708
Mean power delivered (Watts)	30.4 ± 1.2	29.2 ± 1.3	0.024
Maximum power delivered (Watts)	35.6 ± 1.6	35.3 ± 1.1	0.787
Mean temperature delivered (°C)	35.9 ± 0.7	38.4 ± 1.9	<0.001
Maximum temperature delivered (°C)	46.2 ± 2.8	44.5 ± 11.0	0.672
Mean contact force applied (grams)		17.8 ± 2.2	
Total lesion set length (mm)	267.8 ± 14.1	265.7 ± 31.1	0.831
Lesion set length left PV pair (mm)	122.5 ± 13.4	123.1 ± 22.0	0.937
Lesion set length right PV pair (mm)	145.3 ± 10.9	142.6 ± 14.0	0.583

Data are presented as mean ± standard deviation or absolute number (n) + percentage (%)
 CF-: group in which CPVI is performed with the NaviStar® Thermocool® ablation catheter;
 CF+: control group in which CPVI is performed with the Thermocool® SmartTouch™ catheter;
 PV: pulmonary vein; RF: radiofrequency

The touch-ups characteristics and distribution are detailed in Table 3a and 3b. Touch-up applications of the left PV were necessary in 4 patients (11.1%) and of the right PV in 5 patients (13.9%). The most frequent locations of 22 gaps following the first lesion set were on the left PV pair the anterior segment (4 patients, 11.1%) and on the right PV pair the posterior segment (4 patients, 11.1%). The frequency of gaps in the right anterior (CF+: 0/24 vs. CF-: 3/12, p=0.031) and the right inferior segment (CF+: 0/24 vs. CF-: 3/12, p=0.031) was significantly higher in the CF- group. The frequency of gaps in the other PV segments did not significantly differ between the two groups.

Table 3a. Touch-up characteristics

#	CF group	LPV/RPV pair	Antral touch-up region	RF time first lesion set (single PV pair)	RF time touch-up (single PV pair)	Adenosine-induced PV reconnection	RF time touch-up after adenosine	Mean CF (g)
1	CF+	LPV	Left superior Left anterior Left posterior	13' 06"	6' 05"			14.8
2	CF+	RPV	Right posterior	14' 25"	3' 51"			15.6
3	CF-	RPV	Right anterior Right inferior	12' 52"	4' 10"			/
4	CF-	RPV	Right superior Right anterior Right posterior	10' 27"	11' 06"			/
5	CF-	LPV	Left anterior	14' 05"	1' 14"			/
6	CF-	RPV	Right superior Right inferior Right posterior	13' 57"	13' 25"			/
7	CF-	RPV	Right posterior Right anterior Right inferior	14' 09"	4' 16"			/
8	CF-	LPV	Left anterior Left superior Left posterior	9' 53"	10' 21"	LPV: Left anterior & Left posterior	7' 30"	/
9	CF-	LPV	Left anterior Left superior Left posterior	12' 42"	16' 02"			/

AF: atrial fibrillation; CF: contact force; LPV: left pulmonary veins;; vein; RPV: right pulmonary veins;
RF: radiofrequency

Table 3b. Distribution of conduction gaps requiring touch-ups.

	CF- group (n=12)	CF+ group (n=24)	P-value
Right pulmonary veins			
Anterior	3 (25.0)	0	0.031
Posterior	3 (25.0)	1 (4.2)	0.253
Superior	2 (16.7)	0	0.105
Inferior	3 (25.0)	0	0.031
Left pulmonary veins			
Anterior	3 (25.0)	1 (4.2)	0.098
Posterior	2 (16.7)	1 (4.2)	0.253
Superior	2 (16.7)	1 (4.2)	0.253
Inferior	0	0	n/a

CF-: group in which CPVI is performed with the NaviStar[®] Thermocool[®] ablation catheter; CF+: control group in which CPVI is performed with the Thermocool[®] SmartTouch[™] catheter

The left atrial procedure time was significantly lower in the CF+ group (CF+: 117.9 ± 23.3 min vs. CF-: 134.1 ± 25.3 min, $p = 0.033$). RF time (CF+: 31.5 ± 7.1 min vs. CF-: 31.8 ± 7.0 min) and fluoroscopy time (CF+: 11.8 ± 5.6 min vs. CF-: 11.0 ± 5.8 min) did not differ between groups.

The mean applied CF was 17.8 ± 2.2 grams. The mean delivered temperature was higher in the CF+ group (CF+: 38.4 ± 1.9 vs. CF-: 35.9 ± 0.7 , $p = <0.001$), with a lower mean power (CF+: 29.2 ± 1.3 vs. CF-: 30.4 ± 1.2 W, $p = 0.024$).

One patient (CF+ group) developed anterior ST elevation near the end of the PVI due to an underlying LAD stenosis and percutaneous coronary intervention (PCI) was performed immediately following the PVI. In one patient (CF+ group) a small arterio-venous fistula was discovered following the inguinal puncture, which was treated conservatively. One patient (CF+ group) had complaints of pericarditis the day following the procedure. No patients experienced cerebral ischemic events or pericardial perforation or tamponade.

Pericardial effusion was assessed on transthoracic echocardiography the day after the procedure. None of the patients had a hemodynamically significant pericardial effusion. There was no difference in the periprocedural hospitalization duration between the two groups (CF+: 4.0 ± 1.6 vs. CF-: 4.0 ± 2.3 days, $p = 0.679$).

Discussion

Superior efficacy of online CF measurement in CPVI

The TOCCATA [19] and EFFICAS-I studies [20] demonstrated a positive correlation between applied CF and clinical efficacy endpoints as the occurrence of pulmonary vein reconnection and recurrence of AF after PVI. Based on these results current strategies to achieve durable PVI target higher CF values by adjusting catheter position to improve contact [19-20]. If in spite of repositioning a low CF remains, effective lesion formation might be achieved by increasing the power and/or duration of the RF application. Recently, 6 small non-randomized and 1 randomized clinical studies compared online CF measurement with CF sensing catheters to standard open-irrigated-tip catheters for PVI. In 5 of these studies the SmartTouchTM catheter [13-15, 17-18] and in 2 studies the TactiCath[®] catheter (Endosense SA, Geneva, Switzerland) [9,16] was used. In these studies the use of CF sensing catheters was associated with better procedural parameters and outcome as a significant reduction in procedure time [9, 13-17] and RF ablation time [13-15], as well as of fluoroscopy time [9, 14-15] and acute PV reconnection rate [14, 18] were observed. A mid-term clinical benefit with a significant reduction of the AF recurrence rate at 12 months after PVI was recently demonstrated in 2 studies [15-16].

Requirement of touch-up lesions

The EFFICAS-I trial recently demonstrated that in spite of acute complete PV isolation conduction recurs at sites with low CF application. It was suggested that edema formation during the first low force applications might prevent durable transmural lesion formation of subsequent repeat applications at the same site. At these sites conduction gaps recurred [20-21]. Based on these results current strategies include first ablation attempts with optimal CF to achieve lesion transmural with the first application [20]. PVI with entry and exit block following the first circumferential lesion set as the primary endpoint in the current study reflects this strategy. The main finding of our study is that the use of CF technology significantly reduced the need for touch-up lesions to achieve electrical isolation after the first circumferential lesion set from 29% to 4% per PV pair. The most frequent gap locations were in the regions previously reported prone to low contact (the left anterior and right posterior PV segments). Touch-up applications in the right anterior and right inferior PV segments were more frequent in non-CF guided CPVI procedures.

In a recently published prospective, non-randomized, single-center study, Marijon et al. compared CPVI with the SmartTouchTM catheter to a regular irrigated-tip ablation catheter in 60 patients with paroxysmal AF. In their study bidirectional PV isolation using solely an anatomical approach was achieved in 80.0% (24/30) of patients with CF technology compared to only 36.7% (11/30) of patients when CF measurement was not used. The use of online CF measurement was also associated with a reduction of AF recurrence at 12 months of follow up [15]. In a similar study Haldar et al. included 40 patients undergoing CPVI. 20 patients underwent CF guided and 20 patients CF blinded procedure. After 60 min waiting and adenosine administration 70% of patients (21% of the veins) had acute reconnection in the CF blinded vs. 15% of patients (4% of veins) in the CF guided group.

In the current study bidirectional PV isolation was achieved with the first circumferential lesion set in 95.8% of the PV pairs and in 91.6% of the patients with CF technology compared to 70.8% of the PV pairs and in 41.6% of the patients without CF. The PV isolation rates with first circumferential lesion set in both the CF+ and CF- group in our study are very similar to the previous two studies (92% vs. 80% and 85%, and 42% vs. 37% and 30% of patients in the CF+ and CF- group respectively). The slight differences between the studies might be explained by the slightly different ablation strategies. In our study the electrograms from the Lasso catheter within the PV are displayed during PV isolation, allowing longer applications at the site of PV delay or isolation similar to the study by Haldar et al. as opposed to the study by Marijon et al. In our approach the power settings were higher between 30 and 40 Watts as opposed to 25 to 30 Watts in the study by Marijon et al. and 30 Watts in the study by Haldar. Additionally, in our study we adjusted the power settings according to obtained CF.

In addition to improving CF before RF delivery, CF guided ablation allows recognition of application sites where the obtained CF remains low after attempts to improve contact. Despite the lower CF (between 5 and 10g) a durable transmural lesion could still be achieved by increasing the RF duration along with RF power for these specific applications. This strategy explains the higher RF time of the

first circumferential lesion set in the CF+ group as compared to the CF- group (CF+: 31.4 ± 7.1 min vs. CF-: 25.6 ± 2.5 min, $p = 0.015$). The study of Halder et al. reported similar findings; total mean RF time was (non-significantly) higher in the CF guided procedures (CF+: 60.7 ± 20.6 min vs. 52.9 ± 23.1 min, $p = 0.29$) despite the lower incidence of acute PV reconnection requiring touch-up ablations. In addition to the online CF feedback, the higher RF duration of first lesion set might have resulted in the lower incidence of touch-up applications in CF guided procedures.

Sustainable superior efficacy of online CF measurement after the learning period

CF sensing catheters allow online tactile feedback at different CF values, which might teach the operators to better estimate contact quality in the absence of online CF measurement. Experience with the CF catheters might also teach the operators which catheter and sheath maneuvers result in improved tip-tissue contact. The use of CF measuring catheters identified which PV segments are prone to low CF applications if no online CF feedback is available [19, 20]. Individual experience with these catheters also has the potential to identify operator specific CF differences. For these reasons in the current study we tested the hypothesis whether an extensive training period with real-time direct CF feedback from the SmartTouch™ catheter could replace the use of CF sensing catheters.

The large majority of the previously mentioned studies were performed early after the introduction of the CF measuring catheters, thus operators had no or little experience with the CF technology. In only one study by Halder et al. the operators had medium-term experience with the SmartTouch™ catheter before enrollment [18]. Furthermore, in most of the non-randomized trials the control group procedures without CF measurement were performed before the procedures with CF technology [9, 13-14, 16]. Hence, in contrast to the current study, no learning effect from procedures with online CF measurement feedback on procedures without availability of CF technology was present in these studies. The recall period of the SmartTouch™ catheter allowed us to compare CPVI with and without CF measurements beyond the learning curve period of the CF technology. The second main finding of our study is that even after gaining experience in CPVI with CF measuring catheters, procedural parameters remain superior with this technology. An extensive training period with real-time direct CF feedback from the SmartTouch™ catheter did not result in equal quality CPVI when returning to standard open-irrigated-tip RF ablation catheters with adjusting catheter position, RF power or time in regions typically known for difficulty to achieve good CF. This indicates that even after a training period with direct CF feedback, mere tactile feedback remains unreliable to estimate firm tip-to-tissue contact as it may be influenced by the catheter shaft, deflection, torque, and by the different sheaths used.

Adenosine-induced acute PV reconnection

The incidence of adenosine-unmasked dormant conduction was very low in our study. Adenosine provoked PV reconnection occurred only in 1 patient in the CF- group (8% of patients in non-CF guided procedures). In a published, prospective non-randomized two-center study Andrade et al. compared the prevalence of dormant conduction after CPVI with a non-CF sensing catheter (Thermocool®) to CPVI with a CF sensing catheter (SmartTouch™) in 75 paroxysmal AF patients [22]. The use of CF catheters led to a significant reduction of adenosine-induced acute PV reconnection. Adenosine-unmasked dormant conduction was present in 4 out of 50 PV pairs (8%) in 4 out of 25 patients (16%) in the CF% group, and in 35 of 100 PV pairs (35%) and 26 of 50 patients (52%) in the CF- group ($p = 0.0004$ per PV pair, $p = 0.0029$ per patient). The lower incidence of adenosine-induced acute PV reconnection in our study could be partly explained by a difference in RF parameters. In our study applications were made with a power of 35 Watts along the anterior wall and 30 Watts along the posterior wall as opposed to 30-35 watts on the anterior and 25 Watts on the posterior wall in the study by Andrade et al. Moreover in CF guided procedures if it was not possible to attain $CF \geq 10g$, in our study an extension of the duration of the RF application was applied, along with a power increase up to 40 Watts on the anterior wall and 35 Watts on the posterior wall. Also we aimed the CF between 10 and 30g as opposed to a targeted CF between 5 and 50g in the study of Andrade et al. An additional reason for the low adenosine reconnection in our study is likely the shorter waiting time. In the study of Andrade et al. adenosine was administered at least 20 minutes after obtaining PV pair isolation, while in our study adenosine-induced reconnection was checked 30 minutes after isolation of left PVs and only 10 minutes after isolation of the right PVs. Lastly for the non-CF guided procedures, it is possible that the experience gained with using CF catheters improved the results of procedures without CF measurements, resulting in a lower incidence of adenosine-unmasked dormant conduction in our study.

Procedural parameters

In our study the procedure time (the LA procedure time) of CPVI was significantly reduced with the CF technology (CF+ group: 117.9 ± 23.3 min vs. CF- group 134.1 ± 25.3 min, $p = 0.033$), largely because looking for residual gaps (for touch-up lesion target) after completion of first circumferential lesion set is time consuming. Although less additional touch-up RF applications were required in the CF+ group, the total RF time was equal in both groups (CF+: 31.5 ± 7.1 min vs. CF-: 31.8 ± 7.0 min, $p = 0.919$). This is because in the CF+ group ablation points with lower CF, due to difficulty in the catheter position, were compensated with longer RF duration of the RF application.

The use of CF did not result in a reduction in fluoroscopy time in our study (CF+: 11.8 ± 5.6 min vs. CF-: 11.0 ± 5.8 min). However, the fluoroscopy time in both groups was low and was mostly used for the catheter insertion and the transseptal puncture, which are not affected by CF technology.

The mean delivered temperature was higher in the CF+ group (CF+: $38.4 \pm 1.9^\circ C$ vs. CF-: $35.9 \pm$

0.7°C, $p = <0.001$), with a lower mean power (CF+: 29.2 ± 1.3 Watts vs. CF-: 30.4 ± 1.2 Watts, $p = 0.024$). This finding suggests that higher temperatures are achieved with less power when optimal CF is pursued. In general catheter tip temperature in irrigated-tip catheters is not considered an indicator of neither tissue temperature nor contact.

Pulmonary vein isolation with operators blinded to contact force measurements

Because in the CF- group CPVI was performed with a conventional non-CF sensing catheter in a clinical scenario when the SmartTouch™ catheter was unavailable, assessment of the obtained CF in the CF- group was not possible. Two previous clinical studies compared CPVI performed with CF sensing catheters with operators guided by vs. blinded to the CF measurements. In the previously mentioned study, Halдар et al. compared CF guided to CF blinded CPVI in 40 non-randomized patients [18]. CF guided CPVI reduced the rate of PV reconnection after a waiting period of 1 hour and adenosine challenge after PV isolation was achieved. The mean CF was significantly lower in the CF blinded group as compared to the CF guided group (11.6g (10.5-12.9g) vs. 14.4g (13.3-15.7g)), and mean contact force was significantly lower at the segments that experienced reconnection (almost all in the blinded group) (14.5g (13.3-15.7g) vs. 19.6g (14.6-26.3g)). The majority of reconnection sites were on the left side the anterior and superior segments and on the right side the carina. In our study we report similar gap locations.

In another recently published single-center study, Kimura et al. compared CF to non-CF guided CPVI in 38 randomized patients with paroxysmal (28) and non-paroxysmal (10) AF [17]. All procedures were performed with the SmartTouch™ catheter, but in the non-CF group the operators were blinded to the online CF measurement. Blinding to CF measurement lead to a significant reduction in the mean applied CF (5.9 ± 4.5 vs. 11.1 ± 4.3 g in blinded and unblinded procedures respectively). In this study, online CF feedback reduced the mean number of residual conduction gaps requiring touch-up applications after the first circumferential lesion set to achieve PV isolation from 6.3 ± 3.0 to 2.8 ± 1.9 per patient ($p < 0.001$). In addition procedure time (defined from initial the RF application to completion of CPVI) was significantly shorter in CF guided procedures (59 ± 16 vs. 96 ± 39 min in blinded and unblinded procedures, $p < 0.001$). The results in the CF blinded groups in these 2 studies suggest that the inferior efficacy in our CF- group is likely due to uncorrected lower contact during CPVI. In contrast to our study, all patients in the study of Kimura et al. had conduction gaps after the first circumferential lesion set, although significantly less in the CF guided CPVI group. These important differences in results could be explained by different ablation strategies. In our approach point-by-point applications ranging from 20 to 60 seconds were applied as opposed to dragging lesion applications of 20-25 seconds in the study of Kimura et al. The power settings in our study were higher between 30 and 40 Watts as opposed to 25 to 30 Watts. We used a long sheath in the left atrium. We aimed a contact force between 10 and 30g as opposed to a targeted CF between 10 and 20g. The mean obtained CF in the CF guided group was in our study significantly higher as compared

to the study of Kimura et al. (17.8 ± 2.2 . vs. 11.1 ± 4.3 g).

In addition in the study of Kimura et al. the operators blinded to CF had a learning curve of 5 cases. In a subsequent phase of their study an additional 20 patients underwent CF guided CPVI. In these patients the mean CF and number of gaps was not significantly different as compared to the first 20 patients suggesting that there was no learning curve effect between the first and second 20 CF guided cases. However, Kimura et al. also examined the CF at each segment of the left PV under CF blinded CPVI in 5 cases, performed by operators having experienced >30 CF guided procedures. The CFs were in all segments similar to those in the CF guided CPVI suggesting a learning effect. Although only the left sided CF in a small number of cases was investigated, the authors hypothesized that accumulating experience with CF guided CPVI may favorably affect outcomes in non-CF guided CPVI. In our study we report that even if this improvement is present CF guided CPVI remains superior to CF blinded CPVI even after an extensive learning curve.

Although the blinded studies demonstrate that applied CF was lower if operators were blinded to the CF measurements, it must be noted that due to the incorporation of the CF sensor, the distal 3 cm of the SmartTouch™ catheter is stiffer compared to the NaviStar® Thermocool® catheter. Without the online CF feedback, tactile sensation of CF might be further impaired by the increased catheter stiffness in the blinded study group procedures with the SmartTouch™ catheter compared to the NaviStar® Thermocool® catheter. Additionally the CF sensing catheter has a significantly higher cost price. Given these differences, it is a clinically relevant question if after the learning curve the CF sensing catheter could be replaced by a non-CF sensing catheter without risking the efficacy of the procedure. Our study compared two different commercially available catheters, with and without CF sensing, as opposed to the two blinded studies where the same CF catheter is used.

Limitations

Our study has several limitations. The number of patients included in both groups was relatively small. The study was non-randomized and we did not include clinical follow-up. Further as a single-center, single-operator trial it is not known to what extent these results can be generalized. However, it is reasonable to speculate that the benefits of CF sensing catheters, both regarding efficacy and safety, are only greater with less experienced operators. Additionally, the study design did not allow assessment of the obtained CF in the CF- group. Finally, we did not compare procedural parameters without online CF measurements between patients undergoing PVI prior to patients undergoing PVI after the introduction of the CF sensing catheters. It cannot be excluded that the experience gained with using CF catheters improved the results of procedures without CF measurements.

Conclusion

Our results suggest that with the use of online CF measurement PVI is more frequently complete following the first circumferential lesion set. After gaining experience with CF-measuring catheters, procedural CPVI parameters remain superior with this technology when compared to non-CF guided CPVI procedures. An extensive training period with real-time direct CF-feedback was not a substitute for real-time direct CF measurement to maintain this advantage.

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I

Part I

ABLATION OF ATRIAL FIBRILLATION AND ATRIAL TACHYCARDIA

Part IB

A protocol for pulmonary vein isolation with
contiguous and optimized radiofrequency
applications: “CLOSE-PVI”

3

Chapter 3

Evaluation of optimal ablation
parameters for radiofrequency PVI:
inter-tag distance and ablation index

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ABSTRACT

Background: Pulmonary vein reconnection (PVR) still determines recurrences of atrial fibrillation (AF) after contact force (CF)-guided PV isolation (PVI). We studied whether acute PVR (adenosine and/or waiting time) and late PVR (at repeat) are explained by incomplete transmural and/or contiguity within the deployed RF circle.

Methods: We analysed 42 CF-guided ipsilateral PVI procedures. For each RF tag within the circle, we collected data on transmural (time of application, power, impedance drop (ΔImp), CF, force-time integral (FTI), ablation index (AI)) and contiguity (automated interlesion distance, AILD). Ablation line contiguity index (ALCI) was developed as a novel automated algorithm combining transmural and contiguity into one single criterion. Each circle was subdivided into 10 segments. For each segment we determined its “weakest link” by annotating: $\text{Time}_{\min}$, $\text{Power}_{\min}$, $\Delta\text{Imp}_{\min}$, $\text{CF}_{\min}$, $\text{FTI}_{\min}$, $\text{AI}_{\min}$, $\text{AILD}_{\max}$, $\text{ALCI}_{\min}$.

Results: Compared to segments without PVR ($n=758$), segments with PVR ($n=44$) were characterized by lower $\Delta\text{Imp}_{\min}$ (4.8 vs. 7.4 Ω), $\text{CF}_{\min}$ (8.5 vs. 11.8g), $\text{FTI}_{\min}$ (351 vs. 473gs), $\text{AI}_{\min}$ (367 vs. 408 arbitrary unit) and higher $\text{AILD}_{\max}$ (6.8 vs. 5.5mm), all $p<0.001$. $\text{ALCI}_{\min}$ was significantly lower in segments with PVR (74 vs. 104%, $p<0.001$) and was associated with the highest accuracy to predict durable segments ($\text{AUC}=0.73$).

Conclusion: In CF-guided PVI, PVR is explained by lack of both transmural and contiguity within the deployed RF circle. ALCI, a novel parameter combining contiguity and transmural, is the most accurate predictor for durable segments. By avoiding weak links in the ablation chain, ALCI-guided ablation is expected to improve success rate of point-by-point RF ablation.

INTRODUCTION

Catheter based pulmonary vein isolation (PVI) is associated with a single procedure freedom of atrial fibrillation (AF) in $\approx 70\%$ of patients with paroxysmal AF.[1-2] Lack of durability of PVI, a major determinant of AF recurrence, is evidenced by acute PV reconnection at the time of the procedure and late PVR during follow-up.[3-5] The use of contact force (CF) sensing catheters, allowing to better control stability and lesion depth during point-by-point PV encircling, has improved freedom of AF now amounting to $\approx 80\%$.[6-8] Nevertheless acute and late PVR still occur and data on outcome are not unequivocal.[9]

We aimed to investigate whether acute and late PVR in CF-guided ablation are due to incomplete transmural or discontinuous RF lesions within the deployed PV circle and whether criteria can be set forward as targets to avoid weak links in the ablation chain. Criteria for transmuralty implied time of application, median delivered power, impedance drop, average CF, force-time integral and ablation index.[10-11] Contiguity was assessed by calculating automated interlesion distance (AILD). Ablation line contiguity index (ALCI) was developed as a novel automated algorithm to assess both transmuralty and contiguity and was defined as the ratio of the estimated width of a transmural lesion over its distance to the closest transmural lesion.

METHODS

Study population

From august 2013 all patients undergoing CF-guided ablation for AF are followed in a prospective database approved by the local institutional review committee. This database implies collecting patients' informed consent, a detailed case report form of the procedure and follow-up at 1, 3, 6 and 12 months. In the present manuscript we present retrospective analysis of 42 patients that underwent CF-guided catheter ablation for drug-resistant or drug-intolerant symptomatic paroxysmal AF between December 2013 and July 2014 in the St Jan Hospital Bruges.

Contact force-guided pulmonary vein isolation

PVI was performed under conscious sedation or general anaesthesia. In patients undergoing anaesthesia, transesophageal echocardiogram and thermal probing (SensiTherm™, St Jude Medical Inc, Minnesota, US) were performed. After femoral access, intravenous heparin (100 IU/kg) was administered and continuously infused (ACT > 300 sec). After double transseptal puncture, a decapolar Lasso catheter and an 8F open-tip irrigated RF catheter with tip-integrated CF sensor (Thermocool SmartTouch®, Biosense-Webster Inc., Diamond Bar, CA, USA) were positioned in the left atrium. Calibration of CF catheter and respiratory gating were performed. After reconstructing 3D-

geometry (Carto System ®, BSW), point-by-point ipsilateral PVI was performed using real-time automated display of RF applications (Visitag®, Biosense-Webster Inc.), with predefined settings of catheter stability (3 mm for 8 sec) and minimum CF (30 % of time > 4 gr). RF was delivered in a power-controlled mode with maximal 25 W for 30 s on the posterior wall and roof, and maximal 35W for 60s on the anterior wall (irrigation flow of 17 to 30 cc/min). According to data from the EFFICAS studies, CF target was >10 g.[12-13] In case of chest pain or significant intra-esophageal T° rise (> 38.5°C) during posterior wall ablation, RF delivery was stopped prematurely. No strict criteria for contiguity were available at that time. Ablation index and ALCI were not available to the operators.

After electrical isolation within the ipsilateral circle (i.e. entrance block verified by Lasso catheter) we waited for 20 minutes after which adenosine (dose resulting in atrio-ventricular block) was given. In case of reconnection during waiting or after adenosine (acute PVR), ablation was continued until PVI was resistant to subsequent waiting and adenosine. The anatomical site of reconnection within the circle (i.e. site of earliest activity and where touch-up RF eliminated PVR or markedly changed activation pattern) were carefully annotated.

Follow-up

After ablation, anticoagulation and previously failing anti-arrhythmic drugs were continued. At 3 months, anticoagulation was continued according to the stroke risk. Clinical evaluation and ECG were performed at 1, 3, 6 and 12months. Holter was performed at 3 month (24 h), 6 month (24 h) and 12 month (7 day) or in case of symptoms. In case of recurrence, defined as any documented atrial tachyarrhythmia lasting more than 30 seconds, repeat ablation procedure was advised. In case reconnection was observed at the beginning of the repeat procedure (late PVR), ablation was performed until PVI was obtained. The sites of reconnection within the circle (i.e. site of earliest activity and where RF eliminated PVR) were annotated.

Criteria for transmuralty and contiguity

Each procedure was exported and analyzed offline. For each RF tag within the circle we determined offline criteria for transmuralty: time of application (s), median delivered power (W), impedance drop (Δ -Imp, Ω), average CF (CF, g), force-time integral (FTI, gs) and ablation index (AI, arbitrary unit, au). AI is an indirect parameter for prediction of lesion quality based on a logarithmic formula integrating power and CF over time, which was available as an offline research tool.[12,13]. In addition, we determined contiguity by measuring interlesion distance in between neighboring ablation tags (center-to-center distance, mm). To combine both transmuralty and contiguity in one single criterion we developed in Matlab (Mathworks, Natick, MA, USA) a new algorithm to assess ablation line contiguity (ALC). ALC index (ALCI) is defined as the ratio of the estimated width of a

transmural lesion (determined by the AI) over its distance to the closest transmural lesion and calculated as

$$ALCI_{ij} \% = \frac{OC \times Conv \times \frac{AI_i + AI_j}{2}}{100 \times AILD_{ij}} \times 100; \text{ where 'OC' is the overlapping coefficient of the 2}$$

neighboring tags and 'Conv' is the conversion factor specific to anatomical location (anterior or posterior wall).

Determination of the weakest link within the deployed RF circle

Each PV circle was divided into 10 anatomical segments (Fig.1, top panel). For each segment, the “weakest link” was defined as the minimal or maximal value for each criterion ($Time_{min}$, $Power_{min}$, $\Delta-Imp_{min}$, CF_{min} , FTI_{min} , AI_{min} , $AILD_{max}$, $ALCI_{min}$). A representative example of the “weakest link” analysis is shown in (Fig.1, lower panel). In this patient (without acute or late PVR), the weakest link in segment 9 (anterior segment of the right circle encompassing 4 RF tags) was characterized by $Time_{min}$ of 60 s, $Power_{min}$ of 30 W, $\Delta-Imp_{min}$ of 11 Ω , CF_{min} of 8.6 g, FTI_{min} of 515 gs, AI_{min} of 529 au, $AILD_{max}$ of 6.4 mm and $ALCI_{min}$ of 95 %.

Ablation tags belonging to additional RF applications delivered to treat acute PV were ignored for analysis in case of acute PVR, but were included in the analysis of late PVR.

The weakest link values of segments revealing acute or late PVR were compared to those values within segments without PVR. Out of 84 circles, 4 (40 PV segments) were excluded from analysis due to incomplete RF/VisiTag® data. The remaining 80 circles (800 PV segments) were analyzed. Results are presented for all segments, per segment and for posterior wall (segments 1-2-3-4-5 and roof segment 10) and anterior wall (segments 6-7-8-9) separately.

Figure 1: A representative example of “weakest link” analysis in a given segment. Each circle is divided into 10 segments (upper panel). Per segment we defined the minimal value for time (Time_{min}), power (Power_{min}), impedance drop (Δ -Imp_{min}), contact force (CF_{min}), force-time integral (FTI_{min}), ablation index (AI_{min}) and ablation line contiguity index (ALCI_{min}) and maximal value for automated interlesion distance (AILD_{max}). RS, right superior pulmonary vein; RI, right inferior pulmonary vein; LS, left superior pulmonary vein; LI, left inferior pulmonary vein.

Statistics

Continuous variables are expressed as mean $\pm$ SD (or medians with IQR for non-normal distributions) and dichotomous variables as percentage. Normality of data distribution was tested with Shapiro-Wilk test. Mann-Whitney U test or Kruskal-Wallis test were used to evaluate significant difference between segments with and without PVR. For parameters showing significant difference, receiver operator characteristics (ROC) curves were plotted and analyzed to determine the diagnostic accuracy to predict durable isolation at different clinical cutoffs.[11,12,14] Multivariable logistic regression was used to assess the association between the different parameters and PVR. P values < 0.05 were considered statistically significant. All statistical analyses were performed in SPSS Statistics 22 (IBM Corporation, Armonk, New York, USA).

RESULTS

Patients, procedure and follow-up

Clinical characteristics are given in Table 1. All patients had paroxysmal AF. General anesthesia was used in 15 procedures (36 %). Procedure time was 189 ± 41 min, RF time per procedure was 55.0 ± 11.8 min and RF time per circle was 27.6 ± 7.7 min. All ipsilateral pairs of veins (84 circles) were electrically isolated at the end of the procedure.

In 7 patients recurrence of AF was documented (freedom of AF 81 %). In 6 patients, a repeat ablation was performed. Mean time from the first PVI procedure to repeat procedure was 287 ± 17 days.

Table 1: Clinical characteristics of study subjects

Characteristic	CF-guided PVI (n=42)
Mean age, y	63 ± 10
Male, n (%)	24 (57%)
Mean BMI, kg/m ²	27 ± 5
HTN, n (%)	16 (38%)
CHA2DS2-VASc score	
≤ 1 , n (%)	20 (48%)
2-3, n (%)	20 (48%)
≥ 4 , n (%)	2 (4%)
Time of first AF episode to PVI, months	24 [range 3-28]
Mean LVEF, %	63 ± 3
Mean LAD, mm	40 ± 5

Comparison of segments with PVR vs. durable segments without PVR

In total, acute PVR occurred in 25 segments (14 circles in 11 patients) whereas late PVR occurred in 19 segments (6 circles in 6 patients). All patients at repeat revealed at least one reconnected circle. The spatial distribution of acute and late PVR is given for each segment in Fig.2. Out of 44 PVR, we observed 17 PVR at anterior wall vs. 27 PVR at the posterior wall ($p = 0.143$), and 25 PVR at the right circle vs. 19 at the left circle ($p = 0.176$). No PVR was seen at the superior and inferior segments of the posterior left circle (segment 1, 4 and 5). Out of 19 segments with late PVR, only 2 were also characterized by acute PVR.

Figure 2: Number of acute (orange stars) and late (purple stars) pulmonary vein reconnections (PVR) observed for each segment. See text for further explanation. PA, postero-anterior projection.

In those 44 segments with acute or late PVR (vs. 758 segments without PVR) we observed lower $\Delta\text{Imp}_{\min}$, $\text{CF}_{\min}$, $\text{FTI}_{\min}$, $\text{AI}_{\min}$, higher $\text{AILD}_{\max}$ and lower $\text{ALCI}_{\min}$. A representative example is given in Fig.3. In this patient, adenosine revealed acute PVR at the left circle with the site of reconnection in segment 8 (anterior). The weakest link in segment 8 was characterized by the lowest $\text{ALCI}_{\min}$ (51 %) due to the combination of low $\text{AI}_{\min}$ and high $\text{AILD}_{\max}$ (6.8 mm).

Figure 3: Acute pulmonary vein reconnections (PVR) in the left circle, eliminated by touch-up ablation in segment 8. This segment is characterized by a low minimal ALCI value. In the lower panel, bipolar electrograms from the circular mapping catheter at the LSPV together with surface ECG Lead II are presented. * AV block induced by Adenosine. ** PVR. Abbreviations similar to Figure 1.

Overall results are summarized in Figure 4. Compared to segments without PVR ($n = 758$), segments with PVR ($n = 44$) had comparable Time_{min} (33 s vs. 35 s, $p = 0.054$) and Power_{min} (20 vs. 22 W, $p = 0.513$). In contrast, segments with PVR were characterized by significantly lower Δ-Imp_{min} (4.8 vs. 7.4 Ω, $p = 0.002$), CF_{min} (8.5 vs. 11.8 g, $p = 0.001$), FTI_{min} (351 vs. 473 gs, $p < 0.001$) and AI_{min} (367 vs. 408 au, $p = 0.001$). Furthermore, segments with PVR were characterized by higher AILD_{max} (6.8 vs. 5.5 mm, $p < 0.001$). Minimal ALCI per segment was significantly lower in segments with PVR (74 vs. 104 %, $p < 0.001$).

Differences (except of Δ-Imp) remained significant when analyzed for acute PVR and late PVR separately (Table 2). When analyzed per segment and circle separately (Tables 3a and 3b), a similar trend was observed although statistically not invariably significant (due to low number of PVR within a segment ranging from 7 to as low as 0).

Figure 4: Difference in $Time_{min}$, $Power_{min}$, $\Delta-Imp_{min}$, CF_{min} , FTI_{min} , AI_{min} , ILI_{max} , and $ALCI_{min}$ between all segments without PVR vs. all segments with PVR. Red scatter markers represent anterior segments. Pink scatter markers represent posterior segments. Abbreviations similar to Figure 1. See text for further explanation.

Comparison of segments with or without PVR in anterior and posterior segments

Weakest link analysis was performed on anterior wall and posterior wall separately (box and whisker plots, Fig. 5). Compared to durable anterior segments ($n = 303$), anterior segments with PVR ($n = 27$) were characterized by significantly lower $\text{Time}_{\min}$ ($p < 0.001$), lower $\Delta\text{-Imp}_{\min}$ ($p = 0.005$), $\text{FTI}_{\min}$ ($p = 0.005$), $\text{AI}_{\min}$ ($p < 0.001$), higher $\text{AILD}_{\max}$ ($p = 0.001$) and lower $\text{ALCI}_{\min}$ ($p < 0.001$). Compared to durable posterior segments ($n = 455$), posterior segments with PVR ($n = 17$) were characterized by significantly lower $\text{Power}_{\min}$ ($p = 0.02$), $\text{CF}_{\min}$ ($p = 0.003$), $\text{FTI}_{\min}$ ($p = 0.011$), higher $\text{AILD}_{\max}$ ($p < 0.001$) and lower $\text{ALCI}_{\min}$ ($p = 0.001$).

Figure 5: Upper panels: difference in $\text{Time}_{\min}$, $\text{Power}_{\min}$, $\Delta\text{-Imp}_{\min}$, $\text{CF}_{\min}$, $\text{FTI}_{\min}$, $\text{AI}_{\min}$, $\text{AILD}_{\max}$, and $\text{ALCI}_{\min}$ between anterior segments without PVR vs. anterior segments with PVR. Lower panels: idem for posterior segments. Abbreviations similar to Figure 1.

Table 2: Comparison of overall segments with and without PV reconnection

Median [IQR]	Overall segments without PVR vs. segments with PVR			Segments without PVR vs. segments with acute PVR only			Segments without PVR vs. segments with late PVR only		
	No PVR (n = 758)	PVR (n = 44)	p value	No PVR (n = 775)	Acute PVR (n = 25)	p value	No PVR (n = 781)	Late PVR (n = 19)	p value
Time_{min}(s)	35 [29-49]	33 [17-43]	0.054	35 [26-49]	34 [22-44]	0.368	35 [26-48]	25 [11-43]	0.18
Power_{min} (W)	20 [20-26]	22 [20-25]	0.513	20 [20-25]	20 [20-25]	0.852	20 [20-26]	23 [20-25]	0.316
Δ-Imp_{min} (Ω)	7 [4-11]	5 [3-7]	0.002	7 [4-11]	5 [4-8]	0.057	7 [4-11]	4 [3-6]	0.11
CF_{min} (g)	11.8 [8.8-16.3]	8.5 [7.0-11.8]	0.001	11.7 [8.8-16.3]	8.0 [6.6-11.5]	0.002	11.7 [8.7-16.3]	9.0 [7.1-12.2]	0.015
FTI_{min} (au)	473 [393-607]	351 [155-802]	<0.001	472 [390-606]	360 [200-503]	0.006	472 [390-605]	341 [100-486]	0.002
AI_{min} (au)	408 [377-495]	367 [307-417]	0.001	408 [376-489]	367 [317-420]	0.013	408 [376-491]	352 [267-414]	0.003
AIID_{max} (mm)	5.5 [4.6-6.6]	6.8 [5.6-8.8]	<0.001	5.6 [4.6-6.7]	6.7 [5.5-8.7]	0.001	5.5 [4.6-6.7]	7.1 [5.6-8.8]	0.002
ALCI_{min} (%)	104 [74-132]	74 [45-94]	<0.001	103 [73-132]	60 [44-89]	<0.001	103 [73-132]	82 [46-105]	0.007
									0.204

Table 3a: Overall results per segment - right side

Median [range]	Time _{min} (s)		Power _{min} (W)		Δ Imp _{min} (Ω)		CF _{min} (g)		FTI _{min} (au)		AI _{min} (au)		AILD _{max} (mm)		ALCI _{min} (%)	
	No PVR	PVR	No PVR	PVR	No PVR	PVR	No PVR	PVR	No PVR	PVR	No PVR	PVR	No PVR	PVR	No PVR	PVR
Segment 1	31 [45]	41 [32]	20 [14]	20 [0]	7 [17]	4 [5]	12 [6]	8 [5]	475 [842]	392 [101]	392 [287]	383 [62]	5.7 [6.6]	5.7 [0.1]	107 [168]	110 [2]
Segment 2	29 [42]	21 [0]	20 [9]	10 [0]*	6 [13]	2 [0]	12 [39]	11 [0]	450 [580]	223 [0]	383 [185]	244 [0]	5.0 [12.5]	5.0 [0]	123 [167]	127 [0]
Segment 3	30 [43]	38 [15]	20 [6]	25 [9]*	5 [17]	5 [2]	9 [23]	8 [4]	427 [606]	360 [147]	396 [183]	387 [66]	5.9 [8.2]	9.9 [1.5]*	103 [124]	71 [48]*
Segment 4	30 [49]	18 [5]*	20 [9]	23 [5]*	4 [9]	4 [11]	9 [10]	7 [5]	376 [418]	133 [137]*	375 [189]	267 [76]*	5.4 [5.6]	7.3 [3.4]*	94 [198]	45 [58]*
Segment 5	30 [48]	32 [37]	20 [10]	22 [3]	6 [15]	4 [1]	12 [20]	9 [0]	437 [540]	377 [146]	385 [247]	382 [62]	6.1 [7.3]	5.5 [1.1]	100 [165]	126 [43]
Segment 6	43 [68]	34 [0]	25 [15]	25 [0]	10 [32]	12 [0]	18 [29]	23 [0]	863 [1147]	788 [0]	525 [168]	504 [0]	4.3 [5.4]	4.7 [0]	143 [234]	82 [0]
Segment 7	37 [51]	32 [0]	29 [15]	20 [0]	9 [18]	4 [0]	14 [22]	12 [0]	583 [977]	534 [0]	487 [279]	423 [0]	5.8 [5.0]	5.0 [0]	100 [316]	- [-]
Segment 8	55 [53]	44 [0]	30 [17]	30 [0]	11 [31]	27 [0]	14 [37]	20 [0]	694 [2177]	1199 [0]	548 [328]	646 [0]	5.5 [5.4]	7.9 [0]	113 [161]	94 [0]
Segment 9	49 [47]	34 [0]	25 [16]	30 [0]	10 [14]	3 [0]	11 [15]	5 [0]	544 [1162]	171 [0]	510 [217]	390 [0]	5.4 [5.1]	6.4 [0]	94 [146]	47 [0]
Segment 10	34 [52]	41 [30]	20 [20]	20 [9]	7 [21]	4 [16]	10 [15]	8 [17]	446 [1072]	475 [353]	406 [274]	400 [50]	5.2 [5.4]	6.0 [3.9]	116 [238]	93 [42]

* p < 0.05

Table 3b: Overall results per segment - left side

Median [range]	Time _{min}		Power _{min}		Δ Imp _{min}		CF _{min}		FTI _{min}		AI _{min}		AIID _{max}		ALCI _{min}	
	No PVR	PVR	No PVR	PVR	No PVR	PVR	No PVR	PVR	No PVR	PVR	No PVR	PVR	No PVR	PVR	No PVR	PVR
Segment 1	32 [51]	- [-]	20 [10]	- [-]	9 [28]	- [-]	16 [34]	- [-]	505 [1412]	- [-]	400 [271]	- [-]	5.7 [7.5]	- [-]	110 [262]	- [-]
Segment 2	31 [37]	53 [-]	20 [5]	21 [-]*	8 [21]	11 [-]	16 [31]	15 [-]	476 [615]	794 [-]	395 [103]	468 [-]	5.6 [9.8]	8.8 [-]	106 [221]	76 [-]
Segment 3	25 [37]	33 [34]	20 [9]	20 [0]	6 [10]	4 [2]	15 [26]	9 [4]*	466 [609]	227 [118]*	378 [174]	302 [95]*	5.8 [5.6]	4.6 [1.1]	96 [131]	86 [41]
Segment 4	26 [56]	- [-]	20 [15]	- [-]	5 [14]	- [-]	12 [27]	- [-]	422 [670]	- [-]	367 [243]	- [-]	5.9 [4.7]	- [-]	92 [118]	- [-]
Segment 5	27 [48]	- [-]	20 [18]	- [-]	8 [23]	- [-]	11 [17]	- [-]	391 [524]	- [-]	371 [169]	- [-]	5.7 [7.8]	- [-]	93 [204]	- [-]
Segment 6	59 [40]	- [-]	30 [16]	- [-]	12 [20]	- [-]	15 [46]	- [-]	779 [2026]	- [-]	535 [240]	- [-]	4.2 [6.0]	- [-]	142 [491]	- [-]
Segment 7	48 [57]	11 [0]	30 [15]	34 [0]	8 [19]	8 [0]	8 [29]	8 [0]	474 [1265]	100 [0]	520 [346]	306 [0]	5.6 [11.3]	6.4 [0]	98 [260]	62 [0]
Segment 8	44 [60]	28 [31]	30 [15]	27 [15]	7 [35]	6 [9]	10 [23]	10 [14]	478 [1664]	191 [1037]	505 [296]	367 [331]	6.6 [11.3]	6.8 [5.6]	81 [261]	63 [40]
Segment 9	52 [39]	36 [39]*	25 [15]	25 [10]	6 [15]	5 [6]	9 [12]	9 [8]	513 [674]	315 [457]	485 [199]	377 [259]*	6.0 [11.1]	8.0 [6.4]	84 [115]	45 [100]
Segment 10	35 [55]	50 [14]	20 [15]	20 [1]	8 [24]	10 [7]	12 [25]	7 [1]	481 [934]	372 [168]	402 [273]	369 [89]	5.9 [6.4]	8.0 [1.1]	106 [161]	44 [4]

* p < 0.05

Diagnostic accuracy of transmural/contiguity criteria to predict a durable segment

In multivariable analysis, all parameters significantly predicted durability except for time and power. Overall, ROC curve analysis for all segments together showed the highest diagnostic accuracy for ALCI (area under the curve, AUC = 0.73), compared to AILD (0.70, $p = 0.601$), FTI (0.69, $p = 0.460$), CF (0.68, $p = 0.339$), AI (0.67, $p = 0.331$), and Δ -Imp (0.64, $p = 0.126$).

ROC curve analysis for anterior and posterior wall separately is given in Figure 6. In the lower panels, we plotted the specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) to predict durable segments at known clinical cutoffs.[11,12,14] Both at the anterior and posterior wall, ALCI was invariably associated with the highest specificity and PPV to predict a durable segment.

The relatively low sensitivity of each parameter is evident from the significant overlap in values below or above the cutoffs of segments with and without PVR (Fig. 5).

Figure 6: Diagnostic accuracy of transmural/contiguity parameters to predict durable isolation within a given segment for the anterior wall (left upper panel) and posterior wall (right upper panel). In the lower panels we plotted the specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) to predict durable segments at known clinical cutoffs.[11,12,14]

DISCUSSION

Main findings

This study is the first to objectively show that criteria for both transmural and contiguity are major determinants of durable PVI in CF guided ablation. The combination of interlesion distance and parameters of lesion depth (power, time and contact force) into a unique variable, the ablation line contiguity index (ALCI), provides the best criterion to predict durable PVI. Therefore, an ALCI-guided ablation procedure has the potential to further reduce significantly the need for repeat procedures after ablation for paroxysmal AF.

Time of RF application, power and contact force as targets for RF ablation

The depth of RF lesions is dependent on the time and delivered power of the RF application.[15-16] The present observation that segments with acute or late PVR are not characterized by shorter time nor minimal power of RF application, can be explained by the nature of the ablation protocol allowing only limited variation in time and power at the anterior and posterior wall. Also contact force (or force-time integral) has been shown as a major determinant of RF lesion volume in experimental studies.[17-19] In the EFFICAS I study, the site of late PVR correlated strongly with minimal CF and FTI. Minimal CF of 20g and minimal FTI > 400 gs at each PV segment correlated with a 95 % probability of durable PV isolation (at 3 months after index procedure).[12] Likewise Park et al showed that a cutoff value of 10g CF (and a minimum FTI of 400 gs) has high sensitivity and specificity for acute durability of PVI.[20] Our data confirm that segments with acute or late PVR are characterized by RF applications with lower minimal CF and FTI. However our data suggest that FTI > 400 gs is associated with a poor accuracy to predict durable segments (specificity of 47 % at anterior wall and 59 % at the posterior wall). Other limitations speak against the use of CF and FTI to guide point-by-point RF ablation for PVI. Practically it is impossible to reach 10 to 20 g at each RF site (as evidenced by the current distribution of CF values) and, by targeting 20 g, one might introduce catheter dislocation, unnecessary tissue compression, and longer procedure time. Moreover calculation of contact force (and FTI) might be inaccurate due to inadequate calibration, contact with neighboring electrodes or the angle of incidence (underestimation when parallel contact).[21] Finally, FTI as a marker of lesion quality suffers from two major limitations: first, FTI (calculated as the product of force by application time) suggests a linear lesion formation during ablation whereas it is known that lesion volume growth describes a mono-exponential curve.[15] Second, FTI ignores the important and evident role of power delivery in lesion creation. Guerra et al. showed that lesions with an FTI value of 300 gs at 35 W had a volume more than three times that of the lesion created with 20 W.[22] As such it was surprising that FTI 400gs was found to be predictive for gaps in a multi-center study in which power was reported to vary from 10 to 40 W.[12]

Impedance drop

In experimental studies, initial impedance decrease is a good correlate for RF lesion volume [15-19] and in patients, initial impedance decrease is an indicator of good catheter contact.[23] Chinitz et al showed that areas of late PVR were associated with sites with small impedance decrease ($< 10 \Omega$) during point-by-point PVI.[14] The present data – obtained in exclusively paroxysmal AF undergoing only CF-guided PVI - confirm these findings and imply that obtaining/targeting a minimal impedance decrease of $> 10 \Omega$ is likely to result in a durable segment. The fact that impedance decrease is often an observation (rather than a modifiable parameter) speaks against the use of impedance decrease as an optimal ablation target.

Ablation index and its putative role as ablation target values

Ablation index is based upon the experimental work of Nakagawa et al.[10] This index, incorporating contact force, power and time in a weighted formula, predicted lesion depth in the canine ventricle with high accuracy. By taking into account the greater contribution of power (over contact force) and of the initial time of ablation, it differs from force-power-time integral calculated at the multiplication of force, power and time.[20] Gupta et al recently showed that ablation index correlated with impedance drop and that minimal ablation index within a segment was predictive of reconnection at that segment at repeat EP study.[11] Our data confirm that there is a significant difference in minimal AI values required to obtain durable segments in the anterior part of the circle (> 644 au) compared with the posterior segments (> 437 au), suggestive of thicker atrial tissue in anterior regions. In the present study the accuracy of AI was at the higher end of the spectrum but in absolute values not so much higher compared to CF and FTI. AI-guided ablation might have the following advantages; (1) the target can be reached readily at each site within the circle (e.g. by increasing power at sites with low but stable contact). (2) In contrast to FTI, lesion quality is expected to be similar at a certain AI value (despite differences in power, force and time of application required to reach that value). Several observations speak against the ablation index as the sole target: (1) it does not take into account characteristics of underlying atrial tissue (composition, thickness), (2) it ignores the importance of lesion contiguity.

Contiguity of RF applications

One of the key findings of this study is that interlesion distance is predictive of reconnection of that segment. Automated interlesion distance is a new and objective criterion defined as the center-to-center distance between two, automatically acquired, neighboring RF tags. Our data suggest that

targeting AILD's of < 5 mm might be the 'missing link' towards durable PVI. Prior studies already hinted to the importance of contiguous lesions to obtain acute durable isolation. Reddy et al showed that closing the "visual" gap was essential for acute durable PVI, [24] whereas Park et al showed that acute PVR despite $CF \geq 10$ g was explained by ablation sites with a long interlesion distance (≥ 5 mm).[20] Those studies however were limited by the fact that RF tags were taken manually throughout the procedure, whereas in the present study tags were acquired automatically based upon preset criteria of force and stability (Visitag®). The observation that segments can be durable despite higher AILD values (limited sensitivity), might be explained by inaccuracy in 3D electro-anatomical mapping, or the presence of underlying tissue not relevant to atrio-venous conduction.

Ablation line contiguity index

In the present study we introduced ablation line contiguity index (ALCI), as a novel marker to detect and/or avoid the weakest link in the ablation chain. Based upon AI and AILD, this index combines contiguity and transmuralty to assess integrity of the PV circle. In a multivariable model, ALCI remained independently predictive of segment reconnection. Moreover ROC curve analysis suggested that ALCI (target ≈ 100 %) has the highest accuracy to predict durable segments. ALCI as ablation target has the following advantages; 1) ALCI cutoff value is similar for the anterior and posterior wall. 2) In keeping with the concept that the chain of ablation lesions is only as strong as its weakest link, we hypothesize that integrity of the complete RF circle can be quantified by one single, fully-automated value (i.e. lowest ALCI value within the circle). As such it is expected to enhance outcome (and its reproducibility) after CF guided ablation. Obvious limitations are that it is dependent on CF, AI, AILD (and their inherent disadvantages) and that it still oversimplifies the holistic nature of lesion formation in atrial tissue.

Clinical implications

We hypothesize that AILD and ALCI-guided ablation will increase freedom of AF after CF-guided PVI. Whether this will be associated with higher reproducibility in outcome and safety, is currently being evaluated in a multi-center study. The present findings are an impetus for further research: the moderate sensitivity of ablation targets points to oversimplification of the holistic nature of lesion formation and points to ignoring intra- and inter-patient variation.

Limitations

Sample size of this study was small, which limits the strength of the analysis per segment. The chosen analysis methodology did not take clustering of effects by patients into account. Finally it is possible

that segments were misclassified as durable, knowing that some patients free of AF (not undergoing repeat ablation) have reconnected PVs.

The present clinical cutoffs are all associated with moderate sensitivity. This implies that RF applications with values below the target (or above in case of AILD) might still be associated with durability. As such, cutoff-guided ablation strategies might result in durable isolation at the cost of overshoot and potential safety issue. This needs to be evaluated in prospective clinical studies.

Conclusions

Minimal ablation line contiguity index, a novel ablation quality marker integrating interlesion distance into a weighed formula, is independently predictive of PV reconnection. Similar ALCI values are required to prevent reconnection of anterior and posterior segments. ALCI-guided ablation warrants prospective evaluation for improving freedom of AF.

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4

Chapter 4

Comparison of CLOSE-PVI to conventional contact force-guided PVI

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ABSTRACT

Background: We have recently shown that a contact force (CF) guided ablation protocol respecting region-specific criteria of lesion contiguity and lesion depth ('CLOSE' protocol) is associated with high incidence of acute durable pulmonary vein (PV) isolation and a high single-procedure arrhythmia-free survival at 1 year. In the present study, we compared efficiency, safety and efficacy of 'CLOSE'-guided PVI to conventional CF guided PVI.

Methods: 50 consecutive paroxysmal atrial fibrillation (AF) patients underwent PV encircling using a CF-sensing catheter targeting an interlesion distance (ILD) $\leq 6\text{mm}$ and ablation index ≥ 400 and ≥ 550 at posterior and anterior wall ('CLOSE' group). Results were compared to the last 50 patients undergoing conventional CF-guided PVI ('CONV-CF' group). All patients underwent adenosine testing after PVI. Arrhythmia recurrence was defined as any atrial tachyarrhythmia (ATA) $>30\text{s}$ on Holter at 3, 6 and 12 months.

Results: Clinical characteristics did not differ. Contact force variability was comparable in between both groups (proportion of applications with intermittent contact 2% in 'CLOSE' vs 1% in CONV-CF, $p=0.67$). In the 'CLOSE' group, procedure time and RF time per circle were shorter (respectively $149\pm 33\text{min}$ vs $192\pm 42\text{min}$, $p<0.0001$ and $18\pm 4\text{min}$ vs $28\pm 7.5\text{min}$, $p<0.0001$) and incidence of adenosine-proof isolation was higher (97% vs 82%, $p<0.001$). No complications were observed in the 'CLOSE' group, 1 tamponade in the 'CONV-CF' group. At 12 months, single-procedure freedom from ATA was 94% in 'CLOSE' vs 80% in 'CONV CF' group ($p<0.05$). In both groups, the majority of reconnections at repeat were associated with either $\text{ILD}>6\text{mm}$ and/or $\text{AI}<400/550$ (100% vs 83%, $p=0.99$).

Conclusions: 'CLOSE'-guided PVI improves procedural and 1-year outcome in CF-guided PVI while shortening procedure time. Improvement cannot be explained by differences in CF variability and is most likely due to the strict application of criteria for contiguity and ablation index. A randomized controlled trial is needed to exclude the possible contribution of a learning curve.

Introduction

Pulmonary vein isolation (PVI) is the cornerstone for successful treatment of paroxysmal atrial fibrillation (AF).^{1,2} We have recently shown that a contact force (CF)-guided ablation protocol aiming to enclose the veins with contiguous (interlesion distance ≤ 6 mm, ILD) and optimized RF lesions (ablation index $\geq 400/550$, AI) is associated with a high incidence of acute durable PV isolation and a high single-procedure arrhythmia-free survival at 1 year (the 'CLOSE' protocol).^{3,4}

Randomized data on the superiority of 'CLOSE'-guided PVI are lacking. In the present study, we provided comparative data on the efficiency, safety and efficacy of 'CLOSE'-guided PVI to a historical control group of conventional CF guided PVI.

Methods

Study subjects

From August 2013 all patients undergoing CF-guided ablation for AF at the St-Jan Hospital Bruges are followed in a prospective database approved by the local institutional review committee. This database implies collecting patients' written informed consent, a detailed case report form of the procedure and follow-up with Holter-ECGs at 3, 6 and 12 months. In this manuscript we present the analysis of the first 50 cases performed according to the 'CLOSE'-criteria. Results were compared to the last 50 cases performed with conventional CF-guided PVI (in which the operator was blinded to AI and no formal ILD criterion was put forward).

'CLOSE'-guided PVI

PVI was performed by 4 operators. In anaesthetized patients esophageal temperature monitoring (SensiTherm™, St Jude Medical Inc, 76 Minnesota, US) was performed. To avoid discomfort, we did not use temperature monitoring under conscious sedation. Intravenous heparin (100IU/kg) was administered and continuously infused (ACT > 300sec). After transseptal puncture, a decapolar Lasso catheter and a CF catheter (Thermocool SmartTouch®, Biosense-Webster Inc., Diamond Bar, CA, USA) were positioned in the left atrium and calibration of CF and respiratory gating were performed. Then we predefined the RF circle around the PVs (nephroid shape) on the 3D-geometry (Carto System®, Biosense Webster Inc.). Point-by-point RF delivery was performed during sinus rhythm aiming for a contiguous circle enclosing the veins. Real-time automated display of RF applications (Visitag®, Biosense Webster Inc.) was used with predefined settings of catheter stability (3mm for 8sec) and minimum CF (30% of time > 4gr). RF was delivered (EP Shuttle ST-3077, Stockert GmbH, Freiburg, Germany) in a power-controlled mode (without ramping) aiming for 35W (irrigation flow up to 30cc/min) irrespective of posterior or anterior ablation. Reasons for occasional lowering of RF power were high CF at baseline (≥ 30 g) and increase in the tip T° during RF ($> 40^\circ$). RF was delivered until an AI of ≥ 400 at the posterior wall/roof and ≥ 550 at the anterior wall (Fig.1, right panel). Once the target AI was reached, the RF application was stopped and the catheter was moved to an adjacent

spot. Only after verifying stability, contact force and ILD, a new application was started (no catheter dragging). In case of instability leading to an RF tag not reaching the AI target, a new RF application reaching the AI target was applied. Maximal ILD between two neighboring lesions was $\leq 6\text{mm}$ (Fig.1, right panel). In case of chest pain or intra-esophageal T° rise $>38.5^\circ\text{C}$ during posterior wall ablation, RF delivery was stopped at an AI of 300 (but not before). In the absence of first-pass isolation (i.e. no isolation after completing the circle), touch-up ablation was delivered until PVI. After PVI we waited for 20 minutes after which adenosine (dose resulting in atrio-ventricular block) was given 4 times (with the Lasso in its corresponding position). In case of reconnection during waiting time or during adenosine (acute PVR), the site of reconnection was allocated and treated with touch-up ablation until PVI was resistant to subsequent adenosine challenge. In case of pre-procedural or procedural documentation of typical flutter, cavotricuspid isthmus (CTI) ablation was performed until bidirectional block.

Conventional CF-guided PVI procedure

Ablation was performed by the same 4 operators, using the same anesthesia protocol, transseptal access and catheters. Also identical were calibration of CF catheter, respiratory gating, reconstructing of 3D-geometry, the predefined nephroid RF circle, Visitag® settings, RF generator, and RF mode. In contrast to ‘CLOSE’, RF was delivered for 30sec (at 25W) at the posterior wall and roof, and for 60 sec (at 35W) at the anterior wall. According to data from the EFFICAS studies, CF target was $>10\text{ g}$ (Fig.1, left panel). No specific force-time-integral (FTI) threshold nor strict criteria for contiguity were targeted. AI was not available to the operators at the time of the procedure. In case of chest pain or intra-esophageal T° rise $>38.5^\circ\text{C}$ during posterior wall ablation, RF delivery was stopped prematurely. Assessment and management of first-pass isolation and acute PVR was identical as for the ‘CLOSE’ group. CTI ablation was performed if appropriate.

Conventional CF guided PVI

CLOSE guided PVI

Figure 1: Left panel: Conventional CF-guided PVI group, Right panel: ‘CLOSE’-guided PVI. See text for explanation. In the ‘CLOSE’ protocol, 42% of circles are characterized by one or more applications with an AI target of 300 at the posterior wall. PVI=PV isolation, ILD=interlesion distance.

Off-line analysis of criteria to assess integrity of the deployed RF circle

Each procedure was exported and analyzed offline. For each RF tag within the circle we determined time of application (s), median delivered power (W), impedance drop (D-Imp, Ω), average CF (CF, g), force-time integral (FTI, gs) and AI (arbitrary unit, au). Custom-made software was used to automatically determine the path of encircling, the perimeter of the RF circle, ILD (center-to-center distance, mm) and ablation line contiguity index (ALCI). ALCI was developed as a criterion to algorithmically score the combination of contiguity and lesion depth and is defined as the ratio of the estimated width of a transmural lesion (determined by the AI) over its distance (ILD) to the closest transmural lesion.

To determine the weakest link in a given RF circle, each circle was divided into 10 segments, each encompassing 3 to 5 RF tags. [13] For each segment we determined for each measure the 130 minimal (Time_{min}, Power_{min}, D-Imp_{min}, CF_{min}, FTI_{min}, AI_{min}, ALCI_{min}) or maximal value (ILD_{max}). In the CF group 10 procedures were not available for off-line analysis.

We analyzed CF variability using custom-made algorithm (Fig.2). For each application thereconstructed instantaneous CF curve and histogram were analyzed.^{5,6} Constant contact was defined as CF60% variability of absolute CF $\leq$ 10g. Variable contact was defined as the CF60% variability of absolute CF $>$ 10g. Intermittent contact was classified when the percentage of absolute CF dropping below 3g is more than 25% of the application.

Figure 2: Representative examples of applications with constant contact, variable contact and intermittent contact. Right lower panel: the proportion of applications with intermittent contact is equally low in both groups. CF, contact force; CONV-CF, conventional contact force.

Follow-up

Complications were reported on the CRF and collected during follow-up. After ablation, anticoagulation and previously failing anti-arrhythmic drug therapy (ADT) were continued. At 3 months, anticoagulation was continued according to stroke risk, whereas ADT was continued at the discretion of the treating physician. Clinical evaluation and ECG were performed at 1, 3, 6 and 12 months. Holter-ECG was performed at 3 months (24h), 6 months (24h) and 12 months (7 day) or in case of symptoms. Freedom from recurrence was defined as 1-year absence from AF/AT/AFL >30 seconds beyond a 3-month blanking period.

Statistical analysis

Normality of data distribution was tested with Shapiro-Wilk test. Continuous variables are expressed as mean±SD if normally distributed, medians with IQR if non-normally distributed, and dichotomous variables as percentage. Respectively, variables were compared using Student's t test, Mann–Whitney U test, and Fisher's exact test. Linear mixed model tests were used to evaluate difference of ablation parameters between the CF-group versus the CLOSE group. Kaplan–Meier estimate was used to compare freedom from AF between both groups during 12 months follow-up period. Multivariable logistic regression was used to assess the association between the different parameters and PVR. P values <0.05 were considered statistically significant. All statistical analyses were performed in SPSS Statistics (IBM Corporation, Armonk, New York, USA).

Results***Patient characteristics***

All patients had paroxysmal AF. There were no differences in baseline clinical characteristics between two groups (Table 1).

Table 1. Patient characteristics

	Conventional CF group (n=50)	CLOSE group (n=50)	p value
Paroxysmal AF	50 (100 %)	50 (100 %)	> 0.99
Age, y	62±10	61±11	0.466
Male, n	31 (62%)	36 (72 %)	0.395
BMI, kg/m ²	26.6±4.3	27.0±3.7	0.678
Arterial hypertension, n	20 (40%)	15 (30%)	0.402
Structural heart disease, n	7 (14%)	3 (6%)	0.318
Diabetes, n	0 (0%)	2 (4%)	0.495
CHA ₂ DS ₂ VASc score ≥2, n	25 (50%)	16 (32%)	0.068
Left atrial diameter, mm	40.4±4.4	39.9±3.9	0.597
Electrical cardioversion, n	7 (14%)	3 (22%)	0.436
1 st AF episode to PVI, months	24 [12-72]	24 [12-84]	0.623
Resistance to ADT, n	47 (94%)	45 (90%)	0.715

RF characteristics and integrity of the RF circle

Two representative cases illustrating the difference in RF parameters and integrity of the deployed RF circles are given in Fig.3. Compared to the conventional CF-guided procedure (left panel), the ‘CLOSE’ procedure (right panel) is characterized by applications with shorter duration (ranging from 11 to 61s), a higher rate of applications with high power (≥ 30 W), a higher rate of RF tags with a marked impedance drop (≥ 7 W), applications with lower FTI values (ranging from 184 to 875gs) and a higher rate of applications with an AI of ≥ 550 . The range of obtained CF values (5 to 37g) is not different from the conventional CF case. Finally, whereas the perimeter of the circles is comparable, the ‘CLOSE’-guided circles are characterized by enclosing lesions all with 172 and ILD ≤ 6 mm and an ALCI of $>100\%$.

Conventional CF guided PVI

CLOSE guided PVI

Figure 3: RF characteristics obtained during CF-guided PVI procedure (left panels) vs ‘CLOSE’-guided PVI procedure (right panels). The deployed circles are represented color-coded (dichotomous or continuous) for each of the following criteria: application time, power, impedance drop (Delta-Imp), contact force (CF), force-time integral (FTI), ablation index (AI), perimeter, interlesion distance (ILD) and ablation index contiguity index (ALCI). See text for further explanation.

Weakest link analysis for all segments is summarized in Fig.4. Compared to the CF group, segments in the ‘CLOSE’ group are characterized by lower application time_{min} ($p<0.001$), higher delivered power_{min} ($p<0.001$), higher obtained $\Delta\text{-Imp}_{\text{min}}$ ($p<0.001$), similar CF_{min} ($p=0.401$), lower FTI_{min} ($p<0.001$), higher AI_{min} ($p<0.001$), lower ILD_{max} ($p=0.032$), and higher ALCI_{min} ($p<0.001$). RF characteristics for the posterior and anterior segments separately are illustrated in the scatter plots.

Compared to the CF group, applications in the ‘CLOSE’ group were characterized by the same proportion of applications with intermittent contact (2% vs 1%, $p=0.67$) (Figure 2, right panels).

In the ‘CLOSE’ group, applications at the posterior wall lasted 23 ± 6 s overall. In 42 out of 100 circles (42%), there was at least one application with an AI target of 300. In those ‘low AI183 target’ lesions, applications lasted for 13 ± 4 s only.

Figure 4: Weakest link analysis. Difference in $Time_{min}$, $Power_{min}$, $\Delta-Imp_{min}$, CF_{min} , FTI_{min} , AI_{min} , ILD_{max} , and $ALCI_{min}$ between segments from the CF group (blue box) vs segments from the ‘CLOSE’ group (red box). Scatter markers represent anterior (blue and red) and posterior (light blue and pink) segments separately. Abbreviations similar to Figure 2. See text for further explanation.

Procedural characteristics

Characteristics are given in Table 2. PVI was obtained in all circles. CTI ablation was performed in 11 patients in the CF group and 4 in the ‘CLOSE’ group ($p=0.091$). The use of general anesthesia was comparable between groups. Compared to CONV-CF group, ‘CLOSE’ group was associated with a shorter procedure time (149 ± 33 min vs 192 ± 42 min, $p<0.0001$) (Fig.5). Perimeter of the right and left circles and number of applications per circle were not different. Compared to CONV-CF group, ‘CLOSE’ group was associated with shorter RF time per circle (17 ± 3 min vs 29 ± 8 min, $p<0.0001$ for the right circles, 19 ± 4 min vs 26 ± 6 min, $p<0.001$ for the left circles).

Table 2. Procedure characteristics

	Conventional CF group (n=50)	CLOSE group (n=50)	p value
PV isolation, n	50 (100%)	50 (100%)	> 0.99
CTI ablation, n	11 (22%)	4 (8%)	0.091
General anesthesia, n	18 (36%)	25 (50%)	0.225
Procedure time, min	192±42	149±33	< 0.001
Fluoroscopy time, min	21.3±9.0	26.4±7.8	0.003
Right circles			
Perimeter, mm	138±24	129±19	0.068
RF tags, n	41±10	38±8	0.077
RF time, min	29±8	17±3	< 0.001
First-pass isolation, n	25 (50%)	50 (100%)	< 0.001
Waiting/adeno. proof isolation, n	41 (82%)	49 (98%)	0.008
Left circles			
Perimeter, mm	123±26	122±27	0.985
RF tags, n	37±10	40±10	0.068
RF time, min	26±6	19±4	< 0.001
First-pass isolation, n	29 (58%)	48 (96%)	< 0.001
Waiting/adeno. proof isolation, n	41 (82%)	48 (96%)	0.025

Figure 5: Upper panels. Procedure time and radiofrequency (RF) time per circle. Lower panels. Incidence of first-pass isolation and waiting time/adenosine- proof isolation in both groups. See text for further explanation.

First-pass and waiting time/adenosine-proof isolation

Results are summarized in Fig.5. A limited number of patients did not receive adenosine because of a history of asthma or COPD (5 in the CONV-CF group vs 3 in the 'CLOSE'-group). Compared to CONV-CF group, 'CLOSE' group was associated with higher incidence of first pass isolation (98% vs 54%, $p < 0.0001$) and waiting time/adenosine-proof isolation (97% vs 82%, $p < 0.001$).

1-year freedom from AF/AT/AFL

Kaplan Meier analysis was plotted in Fig.6. At the end of the blanking period 23 patients continued ADT in the CONV-CF group (46%) vs 18 patients in the 'CLOSE' group (36%). Overall, single-procedure 12-month freedom from AF/AT/AFL was 94% in CLOSE compared to 80% in CONV-CF group ($p < 0.05$). Both in patients with and without ADT, 'CLOSE' was associated with a higher freedom from AF/AT/AFL (Fig.6, right panels).

Figure 6: Left panel: Kaplan-Meier curves depicting time to first recurrence of atrial fibrillation (AF), atrial flutter (AFL), or atrial tachycardia (AT) (including a 3-month blanking period) in patients undergoing 'CLOSE'-guided ablation and conventional CF-guided ablation. Right panels: Arrhythmia-free survival for patients that continued anti-arrhythmic drug therapy (ADT) at the end of the blanking period (upper panel) and patients without ADT (lower panel).

Safety of 'CLOSE'-guided vs conventional CF-guided PVI

No symptomatic complications were observed in the 'CLOSE' group. In the conventional CF group we observed 1 tamponade during transseptal puncture requiring pericardiocentesis and prolonged hospitalization. Finally there was no significant difference in hospitalization length.

Predictors of AF recurrence and mechanism of reconnections at repeat

Compared to patients with successful 1-year outcome ($n=87$), patients with recurrence ($n=13$) had similar baseline clinical characteristics. Use of 'CLOSE' protocol was an independent predictor for maintenance of sinus rhythm (54% vs 23%; OR=3.917; 95% CI: 1.008-15.220).

In the CONV-CF group (7 patients undergoing repeat) there were 216 23 sites of reconnection in 18 veins, in the CLOSE group (3 patients undergoing repeat), we observed 7 sites of reconnection in 7 veins. We observed no difference in spatial distribution of reconnection sites in between both groups (43% posterior in the CLOSE group vs 48% posterior in the CF group) (Figure 7). In both groups majority of reconnections were associated with either $ILD > 6\text{mm}$ and/or $AI < 400/550$ (7 out of 7, 100% in 'CLOSE' vs 19 out of 23, 83% in 'CONV-CF', $p=0.99$).

Figure 7: Spatial distribution of the sites of reconnection in both treatment groups and their putative mechanism for reconnection. See text for explanation. CONV-CF, conventional contact force; LI, left inferior; LS, left superior; PA, postero-anterior; PVI, pulmonary vein isolation; PVR, pulmonary vein reconnection; RI, right inferior; RS, right superior.

Discussion

Main findings

This study shows that, compared to conventional CF-guided ablation, an ablation strategy aiming to enclose the PVs with contiguous and optimized RF lesions results in a higher rate of adenosine-proof isolation and higher single-procedure arrhythmia free survival. A single procedure freedom of 94% at 1-year is obtained without compromising safety and with shorter procedure and RF times. Whereas in the absence of randomization this study should be interpreted as hypothesis generating only, our data might provide the necessary base to setup a randomized control trial.

Single-procedure freedom of AF after point-by-point RF PVI

The recent FIRE and ICE study confirmed a 64% single-procedure freedom from AF after point-by-point RF ablation.^{7,8} Since the introduction of CF-sensing technology in ablation catheters, several studies suggested enhanced 1-year freedom from AF.⁹⁻¹² In a 2-centre prospective parallel cohort study, CF-guidance was associated with better 1-year arrhythmia free survival (88% v 66%).⁹ In a single center controlled study including 60 paroxysmal AF patients, CF-guidance was associated with higher 1-year freedom from AF (90% vs 67%).¹⁰

Although randomized controlled studies failed to demonstrate a beneficial effect of CF239 guidance on AF free survival at 1 year,¹³⁻¹⁴ our data confirm the $\approx 80\%$ single-procedure freedom of AF after CF-guided PVI (historical control group).

More importantly, the present data suggest that further optimization of CF-guided ablation by adding objective criteria (the 'CLOSE' criteria of ILD and AI) further improves acute durable isolation rates and 1-year single-procedure outcome. Several observations speak for the reliability of the currently reported $>90\%$ single-procedure freedom of AF after 'CLOSE'-guided PVI. First, this high success rate is in line with the hypothesis that avoiding weak links within the deployed RF circle is the key to durable PVI and clinical success.³ Second, also other research groups, respecting a contiguous encircling, reported a $>90\%$ single-procedure arrhythmia-free survival in CF-guided PVI. A recent sub-analysis of SMART-AF in 40 paroxysmal AF patients showed 93% freedom from arrhythmia in those patients with short ILD.¹⁵ Likewise, Itoh et al reported single-procedure freedom of 96% at 1 year after a procedure in which CF-guided PVI was performed using catheter tip dragging in steps of $\approx 2\text{mm}$.¹⁶ Finally, the currently reported high single-procedure freedom after PVI for paroxysmal AF is in line with what one can expect after durable PVI. On the one hand it is known that non-PV triggers account for $<10\%$ of paroxysmal AF,¹⁷ on the other hand a strategy of aiming for durable PVI with repeat ablations is known to cumulate in a $>90\%$ freedom of AF.¹⁸

Conducting a randomized controlled trial confirming the superiority of the 'CLOSE'-protocol will be challenging. In a prospective control group claiming 'conventional CF' only, it seems impossible to avoid the bias of previous experience with AI and ILD. Also other study designs using other control groups will face challenges. Although no randomized trial showed incremental benefit of CF-sensing catheters, it seems unethical to design a control group using catheters without CF sensing. Finally, a control group using catheters with other energy sources will be prone to the obvious criticism of bias introduced by operator experience or preference. Therefore, we believe that the current database of 100 consecutive cases offers a unique cross-sectional view allowing the comparison of both strategies.

What could explain the higher success rate of the ‘CLOSE’ protocol?

The improved procedural and 1-year outcome in ‘CLOSE’ are in line with the weakest link hypothesis.³ Whereas in the conventional CF group there were no objective ranges (not even 268 for contact force), the RF circle in the ‘CLOSE’ protocol was characterized by lesions all with an ILD $\leq$ 6mm and an AI $\geq$ 400(300) at posterior 269 and 550 at anterior wall. Those target values, resulting in an ablation line contiguity index of 100%, were found to be predictive for durable isolation in CF-guided PVI.³ The observation that the majority of reconnections in both groups were due to either ILD > 6mm and/or AI < 400/550 also supports this hypothesis.

Nevertheless, improved outcome might be (partly) due to other factors beyond ILD and AI as well. First, one might speculate that the improvement in the ‘CLOSE’ protocol is mediated by the use of higher power (35W at the posterior wall instead of 25W) and shorter application times to obtain AI targets. Although we did not observe any major shift in the spatial distribution of gaps at repeat in between both groups and although there exists preclinical evidence that lesion size is similar at a certain AI value (despite differences in power, force and time of application to reach that value),¹⁹ no clinical study compared quality of lesions being delivered with different settings. Second, one might hypothesize that improved outcome is due to reduced contact force variability during RF delivery in the ‘CLOSE’ protocol. Stability of lesion delivery, as shown by Shah et al. is a critical determinant of lesion size,⁵⁻⁶ and one might expect less CF variability during shorter applications. Of interest however, we did not observe any difference in CF variability in between both groups. In fact, the proportion of applications with intermittent contact was equally low in both groups, due to the use of combined stability and force criteria in VisiTag module. Finally, improved outcome could be (partly) due to a learning curve promoted by the experience of technology and algorithm application. In the absence of a randomized trial this hypothesis can never be refuted.

Safety precautions during ‘CLOSE’-guided ablation at the posterior wall

The present patient cohort is too small to draw any definitive conclusions regarding safety in ‘CLOSE’-guided PVI. In a recent study, CF catheters were associated with a high incidence of atrial-esophageal fistula.²⁰ Therefore one could argue that a CF-guided strategy with higher power ablation on the posterior wall aiming at fixed AI target values might be imprudent. So far however we did not detect any clinically relevant esophageal injury using the ‘CLOSE’ protocol.⁴ This might be due to the following reasons: (1) in the ‘CLOSE’ protocol, we strive for high stability rather than high contact force during RF delivery. Avoiding high force might avoid pushing the posterior wall towards the esophagus; (2) In our approach, RF is delivered at the left atrial-PV junction rather than at the thin free wall of the posterior left atrium; (3) AI target was reduced to 300 at the posterior wall in the presence of pain perception or temperature rise (general anesthesia). This lower target was also maintained for the rest of the posterior wall lesions of that circle. As a result, 42% of ‘CLOSE’ circles were characterized by one or more lesions with an AI < 400; (4) Finally, due to the use of relatively higher

power (35W), the ‘CLOSE’ protocol is associated with short applications at the posterior wall (23 ± 6 s), even as short as 13 ± 4 sec in case of possible signs of esophageal injury. Short applications might be associated with a lower risk of deep penetration of conductive heating to adjacent structures such as the esophagus.

Of course, safety (and its putative determinants) need to be investigated in properly powered clinical trials or in studies investigating esophageal thermal asymptomatic lesions using esophageal endoscopy.

Towards a short and standardized PVI procedure

In the present study, we observed that ‘CLOSE’-guided PVI is associated with a significant 30% reduction in procedure time and nearly 50% reduction in RF time. A shorter procedure time in the ‘CLOSE’ protocol is explained by the absence of PV reconnections (no time spent chasing gaps at the junction) and a reduction in RF time. Shorter RF time is explained by the markedly shorter applications (use of AI allowing delivery of higher power) and a trend towards less applications. Although the 192 ± 42 min procedure time and 56 ± 11 min total RF time, as observed in the ‘CONV-CF’ group, are in line with procedure time and RF time previously reported in CF-guided procedures (223 ± 86 min and 61 ± 36 min in the SMART-AF study,¹¹ and 194 ± 23 min and 41 ± 7 min in the multicenter UK study¹³) we can never exclude the contribution of a learning curve.

Finally, we believe that the ‘CLOSE’ protocol offers the base for a straightforward and standardized PVI procedure. Rather than isolation of the veins, the endpoint for the procedure is a perfect circle leading invariably to PVI. Introduction of objective and verifiable criteria (AI and ILD) should lead to reproducible outcome across centers and operators.

Limitations

Although 100 patients were enrolled in this pragmatic parallel cohort study, several limitations need to be underlined: our study is monocentric, non-randomized and small-sized. Despite a 24h-Holter ECG at 3, 6 months and a 7-day Holter-ECG at 12 months and the symptomatic nature of PAF, the discontinuous nature of monitoring can underestimate AF recurrence. Finally anti-arrhythmic drug therapy was not systematically withdrawn after the blanking period, and may have improved clinical success in both groups. The limitations of discontinuous monitoring and single-center nature of the study are being tackled by two ongoing clinical studies (a study monitoring arrhythmia-free survival using subcutaneous loop recorders and a multicenter clinical trial in >300 patients). Finally, the present comparison is too small to draw any definitive conclusions regarding safety.

Conclusions

In the present study we evaluated the feasibility of an ablation protocol aiming to enclose the pulmonary veins with contiguous and optimised RF lesions. Compared to conventional CF guided PVI, we observed a shorter procedure time, significant improvement in acute PVI durability and a higher single-procedure arrhythmia free survival at 1 year.

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5

Chapter 5

Evaluation of clinical outcome of CLOSE-PVI in a larger patient cohort

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Abstract

Background: Reconnections after PV isolation (PVI) are explained by insufficient lesion depth and/or discontinuity of radiofrequency (RF) lesions.

Objectives: To evaluate safety, acute and 1-year outcome of an ablation protocol aiming to enclose the PVs with a contiguous and optimized RF circle by targeting region-specific criteria for (1) lesion depth assessed by ablation index and (2) interlesion distance (ILD).

Methods: 130 consecutive patients with paroxysmal atrial fibrillation (AF) underwent PV encircling using a contact force (CF)-sensing catheter. RF was delivered targeting ILD ≤ 6 mm and ablation index ≥ 400 at posterior and ≥ 550 at anterior wall. Recurrence was defined as any AF, atrial tachycardia or flutter (AF/AT/AFL > 30 s) on Holter at 3, 6 and 12 months.

Results: Procedure and RF time per circle were 155 ± 28 min and 17 ± 5 min respectively. Incidence of first-pass and adenosine-proof isolation were 98% and 98% respectively. One short-lived TIA was observed. At 12 months, single-procedure freedom from AF/AT/AFL was 91.3% in those 104 patients off antiarrhythmic drug therapy (ADT) and 96.2% in those 26 patients on ADT. Single-procedure freedom from both AF/AT/AFL and ADT was 73.1%.

Conclusions: This study suggests that an ablation protocol respecting strict criteria for lesion depth and contiguity results in acute durable PVI followed by a high single-procedure arrhythmia-free survival at 1 year. A prospective, multi-center trial is ongoing.

Introduction

Single procedure freedom from atrial fibrillation (AF) after radiofrequency (RF) pulmonary vein isolation (PVI) is $\approx 70\%$ in patients with paroxysmal AF.(1-3) PV reconnection (PVR) is the major determinant of AF recurrence during follow-up.(4-6) The use of contact force (CF) sensing catheters, allowing to better control energy delivery during point-by-point PV encircling, seems to improve freedom from AF to $\approx 80\%$.(7-10) Nevertheless, acute and late PVR still occur, and data on 1 year outcome are not consistent across studies.(11-12)

We recently showed that acute and late PV reconnections after CF-guided PVI are explained by lack of contiguity and insufficient lesion depth, as assessed by ablation index, within the deployed RF circle.(13-15) Ablation index is based upon the experimental work of Nakagawa et al.(14) This index, incorporating contact force, power and time in a weighted formula, predicted lesion depth in the canine ventricle with high accuracy.

The ‘CLOSE’ protocol is a new approach aiming to enclose the PVs with contiguous and optimized RF lesions by targeting an $ILD \leq 6\text{mm}$ and ablation index (AI) ≥ 400 at the posterior wall and ≥ 550 on the anterior wall. We evaluated safety, acute and 1-year single-procedure outcome after ‘CLOSE’-guided PVI in 130 patients with paroxysmal AF.

Methods

Study subjects

From August 2013, all patients undergoing CF-guided ablation for AF at the St Jan Hospital Bruges are followed in a prospective database approved by the local institutional review committee. This database implies collecting patients’ written informed consent, a detailed case report form of the procedure and follow-up with Holter-ECGs at 3, 6 and 12 months. In this manuscript, we present the analysis of 130 consecutive cases of PVI for paroxysmal AF using the ‘CLOSE’ protocol.

‘CLOSE’-guided PVI

PVI was performed by 4 operators under conscious sedation or general anesthesia. In anesthetized patients esophageal temperature monitoring (SensiTherm™, St Jude Medical Inc, Minnesota, US) was performed. After transseptal puncture (SL0, St Jude Medical), a Lasso catheter and CF catheter (Thermocool SmartTouch®, Biosense-Webster Inc., Diamond Bar, CA, USA) were positioned in the left atrium and calibration of CF and respiratory gating were performed. Then we predefined the RF circle around the PVs (nephroid shape) on the 3D-geometry (Carto System®, Biosense Webster Inc.). Point-by-point RF delivery was performed during sinus rhythm aiming for a contiguous circle

enclosing the veins. Real-time automated display of RF applications (Visitag®, Biosense Webster Inc.) was used with predefined settings of catheter stability (3 mm for 8 sec) and minimum CF (30% of time > 4gr). RF was delivered (EP Shuttle ST-3077, Stockert GmbH, Freiburg, Germany) in power-controlled mode (without ramping) with 25 to 35W (irrigation flow up to 30cc/min). RF was delivered until an AI of ≥ 400 at the posterior wall/roof and ≥ 550 at the anterior wall (Figure 1). In case of dislocation, a new RF application reaching the AI target was applied. Maximal ILD between two neighboring lesions was ≤ 6 mm. In case of chest pain or intra-esophageal T° rise $> 38.5^\circ\text{C}$ during posterior wall ablation, RF delivery was stopped at an AI of 300. In the absence of first-pass isolation (i.e. no isolation after completing the circle), touch-up ablation was delivered until PVI. After PVI we waited for 20 minutes after which adenosine (dose resulting in atrio-ventricular block) was given 4 times (with the Lasso in its corresponding position). In case of reconnection during waiting time or during adenosine, the site of reconnection was located and treated with touch-up ablation until PVI was resistant to subsequent adenosine challenge. In case of (pre-)procedural documentation of typical flutter, cavotricuspid isthmus (CTI) ablation was performed.

CLOSE guided PVI

Figure 1: Illustration of 'CLOSE'-guided PVI. PVI=pulmonary vein isolation, ILD=interlesion distance.

Offline analysis of criteria to assess integrity of the deployed RF circle

Each procedure was analyzed offline. For each RF tag within the circle we determined time of application (s), median delivered power (W), impedance drop (D-Imp, Ω), average CF (CF, g), force-time integral (FTI, gs) and ablation index (AI, arbitrary unit, au). Custom-made software was used to automatically determine the path of encircling, perimeter of the RF circle, ILD (center-to-center distance, mm) and ablation line contiguity index (ALCI). ALCI was developed as a criterion to algorithmically score the combination of contiguity and lesion depth.(13)

To describe the overall quality for a given circle, we determined for each circle the median value of all analyzed ablation parameters. Four circles from 2 patients were not available for off-line analysis.

To describe the weakest link in a given circle we determined for each circle the minimal value for ablation index and the maximal value for ILD.

Follow-up

Complications were reported on the CRF and collected during follow-up. After ablation, anticoagulation and anti-arrhythmic drug therapy (ADT) were continued. At 3 months, anticoagulation was continued according to stroke risk, whereas ADT was continued at the discretion of the treating physician. Clinical evaluation and ECG were performed at 1, 3, 6 and 12 months. Holter-ECG was performed at 3 and 6 months (24h) and 12 months (7 day) or in case of symptoms. Freedom from recurrence was defined as 1-year absence from AF/AT/AFL >30 seconds beyond a 3-month blanking period.

Statistical analysis

Normality of data distribution was tested with Shapiro-Wilk test. Continuous variables are expressed as mean $\pm$ SD if normally distributed, medians with IQR if non-normally distributed, and dichotomous variables as percentage. Kaplan–Meier estimate with 95% confidence intervals ($\pm$ 1.96 standard error) was used to assess freedom from AF during 12-month follow-up period. All statistical analyses were performed in SPSS Statistics 24 (IBM Corporation, Armonk, New York, USA).

Results

Patient characteristics

All 130 patients had paroxysmal AF. Baseline clinical characteristics are given in Table 1.

Table 1. Patient characteristics (n= 130)

Paroxysmal AF, n (%)	130 (100%)
Age, y	59 ± 13
Male, n (%)	84 (65%)
BMI, kg/m ²	26.5 ± 4.1
Arterial hypertension, n (%)	42 (32%)
Structural heart disease, n (%)	11 (9%)
Diabetes, n (%)	5 (4%)
CHA ₂ DS ₂ VASc score ≥2, n (%)	47 (36%)
Left atrial diameter, mm	39.7 ± 3.7
Electrical cardioversion, n (%)	26 (20%)
1 st AF episode to PVI, months	24 [9-84]
Resistance to ADT, n (%)	103 (79%)

Procedural characteristics

Characteristics are given in Table 2. PVI was obtained in all cases. CTI ablation was performed in 5 patients (3.8%). General anesthesia was used in 72 out of 130 patients (55%). Procedure time was 155±28min (Figure 2, panel A). RF time per circle was 17±5min (panel B). Perimeter of the deployed circle was 115.7±22.3mm (panel C). The number of RF tags to enclose the PVs was 28±5 (panel D). The number of dislocations per circle was 3±3. Procedural characteristics for the right and left circles separately are given in Table 2.

Table 2. Procedure characteristics (n= 130)

PV isolation, n	130 (100%)
CTI ablation, n	5 (4%)
General anesthesia, n	72 (55%)
Procedure time, min	155±28
Fluoroscopy time, min	16.7 ±7.1
Dose area product (DAP), mGy/cm ²	11314 ± 8687
Total hospitalization time, hrs	39±12
Right circles	
Perimeter, mm	123±19
RF tags, n	29±5
RF time, min	16±4
First-pass isolation, n	130 (100%)
Waiting/adeno. proof isolation, n	128 (99%)
Left circles	
Perimeter, mm	108±23
RF tags, n	27±5
RF time, min	18±6
First-pass isolation, n	126 (97%)
Waiting/adeno. proof isolation, n	128 (99%)

Compared to conscious sedation, procedures with general anesthesia were characterized by shorter procedure time (147±22min vs. 164±31min, $p=0.001$), shorter fluoroscopy time (16±7min vs. 17±8min, $p=0.725$), lower dose area product (DAP) value (9312±7538mGy/cm² vs. 15850±9644mGy/cm², $p=0.014$) and shorter RF time for the right circle (15±3min vs 18±4, $p<0.001$) and left circle (16±4 vs 21±7, $p<0.001$).

Figure 2: RF characteristics and incidence of acute durable PV isolation

Procedure time (A). RF time per circle (B). Perimeter of the deployed circle (C). Number of RF tags within the circle (D). Obtained minimal ablation index per circle (E). Obtained maximal ILD (F). Incidence of first-pass isolation (G). Incidence of waiting time/adenosine-proof isolation (H). See text for further explanation.

RF characteristics and integrity of the RF circle

A representative case illustrating the integrity of the RF circle given in Figure 3. The ‘CLOSE’ procedure is characterized by applications with relatively short duration (ranging from 11 to 61s), a high rate of applications with high power (≥ 30 W) and a high rate of RF tags with a marked impedance drop ($\geq 7\Omega$). There is a wide range of obtained CF values (5 to 37g) and FTI values (ranging from 184 to 875gs). Due to the nature of the protocol, applications at the anterior wall are all with an AI of ≥ 550 . Finally, the ‘CLOSE’-guided circle is characterized by enclosing lesions all with ILD ≤ 6 mm and ALCI of $>100\%$.

Figure 3: Representative examples of RF characteristics in ‘CLOSE’-guided PVI

The deployed circles are represented color-coded (dichotomous or continuous) for each of the following criteria: application time, power, impedance drop (D-Imp), contact force (CF), force-time integral (FTI), ablation index (AI), perimeter, interlesion distance (ILD) and ablation index contiguity index (ALCI). See text for further explanation.

Overall, RF characteristics of lesion quality were as follows; median application time=25s, [23-35], median power=35W, [35-35], median obtained $\Delta\text{-Imp}$ =12.7 Ω , [10.6-14.5], median CF=15.0g, [13.4-17.4], median FTI 375gs, [326-446], median AI 456 au, [449-469], median ILD 4.1mm, [3.8-4.4] and median ALCI 163, [150-179].

Overall, weakest link analysis (Figure 2, panels E and F) showed a minimal ablation index of 408au, [378-425] and 556au, [517-565] at the posterior and anterior wall separately, whereas maximal ILD was 6.5mm, [5.9-8.0].

Of interest, in 105 out of 260 circles (40%), we did not target/reach the 400 AI value at the posterior wall because of chest pain and/or intra-esophageal T° rise.

First-pass and waiting time/adenosine-proof isolation

Results are summarized in Figure 2 (panel G and H). Only 5 patients did not receive adenosine because of a history of asthma/COPD. The ‘CLOSE’-protocol was associated with high incidence of

first-pass isolation (98%) and waiting time/adenosine-proof isolation (98%).

1-year freedom from AF/AT/AFL after ‘CLOSE’-guided PVI

Kaplan-Meier analysis was plotted in Figure 4 and 5. Overall, single-procedure 12-month freedom from AF/AT/AFL was 92.3% (Figure 4). Throughout the course of the study, 26 patients were on ADT. Those patients had continued taking ADT at the end of the blanking period. Conversely, no patient was taking ADT to treat a recurrence documented while being off ADT. In those 26 patients on ADT, freedom from AF/AT/AFL was 96.2% (Figure 5, left lower panel). In those 104 patients off ADT, freedom from AF/AT/AFL was 91.3% (Figure 5, left upper panel). Single-procedure freedom from both recurrence and ADT was 73.1%.

Figure 4: Survival plot in ‘CLOSE’-guided PVI
Kaplan-Meier curve depicting time to first recurrence of atrial fibrillation (AF), atrial flutter (AFL), or atrial tachycardia (AT) (including a 3-month blanking period) in all 130 patients undergoing ‘CLOSE’-guided ablation.

Figure 5: Survival plots for patient subgroups

Kaplan-Meier curves depicting time to first recurrence of atrial fibrillation (AF), atrial flutter (AFL), or atrial tachycardia (AT) in patients undergoing ‘CLOSE’-guided ablation for subgroup of patients not taking ADT (left upper) or taking ADT (left lower), and without arrhythmia during the 3 months blanking (right upper) or with arrhythmia during blanking (right lower).

Single-procedure freedom from AF/AT/AFL was comparable amongst operators ($92.3 \pm 1.3\%$) and type of anesthesia (general = 90.3% , conscious sedation = 94.8% , $p = 0.511$).

Of interest, 16 patients (12%) showed early recurrence during the 3 months blanking period. Kaplan-Meier analysis for patients with ($n=16$) and without ($n=114$) arrhythmia during the blanking period is given in Figure 5 (right panels).

Safety of ‘CLOSE’- guided PVI

One short-lived event, diagnosed as TIA, occurred at day 8 after the ablation. Mean hospitalization length was 39 ± 12 hrs.

Findings at repeat ablation

All 10 patients with documented recurrence underwent repeat ablation. Out of 10 patients, 9 revealed a normal bipolar voltage map during high-density mapping (>200 points). In 6 out of 10 patients (60%) we observed a status of permanent isolation of all veins. In those 4 patients with reconnection of the veins we observed 5 gaps in 4 out of 8 circles. Relative to the RF characteristics of the first procedure, 1 gap could not be explained (adequate AI and ILD according to the 'CLOSE' criteria), whereas 4 gaps were explained by a weak link in the initial ablation circle (all IL distance >6mm).

Discussion

Main findings

This study, evaluating the 'CLOSE' protocol in 130 patients, shows that an ablation strategy aiming to enclose the PVs with a contiguous ablation line with optimized RF lesions results in a high rate of adenosine-proof isolation. This is translated into a single-procedure arrhythmia-free survival of 91% at 1-year without ADT. These results are obtained without compromising safety and with relatively short procedure and RF times. The above findings are in line with the hypothesis that avoiding weak links within the deployed RF circle is the key to durable PVI and clinical success.(13)

Single-procedure AF freedom after point-by-point RF ablation

PVI is simultaneously the cornerstone and Achilles heel of ablation for paroxysmal AF. Despite acute isolation, late PV reconnection results in AF recurrences with the ensuing need for repeat ablations. The recent FIRE and ICE study confirmed a 64% single-procedure freedom from AF after point-by-point RF ablation.(2,3)

Since the introduction of CF-sensing technology, several studies suggested enhanced acute durability of PVI and 1-year freedom from paroxysmal AF.(7-10) In a parallel cohort study, CF-guidance was associated with lower incidence of dormant conduction (8% vs 35%) and better 1-year arrhythmia-free survival (88% v 66%).(7) In a single-center controlled study, CF-guidance was associated with higher acute procedural success (80 % vs 36%) and 1-year AF-freedom (90% vs 67%).(8)

The above studies are in line with work from Michaud et al, showing 84% AF-freedom if PVI is guided by initial impedance decrease, as an indicator of good catheter contact.(9) Improved outcome is

also in line with experimental data showing that for a given stable catheter position and for a given power, lesion depth, width and volume increase with higher CF.(18-22)

However, data on 1-year outcome are not consistent across all studies.(11-12) A recent multicenter randomized controlled study in 117 paroxysmal AF patients, failed to demonstrate a beneficial effect of CF-guidance on AF-free survival. (11) Also Reddy et al failed to demonstrate a benefit of CF-guided ablation in a multicenter randomized trial.(12) Only in the subgroup of patients with at least 90% of RF applications ≥ 10 g, AF-freedom was superior compared to non-optimal CF (76% vs 58% at 1-year).

On top of these conflicting results, even in the most promising scenario, still $\approx 20\%$ of the patients require a repeat procedure after CF-guided PVI.

Determinants of gap in CF-guided PVI

The conflicting results indicate that CF alone cannot preclude the presence of weak links in the ablation chain. Recently, our group demonstrated that in CF-guided PVI, acute and late PVR are explained by discontinuity (interlesion distance) and/or insufficient lesion depth (ablation index) of the lesions within the deployed RF circle.(13)

Prior studies already hinted to the importance of contiguous lesions to obtain acute durable isolation. Miller et al showed that closing the “visual” gap was essential for acute durable PVI, (23) whereas Park et al showed that acute PVR despite CF ≥ 10 g was explained by ablation sites with an ILD of ≥ 5 mm.(24) A recent sub-analysis of SMART-AF in 40 paroxysmal AF patients also showed that ILD correlates with success rate (1-year outcome ranging from 33% to 93%).(25)

The above findings support the concept of superiority of contiguous overlapping lesions with sufficient energy delivery. This concept is also in line with human MRI studies showing that acute isolation can be achieved by a combination of ablation-induced reversible (edema) and irreversible atrial injury (necrosis).(26) Likewise, experimental data showed that tissue heating can lead to acute changes in electrophysiological properties allowing for larger gaps to have conduction block, but as the tissue recovers, to become conductive again.(27) This reversible atrial injury is more likely to occur at the periphery of the lesion (where the tissue temperature is lower) but can also occur at the center of the ablation point when insufficient energy is delivered.

The key observation that lower ablation index values are associated with reconnection - even in segments characterized by closely spaced lesions - suggests that ablation index can be used to titrate delivery of sufficient energy.(13) By taking into account the greater contribution of power (over

contact force) and of the initial time of ablation,(28) ablation index differs from force-power-time integral calculated as the multiplication of force, power and time.(29) Of interest, El Haddad et al observed that there is a significant difference in minimal AI values required to obtain durable segments in the anterior part of the circle compared with the posterior segments, suggestive of thicker atrial tissue in anterior regions.(13)

Based upon the findings by El Haddad et al, we hypothesized that, in order to obtain durable PVI, maximum ILD should not exceed 6mm and that minimal lesion depth defined by the AI should reach the value of at least 400 at the posterior wall and 550 at the anterior wall (the ‘CLOSE’ criteria).

Strengths and weaknesses of the ‘CLOSE’ protocol

In the present relatively large patient cohort, we observed a high rate of acute durable isolation and a high 91% single-procedure, 1-year freedom from AF/AT/AFL without ADT. If continuing ADT (without evidence of recurrence) is considered as failure,(1) single-procedure freedom from both arrhythmia recurrence and ADT was 73.1%. Also the 60% prevalence of permanent and complete PV isolation at repeat is at the higher end compared to prior studies reporting on the status of complete PV isolation in patients undergoing a repeat procedure for arrhythmia recurrence.(4-6, 30) Taken together, these data suggest that the ‘CLOSE’ protocol results in acute and late durable PVI.

The ‘CLOSE’ protocol describes a method to obtain PVI with objective and quantifiable criteria (AI, ILD and ALCI). Although integrity of the deployed RF circle is expected to be similar when all parameters are met, reproducibility across centers requires further study.

We surmise that the ‘CLOSE’ protocol is different from currently used ‘dragging’ or point-by-point RF strategies. Although anecdotally some operators already pursue a contiguous ablation approach with overlapping lesions, this claim is not justified by objective measures. In the SMART-AF sub-analysis - most likely reflecting expert use of CF-guided PVI – more than half of the patients were treated with RF circles characterized by any ILD of >10.6mm.(25) Lack of verification of ILD is reflected in the ongoing need for touch-up ablation after first encirclement or adenosine challenge.

Also the use of ablation index to optimize RF delivery is different from conventional CF- or FTI-guided strategies. In the ‘CLOSE’ protocol, low CF values per se do not preclude delivery of RF at that site. In contrast to prior studies, obtained FTI values at the posterior wall are as low as 200gs.(16,17) The use of higher power implies that lesions can be deployed with a relatively short application time (resulting in few dislocations), even at sites with low but stable contact. Finally, in contrast to FTI or CF targets, lesion quality is expected to be similar at a certain AI value (despite

differences in power, force and time of application required to reach that value).(29)

Our data suggest that durable PV isolation can be obtained with relatively short procedure and RF times. This is explained by the fact that AI allows use of higher power during RF delivery (shorter applications) and by the fact that no time is lost for chasing and managing acute PV reconnection. Although our data suggest that procedural efficiency is higher using general anesthesia, outcome was found to be similar.

The present population is too small to draw any definitive conclusions regarding safety. There is no pre-clinical data to support the safety of any strategy using higher power RF delivery. Nevertheless, in those 130 patients undergoing the 'CLOSE' protocol we observed no complications, especially no audible steam pop, no signs of clinical PV stenosis, no cardiac perforation, permanent stroke, atrio-esophageal fistula or death. Absence of esophageal injury despite relatively high power can be explained by short application times at the posterior wall (max 20s) and esophageal T° monitoring.

Finally, we retain considerable challenges for future RF-guided PVI. (1) Our strategy requires validation and optimization using other ablation catheters and/or ablation parameters settings (lower irrigation, higher power...). (2) Although we observed a limited number of dislocations during encircling, it remains to be seen whether this is reproducible across centers. (3) The 'CLOSE' protocol seems appropriate to obtain durable PVI using this strategy of deploying ≈30 RF lesions following a 10 to 12cm path around the PVs. Whether the 'CLOSE' criteria (AI, ILD and ALCI) might offer an ideal platform to guide wider encirclement of the PVs requires further study. (4) Cutoff-guided ablation strategies, as advocated in the present study, might result in durable isolation at the cost of overshoot and potential safety issue. The current observation of acute durability despite the delivery of AI values lower than 400 at the posterior wall, might be a first step towards avoiding this overshoot. Moreover AI is an estimate and not a direct measure of lesion depth. To minimize RF delivery, each application should be individualized according to on-line in vivo characterization of the tissue before, during and after RF delivery. Only then the unique advantage of point-by-point ablation will be exploited to its full potential.

Limitations

Although 130 patients were enrolled, several limitations need to be underlined.

First, as many pilot studies, this study was monocentric. We believe however that this feasibility study in a relatively large cohort of 130 patients undergoing 'CLOSE'-PVI was a first and necessary step towards adequately powered multi-center studies.

Despite a 24h-Holter ECG at 3, 6 months and a 7-day Holter-ECG at 12 months and the symptomatic nature of PAF, the discontinuous nature of monitoring can underestimate AF recurrence.

In the present study, we did not perform voltage mapping at baseline. No pre-ablation imaging with CT or MRI was performed. Therefore we cannot exclude the possibility of an aberrant PV.

Finally, ADT was not systematically withdrawn after the blanking period. Due to the large sample size however, we could report on outcome in 104 ‘CLOSE’ patients not taking ADT.

The above limitations are tackled by ongoing clinical studies evaluating the safety and efficacy of the ‘CLOSE’ protocol (a multicenter trial, and a study using subcutaneous loop recorders).

Conclusions

In the present study, we evaluated the feasibility of an ablation protocol aiming to enclose the pulmonary veins with contiguous and optimized RF lesions. We observed a relatively short procedure time, high rate of acute PVI durability and a high single-procedure arrhythmia free survival at 1 year.

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6

Chapter 6

Safety evaluation of CLOSE-PVI concerning oesophageal and mediastinal lesions

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Abstract

Background: The incidence of endoscopically detected esophageal lesions after pulmonary vein isolation (PVI) is as high as 18%. Intra-esophageal temperature rise (ITR) during ablation is a predictor for esophageal injury.

Objective: We recently described an ablation strategy aiming to enclose the PVs with contiguous, stable and optimized RF applications (referred to as CLOSE-PVI). We evaluated esophageal and peri-esophageal injury with endoscopy in patients revealing ITR during CLOSE-PVI.

Methods: 85 patients with ITR during CLOSE-PVI underwent endoscopy of the esophagus (with ultrasound in 38 patients). PVI consisted of contact force (CF)-guided encircling of the veins using 35W applications respecting strict criteria of intertag distance ($\leq 6\text{mm}$) and ablation index (AI 550au anterior wall, 400au posterior wall, 300au if $\text{ITR} > 38.5^\circ\text{C}$).

Results: Endoscopy was performed 9 ± 4 days after PVI. At the posterior wall, median power was 35W [IQR 35-35], application time $18 \pm 5\text{s}$, CF $13 \pm 6\text{g}$, AI $403 \pm 38\text{au}$. Median 5 applications [IQR 4-7] per patient over a length of $21.8 \pm 6.8\text{mm}$ resulted in $\text{ITR} > 38.5^\circ\text{C}$ (median 39.9°C , IQR $39.2\text{--}41.2^\circ\text{C}$, range $38.6\text{--}50.0^\circ\text{C}$). For these applications median power was 35W [IQR 30-35], application time $14 \pm 3\text{s}$, CF $12 \pm 5\text{g}$, AI $351 \pm 38\text{au}$. The incidence of esophageal erythema/erosion on endoscopy was 1/85 (1.2%) and of ulceration 0/85 (0%). The incidence of mediastinal or esophageal injury on ultrasound was 0/38 (0%).

Conclusions: The occurrence of esophageal or peri-esophageal injury after CLOSE-PVI is markedly low (1.2%). Absence of esophageal ulceration in patients with ITR suggests that this strategy of delivering contiguous, relatively high-power, and short-duration applications at the posterior wall is safe.

Introduction

Atrio-esophageal fistula (AEF) is a life-threatening complication of pulmonary vein isolation (PVI) for treatment of atrial fibrillation (AF).¹ Whereas the incidence of AEF is low (0.02 to 0.11%),² there is a high (2 to 30%) incidence of subclinical esophageal or peri-esophageal injury on endoscopy performed within 7 days after radiofrequency or cryoenergy ablation.³⁻¹⁴ Halbfass et al showed that the only risk factor associated with the occurrence of esophageal injury or ulcer is intra-esophageal temperature rise (ITR).³ Furthermore they found that an esophageal ulcer is a necessary precursor for AEF.³

We recently introduced a new strategy to enclose the veins with contiguous and optimized RF applications.¹⁵⁻¹⁷ This strategy referred to as CLOSE-PVI is characterized by relatively high-power (35Watts), short-duration applications to target a prespecified ablation index (AI) and is associated with high rate of adenosine-proof, first-pass isolation, favorable 1-year freedom of AF and high rate of durable isolation at repeat procedure.¹⁶⁻¹⁸ To assess the incidence of esophageal injury (and potential risk of AEF) using this ablation strategy, we performed echo-endoscopy in those patients revealing ITR during CLOSE-PVI.

Methods

Patient population

All patients undergoing AF ablation in the St-Jan Hospital Bruges are followed in a prospective database approved by the local institutional review committee. This database implies collecting patients' written informed consent and detailed case report form. From September 2017 to May 2018, 185 patients with paroxysmal or persistent AF underwent a first CLOSE-guided PVI monitored with a luminal esophageal temperature probe. According to institutional protocol (implemented after the study by Halbfass et al),³ all patients revealing ITR >38.5°C were advised to undergo endoscopic evaluation of the esophagus within the first 2 weeks after PVI.

PVI according the CLOSE protocol

The CLOSE-PVI protocol was previously described.¹⁶⁻¹⁷ Under general anesthesia double transseptal puncture (SL0, St. Jude Medical, St. Paul, Minnesota) was guided by trans-esophageal echocardiography (TEE). After puncture, TEE was removed and a temperature probe with 5 electrodes (SensiTherm, St. Jude Medical) was advanced into the esophagus until positioned at the LA level. Each of the 3 intermediate electrodes has a thermocouple for independent detection of intraluminal temperature. After 3-dimensional-reconstruction of LA geometry (Carto System, Biosense Webster, Diamond Bar, California), a Lasso and contact force (CF) catheter (Thermocool SmartTouch, Biosense Webster,) were used to predefine the RF circle around the PVs (nephroid shape). Identification of the LA-PV junction was based upon anatomy, CF, CF vector, catheter jump during

pull-back maneuvers, position relative to the Lasso, impedance and local electrogram characteristics (fusion of atrial and PV potentials).

Point-by-point RF delivery was performed aiming for a contiguous circle enclosing the PVs (maximal inter-tag distance between 2 neighboring applications $\leq 6\text{mm}$). Real-time automated display of RF applications (Visitag, Biosense Webster) was used with predefined settings of catheter stability (3mm for 8s) and minimum CF (30% of time $>4\text{g}$). RF was delivered in power-controlled mode (without ramping) at 35W (irrigation flow 30ml/min) targeting AI of $\geq 550\text{au}$ at the anterior wall and AI of $\geq 400\text{au}$ at the posterior wall/roof. In case of dislocation, a new RF application reaching the pre-specified AI target was applied. During encirclement of PVs, the position of the temperature probe was manually adjusted in order to place the 3 sensors as closely as possible to the respective ablation site (Figure 1). In case of early ITR $>38.5^\circ\text{C}$, RF was continued until target AI $\geq 300\text{au}$ (Figure 2). In case of ITR $>38.5^\circ\text{C}$ observed between AI 300 and 400au, RF was stopped, in case of ITR $>38.5^\circ\text{C}$ after reaching 400au, the site was noted. Before applying RF energy to the next adjacent position, we waited for temperature dropping $<38.5^\circ\text{C}$. During this waiting time, the operator could stay on site and wait for temperature drop (preferred strategy if minor ITR and quick decline of temperature after RF cessation) or choose to ablate at a remote locus before going to the adjacent position (preferred strategy if high ITR and/or slow decline). RF power, as previously described, was only reduced in case of catheter tip temperature rise $>43^\circ\text{C}$ or in case of high CF ($\geq 20\text{g}$) that might lead to overshoot of the AI target. In the absence of first-pass isolation, touch-up ablation was delivered guided by the earliest PV potential on the Lasso-catheter until PVI was achieved.

Figure 1: Luminal esophageal temperature probe.

During encirclement of the right veins, a circular mapping catheter is positioned in the right superior pulmonary vein. The position of a luminal esophageal temperature probe (SensiTherm, St. Jude Medical, St. Paul, Minnesota) is adjusted so that the 3 thermosensors are as close as possible to the respective ablation site.

Figure 2: CLOSE-guided PVI.

Representative example of CLOSE-PVI and off-line analysis. In this patient, applications on the posterior wall of the right circle did not result in temperature rise, whereas six applications on the posterior wall of the left circle resulted in intra-esophageal temperature rise $>38.5^{\circ}\text{C}$. The ablation index target was reduced to $\geq 300\text{au}$ (pink VisiTags). (AI: ablation index; CF: contact force; FTI: force-time integral; ITR: intra-esophageal temperature rise; P: power; t: radiofrequency time)

Post-procedural care and follow-up

Complications were reported and collected during follow-up. According to institutional protocol all PVI patients were prescribed omeprazole 40mg daily for 1 month. Follow-up consisted of clinical visit at 1, 3, 6 and 12 months.

Endoscopic evaluation of the esophagus

Endoscopic examinations were scheduled <14 days after PVI and performed by 4 experienced operators. All patients were kept fasting overnight prior to examination. As standard of care all patients underwent clinical evaluation of symptoms (chest pain, dysphagia, fever or neurological symptoms) before endoscopy. They were examined in left lateral position under conscious sedation with midazolam 2.5mg and/or alfentanil 0.5mg IV. Oxygen saturation, pulse rate and blood pressure were monitored. Evaluation of the esophagus, stomach and duodenum was performed using a standard video endoscope (Pentax EG 29-i10 and Olympus GIF-H180). Endoscopic lesions were attributed to AF ablation if they were located on the anterior wall of the mid-esophagus. Esophageal lesions were classified into erythema/erosion, ulcer or perforation.^{3,4}

Endoscopic ultrasound investigation (EUS) was performed using a radial scanning ultrasound endoscope (Pentax EG 3670URK) and the Hi Vision AVIUS ultrasound system from Hitachi. Careful

examination of mediastinum and esophageal wall was performed to assess mucosal and peri-esophageal/mediastinal lesions.

Off-line analysis of the deployed RF circle

Procedures from all patients with ITR were analyzed off-line. For each RF tag on the posterior wall we determined application time (s), power (W), CF (g), force-time integral (FTI) (gs), AI (arbitrary unit, au) and the maximum intra-esophageal temperature (°C) (Figure 2). To anatomically allocate sites with ITR, the posterior hemisphere of each circle was divided into 5 segments. To assess the lesion length associated with ITR, we calculated the distance between most cranial and caudal RF tags causing ITR.

Results

Patient population and procedural characteristics

From October 2017 to May 2018, 185 patients underwent first-time CLOSE-guided PVI with luminal esophageal temperature probe. ITR >38.5°C was observed in 133 procedures (72%). 85 patients consented for endoscopic evaluation. In the first 38 patients, additional EUS was performed. Patient and procedural characteristics are detailed in Supplementary Table S1. Mean number of applications per circle was 57±15, mean number of dislocations was 2±1, and mean number of dislocations on the posterior wall was 0±1. First-pass isolation was obtained in 162/170 circles (95%). During a median follow-up of 8.9 months [IQR 7.1-11.1] no complications of esophageal fistula, stroke or death were noted.

Characteristics of the RF applications

A representative example is given in Figure 2. Results are summarized in Table 1. At the posterior wall, median power was 35W [IQR 35-35], application time 18±5s, CF 13±6g, AI 403±38au. Due to high baseline CF, power was reduced to <35W (25W [IQR 25-30] in median 1 [IQR 0-3] RF application per patient. For the left PV circle median 10 [IQR 9-12] and for the right PV circle median 12 [IQR 10-14] RF applications were located on the posterior wall. Median 5 [IQR 4-7] RF applications per patient resulted in ITR >38.5°C, covering a mean length of 21.8 ± 6.8mm along the posterior wall.

Table 1: RF characteristics of all applications on the posterior wall and of applications with intra-esophageal temperature rise

	Applications posterior wall	Applications with ITR
Number of tags, n	22 [19–26]	5 [4–7]
RF time, s	18±5	14±3
CF, g	13±6	12±5
Power, W	35 [35–35]	35 [30–35]
FTI, gs	219±88	165±77
AI, au	403±38	351±38

AI: ablation index; CF: contact force; fore-time integral; ITR: intra-esophageal temperature rise >38.5°C

The spatial distribution of sites with ITR is shown in Figure 3. In 53 patients ITR was observed deploying the left PV circle and in 36 patients deploying the right (in 4 patients in both circles). Baseline esophageal temperature at those sites was 36.2±0.3°C. Maximal temperature observed was 39.9°C ([IQR 39.2–41.2°C] and range 38.6–50.0°C, Figure 4). Of interest, out of 405 RF applications resulting in ITR, only 36 (8.9%) were characterized by delayed ITR (i.e. occurring only after stopping RF at the AI target of 400au).

For applications resulting in ITR, median power was 35W [IQR 30–35], application time 14±3s, CF 12±5g, AI 351±38au. In case of ITR, the median time in between neighboring applications was 22s [IQR 14–34]. In 14 patients with ITR, the operator chose to ablate at a remote locus (3 [IQR 2–4] applications) before resuming RF at the neighboring spot.

Figure 3: Spatial distribution of intra-esophageal temperature rise in 85 patients.

Number of patients showing ITR >38.5°C: frequency per circle and per segment.

405 RF applications with ITR >38.5° C

Figure 4: Maximum intra-esophageal temperature rise.

All applications resulting in ITR >38.5°C and their respective maximum intra-esophageal temperature.

Endoscopic evaluation

Endoscopy was performed after mean 9 ± 4 days after PVI. In none of the 85 patients an esophageal ulcer was detected. In one patient we observed two erythematous lesions at day 4 after ablation (Figure 5). In this patient RF was applied on the posterior wall for 26 applications (RF duration 8.4 min). ITR was observed during three applications along the left inferior PV (max. ITR 39.5, 40.1 and 41.2°C respectively).

Furthermore endoscopy revealed following findings in 28 of 85 patients: peptic esophagitis in 16 patients (grade A, B, C and D in respectively $n=13$, $n=1$, $n=1$, $n=1$), short Barrett esophagus in 3 patients, esophageal moniliasis in 3 patients, gastric antritis/gastritis in 8 patients, gastric erosion/ulcer in 4 patients, duodenal erosion/ulcer in 2 patients, an ampulloma in 1 patient. Findings were classified as incidental, and not related to the ablation procedure, based upon the anatomical location (distant from the left atrial wall).

Figure 5: Results of endoscopic evaluation.

In only 1/85 patients endoscopy revealed two erythematous lesions at day 4 after ablation.

Ultrasound evaluation

In none of the 38 patients undergoing additional sonographic evaluation, we observed direct signs of injury to the esophageal wall. Peri-esophageal lymph nodes at the atrial level were observed in 13 patients, minimal pleural effusion in 17 patients, physiological pericardial effusion in 7 patients and focal pleural thickening in 2 patients.

48 patients not undergoing endoscopy

In the present study, 48 ITR patients did not undergo endoscopy because of decline by the patient (large distance home-hospital, undesired absence from work or aversion for endoscopy). Of interest, clinical, RF and ITR characteristics were not different from the 85 patients undergoing endoscopy. More specifically, at the posterior wall, median power was 35W [IQR 35-35], application time 18±6s, CF 12±6g, AI 404±44au, with a median of 4 [IQR 4-6] RF applications per patient resulting in ITR. Finally in none of the patients an adverse event was noted at follow-up.

Discussion**Main findings**

The incidence of esophageal injury on endoscopy after CLOSE-PVI is low (1.2%) despite significant ITR during the procedure. Absence of esophageal ulceration and lack of changes on ultrasound suggest that this specific strategy of delivering relatively high-power, short-duration optimized applications at the posterior wall might be safe. These findings require confirmation in a larger patient cohort.

Prior studies reporting on the incidence of esophageal injury on endoscopy

The incidence of endoscopically detected esophageal injury after catheter ablation is high, both after PVI guided by cryoballoon (from 3 to 19%)¹³⁻¹⁴ and by RF energy (from 2 to 30%).³⁻¹² The majority of reports on esophageal injury are based upon endoscopy performed within two to three days after PVI and describe both erythema and ulceration. In the present discussion we focus on the incidence of ulceration (1) because ulceration and not erythema is a known precursor of fistula and (2) because erythema (in contrast to ulceration) is potentially underestimated in the present paper due to relatively late timing of endoscopy (see below). Several papers reported on injury after RF-guided PVI performed with ≤ 25 W on the posterior wall without esophageal temperature probe. Whereas Martinek et al⁵ (267 patients, non CF) and Blockhaus et al⁶ (70 patients, CF range 10-40g) reported injury in only 2.2% (1.5 ulceration) and 2.9% (1.4% ulceration) respectively, Halbfass et al (100 patients, CF 10-40g) reported an incidence of 13% (with 8% ulceration).⁷ The incidence is equally high after PVI in which RF delivery is guided by an esophageal temperature probe and ITR. Di Biase et al (50 patients, 35W over the posterior wall with discontinuation of RF in case of ITR $>39^{\circ}\text{C}$) reported esophageal injury in 26% of patients.⁸ Muller et al (40 patients, ≤ 25 W posterior wall, CF target 10-40g, discontinuation of RF delivery if ITR $\geq 39.5^{\circ}\text{C}$) reported an incidence of esophageal injury in 30% (7.5% ulceration).⁹ Halbfass et al (40 patients, ≤ 25 W, CF 10-20g and RF time ≤ 20 s on posterior wall, discontinuation of RF delivery at ITR $>39^{\circ}\text{C}$) reported an incidence of 7.5% (2.5% ulceration).¹⁰ The high incidence of endoscopically detected esophageal injury after PVI is reflected in a recent meta-analysis including 3921 patients (mainly RF-ablation).⁴ The overall incidence of endoscopic injury after ablation was 15% with 5.2% incidence of erythema, 5.7% superficial ulceration and 3.6% deep ulceration. The high incidence is also in line with the recently published largest single-center registry (832 patients), in which Halbfass et al demonstrated that endoscopically detected esophageal injury early after RF ablation (performed within 7 days) is as high as 18% (12% erythema, 6% ulceration).³

There is only limited data on predictors for esophageal injury. Smaller studies have identified lower body mass index¹⁹, general anesthesia⁸, use of a nasogastric tube for visualisation of the esophagus²⁰, use of TEE probe²¹ and maximal energy at the posterior wall²⁰ to be predictors of esophageal injury. In the study from Halbfass et al, the only risk factor associated with the occurrence of esophageal injury

was ITR $>40.5^{\circ}\text{C}$.³ This study underscores the relevance of performing and reporting on endoscopy in those specific patients with ITR during ablation.

Performing endoscopy in patients with intra-esophageal temperature rise during ablation

We observed a low incidence of esophageal injury after CLOSE-PVI with ITR (1.2%), despite reaching a median temperature of 39.9°C and despite using relatively high power. This incidence is at the lower end compared to prior studies on esophageal injury,^{3,12} and more specifically compared to prior reports on endoscopy performed in ITR patients.

Contreras-Valdes et al (82 patients with ITR $\geq 39^{\circ}\text{C}$, 25W on the posterior wall, discontinuation of RF delivery at ITR $>38^{\circ}\text{C}$) reported esophageal injury in 27% (8.5% deep ulceration) of ITR patients.¹¹ Knopp et al. (425 patients with ITR $>41^{\circ}\text{C}$, 30W on the posterior wall in proximity to the esophageal temperature probe) found thermal esophageal lesions in 11% of ITR patients.¹²

One might speculate that a protocol of performing endoscopy only in patients with ITR underestimates the true incidence of injury after all CLOSE-PVI procedures. It seems however unlikely that the incidence of injury would be higher in patients without ITR. Indeed, Halbfass et al determined ITR as the only risk factor for injury. Moreover, due to careful positioning of the probe, patients with ITR represent the large majority of CLOSE-PVI patients (72% of cases).

Finally, it seems unlikely that we missed esophageal injury (and more specifically ulcer) due to the relatively late timing of endoscopy (9 ± 4 days). In those patients with endoscopy within 7 days we also did not observe any ulceration. Moreover, also in the study by Halbfass et al, reporting 18% of injury, endoscopy was performed up to 7 days after ablation.³ Finally in that latter study, 47 patients with documented esophageal injury underwent a control endoscopy at 12.3 ± 8.9 days. Whereas in those patients with initial erythema/erosion, the site of injury was still detectable in 21% of patients, in those patients with initial ulcer the site of injury was still apparent in 83% of patients. As such it is unlikely that ulceration was missed in the present study. This hypothesis is further supported by the absence of esophageal or peri-esophageal wall injury on ultrasound. A prior study has shown that ultrasound has the potential to detect thermal injury-induced changes to the esophagus (submucosal and mucosal) and to the peri-esophageal tissue in patients with normal endoscopy.²²

What explains the present findings?

Most likely the low incidence after CLOSE-PVI is explained by the ablation protocol itself. (1) Due to the automated ablation tag, stability and contiguity criteria (resulting in limited dislocations and high incidence of first-pass isolation), there is a minimal amount of applications required to isolate the PVs. On average 10 applications per circle cross the posterior wall and only 5 of those are associated with ITR. (2) In contrast to prior RF strategies, CLOSE-PVI is characterized by short-duration, relatively higher power (35W) applications. Due to the pre-specified AI targets, RF applications at the posterior wall can be as short as 10s (mean 18s) for AI 400au and as short as 8s (mean 14s) for AI 300au. It has

been hypothesized that short duration-high power (SD-HP) applications favor the balance in resistive to convective heating thus preventing the risk of collateral damage.²³ At least in experimental models, SD-HP applications result in more shallow lesions.^{24,25} (3) Also inherent to CLOSE-PVI, in contrast to prior RF studies, is the concept of striving for high stability rather than high CF. Excessive CF by the ablation catheter (applied in non-CF guided procedures or in earlier CF studies) might result in inadvertent displacement of the posterior wall towards the esophagus.²⁶ (4) Finally CLOSE-PVI is characterized by ablation at the LA-PV junction. Avoiding a wider encirclement reduces potential overlap with the esophagus and limits the number of procedures in which ITR is observed during both the left and right circle. Indeed only in 4 patients we observed ITR during both left and right PV encirclement.

Clinical implications

Esophageal injury and AEF are obstacles in the search for durable PVI. In the past, powerful energy to isolate the veins was associated with fistulisation.²⁷ In order to avoid thermal esophageal lesions, the 2017 expert consensus statement advises 1) reduction of RF power along the posterior wall (class I indication) and 2) use of an intraluminal temperature probe to monitor ITR to help guide energy delivery (class IIa indication).² Reduction of RF power however might lead to non-durable PVI and more repeat ablations. Moreover, during the procedure itself lower power might lead to non-adenosine-proof or non-first-pass isolation with the ensuing need for touch-up applications (with possible accumulation of RF delivery and conductive heating at particular locations, even paradoxically increasing the risk for AEF formation).

The findings of the present study suggest that CLOSE-guided ablation could offer a strategy in which efficacy and safety go hand in hand despite relatively higher power at the posterior wall. Indeed, in a prospective cohort study CLOSE-PVI was associated with a very high rate of first-pass and adenosine-proof PV isolation and a single-procedure arrhythmia-free survival of 92.3% at 1-year for paroxysmal AF.¹⁷ The present data suggest that CLOSE-PVI is safe from the esophageal perspective, because the risk for AEF development is unlikely in absence of ulceration. The low incidence of erythema/erosion and the absence of ultrasound lesions suggest that our observations are not a matter of sample size.

These initial results however need confirmation. The safety and efficacy of the CLOSE-PVI protocol are currently being investigated in a multi-center randomized controlled trial (the VISTAX-study, ClinicalTrials.gov Identifier: NCT03062046). Furthermore it remains to be seen whether our data can be extrapolated to other patient populations (dilated atria, more thin-walled atria, fibrosis) and other strategies using higher power applications (but without following specific criteria inherent to the CLOSE-PVI protocol like contiguity, temperature monitoring, optimized AI target).

Limitations

- 1) The number of patients evaluated with endoscopy was limited (n=85). Furthermore, to prevent long waiting time between PVI and endoscopy, evaluation by ultrasound was not continued after the first series of 38 patients. The absence of ulcer and lack of morphological changes in the peri-esophageal connective tissue evaluated with EUS however are reassuring compared to other studies with the same sample size.
- 2) Only patients with ITR were evaluated as per institutional protocol. Those patients however represent the majority of CLOSE-PVI cases (ITR was observed in 72% of the cases). This is explained by dynamic, optimal positioning of the esophageal temperature probe. Moreover ITR has been shown to be a predictor of injury.
- 3) Only one type of luminal temperature probe (a non-insulated multi-electrode with fast response time) was used in our study. Non-insulated probes have been shown to increase esophageal injury.^{3,9,10,28,29,30}
- 4) As the temperature probe was only used in anesthetized patients, the conclusion of safety of the CLOSE-PVI protocol with regards to esophageal injury cannot be generalized to unmonitored and awake patients.
- 5) In none of the patients we did perform pre-procedural imaging to define LA-PV junction or esophagus. Ablation closer to the PVs might explain the minimal number of applications required to isolate the veins and lack of esophageal injury.
- 6) Finally, 48 patients with ITR did not undergo endoscopy. It is unlikely however that those patients would have a different risk for esophageal injury because the reason not to perform EGD was not procedure or operator related, but simply due to decline of the patient. This is in line with the observation that those 48 patients had similar clinical, procedural and ITR characteristics.

Conclusion:

The absence of esophageal ulceration after CLOSE- and ITR-guided PVI suggests that this strategy of delivery of contiguous relatively high-power and short-duration applications is safe.

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7

Chapter 7

Evaluation of the durability of pulmonary vein isolation in CLOSE-PVI

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Abstract

Objectives: This study sought to determine the prevalence of patients with 4 isolated veins at repeat ablation after ‘CLOSE’-guided pulmonary vein isolation (PVI), a strategy based upon delivery of contiguous and optimized radiofrequency lesions.

Background: The likelihood of finding 4 isolated veins at a repeat ablation for atrial fibrillation (AF) recurrence after a first PVI is low.

Methods: Patients undergoing repeat ablation for AF recurrence after first ‘CLOSE’-guided PVI were included. At repeat, 1) the status of the PVs was evaluated and 2) high density voltage mapping was performed. In case of pulmonary vein reconnection (PVR), veins were re-isolated. In patients with 4 isolated veins, empirical trigger or substrate ablation was performed.

Results: Out of 326 patients undergoing CLOSE-guided PVI for paroxysmal AF, 45 patients underwent repeat ablation for AF recurrence (11 ± 7 months after first PVI). In 28 patients all veins were still isolated (62%). They showed similar clinical characteristics and similar time from first PVI to AF recurrence (8 ± 7 versus 6 ± 6 months respectively, $p=0.453$) compared to patients with PVR. In contrast, they were characterized by a higher incidence of low voltage (57% versus 17%, $p=0.033$). Patients with 4 isolated veins showed a lower 12-month freedom from AF after repeat ablation compared to patients treated for PVR (61% vs 88%, $p=0.045$).

Conclusion: After ‘CLOSE’ guided ablation, PVR is no longer the rule in patients with AF recurrence. Patients with AF recurrence and 4 isolated veins present with a similar clinical profile and time to recurrence that compared to patients with PVR.

Introduction

Pulmonary vein isolation (PVI) is considered the cornerstone for successful ablation in atrial fibrillation (AF). (1) AF recurrence after PVI is assumed to be mediated by PV reconnection (PVR). (2-4) This assumption is based upon the observation that (1) the likelihood of finding 4 isolated veins at repeat ablation is extremely low (varying from 41% to as low as 0%) and (2) upon the good outcome after re-isolation of reconnected veins. (3-17)

The ‘CLOSE’-protocol is a contact force guided ablation protocol aiming to enclose the veins with stable, contiguous, and optimized (ablation index-guided) radiofrequency (RF) applications. (18) This new approach of PVI is associated with a high rate of first-pass and adenosine-proof isolation and a high single-procedure arrhythmia-free survival at 1 year. (18-20)

In the present study we determined the prevalence of patients presenting with 4 isolated veins at repeat ablation for AF recurrence after ‘CLOSE’-guided PVI. This endpoint is a relevant and objective parameter to evaluate effectiveness of any PVI strategy. We further investigated whether those patients (with non-PV mediated AF recurrence) are characterized by specific clinical, first procedural or post-procedural characteristics and whether outcome of repeat ablation is different from patients with reconnected veins.

Methods

Patient recruitment

All patients undergoing ablation for AF at the St-Jan Hospital Bruges are followed in a prospective database approved by the local ethical committee. This study enrolled all consecutive patients undergoing repeat ablation for AF recurrence after a first CLOSE-guided PVI for paroxysmal AF. All patients were recruited at the St-Jan Hospital Bruges between November 2014 and December 2017. AF recurrence was detected at ambulatory ECG, Holter or implantable loop recorder.

‘CLOSE’-guided pulmonary vein isolation

First PVI was performed under general anesthesia or conscious sedation. The CLOSE strategy has been described in detail previously. (18) Esophageal temperature monitoring (SensiTherm™, St Jude Medical Inc., St. Paul, MN, USA) was used in anaesthetized patients. Intravenous heparin bolus (100IU/kg) and continuous infusion (ACT >300 s) was administered after groin puncture. After transseptal puncture, a decapolar lasso catheter and a contact force guided ablation catheter (Thermocool Smart Touch®, Biosense-Webster Inc., Diamond Bar, CA, USA) were positioned in the left atrium (LA). Calibration of contact force and respiratory gating were subsequently performed. A 3D-geometry of the LA was constructed using the CartoSystem® (Biosense-Webster Inc.) and the RF circle around the pulmonary veins was predefined on this 3D-geometry. Point by point RF delivery

was performed aiming for a contiguous circle enclosing the ipsilateral veins, respecting a maximal interlesion distance (ILD) of $\leq 6\text{mm}$. Real-time automated display of RF applications (Visitag®, Biosense Webster Inc.) was used with predefined settings of catheter stability (3 mm for 8 sec) and minimum CF (30% of time $> 4\text{gr}$). RF was delivered (EP Shuttle ST-3077, Stockert GmbH, Freiburg, Germany) in a power-controlled mode aiming for 35W (irrigation flow up to 30 cc/min). RF was delivered until an ablation index (AI) target of ≥ 550 at the anterior wall and ≥ 400 at the posterior wall. In case of chest discomfort or intra-esophageal temperature rise ($> 38.5^\circ$), AI target was limited to 300 at the posterior wall. After encircling the ipsilateral veins, PVI was ensured using the decapolar lasso catheter at the ostium of all four veins. In case of remaining PV potentials, touch-up ablation was delivered until PVI. Intravenous adenosine was administered to assess dormant PV conduction in the majority of patients. Voltage mapping was not systematically performed at the time of the first procedure.

Repeat procedure: high-density voltage mapping and ablation strategy

Repeat ablation was performed using the same modalities as the first procedure (general anesthesia or conscious sedation, double transseptal puncture, 3D-geometry of the LA, use of a Thermocool Smart Touch® catheter and decapolar lasso catheter, ablation index and ILD targets).

At repeat procedure, high-density, point-by-point, bipolar voltage mapping of the LA was performed by acquiring > 300 points during sinus rhythm homogeneously distributed around the surface of the LA (pre-specified color fill of 5 and after exclusion of the pulmonary veins). To ensure reliable mapping during automated acquisition of the points (Confidence, Biosense-Webster Inc) pre-specified filter settings were used: a mapping window set to the sinus rhythm cycle length minus or plus 100ms, minimum contact force of 4 grams and LAT stability of maximal 3ms. Off-line we determined, the area (cm^2) with low bipolar voltage ($< 0.5\text{mV}$) using the area measurement tool embedded in the Carto system®. A low voltage area was defined as an area of $> 1\text{cm}^2$ with bipolar voltage $< 0.5\text{mV}$.

PV reconnection was defined as residual PV potentials at the LA-PV junction detected by the decapolar lasso catheter or by the Thermocool Smart Touch catheter. Patients with PVR underwent re-isolation of the reconnected vein(s). Patients revealing four isolated veins were treated by ablation of the empirical trigger or substrate. Empirical trigger ablation consisted of superior vena cava isolation and/or widening of the circle around the veins. Adenosine or isoproterenol to elicit triggers was not systematically used. Substrate ablation was preferred in patients with ongoing AF at the time of procedure or in case of AF episodes lasting longer than 24hours. Empirical substrate ablation consisted of deployment of linear lesions (i.e. CLOSE-guided linear ablation at the roof, mitral isthmus and anterior wall) during sinus rhythm or AF. Ablation was continued until proven block over the roof and mitral isthmus line.

Radiofrequency characteristic of the ablation circles during the first PVI procedure

For each repeat patient, we exported the first procedure and analyzed offline the RF characteristics of the initial RF circles using custom made software. (19) For each RF tag within the circle we calculated the time of RF delivery (Time, s), ablation index (AI, arbitrary unit, au), force time integral (FTI, gs), interlesion distance (ILD, mm), mean contact force (CF, g), and drop in impedance (Δ -Impedance, Ω). To assess quality of RF applications, we determined for each circle the median value of each RF parameter (Time_{Med}, AI_{Med}, FTI_{Med}, CF_{Med}, ILD_{Med}, Δ -Impedance_{Med}). (18)

Follow up after repeat procedure

All patients had standard follow up with clinical evaluation and 12-lead electrocardiograms at 1, 6 and 12 months and Holter at 6 months after repeat procedure. In case of symptoms, additional Holter analyses were performed. Recurrence of AF was registered after a 3 month blanking window. Of interest, 12 (27%) patients had continuous rhythm evaluation by implantable loop recorders (ILR).

Statistical Analysis

Continuous variables are expressed as mean $\pm$ standard deviation or median [interquartile range (IQR)] if data were non-Gaussian distributed. Categorical variables are expressed as absolute number with percentage (%). Comparison among groups for continuous variables is done by the Student T test or Mann-Whitney U test (in case of non-Gaussian distribution). Comparison of categorical variables among groups is performed by Chi square test. Kaplan-Meier estimate was used to compare freedom of AF after repeat ablation. Statistical significance is set at a 2-tailed probability level of <0.05 . All statistical analysis is performed using SPSS software (Version 24.0, IBM, Armonk, NY, US).

Results**Status of the pulmonary veins at repeat ablation for AF recurrence after first 'CLOSE'-guided PVI**

Of 326 patients undergoing first CLOSE-guided PVI for paroxysmal AF, 45 patients underwent repeat ablation for AF recurrence (Figure 1). Out of those 45 patients, 28 (62%) patients revealed 4 isolated veins. In patients with PVR (n=17) the mean number of reconnected veins was 2 ± 1 with no predilection sites of PV reconnection (Figure 2, left).

Figure 1: High incidence (28/45, 62%) of four isolated veins in patients with atrial fibrillation recurrence after first CLOSE-guided pulmonary vein isolation.

Figure 2: Left panel: Localization of gaps in the ablation circles among patients (17 patients, 27 gaps) with AF recurrence and pulmonary vein reconnection (PVR). No predilection sites of PVR could be identified. **Right panel:** Circles with gaps showed similar lesion quality compared to circles with durable pulmonary vein isolation.

Patients with four isolated veins: clinical characteristics, first procedural characteristics and time to recurrence after first PVI

Baseline clinical characteristics of all patients undergoing repeat ablation are listed in Table 1. Patients revealing 4 isolated veins at repeat had similar clinical characteristics compared to patients with PVR. Also the arrhythmic profile of the initial paroxysmal AF was not different, with similar AF burden, both in terms of frequency and duration of AF episodes.

Compared to patients with PVR, patients revealing four isolated veins had also similar first procedural and RF characteristics (Table 2). We did not observe any difference in the radiofrequency characteristics (RF time_{Med}, AI_{Med}, FTI_{Med}, ILD_{Med}, CF_{Med} or Δ -impedance_{Med}) of the RF circle deployed during the first procedure. Comparing circles with PVR to circles without reconnection could also not identify any differences in RF time_{Med}, AI_{Med}, FTI_{Med}, ILD_{Med}, CF_{Med} or Δ -impedance_{Med} (Figure 2, right).

Finally, also the mean time to recurrence after prior PVI did not differ among both groups (8 $\pm$ 7 vs 6 $\pm$ 6 months, p=0.453, Figure 3). Of interest, patients revealing four isolated veins at repeat (i.e. non-PV mediated AF recurrence) presented with a wide variation in time to AF recurrence after initial PVI.

Table 1: Clinical characteristics of patients undergoing repeat procedure

	All repeat patients (n=45)	Patients with 4 isolated veins (n=28)	Patients with reconnected veins (n=17)	P value
Patient characteristics				
Age, yrs	61 $\pm$ 10	63 $\pm$ 10	59 $\pm$ 10	0.153
Male gender, n (%)	23(51)	12(43)	11(65)	0.221
BMI, kg/m ²	27 $\pm$ 5	26 $\pm$ 5	28 $\pm$ 4	0.271
Obesity (BMI>25), n(%)	26 (58)	15(54)	11(65)	0.543
CHA ₂ DS ₂ -VASc-score	1 $\pm$ 1	1 $\pm$ 1	1 $\pm$ 1	0.617
Arterial Hypertension, n(%)	13 (29)	9(32)	4(24)	0.737
Diabetes, n(%)	2(4)	1(4)	1(6)	1.00
Obstructive sleep apnea, n(%)	2(4)	0(0)	2(12)	0.137
Left atrial diameter, mm	41 $\pm$ 4	41 $\pm$ 5	41 $\pm$ 4	0.811
Characteristics of paroxysmal AF before PVI				
Paroxysmal AF, n (%)	45(100)	27(100)	17(100)	1.00
AF duration, months	67 $\pm$ 86	75 $\pm$ 100	55 $\pm$ 61	0.916
ADT resistant, n (%)	39(87)	25(89)	14(82)	1.00
Frequency of AF episodes, n (%)				
<1 episode/ month	20(45)	14(50)	6(35)	0.336
>1 episode/month	16(36)	8(29)	8(47)	0.209
>1 episode/week	3(7)	2(7)	1(6)	0.869
>1 episode/day	6(13)	4(14)	2(12)	0.809
Duration of AF episodes, n (%)				
>24 hours	8(18)	4(14)	4(24)	0.431
12-24 hours	7(15)	2(7)	4(24)	0.116
1-12 hours	16(36)	13(47)	4(24)	0.124
<1 hour	14(31)	9(32)	5(29)	0.848
Characteristics of recurrence of AF after first PVI				
Time to recurrence, months	7 $\pm$ 7	8 $\pm$ 7	6 $\pm$ 6	0.453
Initial responder (> 1 month free of AF) , n (%)	28(62)	18 (64)	10(59)	0.759

Table 2: Characteristics of the first PVI procedure in patients revealing 4 isolated veins at repeat

	All repeat patients (n=45)	Patients with 4 isolated veins (n=28)	Patients with reconnected veins (n=17)	p value
Procedure characteristics				
General Anaesthesia, n (%)	30(67)	20(74)	9(53)	0.193
Common pulmonary vein, n (%)	4(9)	2(7)	2(12)	0.626
Procedure duration (min)	162±37	158±41	168±29	0.378
N of RF applications (points)	71±13	68±13	75±13	0.114
Total time of RF energy (min)	33±7	32±6	35±7	0.076
Fluoroscopy time (min)	15±8	13±6	16±9	0.211
DAP (mGy/cm ²)	7569±7249	7157±7366	8252±7244	0.398
AK (mGy)	36±35	35±37	38±31	0.353
RF circle characteristics				
Time _{Med} (min)	29[26:32]	29[26:33]	28[27:31]	0.365
Ablation index _{Med} (au)	486[478:494]	484[478:496]	487[479:494]	0.689
Force time integral _{Med} (gs)	426[379:484]	426[370:501]	426[386:451]	0.567
Inter lesion distance _{Med} (mm)	3.9[3.7:4.4]	4.1[3.7:4.4]	3.9[3.7:4.3]	0.907
Contact force _{Med} (g)	15[13:18]	15[13:18]	16[14:18]	0.716
Δ Impedance _{Med} (ohm)	12[11:13]	12[11:14]	12[11:13]	0.772

Figure 3: Time course to AF recurrence after first CLOSE-guided pulmonary vein isolation. Patients with a status of four veins being isolated, showed similar time course to first AF recurrence compared to patients with pulmonary vein reconnection. Of interest, patients with low voltage (color-coded in red) present with both early and late recurrence after first PVI.

High-density bipolar voltage mapping of the left atrium

Compared to patients with PVR, patients with 4 isolated veins were characterized by a higher incidence of low atrial voltage in the residual left atrial surface. Representative examples are given in Figure 4 (left). Whereas the patient with AF recurrence and PVR showed no low voltage area in the posterior LA, the patient with AF recurrence and complete PV isolation presented with a distinct area of low voltage at the posterior LA (8.3cm²).

Overall results are summarized in the right panels of Figure 4. In patients with AF recurrence and four isolated veins, the incidence of low voltage was significantly higher (57% vs 17% in PVR patients, $p=0.033$) and the area of low voltage was significantly larger (4.6[2.3-7.9] cm² versus 0.0[0.0-0.0] cm²

in PVR patients, $p=0.049$). As can be seen in Figure 3 (in which we color-coded in red those patients with low voltage), patients with low voltage present with both early and late recurrence after first PVI. In 10 out of 45 patients, we could compare the presence or absence of low voltage at repeat to a baseline high-density voltage map created during the first PVI procedure. None of these patients revealed any change in low voltage characteristics between baseline and repeat at 7 ± 6 months. Representative maps are plotted in Figure 5 (left). Overall, in 3 patients presenting with low voltage at baseline, the surface of low voltage remained identical over time. Likewise, none of the 7 patients presenting with normal voltage at baseline developed low voltage (Figure 5, right).

Figure 4: **Left panel:** Representative examples of left atrial (LA) voltage mapping (bipolar voltage cut off 0.5mV) in two patients with atrial fibrillation (AF) recurrence after first CLOSE-guided pulmonary vein isolation. The upper left panel represents a patient with reconnection of the left inferior pulmonary vein. The LA shows a normal bipolar voltage with absence of low voltage zones. The lower left panel shows the voltage map of a patient with AF recurrence despite all four veins isolated. A large area of low voltage at the posterior wall is documented. **Right panel:** Overall, patients with AF recurrence despite isolated veins have more often areas (>1cm²) of bipolar voltage <0.5mV and have larger areas of low voltage compared to patients with pulmonary vein reconnection.

Figure 5: Comparison of the presence or absence of low voltage at repeat to a baseline high-density voltage map created during the first PVI procedure. The patient in the **upper left panel** presented with area of 7cm² on the posterior wall, but showed no progression of this low voltage area 7 months later at repeat procedure. The patient (**lower left panel**) without left atrial low voltage at baseline did not develop low voltage over a period of 4 months. **Right panel:** Overall, in 3 patients presenting with low voltage at baseline, the surface of low voltage remained identical over time. Likewise, none of the 7 patients presenting with normal voltage at baseline developed low voltage.

Outcome after repeat ablation

In patients with PVR, all reconnected veins were re-isolated. Out of 28 patients with 4 isolated veins, 15 (54%) patients underwent empirical ablation of the trigger and 13 (46%) patients underwent ablation of the empirical substrate.

Median follow-up after repeat ablation was 13±11months. Patients with AF recurrence and complete vein isolation, tended to have a lower freedom of AF compared to patients with PVR (61% vs 88%, $p=0.045$) (Figure 6). Time to AF recurrence after repeat procedure was 6.5±4.8 months in the PVR group versus 5.7±2.1 months in patients with a status of four isolated veins ($p=1.00$).

Figure 6: Kaplan-Meier curves depicting time to AF recurrence after repeat ablation for patients with and without pulmonary vein reconnection at repeat ablation. Patients with all four veins being isolated (treated with either ablation of the empirical trigger or substrate) showed worse outcome.

Repeat ablation in patients with implantable loop recorders

Of interest, from the twelve patients who were implanted with an ILR, AF recurrence was paroxysmal in 10 (83%) patients and persistent in 2 (17%). Of these ILR patients, 5 (42%) patients presented with PVR, whereas 7 (58%) of those patients presented with a status of all veins being isolated. In patients with ILR undergoing re-isolation of all reconnected PVs, 80% remained free of AF, whereas in patients with ILR who underwent substrate or trigger ablation 57% remained free of AF ($p=0.636$).

Discussion

Main findings

First, the likelihood of finding 4 isolated veins at the time of repeat ablation for AF recurrence after ‘CLOSE’-guided PVI is 62% - higher than previously reported- and implying that AF recurrence after PVI now is more likely to point to non-PV mediated AF. Second, patients presenting with AF recurrence and 4 isolated veins (i.e. non-PV mediated AF recurrence) have no distinct clinical or first procedural characteristics and also time to AF recurrence after the first PVI is not different from patients presenting with PVR. Third, the association with low voltage and the moderate outcome after empirical ablation suggest that a patient-specific repeat ablation might be required to optimize outcome in patients presenting with complete vein isolation.

AF recurrence does not longer imply PV reconnection at repeat

It is generally accepted that AF recurrence after PVI is due to reconnection of 1 or more PVs. This is based upon the good outcome after isolation of reconnected veins with repeat ablation for AF and numerous observations that recurrence after PVI is almost invariably associated with reconnection of the vein(s).

Prior studies, predominantly in patients with paroxysmal AF, reported indeed a low incidence of a status of complete vein isolation at repeat ablation for AF recurrence (Figure 7). (3-9,11-17) In the earlier years (using non-irrigated or irrigated non-contact force RF or first generation cryoballoon to isolate the veins) the likelihood of complete isolation was as low as 0% and certainly not exceeding 20%. The likelihood of finding 4 isolated veins at repeat ablation for AF recurrence after predominantly second-generation cryoballoon PVI ranged from 26% to 41%. (5,8,11,17) More recent data on RF-guided PVI still show high reconnection rates. (15-16) Shah et al. showed that the incidence of isolated veins in patients with late AF recurrence (>36 months after first PVI) was only 19%. (16) Of interest, although contact force-guided ablation is associated with higher percentage of complete isolation in study patients undergoing invasive re-evaluation at 3 months regardless of symptoms, (21,22) Buist et al. reported a low incidence of finding 4 veins isolated at repeat for contact force-guided RF (only 3%). (15) Finally, a recent meta-analysis by Nery et al. reported an overall 14% likelihood of finding 4 isolated veins in case of a clinically-indicated repeat ablation after PVI. (2)

Figure 7: Overview of studies assessing the likelihood of finding four isolated veins after single pulmonary vein isolation (PVI). After CLOSE-guided PVI, atrial fibrillation (AF) recurrence no longer implies pulmonary vein reconnection.

The present observation that 62% of repeat patients reveal a status of complete isolation confirms that ‘CLOSE’-guided PVI, by avoiding weak links in the ablation chain, is associated with durable isolation. This finding is in line with prior data from our group reporting favorable acute and 1-year outcome after a PVI strategy based upon stable, contiguous, and optimized RF applications. (18,20) Of interest, the 62% complete isolation is in line with the 64% incidence of complete isolation in 14 patients undergoing repeat ablation for recurrence after a prior video-assisted thoracoscopic PVI (using bipolar RF clamp to ensure transmural and durable isolation). (23)

All of the preceding percentages (Fig. 7) apply to the likelihood of finding 4 isolated veins in patients undergoing repeat study for AF recurrence (clinically-indicated repeat study). Although it is well-known from protocol-mediated repeat studies that PV reconnection can occur in patients free of AF, (7,9,10,13,14,21) the likelihood of finding 4 isolated veins is expected to be higher when evaluating all patients, also those without AF recurrence. Indeed in a recent meta-analysis (combining data of eleven studies) by Nery et al., the likelihood of finding complete isolation was 41.4% in patients without AF recurrence, markedly higher than the reported 14.5% in patients with AF recurrence. (2)

Can we identify upfront those patients that will present with isolated veins at repeat procedure?

Predicting upfront those patients that will represent with four isolated veins at repeat might optimize communication with the patients (expectations regarding repeat ablation outcome, length of the procedure), and repeat procedural planning (cath lab time, mapping strategies, ablation tools). It might even avoid a repeat procedure and favor non-ablative treatment (anti-arrhythmic drugs). (24)

We showed however that patients with four isolated veins (i.e. non-PV mediated AF recurrence) have no distinct clinical characteristics. Also the phenotype of paroxysmal AF before PVI did not show any specific characteristics. These findings are in line with prior studies on non-PV mediated AF, demonstrating that clinical characteristics (i.e. age, gender, LA size) do not differ between patients with PV and non-PV mediated AF. (25,26)

Furthermore we observed no difference in the time to AF recurrence after PVI among both groups, with both early and late recurrence in patients with non-PV mediated AF. One might have anticipated that patients with non-PV mediated AF recurrence would be more likely to present with early recurrence after PVI. We retain two hypotheses to explain why patients presenting with 4 isolated veins at repeat would reveal a late recurrence after initially responding well to PVI; (1) development of non-PV mediated AF at a later stage, with an initial good response because of the initial PV-mediated AF or (2) non-PV mediated AF from the very start, with an initial good response to PVI due to a secondary but transient effect of ablation (like autonomic modulation). This latter hypothesis could explain the striking similarity in the variation in time to recurrence in both patient groups i.e. in

the reconnected group, PV reconnection occurs early, but the time to recurrence is mediated by absence or recovery from autonomic modulation.

We could not detect any difference in procedural characteristics or lesion characteristics between patients/circles with reconnection vs patients/circles with permanent isolation. Lack of difference might be explained by the fact that ablation is meticulously performed according to well-controlled strict criteria (precluding variation in those parameters). The high freedom of AF after first PVI and the currently reported high incidence of complete isolation suggest that those 'CLOSE'-criteria were well-chosen. In case of reconnection after 'CLOSE', PVR must be due to other, unmeasured variables like tissue thickness or tissue composition. Therefore markers of direct tissue contact as intra cardiac echocardiography or sound mapping might further improve CLOSE-guided PVI.

Low voltage assessment at the time of repeat procedure.

We observed that patients with non-PV mediated AF recurrence after first PVI were characterized by a higher prevalence of low voltage areas in the left atrium. Those low voltage areas are suggestive for atrial fibrosis either as a manifestation of structural heart disease or as a result of an intrinsic fibrotic atrial cardiomyopathy. (27,28) Our findings are in line with prior studies reporting lower single procedure outcome after first PVI in patient presenting with fibrosis or low voltage areas in the LA.(29,30) Marrouche et al. showed that both the presence and extent of atrial fibrosis (as detected by delayed enhancement on magnetic resonance imaging), was independently associated with a higher likelihood of AF recurrence. (29) In the study of Verma et al., the presence of left atrial fibrosis (as assessed by electro-anatomical mapping) was the strongest predictor for AF recurrence. (30) It is unknown to what extent low voltage is a risk factor or marker for patients with non-PV mediated substrate and/or trigger. Of interest, Chao et al. reported that patients with higher CHADS2 scores presented with more low left atrial voltage (31) and subsequently reported a higher likelihood of non-PV triggers in patients with a higher CHADS2 score. (32)

Outcome after repeat ablation in patients with 4 isolated veins

Most studies that provided data about outcome after repeat ablation reported outcome data in those patients undergoing re-isolation of reconnected veins with freedom of AF varying between 81 and 97%. (3,6,7,13,14) Two studies reported on outcome in all repeat patients (both patients with re-isolation of reconnected veins and patients undergoing non-PV ablation in case of isolated veins). In these studies long-term freedom of AF was observed in 53% and 66% of the patients undergoing repeat ablation. (12,33) Only 2 studies reported specifically on outcome data after repeat ablation for AF recurrence in patients with a status of all veins being isolated. (4,17) In the first study by Ouyang et al., 5 out of 26 patients revealed a status of isolated veins and underwent repeat ablation (non-PV triggers, focal AT and linear lesions). (4) After a blanking period of one month, all 5 patients remained free of AF recurrence. In a second study by Baldinger et al., freedom of arrhythmia after repeat

ablation depended on whether patients with isolated veins presented with AF recurrence (20% freedom after a repeat strategy consisting of lines and/or antral extension and/or defractionation) or with AT recurrence (67% freedom after a repeat strategy targeting activation time). (17)

The present study showed that outcome after repeat ablation in patients with complete isolation (n=27) was inferior to patients presenting with PVR. Worse outcome was seen independent of whether we performed empirical ablation of either the non-PV trigger or substrate. Poor outcome and its association with low voltage suggests that ablation outcome could be improved by adding patient-specific ablation strategies at repeat ablation.

Study limitations

The major limitations of the study are the small sample size and that we did not report systematically on status of PVs in all patients. Although the number of patients seems limited it is important to state that the sample size is comparable to prior published studies and that it is (and will be more) challenging to provide data on 45 patients given the low probability of recurrence/repeat after durable PVI for paroxysmal AF. Our data on outcome after repeat ablation should be considered as a hypothesis generating only as there was no predefined randomization amongst strategies. Similarly, the data on low voltage require further study by evaluating a larger patient cohort and by assessing its relation with clinical characteristics.

Conclusions

After pulmonary vein isolation with stable, contiguous and optimized (ablation index-guided) radiofrequency lesions (CLOSE-protocol), PV reconnection is no longer the rule in patients experiencing AF recurrence. Patients with AF recurrence and 4 isolated veins present with a clinical profile and time to recurrence that is not different from patients with reconnected veins. The presence of low voltage regions and moderate outcome after repeat suggest that a patient-tailored strategy is required to treat patients with non-PV mediated AF.

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8

Chapter 8

Long-term impact of catheter ablation on
arrhythmia burden in low-risk patients
with paroxysmal atrial fibrillation: the
CLOSE to CURE study

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ABSTRACT

Background: Few studies have evaluated the impact of catheter ablation (CA) on atrial tachyarrhythmia (ATA) burden in paroxysmal atrial fibrillation (AF).

Objective: In the prospective, patient-controlled CLOSE to CURE study we studied longer-term impact of optimized CA on ATA burden using insertable cardiac monitors (ICM).

Methods: 105 symptomatic PAF patients were implanted with an ICM 65 [61-78] days before CA. CA consisted of contact force guided pulmonary vein isolation (PVI) targeting an intertag distance ≤ 6 mm and a region-specific ablation index. Primary endpoint was reduction in ICM-detected ATA burden (relative time spent in ATA), secondary endpoints were single-procedure freedom from ATA, quality of life (QOL), and adverse events.

Results: Mean age was 62 ± 8 y, CHA2DS2-VASc score 1[1-2], left atrial (LA) diameter 43 [39-43] mm. After PVI (1.13 ± 0.39 procedure per patient), ATA burden decreased from 2.68 [0.09-15.02] % at baseline to 0 [0-0] % during the first year and 0 [0-0] % during the second 2-year (reduction in ATA burden 100 [100-100] %, $p < 0.001$). Single-procedure freedom from any ATA was 87% at 1 year and 78% at 2-year. QOL improved significantly across all scores. Adverse events occurred in 5 (4.8%) patients.

Conclusions: CA has become an effective procedure in paroxysmal AF with a major impact on ICM-detected ATA burden. Whereas conventional survival analysis suggests progressive decline in efficacy, we observed that burden reduction is maintained at longer follow-up. These data imply that ATA burden is a more optimal endpoint for assessing ablation efficacy.

Introduction

Catheter ablation (CA) is recommended in patients with drug-resistant symptomatic paroxysmal atrial fibrillation (PAF).(1,2) In PAF, pulmonary vein isolation (PVI) results in a 65% single-procedure one-year freedom from atrial tachyarrhythmia (ATA),(3-6) with progressive decline of efficacy at longer follow-up and recurrence of ATA mainly due to non-durable PV isolation.(7)

Few studies evaluated the impact of PVI on ATA burden in PAF.(8,9) ATA burden, defined as % of time spent in ATA,(1,2,10) is associated with AF-related symptoms, heart failure and stroke.(11-15)

In the prospective, patient-controlled CLOSE to CURE (C2C) study we determine the longer-term impact of PVI on ATA burden in PAF. To reliably quantify ATA burden all patients were implanted with an insertable cardiac monitor (ICM) at least 2 months before PVI. Ablation consisted of a point-by-point contact force (CF)-guided RF approach aiming to enclose the PVs with contiguous, stable and optimized RF lesions. (16-19)

Methods

Study design

The C2C study (NCT02925624) is a single-center, patient-controlled, prospective cohort study. Enrollment started July 2016 until July 2017 at the St Jan Hospital Bruges. Written informed consent was obtained before patient inclusion. The study was approved by the ethics review board.

Patient population

Patients were eligible if there was a history of symptomatic ECG-proven PAF (either resistant, intolerant or unwilling to take ADT) with at least ≥ 3 AF episodes (anamnesic or documented) in the last 3 months.

Exclusion criteria were persistent AF, prior AF ablation, left atrial (LA) diameter > 50 mm, ejection fraction $< 35\%$, AF secondary to reversible causes, unstable angina or uncontrolled heart failure, myocardial infarction or CABG within the last 3 months, awaiting cardiac surgery, diagnosed atrial myxoma or thrombus, acute illness, blood clotting or bleeding abnormalities, life expectancy < 12 months, pregnant or breastfeeding women, and enrollment in any other study.

Implantation and programming of the ICM

All ICMs (Reveal LINQTM, Medtronic Inc.) were inserted parasternal, over the 4th intercostal space, aiming for R-wave > 0.3 mV. Programming of ATA detection was standardized across all patients (AF/AT detection on; sensitivity: balanced; ectopy rejection: nominal; AF/AT recording threshold: all episodes). This algorithm, based upon R-R interval stability and P-wave detection, has an overall accuracy for AF and non-AF detection of 99.4%.(20,21) Because the algorithm makes a rhythm classification within a 2-min window, the minimal length of an ICM-detected ATA is 2-min. To avoid memory overflow and loss of intracardiac electrograms, patients were asked to weekly transmit ICM

data to the Medtronic Care Link® Network.

Mechanical and electrical properties of the LA

All patients underwent at baseline an advanced transthoracic echocardiographic study (Vivid E9, GE-Vingmed, Milwaukee, WI) to determine LA diameter (parasternal long-axis view), LA volume (Simpson's biplane method at end-systole) and LA reservoir strain function assessed by 2-dimensional speckle tracking echocardiography (EchoPAC, GE, Norway, version 110.2). Prior to PVI, we determined atrial refractoriness, AF inducibility, electrogram voltage, and intra-atrial conduction velocity. (22) An area of low voltage was defined as an area of $>1\text{cm}^2$ with $<0.5\text{mV}$.

Catheter ablation

PVI was performed by 6 operators. The CLOSE procedure was previously described in extenso.(17) By preference the procedure was performed under general anesthesia with an esophageal temperature monitor (SensiTherm™, St Jude Medical Inc, Minnesota, US) Further set-up consisted of a contact-force (CF) catheter (Thermocool SmartTouch®, Biosense-Webster Inc., Diamond Bar, CA, USA) and a circular mapping catheter (CMC) (Figure 1, left panel). Identification of LA-PV junction was based upon anatomy, CF, CF vector, catheter jump during pull-back maneuvers, position relative to the CMC, impedance and local electrogram characteristics. Maximal intertag distance between two neighboring lesions was $\leq 6\text{mm}$. In case of (pre-)procedural documentation of typical flutter, cavotricuspid isthmus (CTI) ablation was performed.

Figure 1: Catheter ablation.

Left panel: Fluoroscopic image showing position of the circular mapping catheter and ablation catheter during CA. Right panel: Tags are represented color-coded according to ablation index target. An intertag distance of $\leq 6\text{mm}$ is respected.

Study visits and follow-up after CA

Clinical visits, 12-lead ECG and ICM data review were performed at enrollment, at 1, 3, 6, 12, 18 and 24 months after CA or in case of symptoms. Three months after CA, ADT was stopped whereas anticoagulation was continued according to stroke risk. Quality of life (QOL) was assessed before and every 6 months after CA via the Short Form 36 Health Survey, (23) AF Symptom Checklist,(24) and EHRA symptom score. Repeat ablation was advised in case of symptomatic ATA recurrence and consisted of re-isolation or an empirical trigger or substrate ablation.(18)

Primary endpoint

The primary endpoint, ICM-detected ATA burden, was defined as the % of time spent in ATA (hours of ATA/hours of monitoring) (Figure 2). ATA burden before PVI was compared to ATA burden during the first (excluding a 3-month blanking window) and second year after PVI. All ICM-detected ATA episodes and their corresponding electrograms were revised on a weekly basis by two independent investigators (JDP, MD). This allowed to adjudicate false detection of ATA due to artefact, premature atrial or ventricular beats or sinus arrhythmia (Figure 2, upper panels). For data analysis, all true episodes and their duration were exported to a custom-made C2C-ATA database (Figure 2, lower panels). This allowed to calculate for each patient the daily burden of ATA (black bars) and the relative time spent in ATA (%).

Figure 2: Analysis of atrial tachyarrhythmia burden. Determining atrial tachyarrhythmia (ATA) burden from the insertable cardiac monitor.

Secondary endpoints

Secondary endpoints included alternative measures of ATA burden: ATA burden before adjudication (according to raw ICM data), proportion of patients with reduction in ATA burden (by >50%, >75%, >90% and >95%) and with residual ATA burden >0.5% after CA. In addition, we calculated for each patient the number of days characterized by ATA using different cut-offs i.e. daily burden of ≥ 2 -min, ≥ 1 -hour, ≥ 6 -hours or 24-hours. Other secondary endpoints were single-procedure freedom from any ICM-detected ATA (≥ 2 -min) at 1 and 2 years, QOL among the different scores and ablation-related adverse events.

Sample size and statistical analysis

Normality of data distribution was tested with Shapiro-Wilk test. Continuous variables were expressed as mean $\pm$ standard deviation or medians with interquartile range. Dichotomous variables were expressed as frequency (%). Group comparisons for continuous variables were performed using the paired T test or paired Wilcoxon Signed Rank test. Group comparisons for categorical variables were performed using the Chi square test. Kaplan–Meier survival curves were used to assess time to first documented ATA recurrence. For analysis of QOL, SF 36 data were normalized.(23-25) Statistical significance was set at 0.05 for two tailed tests.

For analysis of ATA burden and its reduction, data were given for all patients (n=105) and for those patients with actual ICM-detected ATA during the baseline monitoring period (n=84). Simple linear regression models using baseline variables were calculated to predict ATA burden after PVI. A multivariable analysis was performed adjusting for potentially confounding variables by selecting variables with at least $p < 0.2$ from the univariable analysis. All analysis was performed using SPSS software (Version 23.0, IBM, Armonk, NY, US).

Results**Clinical characteristics**

The study included 105 patients (Table 1). The median number of monitoring days was 65 [61-78]. Overall, 21 patients did not reveal any ATA episode during monitoring. In these patients the time from diagnosis to CA was 9.0 [6.5-20] months and the last ECG documented-AF episode was 17 [9-28] days before enrollment.

Table 1: Baseline and procedural characteristics (n = 105)

Baseline characteristics	
Age, yrs	62±8
Male gender, n (%)	65 (62)
BMI, kg/m ²	27±4
CHA ₂ DS ₂ -VASc-score	1 [1,2]
Arterial hypertension, n (%)	35 (33)
Diabetes, n (%)	8 (8)
Structural heart disease, n (%)	13 (12)
Coronary artery disease, n (%)	11 (10)
Valvular heart disease, n (%)	2 (2)
Paroxysmal AF, n (%)	105 (100)
Time from 1 st AF episode to PVI (months)	15 [9,28]
Left atrial diameter, mm	43 [39,43]
Left atrial volume, ml	84±22
ADT resistant, n (%)	63 (60)
ADT intolerance or unwillingness, n (%)	42 (40)
Procedural characteristics	
General anaesthesia, n (%)	102 (97)
Procedure duration, min	143±31
Isolation of all PVs, n (%)	105 (100)
Additional ablation of CTI, n (%)	6 (6)
First pass isolation right circle, n (%)	98 (93)
First pass isolation left circle, n (%)	101 (96)
Adenosine challenge performed, n (%)	97 (92)
Adenosine proof isolation, n (%)	93 (96)
RF energy, number of applications	59±11
RF energy, total time of delivery, min	28±6
DAP (mGy/cm ²)	4769±3378

Mechanical and electrical properties of the LA

Results are summarized in Figure 3. In 10 patients (9.5%) we observed a low-voltage area. During premature stimulation, self-terminating ATA was induced in 8 patients (7.6%).

Figure 3: Mechanical and electrical left atrial properties

Histogram plots depicting mechanical (upper panels) and electrical properties (lower panels) of the left atrium (LA).

Procedural characteristics of CA and follow-up

Results are given in Table 1. All patients except one were discharged the day after CA. Within the two-year follow-up period, 0 patients received class I or III antiarrhythmic drugs or cardioversion, 14 patients received a repeat procedure at 150 [100-513] days after PVI.

Primary endpoint: ATA burden before and after ablation

Results for ATA burden for the entire study population are given in the upper panels of Figure 4. After PVI (1.13 ± 0.39 procedure per patient throughout the 2 year follow-up), ATA burden decreased from 2.68 [0.09-15.02] % at baseline to 0 [0-0] % during the first year (reduction in ATA burden 100 [100-100] %, $p < 0.001$, left panel) and 0 [0-0] % during the second 2-year (reduction in ATA burden 100 [100-100] %, $p < 0.001$, right panel). Burden reduction was seen both in patients without (black bars) and with any 2-min ATA recurrence (red and green bars). None of the patients progressed to persistent AF after CA. Results for the subset of 84 patients with documented ATA during the monitoring period were similar (Figure 4, lower panels).

Secondary ATA burden-related endpoints

Results for the 84 patients are given in Table 2. ATA burden without adjudication decreased from 6.61 [1.80-19.00] % to 0 [0-0.03] % during the first 12 months after PVI and to 0 [0-0.03] % during the second year ($p<0.001$ for both). The proportion of patients with $>95\%$ reduction in ATA burden was 94% and 96% at 1 and 2-y FU. Finally, throughout the first and second year after ablation, only 5 (6%) and 1 (1%) had a residual ATA burden $>0.5\%$.

In Figure 5 we plotted the AF calendar plots for the entire study population. Using a cumulative daily ATA burden of 2-min (red), 1-hour (blue), 6-hours (green) and 24-hours (purple), the number of days per patient characterized by ATA decreased significantly (all paired tests $p<0.001$). Of interest, of the 14 patients with ATA during the first year, only 4 patients showed ATA during the second year. Vice versa, of the 13 patients with ATA during the second year, only 4 patients showed ATA during the first year.

A significant but weak regression was found between ATA burden after PVI and ATA burden before PVI (Table 3). In a multivariable model during the 1st year adjusting for both ATA burden before PVI and male gender, only ATA burden before PVI remained statistically significant.

Figure 4: ATA burden plot before and after catheter ablation
Plots showing the % of time spent in ATA during the first and second year compared to baseline in the entire population (upper panels) and subpopulation (lower panels). Each line represents an individual patient. Patients are arranged by recurrences during follow-up, ranging from greatest (bottom) to fewest (top). The horizontal axis is artificially truncated at 30%. See text for explanation.

Table 2: ATA burden before and after PVI (n=84)

	ATA burden before PVI	ATA burden throughout 3-12 months after PVI	ATA burden throughout 12-24 months after PVI	P value
ATA burden (relative time spent in ATA), unadjudicated %	6.61 [1.80, 19.00]	0 [0, 0.03]	0 [0 0.03]	<0.001*
ATA burden (relative time spent in ATA), %	6.56 [1.71, 17.24]	0 [0, 0]	0 [0, 0]	<0.001*
Reduction in ATA burden, %	-	100 [100, 100]	100 [100, 100]	
Proportion of patients with reduction in ATA burden, n (%)				
by > 50%	-	82/84 (98)	82/84 (98)	-
by > 75%	-	81/84 (96)	81/84 (96)	-
by > 90%	-	79/84 (94)	81/84 (96)	-
by > 95%	-	79/84 (94)	81/84 (96)	-
Proportion of patients with ATA burden after PVI, n (%)				
> 0.5 and ≤1 %	-	1 (1)	0 (0)	-
> 1 and ≤5 %	-	3 (3)	1 (1)	-
> 5 and ≤10 %	-	0 (0)	0 (0)	-
> 10%	-	1 (1)	0 (0)	-

* Applies to ATA before PVI vs 3-12M and to ATA before PVI vs 12-24M

Table 3: Linear regression of ATA burden after PVI versus baseline characteristics

	3-12 months after PVI				12-24 months after PVI	
	Simple linear regression		Multiple linear regression		Simple linear regression	
	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value
Age	0.005 (-0.033, 0.043)	0.797			0.001 (-0.006, 0.008)	0.769
Male gender	-0.404 (-1.005, 0.198)	0.186	-0.585 (-1.178, 0.009)	0.053	-0.059 (-0.176, 0.058)	0.318
BMI	0.021 (-0.058, 0.101)	0.594			0.009 (-0.006, 0.025)	0.234
CHA ₂ DS ₂ -VASC-score	-0.042 (-0.3, 0.217)	0.75			-0.008 (-0.058, 0.042)	0.737
Arterial hypertension	-0.136 (-0.771, 0.499)	0.671			-0.043 (-0.166, 0.080)	0.487
Diabetes	-0.215 (-1.368, 0.938)	0.712			-0.033 (-0.257, 0.190)	0.766
Structural heart disease	-0.297 (-1.212, 0.619)	0.521			-0.041 (-0.219, 0.136)	0.644
Left atrial diameter	0 (-0.059, 0.06)	0.988			0.002 (-0.009, 0.014)	0.699
Left atrial volume	-0.003 (-0.019, 0.013)	0.716			0.001 (-0.003, 0.004)	0.746
ADT resistant	0.011 (-0.598, 0.619)	0.972			0.038 (-0.079, 0.156)	0.519
ADT intolerance or unwillingness	-0.163 (-1.419, 1.092)	0.796			-0.032 (-0.275, 0.211)	0.792
Time from 1 st AF episode to PVI	-0.004 (-0.012, 0.005)	0.411			-0.000 (-0.001, 0.001)	0.818
Monitoring days before PVI	0 (-0.014, 0.014)	0.608			0.000 (-0.003, 0.003)	0.904
ATA burden before PVI	0.015 (0.002, 0.027)	0.021	0.018 (0.005, 0.030)	0.007	0.003 (0.001, 0.006)	0.010

Figure 5: ATA calendar plots

ATA calendar plots up to 2 year for all patients. Each row represents data collected from each of the 105 patients. Patients are arranged by time of enrollment. Gray shaded areas correspond to the period of continuous monitoring with ICM. Black dashed line denotes time of PVI as the reference for all patients.

Single-procedure, off ADT freedom from ATA

In Figure 6 we plotted the time to the first day with any 2-min ATA for the entire population (blue curve) and subpopulation (red curve). Single-procedure, off-ADT freedom from any ATA declined from 87% after 1 year to 78% after 2 years ($p = 0.343$).

Figure 6: ATA free survival plot

Kaplan-Meier curves depicting time to first recurrence of any ATA during the first 2 years after PVI (blue curve: entire study population; red curve: 84 patients).

Quality of Life

Results are summarized in Table 4. Physical and mental Health SF36 score, symptom frequency and severity scores, and EHRA score all improved significantly at 1 and 2 year ($p < 0.001$). Improvement in QOL was comparable among patients with and without ATA recurrence.

Table 4: Quality of Life assessment before vs after PVI

	At baseline before PVI	At 12 months after PVI	P value	At 24 months after PVI	P value
SF 36 normalised scores					
Physical health score	47.6 ± 7.4	51.0 ± 6.8	< 0.0001	49.45 ± 7.96	0.192
N of fully completed forms	97	95		96	
Mental health score	48.7 ± 9.1	52.1 ± 7.9	0.002	52.16 ± 8.31	< 0.001
N of fully completed forms	97	95		96	
Symptoms scores					
Symptoms frequency score	18.3 ± 8.7	9.8 ± 7.4	< 0.0001	10.76 ± 8.50	< 0.0001
N of fully completed forms	102	99		102	
Symptoms severity score	13.9 ± 7.4	7.12 ± 7.0	< 0.0001	7.81 ± 7.30	< 0.0001
N of fully completed forms	95	93		96	
EHRA score					
Median score [IQR]	3 [2,3]	1 [1,1]	< 0.001	1 [1,1]	< 0.001

Safety

Ablation-related adverse events were observed in 5 patients (4.7%): three patients with groin-site hematoma (all treated conservatively by mechanical pressure), one patient with femoral pseudoaneurysm (requiring surgery) and one patient with symptomatic left PV stenosis (treated with percutaneous stenting at 104 days after PVI with resolution of symptoms throughout 2-year FU). In none of the patients undergoing repeat ablation narrowing of PVs was observed.

Discussion

Main Findings

The C2C study shows that an optimized CA results in a major overall reduction in ICM-detected ATA burden in patients with PAF. Whereas survival analysis based upon freedom from any ATA recurrence suggests progressive decline of efficacy over time, the impact of CA on ATA burden is maintained at longer-term FU. These data imply that ATA burden is a more optimal endpoint for assessing ablation efficacy.

PAF patients in the C2C study

In the present study, patients were relatively young, had limited structural heart disease, low stroke risk, near-normal left atrial diameter and a relatively short time from diagnose to CA. This low-risk profile however does not differ from the PAF patient enrolled in CA trials,(3-6) or from patients referred for CA in real-life.(26,27). Likewise the ATA burden and its variation (median 2.68%) is not different from prior studies reporting on ATA burden in PAF.(8,9,14,28) Finally, C2C patients were characterized by left atrial electrical and mechanical properties in line with prior studies in

PAF.(29,30) Also the finding of low-voltage areas in $\approx 10\%$ of apparently healthy patients is in line with prior studies in PAF.(2-32) All together, above data suggest that the C2C population reflects the relatively young, symptomatic and otherwise relatively healthy patient referred for ablation of PAF both in studies and real-life.

ATA burden before and after CA: are we close to curing PAF?

Efficacy of CA is commonly expressed as single-procedure freedom from any ATA ($>30s$).⁽¹⁾ This definition (in which one single, even short episode implies permanent failure) most likely underestimates clinically relevant success after CA.⁽¹⁾ In this regard, ATA burden, defined as % of time spent in ATA and preferably measured by continuous monitoring, seems a more reliable estimate of clinically relevant success after CA.^(1,2,10) Indeed, prior studies suggested a dose-effect relation between ATA burden and symptoms, heart failure and stroke.⁽¹¹⁻¹⁵⁾ Glotzer et al showed that ATA burden ≥ 5.5 hours per day ($\geq 20\%$) was associated with a double stroke risk⁽¹⁴⁾, whereas Go et al showed that only the highest tertile of AF burden ($\geq 11.4\%$) was associated with a >3 -fold higher adjusted rate of thromboembolism in PAF patients.⁽¹³⁾

A limited number of prospective studies reported on patient-controlled ATA burden after CA. In the DISCERN AF study, CA reduced mean ICM-detected ATA burden from 8.3% to 1.25% after 18 months.⁽⁹⁾ In MANTRA-PAF, CA reduced estimated ATA burden from a 90th ATA burden of 30% to 13% throughout the first 24 months.⁽²⁷⁾ In the CAPTAF study, CA reduced ICM-detected ATA burden from $24.9 \pm 37\%$ to $5.5 \pm 18.1\%$ at 12 months ($p < 0.001$), not different from medical therapy.⁽⁸⁾

In the present C2C study, optimized CA had a marked and maintained impact on ATA burden (with a low number or repeat procedures and without ADT). In a PAF population in which one quarter of the patients presented with ATA burden $> 15.02\%$, median ATA burden in the 1st two years after CA was 0 [IQR 0-0] % (Figure 4) and also in patients with some ATA recurrence, ATA burden was significantly reduced (because episodes were short-lasting and isolated in nature). The good results of the C2C study, most likely, are explained by durable PV isolation,⁽¹⁹⁾ rather than patient selection (in view of the patient characteristics comparable to prior trials). Also an early intervention strategy during the first year from AF diagnosis (although performed in only 26% of patients) might contribute to improved outcome. Whether reduction in ATA burden by CA might impact AF-related morbidity and mortality requires further study, especially in a sicker population. Marrouche et al recently showed that reduction of burden improves outcome in heart failure patients.⁽¹⁵⁾ Likewise, reduction of burden might be expected to improve symptoms,^(11,12) and reduce stroke.^(13,14)

Single-procedure freedom from ATA, QOL, and safety after CA for PAF

In the C2C study freedom from any ATA was $\approx 85\%$ at 1-year. This relatively high success rate (in the setting of continuous monitoring) ⁽³³⁾ is in line with 1) data from the CLOSE-PILOT study,⁽¹⁷⁾ 2)

prior studies reporting a $\approx 90\%$ 1-year success rate after multiple PVI procedures,(3,4) and 3) the knowledge that non-PV triggers account for $\approx 10\%$ of PAF.(34) The C2C data at 2-year (suggesting decline in efficacy as previously reported) (7) however underscore that this definition of success is not optimal to describe longer-term efficacy of CA.

Prior studies showed that CA improves QOL in AF patients, especially but not exclusively in patients free from ATA.(3,5,6) Recent studies showed that residual ATA burden (i.e. $>4\%$ assessed by Holter; or $>0.5\%$ assessed by ICM) determines poor QOL after CA.(11,12) Also in the CAPTAF study, general health was related to actual ATA burden.(8) Due to the low residual burden after CA in the C2C study, QOL significantly improved both in patients with and without ATA recurrence.

The C2C study confirms the overall safety profile of CA.(3-6) Whereas we did not observe death, stroke or tamponade, there was a limited number of groin-site hematomas, one pseudoaneurysm and one PV stenosis requiring stenting. None of the patients undergoing repeat ablation revealed PV narrowing. The safety profile is in line with prior safety data after CLOSE-PVI.(17,35) Moreover, improvement in safety is underappreciated because safety of CA also depends on the number of repeat procedures required for durable isolation.

Implications of the present study

(1) The C2C study shows that PVI, if meticulously performed, markedly impacts ATA burden and QOL on the longer-term. It suggests that any novel CA strategy resulting in durable isolation will have similar impact; (2) Despite a class I indication, despite superiority over ADT,(3,5,6) and excellent outcome after CA combined with ADT,(24) there is underutilization and late referral of ablative therapy in PAF. The current longer-term data may lower the threshold for CA; (3) Finally, C2C data suggest that ATA burden is more useful measure of the outcome of the ablation than to censor an ablation as a failure after a single 30-second recurrence as is currently recommended by the guidelines. (1) Because of the short duration of false-positive ATA episodes, ATA burden is not sensitive to adjudication. Because of the shorter and isolated nature of late recurrences, ATA burden (in contrast to survival analysis) is more appropriate to assess longer-term efficacy of CA. In this regard, C2C analysis can serve as a methodological guide for future studies on ATA burden, either assessed by implanted or wearable devices.

Limitations

(1) Despite the importance of patient-controlled data, present results require confirmation by multicentric large studies; (2) ATA burden is dependent on the accuracy of ICM detection. Although one can correct for false positive ATA and although adjudication did not affect results on ATA burden, one cannot correct for false negative findings (like asymptomatic AT with slow regular ventricular rate); (3) We did not advise patients to record symptoms in a standardized diary. Therefore the C2C study is less suited to address the issue of symptomatic vs asymptomatic ATA.(9,10); (4) Finally, 21

patients did not have ICM-documented ATA during the monitoring phase. The fact that those patients had a median time from diagnosis to CA of 9.0 [6.5-20] months together with at least 3 episodes before enrollment favors the hypothesis that absence of ATA is the result of the probabilistic nature of PAF rather than spontaneous resolution of the arrhythmia.

Conclusions

We observed that CA aiming for durable pulmonary vein isolation markedly reduces ATA burden assessed by insertable cardiac monitors; in a PAF population in which one quarter of the patients presented with ATA burden >15.02%, median ATA burden in the first two years after CA was 0 [IQR 0-0] %. Finally, our data make a strong case that the “survival” approach to assessing efficacy with time to first recurrence underestimates the benefit of ablation in reducing burden.

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I

Part I

ABLATION OF ATRIAL FIBRILLATION AND ATRIAL TACHYCARDIA

Part IC

Optimizing left atrial linear ablation

9

Chapter 9

Contiguous and optimized
radiofrequency applications for linear
lesions.

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Abstract

Aims: Achieving block across linear lesions is challenging. We prospectively evaluated radiofrequency (RF) linear ablation at the roof and mitral isthmus (MI) using point-by-point contiguous and optimized RF lesions.

Methods: 41 consecutive patients with symptomatic persistent AF underwent stepwise CF-guided catheter ablation during ongoing AF. A single linear set of RF lesions was delivered at the roof and posterior MI according to the 'ALINE'-criteria, i.e. point-by-point RF delivery (up to 35W) respecting strict criteria of contiguity (inter-lesion distance $\leq 6\text{mm}$) and indirect lesion depth assessment (Ablation Index ≥ 550). We assessed incidence of bidirectional block across both lines only after restoration of sinus rhythm.

Results: After a median RF time of 7min [IQR 5–9], first-pass block across roof lines was observed in 38/41 patients (93%). Final bidirectional roof block was achieved in 40/41 patients (98%). First-pass block was observed in 8/35 MI lines (23%), after a median RF time of 8min [IQR 7–12]. Additional endo- and epicardial (54% of patients) RF applications resulted in final bidirectional MI block in 28/35 patients (80%). During a 396-day [IQR 310–442] median follow-up, 12 patients underwent repeat procedures, with conduction recovery in 4/12 and 5/10 previously blocked roof lines and MI lines respectively. No complications occurred.

Conclusion:

Anatomical linear ablation using contiguous and optimized RF lesions results in a high rate of first-pass block at the roof, but not at the MI. Due to its complex 3D architecture, the MI frequently requires additional endo- and epicardial lesions in order to be blocked.

Introduction

Left atrial (LA) linear lesions are one of the main techniques described for ablation of persistent atrial fibrillation (AF) and are also frequently performed for left atrial macroreentrant tachycardia. However, performing linear ablation remains challenging. Indeed, bidirectional block across LA lines should be the ablation endpoint (HRS/EHRA/ECAS recommendation¹) but this is achieved in a limited amount of patients²⁻⁶ and incomplete electrical block can have pro-arrhythmic consequences and cause atrial tachycardia recurrence.³⁻⁴ On the other hand, increased success in completing linear block is often associated with an increased complication rate from higher ablation power and a higher risk of steam pop, perforation, and tamponade.⁷

New studies have recently introduced a new ablation approach of anatomical point-by-point radiofrequency (RF) ablation based upon indirect evaluation of lesion depth (estimated by a specific formula i.e. “Force-Power-Time Index or Ablation Index”) and delivery of *contiguous* RF lesions.⁸⁻⁹ During pulmonary vein isolation (PVI), it has been showed that acute and late pulmonary vein (PV) reconnection resulted from an insufficient Ablation Index (<550 anteriorly and <400 posteriorly) and/or from a too long interlesion distance (>6mm).⁸

However, these criteria on minimal Ablation Index and maximal interlesion distance have never been evaluated and validated for linear lesions yet. Therefore, we sought to assess the efficacy of performing point-by-point left Atrial LINEar RF lesions (the ALINE study) during AF at the roof and at the mitral isthmus (MI) only using criteria for contiguity (interlesion distance ≤ 6 mm) and Ablation Index (≥ 550), i.e. the ALINE criteria.

Methods

Patient population

From October 2015 to May 2016, all patients undergoing ablation for drug-resistant symptomatic persistent AF were prospectively included in the study if a roof line and/or a MI line was required. LA lines were always performed during ongoing AF to avoid bias from electrogram interpretation, and sinus rhythm or atrial tachycardia were exclusion criteria. Patients with previous linear or complex fractionated atrial electrogram ablation in the LA were also excluded. All patients were followed in a prospective database approved by the local institutional review committee. This database implies collecting patients’ informed consent, a detailed case report form of the procedure, and follow-up at 1, 3, 6 and 12 months.

Procedure

All procedures were performed by 4 different operators, under general anesthesia or conscious sedation, and under novel anticoagulants (last dose taken 24 hours before procedure) or uninterrupted warfarin. Antiarrhythmic drugs, with the exception of amiodarone (6 patients), were withdrawn 24 hours before the procedure. No antiarrhythmic medication was administered during the procedure. In

patients under general anesthesia, an esophageal temperature monitoring probe (SensiTherm™, St Jude Medical Inc, Minnesota US) was placed at the discretion of the operator. Intravenous heparin was administered after femoral vein access to achieve an activated clotting time >300s. A decapolar coronary sinus (CS) catheter and quadripolar His catheter were introduced via the right femoral vein and double transseptal puncture was performed with conventional long sheaths (SL0, St. Jude Medical Inc). A decapolar circular mapping catheter (Lasso®, Biosense-Webster Inc, Diamond Bar, CA, USA) and an 8F open-tip irrigated RF catheter with tip-integrated CF sensor (Thermocool SmartTouch®, Biosense-Webster Inc) were positioned in the LA. Then calibration of CF catheter, respiratory gating and 3D-geometry of the LA (Carto System®, Biosense Webster Inc) were performed. Patients in persistent AF undergoing a first catheter ablation procedure underwent PVI first. In patients undergoing a repeat ablation procedure, electrical isolation of the PVs was checked with the Lasso catheter and electrical re-isolation of the PVs was performed if reconnection had occurred. If AF persisted after PVI, LA linear ablation at the roof and MI was subsequently performed.

Protocol for roof and mitral lines using the ALINE criteria

After confirmation of electrical PVI, a single linear lesion at the roof and subsequently the MI was performed during ongoing AF respecting strict criteria for contiguity (interlesion distance $\leq 6\text{mm}$) and Ablation Index (≥ 550). MI lines were only performed if AF continued after PVI and roof line, and if the persistent AF duration was >1 month (operator's preference). Roof lines were carried out at the shortest distance between the superior margins of right and left superior PVs as cranial as possible. The MI line was drawn at the shortest distance between the posterolateral mitral annulus (A/V ratio of 1:1) and the left inferior PV ostium. ALINE-guided ablation consisted of point-by-point RF delivery (EP Shuttle ST-3077, Stockert GmbH, Freiburg, Germany) in a power-controlled mode (without ramping) with a power setting of 35W (adapted based on catheter tip temperature feedback) and with 30mL/min irrigation. Applications targeted if possible a contact force (CF) between 10-30g with stable CF curve during RF delivery with support of a long non-steerable sheath. At each point, energy was delivered in order to reach an Ablation Index (Hiroshi formula¹⁰⁻¹¹, Biosense Webster Inc) of ≥ 550 . No applications were started with a CF value <5g. RF applications were depicted on the anatomical map with automated tagging technology (Carto VisiTag™, Biosense Webster Inc). Attempts were made to create a single line of VisiTag applications with a maximum interlesion distance $\leq 6\text{mm}$ (center-to-center). In case of instability leading to an inadequate RF tag (not reaching the Ablation Index target), the lesion was discarded and a new RF tag reaching the Ablation Index target was applied in order to obtain a contiguous linear ablation set of applications with Ablation Index ≥ 550 (Figure 1). In case of chest pain or significant intra-esophageal temperature rise ($>38.5^\circ\text{C}$) RF delivery was ceased, and no other application with Ablation Index ≥ 550 was attempted at this spot. In some patients, additional substrate ablation was performed, but delivery close to the roof or MI

lines or in the CS was not allowed on or close to the lines which were previously drawn and if necessary, electrical cardioversion was carried out.

After conversion to sinus rhythm (by ablation or electrical cardioversion), first-pass bidirectional block across roof and MI line was assessed by conventional methods consisting of both differential pacing maneuvers and documenting widely separated double potentials across the entire length of the line.²⁻⁷ In patients without documentation of double potentials despite of bidirectional block established by differential pacing, high-density activation mapping was additionally performed.²⁻⁷ Complete block of mitral and roof lines were confirmed by observing the reversal of the expected activation sequence at one side of the line while pacing from the other side as follows: while pacing from LAA, activation of the LA posterior wall ascends with a complete roof line (instead of descending with an incomplete line)⁶ and the CS sequence is activated proximal to distal with a complete mitral line (instead of distal to proximal if incomplete).^{2,3} Differential pacing was then also systematically used to exclude slow conduction on both lines.²

In sinus rhythm, if block was not achieved after a single linear lesion, additional applications were made by mapping the earliest activity during pacing from the contralateral part of the line and until bidirectional block was achieved. For the posterior MI, both additional RF ablation at the endocardium and in the CS (with a power setting of 15-25 Watts, 30ml/min irrigation, CF 10-30g, Ablation Index ≥ 400) were performed. A maximum total duration of RF application of 30min was allowed, after which failure of block was accepted. Bidirectional conduction block was re-assessed ≥ 20 min after the last ablation lesion along the line.

Figure 1: ‘ALINE’-guided first-pass ablation of roof and posterior mitral isthmus line during ongoing AF. Attempts were made to create a single anatomical line of contiguous VisiTag applications with a maximum interlesion distance ≤ 6 mm (center-to-center) and Ablation Index (AI) ≥ 550 (red Visitags). After restoration of sinus rhythm, first-pass block was assessed.

Off-line analysis of RF characteristics of roof and MI lines

Each procedure was exported and analyzed offline. For each RF tag at the roof and MI, we determined time of application (s), median delivered power (W), impedance drop (Δ -Imp, Ω), average contact force (CF, g), force-time integral (FTI, gs) and Ablation Index (AI, no unit). In addition, custom-made software was used to automatically determine the interlesion distance in between neighboring ablation tags (center-to-center distance, mm) and the ablation line contiguity index (ALCI). The ALCI has been previously evaluated during PVI and has been shown to be the most accurate predictor for durable RF segments.⁸ The ALCI algorithmically combines interlesion distance and Ablation Index into one single criterion, and is defined as the ratio of the mean Ablation Index of 2 neighboring RF lesions (multiplied by a 1.5 conversion factor referring to the thickness of the tissue) over their interlesion distance.⁸ The length of the line (as measured on the 3D navigation system) was also measured.

Post-procedural care and follow-up.

Clinical evaluation and ECG were performed at 1, 3, 6 and 12 months or in case of symptoms. Holter recordings were performed at 6 and 12 months. Recurrence of AF and atrial tachycardia (≥ 30 s) was evaluated considering a blanking period of 8 weeks. Repeat procedures were performed based on case-by-case evaluation, but repeat ablation was preferred in patients with atrial tachycardia recurrence.

Statistical analysis

Continuous variables are expressed as mean $\pm$ SD (or medians with interquartile range (IQR, 25th—75th percentile) for non-normal distributions) and dichotomous variables as count and percentage. Normality of data distribution was tested with the Shapiro-Wilk test. Parametric (Student's t-test) or non-parametric tests (Mann-Whitney U) were used when appropriate to evaluate differences in continuous clinical and ablation parameters between groups with bidirectional block vs. remaining conduction after first-pass RF delivery at the roof and MI respectively. Categorical variables were compared with the χ^2 test or Fisher's exact test when appropriate. Univariable and multivariable predictors were examined using logistic regression analysis. Variables with a univariable p-value of 0.1 were included in the multivariable model. All reported p-values were 2-sided, and a p-value of 0.05 was considered significant. All statistical analyses were performed in SPSS Statistics 24 (IBM Corporation, Armonk, New York, USA).

Results

Patient population and procedural characteristics.

The study population included 41 consecutive patients (41 patients with a roof line and 35 with a MI line) according to the pre-established inclusion criteria. The mean age of the study population was 65 ± 9 years, and 68% of patients were male. The mean left atrial volume was 130 ± 37 mL. Further

patient characteristics are summarized in Table 1. Procedures were performed under general anesthesia in 30 patients (73%). An esophageal temperature probe was used in 19 patients (46%). There were no peri-procedural complications.

Table 1: Patient and procedural characteristics

<i>Patient characteristics</i>	
Total number	41
Age, y	64.8 ± 8.5
Male gender, n (%)	28 (68)
BMI, kg/m ²	27.7 ± 5.0
CHA ₂ DS ₂ VASc-score	1.6 ± 1.4
Left atrial volume, mL (Carto System®)	129.6 ± 37.4
Left atrial diameter, mm (ultrasound)	44.1 ± 6.1
Atrial fibrillation	
persistent (<12 mo), n (%)	32 (78)
long standing persistent (>12 mo), n (%)	9 (22)
atrial fibrillation cycle length, ms	172 ± 24
Prior pulmonary vein isolation, n (%)	8 (20)
<i>Procedural characteristics</i>	
General anesthesia, n (%)	30 (73)
Esophageal temperature probe, n (%)	19 (46)
Pulmonary vein anatomy	
4 pulmonary veins, n (%)	39 (95)
LCPV, n (%)	2 (5)

BMI: body mass index; LCPV: left common pulmonary vein

Roof line using ALINE criteria

A roof line was performed in 41 patients. The mean length of the lines was 39±12mm. The median number of RF applications to create a first-pass blocked roof line was 11 [IQR 8 – 13] with a median RF time of 7min [IQR 5 – 9]. The median number of dislocations before reaching the Ablation Index target was 0 [IQR 0 – 1] per patient. First-pass bidirectional block was observed in 38 of the 41 roof lines (93%) (Figure 2). Additional RF (5 - 16 applications, with 2 – 7min duration) resulted in block across 2 of the 3 remaining unblocked roofs. Conduction gaps were located at the middle of the roof in one patient, and near the right PVs in the second patient. Final bidirectional block was achieved in 40 of 41 patients (98%) (Figure 2) and was still present in all patients after a waiting period of ≥20min. In one patient, RF delivery was ceased before reaching the target Ablation Index due to an esophageal temperature rise >38.5°C.

Comparison of clinical and RF lesion characteristics between lines with bidirectional block vs. conduction after first-pass RF are summarized in Table 2 and Figure 3A. Increased length of the roof

was a significant predictor of failure of first-pass roof line block in univariable (OR 0.81, 95% CI 0.66 – 0.99, p-value 0.044), but not in multivariable analysis. No clinical or procedural parameters differed between both groups (Table 2). The characteristics of the ≥ 550 Ablation Index tags (RF time, delivered power, impedance drop, average CF, FTI, AI, interlesion distance and ALCI) did not differ between first-pass blocked and unblocked roof lines (Figure 3A).

Figure 2: Results of first-pass and final roof and mitral isthmus block.

Mitral isthmus lines using ALINE criteria

Posterior MI lines were performed in 35 patients. The mean length of the MI line was 39 ± 13 mm. The median number of RF applications to create a first-pass MI line was 12 [IQR 9 – 14] with a median RF time of 8 min [IQR 7 – 12]. The median number of dislocations prior to reaching the Ablation Index target was 0 [IQR 0 – 2] per patient. An example of a case is illustrated in Figure 4. First-pass bidirectional block was observed in only 8 of 35 MI lines (23%) (Figure 2). Preferential conduction gaps after first-pass RF are shown in Figure 5. In 11 patients no clear preferential gap could be determined and more extensive additional endo- and epicardial ablation was needed in order to obtain block. Additional RF at the epicardial/CS side (median of 7 applications [IQR 5 – 14], during 4 min [IQR 3 – 7]) in 19 patients, and at the endocardial side (median of 8 applications [IQR 6 – 15], during 6 min [IQR 4 – 9]) in 14 patients resulted in block of 20 out of 27 remaining unblocked MI lines. Final bidirectional MI block was achieved in 28 of 35 patients (80%), after a median total RF duration of 15 min [10 – 20] and was still present in all patients after a waiting period of ≥ 20 min. In two patients,

cannulation of the distal CS was not feasible. An esophageal temperature rise $>38.5^{\circ}\text{C}$ (or pain) was never observed during applications along the posterior MI.

Comparison of clinical and RF lesion characteristics between lines with bidirectional block vs. conduction after first-pass RF are summarized in Table 2 and Figure 3B. LA volume was statistically significant in univariable (OR 1.04, 95% CI 1.00-1.07, p-value 0.033), but not in multivariable analysis. No clinical or procedural parameters differed between both groups (Table 2). No difference was observed in the characteristics of the ≥ 550 Ablation Index tags between first-pass blocked and unblocked MI lines (Figure 3B).

Table 2: Determinants of first-pass roof and mitral isthmus block

ROOF LINE		No first-pass roof block (n=3)	First-pass roof block (n=38)	Univariable analysis		Multivariable analysis	
				OR (95% CI)	p-value	OR (95% CI)	p-value
<i>Clinical characteristics</i>							
Age, y		60.0 ± 7.8	65.1 ± 8.6	1.07 (0.94 - 1.21)	0.324		
Male gender, n (%)		3 (100)	25 (66)	0.00 (0.00 - /)	0.999		
CHA2DS2VAsE-score		1.0 ± 1.0	1.6 ± 1.3	1.49 (0.52 - 4.26)	0.462		
Continuous AF duration >12mo, n (%)		2 (67)	7 (18)	0.53 (0.04 - 6.66)	0.625		
Left atrial volume, mL		137.3 ± 20.5	129.0 ± 38.6	0.99 (0.96 - 1.03)	0.706		
Left atrial diameter, mm		44.0 ± 9.5	44.1 ± 5.9	0.95 (0.75 - 1.19)	0.634		
<i>Procedural characteristics</i>							
General anesthesia, n (%)		2 (67)	28 (74)	1.40 (0.11 - 17.2)	0.792		
Length line, mm		55.1 ± 4.1	37.8 ± 11.6	0.81 (0.66 - 0.99)	0.044	0.85 (0.70 - 1.03)	0.097
RF time, s		656.0 ± 102.8	435.3 ± 169.9	0.99 (0.98 - 1.00)	0.062	1.00 (0.98 - 1.01)	0.327
MITRAL ISTHMUS LINE		No first-pass MI block (n=27)	First pass MI block (n=8)	Univariable analysis		Multivariable analysis	
				OR (95% CI)	p-value	OR (95% CI)	p-value
<i>Clinical characteristics</i>							
Age, y		65.5 ± 7.2	60.8 ± 10.0	0.93 (0.84 - 1.03)	0.151		
Male gender, n (%)		19 (70)	4 (50)	0.42 (0.08 - 2.11)	0.293		
CHA2DS2VAsE-score		1.4 ± 1.4	2.0 ± 1.3	1.37 (0.77 - 2.44)	0.462		
Continuous AF duration >12mo, n (%)		7 (26)	1 (13)	1.17 (0.19 - 7.34)	0.870		
Left atrial volume, mL		127.9 ± 30.9	131.6 ± 32.6	1.04 (1.00 - 1.07)	0.033	1.03 (1.00 - 1.07)	0.060
Left atrial diameter, mm		44.1 ± 6.4	43.9 ± 6.5	0.98 (0.84 - 1.13)	0.742		
<i>Procedural characteristics</i>							
General anesthesia, n (%)		19 (70)	7 (88)	2.95 (0.31 - 28.0)	0.347		
Length line, mm		38.8 ± 11.7	34.1 ± 21.9	1.02 (0.89 - 1.17)	0.814		
RF time, s		571.0 ± 194.0	457.1 ± 181.0	1.00 (0.99 - 1.00)	0.156		

AF: atrial fibrillation; CI: confidence interval; OR: odds ratio; RF: radiofrequency

Figure 3: Comparison between lines with vs. without first-pass conduction block at the roof (A) and mitral isthmus (B) concerning the minimal value from all effective RF lesions for the following parameters: application time (Time_{min}), power (Power_{min}), impedance drop (Δ-Imp_{min}), contact force (CF_{min}), force-time integral (FTI_{min}), Ablation Index (AI_{min}) and ablation index contiguity index (ALCI_{min}), and the maximal value of interlesion distance (ILD_{max}). RF points with dislocation during application were excluded from the analysis.

Figure 4: Upper panels: Evaluation of conduction block after first-pass roof and posterior mitral isthmus (MI) line. High density activation map during left atrial appendage (LAA) pacing shows propagation across the MI (arrows), with probable epicardial conduction through the coronary sinus (CS). Distal-to-proximal CS activation is concordant with MI conduction. The roof was blocked after first-pass RF delivery.

Lower panels: After additional RF applications in the CS, MI block was obtained, evidenced by pattern of activation (arrows), presence of widely-spaced double potentials across the MI line and proximal-to-distal activation along the CS catheter.

Follow-up

During a median follow up of 396 days [IQR 310 – 442], 17/41 patients (41%) experienced atrial arrhythmia recurrence (14 patients with AT, 3 with AF) with 22 patients (56%) continuing antiarrhythmic drugs (10 pts class Ic, 5 pts sotalol and 7 pts amiodarone). There was no difference in achievement of final block across roof and MI lines between patients with and without atrial arrhythmia recurrence (19/24 (79%) vs. 14/17 (82%) pts, $p=1.000$). Repeat ablation procedures with assessment of persistent conduction block across roof and MI were performed at 7 ± 4 months after the index procedure in 12 of 14 patients with atrial tachycardia recurrence.

Repeat evaluation of roof lines

Of the 12 evaluated roof lines, all had been blocked after first-pass RF delivery during the index procedure. There was persistent block in 8/12 and there was re-conduction in 4/12 (33%). Conduction

gaps were small, located at the middle of the roof or at the transition between the middle towards the right PVs (Figure 5) and were responsible for roof-dependent macroreentry in 3 of the 4 patients with re-conducting roof lines. Re-ablation using the ALINE criteria resulted in block in all patients after a short duration of application (1.6 ± 0.6 min).

Repeat evaluation of mitral isthmus lines

Of the 12 re-evaluated MI lines, 2 were not blocked during the index procedure and were still conducting. Of the remaining 10 evaluated lines (with block during the index procedure of which 2 with first-pass block), 5 MI lines showed persistent block while 5 had re-conduction (Figure 6). Conduction gaps were short and located in the mid-isthmus region (4 patients) and in the CS (1 patient). Block was re-achieved after endocardial ablation only in 4 patients; in one patient, additional applications in the distal CS were required (Figure 5). Six of the 7 patients with conduction across the MI at re-evaluation presented with a procedural perimitral atrial tachycardia. All re-ablation using the ALINE criteria resulted in block after short application duration (3.1 ± 0.9 min).

Figure 5: Distribution of conduction gaps on the roof and mitral isthmus (MI) after first-pass radiofrequency lesions respecting criteria of contiguity and lesion depth (shown for patients with final block) (**left panel**). Distribution of conduction gaps at the roof and MI in patients with recovered conduction during repeat ablation procedures (**right panel**).

Discussion

Main findings

Our study shows that performing LA linear lesions with contiguous and optimized RF lesions results in a very high rate of first-pass bidirectional block at the roof but not at the mitral isthmus line. During repeat procedures, limited RF delivery was necessary to achieve conduction block and was successful in all re-ablated patients for both lines.

Additional benefit of both contiguous and optimized RF lesions

In studies on RF ablation in the canine heart, Nakagawa et al found that the RF lesion depth was accurately (± 1 mm) described by a logarithmic function of CF, RF power and application time (i.e. the Force-Power-Time Index or Ablation Index).¹⁰⁻¹¹ In a recent retrospective analysis, our research group emphasized that in CF-guided PVI, both indirect lesion depth assessment (as measured via Ablation Index) and lesion contiguity are essential to obtain a durable ablation lesion. El Haddad et al demonstrated that for durable PVI, the maximum interlesion distance should not exceed 6mm and the minimal Ablation Index should be ≥ 400 at the posterior and ≥ 550 at the anterior wall, reflecting the difference in wall thickness between the anterior and posterior PV junction.⁸ Additionally in a prospective cohort study, an ablation strategy respecting contiguous and optimized RF lesions resulted in a very high rate of first-pass and adenosine-proof PV isolation and a single-procedure arrhythmia-free survival of 92% at 1-year, without any complications.⁹ Based upon these findings, we hypothesized that linear ablation respecting strict criteria of contiguity and indirect lesion depth assessment based on the Ablation Index would also improve achievement of both acute and durable block across LA linear lesions.

Conduction block with left atrial linear ablation: technically challenging but essential

Roof and MI lines are the most commonly performed LA linear lesions. Even though achieving bidirectional conduction block is challenging²⁻⁶ (reported block across roof lines of 81 to 95%^{3,6,12} and for the MI line between 57 to 92%^{2-4,13-14}), it is well known that incomplete bidirectional conduction block has been associated with an increase in subsequent arrhythmia during follow-up.³⁻⁴

In our study, even respecting the criteria for contiguity and Ablation Index, we achieved complete block in the roof line in 93% of patients after a single linear lesion set, but only in 23% at the MI line (without CS ablation) confirming this difference for both lines. The very high success rate of first-pass block on the roof in our study can probably be explained by the favorable and uniform anatomy of the roof, which renders the roof quite suitable for a strategy aiming at transmural and contiguity of RF lesions. This was emphasized by the low number of dislocations before reaching Ablation Index target value. In the case of absence of block after the first-pass roof line and during the redo procedures, all conduction gaps were located in the middle of the roof or near the right PVs (never at the left side of the roof). These locations are characterized by lower stability during RF delivery and also by thicker tissue with interatrial muscular bridges.¹⁵

Conversely, the success rate for achieving bidirectional conduction block after a first pass linear lesion at the MI was low. This can probably be explained by the anatomical characteristics of the MI region. Post mortem anatomical and *in vivo* studies have shown that the atrial myocardium at the left mitral line has a wall thickness of up to 10mm at the ostium of the left inferior PV.¹⁶ In comparison, the LA roof is thinner with a range between 3.5 and 6mm.¹⁵ The distance between the endocardium and the overlying inner surface of the CS is even larger than the MI thickness, due to the adipose tissue overlaying the CS along the mitral valve, sometimes with interlaying circumflex artery branches.^{13,17}

Numerous recesses and cavities along the left mitral isthmus have also been reported¹⁸ as well as epicardial muscular connections necessitating ablation within the CS in the majority of patients.^{2,17-18} Blood flow in the CS and circumflex artery may also act as a ‘heat sink’ and reduce the efficacy of radiofrequency ablation.¹⁷ Length of the MI line, increased MI thickness and interposition of the circumflex artery between the CS and the MI were independent predictors of incomplete MI block in previous studies¹³⁻¹⁴ and the need for epicardial CS ablation in order to obtain MI block has been reported in 60 to 84% of cases^{2,13-14} (as compared to 54% in our study).

Recovery of conduction has been reported to occur in up to 90% of MI line and 79% of the roof lines during repeat evaluation for atrial arrhythmia recurrence^{19,20}. In our study, 50% of the MI lines and 33% of the roof lines that were blocked at the end of the index procedure had recovered conduction. Interestingly, among the 8 patients with first-pass MI block in the index procedure, 2 of them had a redo procedure and reevaluation of the MI line showed persistent complete conduction block. The other 6 patients did not have atrial arrhythmia recurrence. Even if the number of patients is really low, these findings might suggest that if first-pass MI block is achieved, the probability of durable MI block is higher, possibly due to favorable patient’s MI anatomy.

Limitations

(1) The criteria for Ablation Index (≥ 550) and interlesion distance ($\leq 6\text{mm}$) were arbitrarily applied for both lines, even if this may oversimplify the complex anatomy of the roof and MI region. These values were selected based on previous studies⁸⁻⁹ and local experience, to minimize the risk of complication and to minimize the risk of dislocation (during longer RF applications) which could have impacted the interpretation of the data. In the future, higher Ablation Index or shorter interlesion distance should be evaluated for the MI line given the low amount of first pass block. (2) Pre-evaluation with imaging technologies might also improve the results by allowing adaptation of the criteria depending on individual anatomical variations and helping avoid RF under- and overshooting. (3) The Ablation Index has been shown to be an accurate marker for lesion depth, but we did not measure the actual lesion depth with imaging or histology. (4) Although no safety-related issues were observed, larger studies are necessary to evaluate the safety and efficacy of this protocol for linear LA lesions. (5) Because evaluation of persistent roof and MI line block was only performed in a limited number of patients who presented with atrial tachycardia recurrence, the rate of conduction recurrence might be underestimated. (6) Previous ablation for PVI may impact the atrial tissue at the roof and MI differently if ostial or antral ablation is performed. However, in all study patients, PVI was performed close to the PV junction.⁹ (7) The use of a steerable sheath might have improved the results mainly by increasing optimizing contact, catheter stability and by decreasing catheter dislocation⁴; however this happened only sporadically in our study.

Conclusion

Anatomical ablation using contiguous and optimized RF lesions is very effective for the roof line but not for the mitral isthmus line. The complex 3D architecture of the mitral isthmus region frequently necessitates epicardial and additional endocardial RF lesions in order to obtain block.

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I

Part I

ABLATION OF ATRIAL FIBRILLATION AND ATRIAL TACHYCARDIA

Part ID

Mapping of drivers in persistent atrial fibrillation

10

Chapter 10

Direct contact activation mapping in persistent atrial fibrillation

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Abstract**Introduction:**

Recent studies have characterized drivers in persistent atrial fibrillation using automated algorithm detection with panoramic endocardial mapping by means of basket catheters. We aimed to identify repetitive atrial activation patterns (RAAPs) during ongoing AF based upon automated annotation of unipolar electrograms recorded with a high-density regional endocardial contact mapping catheter.

Methods:

In 14 persistent AF patients, high resolution electrograms (EGMs) were recorded for 30 seconds at sequential PentaRayTM (Biosense Inc) positions covering the entire bi-atrial surface. All recordings were reviewed off-line with dedicated software allowing automated annotation of the local activation time of the unipolar fibrillatory EGMs (CARTOFINDERTM, Biosense Inc).

RAAPs were defined as a consistent activation pattern (for ≥ 3 consecutive beats) of either focal activity with centrifugal spread (RAAP_{focal}) or rotational activity across the PentaRay splines spanning the AF cycle length (RAAP_{rotational}).

Results:

498 PentaRay recordings were analyzed (35.6 ± 7.6 per patient). The number of PentaRay recordings displaying RAAP was 9.8 ± 3.1 per patient (range 3-15), of which 2.4 ± 2.4 RAAP_{rotational} (range 0-7) and 7.4 ± 4.4 RAAP_{focal} (range 1-13). 77% of RAAPs portrayed focal firing. The median number of repetitions per 30 second recording was 11 (range 3-225) per recording. RAAPs were observed both in the RA (35%) and LA (65%), with the majority being near the left PVs/appendage (35% of all RAAPs) and the SVC/right appendage (23% of all RAAPs).

Conclusions:

High-resolution, sequential endocardial EGM-based mapping allows identification of RAAPs in persistent AF. In our series, focal firing was the most frequently observed pattern.

Introduction

During persistent atrial fibrillation (AF), multiple atrial wavelets and localized (focal or reentrant) sources have been reported to contribute to the maintenance of AF.¹⁻³ In the last few years, there has been progress in mapping AF sources and mechanisms, mostly using phase-based analysis of epicardial or endocardial potentials.⁴⁻¹⁰ However, phase mapping has limitations as it is known to generate false rotational activities, particularly in cases of low voltage, variable contact and when far-field signals are present.¹¹⁻¹²

Recently, AF propagation maps based on direct contact mapping (without phase transformation) with a dedicated software (CARTOFINDER™, Biosense Webster Inc, Diamond Bar, CA) have also been tested.¹³⁻¹⁶ Using a multi-electrode basket catheter, the authors were able to reliably and reproducibly identify repetitive activation patterns in the majority of patients. Nevertheless, the basket catheter had long interelectrode distance and could not reach stable contact with the atrial wall in some regions and therefore, some repetitive activation patterns were probably missed.

This study sought to evaluate a new mapping method for the Cartofinder software, using a regional high-density contact mapping catheter (PentaRay™, Biosense Webster Inc). For the present work, we characterized repetitive atrial activation patterns (RAAPs) during ongoing AF based upon the automated annotation of unipolar electrograms (EGMs) directly obtained by these sequential recordings of the entire bi-atrial endocardial surface.

Methods

Patient population

During a two-fold period of availability of the Cartofinder software in our center (from May to October 2017 and from May to June 2019) consecutive patients who were referred to our institution for a first ablation of ongoing persistent AF and who consented to participate in the protocol, were enrolled in the study. Persistent AF was defined as continuous AF from 7 days to 12 months. Exclusion criteria were 1) sinus rhythm or atrial tachycardia at the onset of the procedure, 2) prior pulmonary vein isolation or atrial substrate ablation (linear lesions or ablation of fragmented signals), 3) presence of intra-cardiac leads, mechanical heart valves, an inter-atrial septum or a left atrial appendage occluder devices, 4) contra-indication for general anesthesia. The study protocol was approved by our institutional Ethics Committee.

Procedure and contact mapping

All procedures were performed under general anesthesia and under novel anticoagulants (last dose taken 24 hours before procedure) or uninterrupted warfarin by three operators (RT, SK and MD). Antiarrhythmic drugs, with the exception of amiodarone, were withdrawn at least five half-lives before the procedure. Intravenous heparin was administered after femoral vein access to achieve an activated clotting time >300s. A decapolar coronary sinus catheter was introduced via the right

femoral vein and double transseptal puncture was performed with conventional long sheaths (SL0, St. Jude Medical Inc). An irrigated mapping catheter with five soft radiating splines with 10 pairs of 1mm electrodes separated by 2-6-2mm interelectrode spacing (PentaRay, Biosense Webster Inc) and an 8F irrigated RF catheter with contact force sensor (Thermocool SmartTouch®, Biosense-Webster Inc) were positioned in the LA. Then calibration of contact force catheter and respiratory gating (Carto System®, Biosense Webster Inc) were performed. After reconstruction of 3D-geometry of the left atrium with the PentaRay catheter, high resolution EGMs during ongoing AF were recorded for 30 seconds at sequential PentaRay positions covering the entire left atrial surface, with each position overlapping the previous recording position with the radius of the PentaRay (Figure 1). Recordings were only obtained after optimal positioning of the PentaRay catheter, aiming maximal and even spread of the five splines with optimal electrode-tissue contact (also guided by the *Tissue Proximity* Indicator (Biosense Webster Inc), which determines the electrode *proximity* to cardiac *tissue* based on impedance measurements). *After sequential mapping of the left atrium, 1 transseptal sheath was pulled back and sequential mapping of the entire right atrium was then performed.* After EGM acquisition, RF ablation was performed with a lesion set consisting of pulmonary vein isolation with entrance block and linear lesions (roof, mitral and cavotricuspid isthmus). Ablation was not guided by the Cartofinder analysis.

Figure 1: Sequential PentaRay recording positions covering the entire bi-atrial surface. Recordings were only obtained after optimal positioning of the PentaRay catheter, aiming maximal and even spread of the five splines with optimal electrode-tissue contact. Sequential positions overlap the previous recording position with the radius of the PentaRay: the center of position 1 (star) becomes the radius of position 2 (top panels). Overlapping recordings enhance detection of repetitive atrial patterns (rotational in position 1 and focal in position 2, bottom panels).

EGM analysis and translation to activation mapping.

All recordings were reviewed off-line with dedicated software allowing automated annotation of the local activation time of the fibrillatory EGMs (CARTOFINDER™, Biosense Webster Inc). Off-line analysis consisted of the following two parts: 1) identification and characterization of RAAPs, 2) Assessment of manual RAAP identification on Cartofinder activation maps and agreement between reviewers.

Part 1: identification of repetitive atrial activation patterns

Cartofinder is based on the assessment of the local activation time of atrial signals during ongoing AF¹³⁻¹⁷. To accurately determine the activation time, the automated Cartofinder software entails the following: 1) first the algorithm filters out the far-field ventricular signals. 2) Then for each electrode, 2 bipolar atrial signals are created by using the nearest two electrodes, which are determined by the Carto matrix (impedance based). For each electrode, the bipolar EGM window is then established based on measurement of the earliest onset to latest offset of its 2 bipolar electrograms. This bipolar EGM window establishes the window to record the unipolar atrial signal from each electrode. 3) Next, a wavelet analysis of unipolar signals recorded from the bipolar electrogram window is performed. This analysis uses a proprietary algorithm to annotate only high-quality unipolar signals^{13,17}. For each electrode the local activation time is established as the maximal negative slope of the unipolar electrogram within its predefined bipolar window, with the purpose of blanking out negative slopes due to far-field potentials. The accuracy of automated annotation of atrial local activation time and V far-field subtraction has been previously validated by experienced electrophysiologists (EPs) as part of the development process and used for the FDA submission, and were not routinely manually verified in our study.

After automated EGM analysis, RAAPs were identified on a 3D propagation map, which was automatically generated for each recording (Figure 2 and 3 and supplementary video recording A and B). RAAPs were defined as a consistent activation pattern (for ≥ 3 consecutive beats) of either focal activity with centrifugal spread along the PentaRay splines (RAAP_{focal}) (Figure 2) or rotational activity across the PentaRay splines spanning the AF cycle length (RAAP_{rotational}) (Figure 3). To classify the spatial distribution of RAAPs, the bi-atrial surface was divided in 7 regions (Figure 4). Four regions were defined in the left atrium, 2 in the right atrium, and 1 in the anterior interatrial septum. Because of their proximity, left PVs were grouped with the left appendage into 1 region en bloc. Similarly, the right atrial appendage was grouped with the upper right atrium. Type, number and location of RAAPs were cataloged per patient.

Figure 2: Example of a $RAAP_{focal}$: PentaRay positioned at the lateral wall of the right atrium. Subsequent panels show the propagation during a time window of 990 to 1030 ms of a 30 s registration during ongoing atrial fibrillation. The color-coding, as well as the unipolar fibrillatory EGMs recorded at each electrode (here organized per PentaRay spline (A to E) with electrode 4 as the most proximal and electrode 1 as the most distal per spline) shows a centrifugal propagation consistent with focal firing ($RAAP_{focal}$).

Figure 3: Example of a $\text{RAAP}_{\text{rotational}}$: PentaRay positioned at the lateral wall of the right atrium. Subsequent panels show the propagation during a time window of 1250 to 1420 ms of a 30 s registration during ongoing atrial fibrillation. The color-coding, as well as the unipolar fibrillatory EGMs recorded at each electrode (here organized per radius with electrode 4 as the most proximal and electrode 1 as the most distal per spline A to E), show a repetitive rotational propagation consistent with a $\text{RAAP}_{\text{rotational}}$.

Part 2: Validation of RAAP identification from the Cartofinder software

This part of the study sought to validate the propagation map as generated by the Cartofinder system with the EGM analysis obtained from automated EGM annotation and reviewed by 4 experienced EPs who were blinded to the Cartofinder results. 46 out of 498 recordings (annotated EGMs and propagation maps) were randomly selected (21 with identified RAAP_{focal}, 18 with identified RAAP_{rotational} and 7 recordings without RAAP identification). Agreement among the individual classification by 4 reviewers was documented and compared to the propagation map generated by the Cartofinder software.

Statistics

Continuous variables are expressed as mean $\pm$ SD (or medians with range for non-normal distributions) and dichotomous variables as count and percentage. Normality of data distribution was tested with the Shapiro-Wilk test. Intraclass correlation coefficient was calculated to determine the agreement amongst the 4 operators. All statistical analyses were performed in SPSS Statistics 24 (IBM Corporation, Armonk, New York, USA).

Results

Part 1: identification of repetitive atrial activation patterns

The characteristics of the 14 patients are detailed in Table 1. In total 498 PentaRay recordings were achieved and analyzed (35.6 ± 7.6 recordings per patient, 13.3 ± 3.5 in the RA and 22.1 ± 3.2 in the LA). The duration to perform all recordings was 44 ± 6 min. Radiation exposure during mapping was 6 ± 3 min. The mean AF cycle per recording was 172 ± 25 ms.

The mean number of PentaRay recordings displaying RAAP was 9.8 ± 3.1 per patient (range 3-15) (6.4 ± 2.5 in the LA and 3.4 ± 2.1 in the RA). Per RAAP, the median number of consecutive cycle repetitions during the 30 s recording was 11 (range 3-225).

Table 1: Patient characteristics

Total patient number	14
Age, y	59.9 ± 9.5
Male gender, n (%)	10 (71)
BMI, kg/m ²	26.7 ± 5.0
CHA2DS2VASc-score	1.8 ± 1.4
Arterial hypertension, n (%)	5 (36)
Diabetes mellitus, n (%)	1 (7)
LV ejection fraction: 35 ≤ LVEF ≤ 50, n (%)	2 (14)
Coronary artery disease, n (%)	2 (14)
Left atrial volume, mL	115.6 ± 37.4
Left atrial diameter, mm	44.5 ± 2.3
Atrial fibrillation persistent (>7days, <12 moths), n (%)	14 (100)
Antiarrhythmic drugs	
bèta-blocker, n (%)	8 (57)
class Ic, n (%)	4 (29)
sotalol, n (%)	3 (24)
amiodarone, n (%)	3 (24)
Oral anticoagulation, n (%)	14 (100)

BMI: body mass index; LV: left ventricular

Focal firing vs. rotational activity:

Per patient, a mean of 7.4 ± 4.4 RAAP_{focal} (range 1-13) and 2.4 ± 2.4 RAAP_{rotational} (range 0-7) were observed. In total 77% of RAAPs showed focal spread and in 7 out of 14 patients only RAAP_{focal} could be observed.

Distribution in left and right atrium:

The distribution of RAAPs is displayed in Figure 4. RAAPs were identified in a mean of 4.5 ± 1.1 regions per patient, in both the right (35%) and the left atrium (65%). RAAPs were most frequently located near the left PV / left atrial appendage region (n=47 or 35% of all RAAPs) and in the superior RA / right atrial appendage region (n=31 or 23% of all RAAPs).

The distribution of RAAP_{rotational} and RAAP_{focal} were similar. In the RA, per patient a mean of 0.9 ± 1.2 RAAP_{rotational} (range 0-3) and 2.4 ± 2.3 RAAP_{focal} (range 0-8) were observed. In the LA, per patient a mean of 1.5 ± 1.8 RAAP_{rotational} (range 0-5) and 4.9 ± 3.1 RAAP_{focal} (range 1-11) were identified.

Figure 4: Panel A: To classify the spatial distribution of RAAPs, the bi-atrial surface was divided in 7 regions. Four regions were defined in the left atrium, 2 in the right atrium, and 1 in the anterior interatrial septum. Because of their proximity, left PVs were grouped with the left appendage into 1 region en bloc. Similarly, the right atrial appendage was grouped with the upper right atrium. **Panel B:** total number of identified RAAPs per region for all 14 patients. **Panel C:** number of RAAP_{rotational} per region for all 14 patients. **Panel D:** number of RAAP_{focal} per region for all 14 patients.

Part 2: Validation of RAAP identification from the Cartofinder software

There was good statistical agreement amongst the 4 operators in identifying RAAP (intraclass correlation = 0.725 [95%CI: 0.571, 0.835], $p < 0.001$).

In the majority of the selected recordings (37 of 46 or 80%), an agreement between reviewers was obtained. This includes a full agreement amongst the 4 reviewers in 19 (41%) recordings and an agreement amongst 3 reviewers in 18 (39%) recordings. In 9 recordings (20%), agreement was achieved amongst only 2 of the 4 reviewers. More precisely, for rotational activity, agreement amongst 4 and 3 reviewers was present in 44 and 50% respectively. For focal activity, agreement amongst 4 and 3 reviewers was present in 53 and 40% respectively. In the 7 recordings without RAAP, agreement amongst 4 and 3 reviewers was present in 43% and 43% respectively. We added two examples of the agreement between reviewers to the supplementary appendix.

Discussion

Main findings

This study shows that in persistent AF, using a high-density direct contact mapping catheter, the Cartofinder software consistently identifies numerous RAAPs (and predominantly focal firing sources), based on an automated acquisition of unipolar fibrillatory EGMs. Sequential high-density mapping may detect a greater number of RAAPs due to better coverage and mapping density in comparison with basket catheters¹³⁻¹⁷.

Localized high-density vs. panoramic mapping using the Cartofinder software.

Recent studies have investigated the feasibility of the Cartofinder software (Biosense Webster) to identify and characterize RAAPs during AF. However, all of those studies used an endocardial 64-electrode basket-catheter (Constellation, Boston Scientific) to cover the entire LA¹³⁻¹⁶ except for one in which the basket catheter was evaluated in combination with the PentaRay catheter¹⁷. In this study, focusing on the LA¹⁷, focal RAAPs detected by the PentaRay catheter were less frequent as compared to our study. This could be explained by the fact that there were less recordings per patient (mean of 13 recordings as compared to 22 in our study) and that all included patients had long-standing persistent AF, while patients with AF >12 months were excluded in our trial.

Using the basket catheter, there has been some inconsistency concerning the amount of RAAP which could be identified by the software: from ~1^{14,15,17} to ~6¹⁶ RAAP, as compared to ~10 in our study (all of the patients had ≥ 3 RAAPs). Moreover, while some investigators used a prolonged recording time (1-minute vs. 30 seconds in our study)¹³, and although RAAP definition was sometimes more flexible (≥ 2 consecutive wavefronts for RAAP_{focal} and ≥ 1.5 rotations for RAAP_{rotational}), RAAPs were only present in 55-65% of the patients in some of those studies using the basket catheter^{14,15}. In addition, RAAPs were mostly rotational¹⁴, while focal RAAPs were more prevalent our study.

With the basket catheter, the interelectrode spacing is larger and there could be an issue with electrode-tissue contact and a predilection to position the basket towards the anterior wall.^{15,16} This can result in a suboptimal coverage of the atrial surface (54 to 72%)^{15,16}, with possible underestimation of RAAPs.

Sequential global mapping using a regional high-density mapping catheter can potentially overcome these issues. The PentaRay catheter used in our study has already demonstrated its usefulness in the analysis of activation patterns during ongoing AF. In a study on AF mapping, complex fractionated electrogram (CFAE) areas were demonstrated to be mostly passive as there was a simultaneous activation in all PentaRay splines in 84% of the CFAE areas¹⁸. In another study, this high-density mapping catheter was used to localize and ablate focal activity in the left atrium during AF, with

encouraging results¹⁹. More recently, focal drivers that were detected in AF on sequential PentaRay recordings were more consistent, showed greater temporal stability and a higher recurrence rate compared with drivers that were not identified as “region of interest” using the basket catheter¹⁷. Furthermore, ablation at these RAAP sites identified with sequential PentaRay maps was more likely to terminate AF than drivers identified on global wavefront maps alone¹⁷.

While localized mapping allows for mapping both entire atria, it is crucial that the catheter remains stable, and with good contact of all 5 catheter splines. In addition, it cannot be excluded that meandering rotors were counted repeatedly with the overlapping mapping approach, resulting in a higher number of detected RAAPs.

Detection of in vivo AF drivers derived from phase transformation analysis

The mechanistic role of RAAPs as AF drivers was first supported by modeling and animal studies.^{20,21} Recently, new technologies have been developed that also allow direct visualization of the mechanisms driving AF in humans. Both the RhythmView (Topera, Menlo Park, CA, USA) and the ECVUE™ system (CardioInsight Technologies Inc, Cleveland, OH) have been developed for automated intra-procedural mapping of RAAPs, and are both based on filtering and phase analysis of a wide-field of view (biatrial) of fibrillatory electrograms. Both systems apply phase transformation to the unipolar fibrillatory electrograms to facilitate the description of complex spatiotemporal fibrillation patterns. This phase transformation potentially results in “falsely” increased detection of temporal and spatial organization during fibrillation, and could facilitate the visualization of non-existent rotors.²³ Furthermore, the basket catheter used with the Topera system has a lack of spatial resolution, which could also potentially result in the detection of false rotors when phase transformation is applied,^{6,23} because data interpolation from the surrounding electrodes is needed. These limitations can potentially explain the mitigated results of ablation strategies based on systems using phase transformation^{7,24}. Importantly, no randomized clinical study using the Cartofinder software has yet evaluated the impact of RAAP ablation during AF and the system therefore has to be validated in the future.

Location of RAAPs

In our study, RAAPs were mostly located in the left PV/left appendage region and the right atrial appendage region, but were not often observed near the right PVs. Also, in the AFACART multicenter study on non-invasive mapping with phase conversion of persistent AF, the right PVs were a much less frequent origin of AF drivers, especially of focal sources, compared to the left PVs and the appendage region⁷. This is in contrast to the findings of Haïssaguerre et al. who identified drivers with ECGi and phase transformation near both left and right PV pairs in >95% of persistent AF patients without prior PV isolation⁶. In addition, foci in the inferior LA and on the roof/anterior wall were less frequent in our study.

Clinical perspectives for ablation of atrial fibrillation

While the pulmonary veins are the predominant source of triggers responsible in the pathogenesis of paroxysmal AF, electrical and structural remodeling is fundamental in the progression to persistent AF, in which multiple atrial wavelets and localized (focal or reentrant) sources have been reported to contribute to the substrate¹⁻³.

Therefore, durable electrical isolation of the pulmonary veins is an effective ablation strategy for paroxysmal AF, but yields less favorable results in persistent AF. In order to improve the outcome in persistent AF patients, several different ablation techniques have been developed to target the atrial substrate including ablation of complex fractionated electrogram (CFAEs) in both atria, left atrial linear lesions, and the so-called 'stepwise' approach.²⁵ Outcomes from ablation of persistent AF using these strategies have given modest results, and each approach lacks specificity, sometimes resulting in extensive ablation with potentially deleterious effects (on atrial hemodynamic function or with pro-arrhythmic consequences).²⁵ This would explain why empirical substrate ablation (with linear or CFAE ablation) on top of PVI did not seem to improve outcome²⁶. These pitfalls encourage development of patient tailored ablation strategies targeting patient-specific AF drivers.

This study shows that direct endocardial high-density contact mapping EGM analysis during ongoing AF allows identification of RAAPs. The automated annotation software has the potential to provide on-line detection of potential bi-atrial AF drivers annotated on the 3D-geometric bi-atrial shell, making patient-tailored substrate ablation possible. Further studies are needed to investigate if ablation of RAAPs as detected by the system might improve clinical outcome.

Limitations

1) It was not always possible to equally spread the 5 spines of the mapping catheter (mostly on the anterior septum), which could have affected the results. 2) Procedures were performed with the PentaRay with 2-6-2 mm interelectrode spacing. We cannot certify that use of the 4-4-4 mm interelectrode spacing would have rendered identical results. 3) It is possible that the detection of rotational RAAPs is decreased by the narrow field-of-view of the PentaRay catheter. 4) Automated electrogram annotations were not manually verified and this could have led to some annotation errors. 5) Although this study suggests the universal existence of RAAPs in persistent AF patients, this study does not clarify whether RAAPs have a mechanistic role in AF maintenance or if they are just an epiphenomenon. The effect of ablation of RAAP was not investigated in our study. A randomized study about the potential benefit of driver ablation as depicted by the Cartofinder software should be performed.

Conclusions

High-resolution and sequential endocardial EGM-based mapping shows the presence of repetitive activation patterns during persistent AF in all patients. In our series, focal firing was the most frequently observed pattern. The PentaRay high-density mapping catheter has the ability to reach all atrial regions and could potentially enhance RAAP detection.

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II

Part II

ABLATION OF VENTRICULAR TACHYCARDIA

11

Chapter 11

Evaluation of long-term outcomes
of substrate modification for post-
myocardial infarction ventricular
tachycardia.

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Abstract

Background: Long-term results of substrate modification for ablation of ventricular tachycardia (VT) have not been reported. We report long-term outcomes of substrate elimination targeting local abnormal ventricular activities (LAVA) for post-myocardial infarction (MI) VT.

Methods & Results: 159 consecutive patients undergoing first ablation were included (65 ± 11 y, 92% ICDs, 54% storms and 73% appropriate shocks). LAVA were identified in 92% and VT was inducible in 73%. Complete LAVA elimination and non-inducibility after ablation were achieved in 64% and 85%. During a median follow-up of 47 months (IQR 34-82), single procedure ventricular arrhythmia (VA)-free survival was 55% (10% storms and 19% shocks). The VA-free survival was 73, 68, 61, 55 and 49% after 1, 2, 3, 4 and 5 years. Complete LAVA elimination was associated with improved outcomes: VA-free survival of 82% at 1 and 61% at 5 years. In the subgroup treated with multi-electrode (ME) mapping and real-time image integration, VA-free survival was 86 and 65% at 1 and 4 years respectively. Including repeat procedures in 18% of pts (1.3 ± 0.6 ablations/pt) outcomes improved to 69% VA-free survival (2% storms and 9% shocks) during median 46 months follow-up. Overall survival was 91 at 1 and 77% at 5 years of follow-up.

Conclusions: In this mono-centric study, substrate modification targeting LAVA for post-MI VT resulted in a substantial reduction of VT storm and ICD shocks and up to 49% of patients free from arrhythmia at 5 years after a single procedure. Complete LAVA elimination, ME mapping and real-time integration were associated with improved VA-free survival.

Introduction

Catheter ablation for sustained monomorphic ventricular tachycardia (VT) after myocardial infarction (MI) has emerged as an effective tool for the control of VT recurrence.¹ Recently few studies have reported long-term follow-up data of VT ablation in ischemic cardiomyopathy (ICMP) patients, guided predominantly by activation and entrainment mapping of inducible and hemodynamically tolerated VTs.²⁻³ However, alternative strategies predominantly based on substrate modification have gained prominence. These strategies not only have the advantage of identifying targets for ablation in patients in whom VT is not inducible or not tolerated, but they may also provide a more comprehensive treatment of the substrate for present but also future VT, as they are not limited to inducible or “clinical” types of VT. Long-term results of substrate modification strategies have not been reported.⁴⁻⁶ The aim of our study was to report the long-term outcomes after single and multiple ablation procedures with elimination of local abnormal ventricular activities (LAVA) for VT ablation in post-MI patients.

Methods

The data, analytic methods, and study materials have been made available to other researchers for purposes of reproducing the results or replicating the procedure.

Definition of LAVA

Our definition of LAVA has been described previously.⁷ LAVA incorporate all abnormal local electrical signals arising from pathological slowly conducting/poorly coupled ventricular tissue, hence potential VT isthmuses. LAVA are defined as sharp high-frequency ventricular potentials, possibly of low amplitude, distinct from the far-field ventricular electrogram occurring anytime during or after the far-field ventricular electrogram in sinus rhythm, or before the far-field ventricular electrogram during VT. They sometimes display fractionation or double or multiple components separated by very-low-amplitude signals or an isoelectric interval and are poorly coupled to the rest of the myocardium.

Study population

From May 2006 to September 2015, all consecutive patients referred to our center for a first catheter ablation procedure for post-MI VT were included. Inclusion criteria consisted of repetitive episodes of drug-resistant sustained monomorphic VT in patients with a history of MI, documented by surface electrocardiography or implantable cardioverter-defibrillator (ICD) tracings. Patients were excluded if ventricular arrhythmias were attributable to an acute or reversible cause or if another type of cardiomyopathy co-existed. Sustained VT was defined as VT lasting ≥ 30 seconds or terminated by external or internal cardioversion or antitachypacing (ATP). VT storm was defined as ≥ 3 VT episodes in 24 hours. Patients with repetitive premature ventricular contractions or non-sustained VT in the

absence of sustained VT were excluded. The study was approved by the Institutional Review Board and all patients gave written informed consent.

Left ventricular access and electrophysiological study

The electrophysiological study and ablation were conducted with conscious sedation with midazolam 0.02mg/kg before femoral puncture, morphine sulfate 0.1 to 0.2 mg/kg, and supplementary analgesia (sufentanil 0.05 – 0.15µg) under supervision of an anesthesiologist for pericardial approach when needed. Non-invasive or intra-arterial blood pressure monitoring and digital pulse oximetry were performed continuously. ICD therapies were inactivated prior to femoral puncture. Antiarrhythmic drug treatment was continued until the ablation procedure. Vascular sheaths were inserted into the right femoral vein (2-3), right femoral artery (1), and/or subxiphoid area (1) under local anesthesia (bupivacaine). A steerable quadripolar/decapolar catheter (Xtrem, Sorin France, or Dynamic, Boston Scientific Inc, Cambridge, LA) was placed in the right ventricular apex or coronary sinus. The left ventricle was accessed by a transseptal (BRK needle, Agilis sheath, St. Jude Medical, St. Paul, MN) and/or retrograde aortic approach with or without additional epicardial mapping (Tuohy Needle, Agilis sheath short curve, St. Jude Medical). The mode of access to the left ventricle (LV) was at the operator's discretion, however dual (transseptal and retrograde) or triple (transseptal, retrograde and epicardial) access was encouraged. In the absence of contraindications, epicardial mapping was specifically encouraged if an epicardial origin was suspected (preprocedural imaging, 12-lead ECG, absence of endocardial LAVA, and/or persistent LAVA after endocardial ablation). Contraindications to epicardial access included previous cardiac surgery, pericardial adhesions, and the use of double antiplatelet therapy or continued oral anticoagulation. Our method of percutaneous pericardial access through anterior subxiphoid puncture has been described previously.⁷ After LV access was obtained, a 50 U/kg heparin bolus was administered intravenously and repeated as necessary to achieve an activated clotting time >250 seconds.

Substrate mapping

Twelve-lead ECG and bipolar intracardiac electrograms were recorded continuously (LabSystem Pro, Bard Electrophysiology, Lowell, MA, or Siemens Axiom Sensis XP Siemens, Munich, Germany). Signals were sampled at 1kHz and filtered at 0.1 to 50Hz for surface ECGs and 30 to 250Hz for intracardiac signals, displayed at an amplification of 0.1mV/cm. Use of 3D-electroanatomical mapping (EAM) systems, multi-electrode (ME) mapping catheters and real-time image integration (RTII) was integrated into the workflow once available for clinical use (if no contra-indication to contrast-enhanced multidetector computed tomography (MDCT) and magnetic resonance imaging (MRI)). Mapping was performed with either a 3.5mm open-irrigated ablation catheter (Biosense Webster, Diamond Bar, CA), but preferably a multipolar high-density mapping catheter (Pentaray 2-6-2mm spacing, Biosense Webster, or Intellamap Orion, Boston Scientific). Peak-to-peak amplitudes of

0.5 to 1.5mV and <0.5mV were used to define low-voltage zones and dense scar zone (adjusted voltage range of 0.2 to 0.8mV was used in 6 patients mapped with the Intellamap Orion⁸). When a 3D-EAM system was used (CARTO3, Biosense Webster; NavX, St. Jude Medical; Rhythmia, Boston Scientific) mapping was performed during sinus rhythm to create a voltage map and annotate LAVA. For RTII, MDCT or MRI images were processed using dedicated software (MUSIC, Liryc - Université de Bordeaux / Inria - Sophia Antipolis, France) to render patient-specific meshes of the cardiac chambers, epicardium, coronary sinus, coronary arteries and left phrenic nerve. Structural substrate (scar) was segmented on imaging as areas of delayed gadolinium enhancement (DE) on MRI and/or areas of wall thinning ≤ 5 mm on MDCT (Figure 1).

Figure 1: LAVA elimination using high-density multi-electrode mapping and real-time image integration in a case of post-anterior myocardial infarction ventricular tachycardia. **Upper panels:** A large anterior scar (<0.5mV) is demonstrated on endocardial bipolar voltage maps (modified RAO and LAO view). **Lower panels:** Integration of 2mm (dark brown), 3mm and 4mm myocardial wall thinning layers derived from multi-detector computed tomography, showing good correlation with scar and border zone on voltage maps. LAVA (*) were recorded with multi-electrode mapping (Pentaray) mostly in scar and border zone (blue tags). Ablation (red tags) resulted in complete LAVA elimination.

VT inducibility

Prior to ablation, VT induction was attempted with programmed stimulation from at least two sites (right ventricular apex or outflow tract, and/or LV apex) at two drive trains (600 and 400ms), with up to 3 extrastimuli decremented to ventricular refractoriness or 200ms. Isoprenaline was not used for the purpose of inducibility. If hemodynamically tolerated VT was induced or originated during substrate

mapping, conventional activation and entrainment mapping and ablation at the critical isthmus was performed first. Induced VTs were classified as clinical or non-clinical based on comparison of the twelve-lead ECG morphology and cycle length to documented tracings of the clinical VTs. When no 12-lead tracings were available, classification was based on the cycle length on ICD tracings. In case of non-inducible or hemodynamically intolerated VT, ablation targeting LAVA elimination was performed in sinus rhythm.

Catheter ablation

Ablation in sinus rhythm targeting complete LAVA elimination was the procedural endpoint in addition to non-inducibility of any VT. Ablation was delivered with open-irrigated catheter (25-50W endocardial and 25-35W epicardial) until targeted sites were rendered electrically unexcitable with pacing at 20mA with 2ms pulse width output. If a sequence of activation of LAVA was mapped, the earliest signals were targeted first. If both endo- and epicardial LAVA were present, ablation from the endocardial side was performed first with subsequent epicardial ablation if LAVA persisted. After ablation, the ventricles were remapped with the original mapping catheter and additional substrate ablation would be performed if residual LAVA were identified and/or if any VT remained inducible. Inducibility testing after ablation was avoided if patients were unstable or if they had required ≥ 2 cardioversions for hemodynamically unstable VT induced during the procedure. In case of epicardial ablation, proximity of coronary arteries and phrenic nerve to the targeted ablation sites was derived from RTII when available. Coronary arteries were injected only if the distance between the ablation catheter and the coronary image was 10mm or less. High-output pacing for the phrenic was also used following the same rule.

Post-procedural care

Venous and arterial sheaths were withdrawn immediately. Pericardial sheaths were retracted after a dry pericardial aspirate was confirmed. ICD therapies were reactivated at the end of the procedure. Patients were monitored in hospital for at least 2 to 5 days. Preprocedural antiarrhythmic drugs were continued unless contraindicated or not tolerated.

Follow-up

Patients were followed up at 1, 3, 6 and 12 months during the first year and every 6 months thereafter. ICD were interrogated at each visit and arrhythmia logs were retrieved. In addition, 64 of 146 (44%) patients with ICD were followed through remote monitoring with weekly transmissions. A detailed history, ECG and Holter monitoring were performed in symptomatic patients without ICD. At each follow-up consultation, reduction or discontinuation of antiarrhythmic drugs was evaluated. The primary endpoint was the ventricular arrhythmia (VA)-free survival. Any documented monomorphic

or polymorphic VT sustaining ≥ 30 s or terminated by appropriate ICD therapy (ATP or shock) was considered a recurrence. In patients with ICD implanted for ≥ 1 year prior to ablation, the VT burden was compared 1 year before and after ablation. Secondary endpoints were recurrence of VT storm, appropriate ICD shocks, all-cause mortality and discontinuation of antiarrhythmic drugs. Mortality during follow-up was categorized as either cardiovascular arrhythmogenic, cardiovascular non-arrhythmogenic or non-cardiovascular. ICDs of all deceased patients were analyzed to exclude an arrhythmogenic cause (monitor zones were programmed to detect to slow VT). Mortality was only adjudicated as non-cardiovascular if a clear non-cardiac cause, directly related to the death could be withheld. Indications for repeat procedures were evaluated on a case-by-case basis.

Statistical analysis

SPSS version 24 (IBM Corp, Armonk, NY) was used for statistical analysis. Continuous variables are summarized by mean $\pm$ standard deviation or median $\pm$ interquartile range (IQR, 25–75th percentile), depending on the normality of distribution. Categorical variables are presented by frequencies and percentages. Kaplan-Meier analysis with log-rank tests were used to calculate VA-free and overall survival over time and compare survival rates between subgroups. Univariable Cox proportional hazards regression was used to identify predictors of VA-free and overall survival (Supplemental Table). Variables significant at the 0.2 level in univariate analyses were considered in an automated stepwise multivariate Cox regression model. All statistical tests were 2-tailed. A p-value < 0.05 was considered statistically significant.

Results

Population (Figure 2, Table 1)

During the study period, 842 ablations for any ventricular arrhythmia were performed in 707 patients. Five hundred and seven pts were excluded because of non-qualifying diagnoses (n=206 non-sustained VT or idiopathic ventricular fibrillation, n=99 idiopathic VT, n=177 non-ischemic, n=6 mixed cardiomyopathy, n=19 ICMP without MI). An additional 31 patients were excluded due to prior VT ablation and 10 patients did not consent. The study population consisted of 159 consecutive patients referred for first ablation of post-MI VT. Eighty-six (54%) had VT storm and 84 of 115 patients with ICD prior to ablation (73%) had appropriate shock(s). Most (n=118, 74%) were treated with amiodarone prior to ablation (usual daily dose 200mg).

Figure 2: Flow diagram of the study population.

Table 1: Characteristics of the study population (n=159)

Age, y	65 ± 11
Male gender	152 (96%)
Coronary risk factors	
Arterial hypertension	99 (62%)
Diabetes	35 (22%)
Dyslipidemia	123 (77%)
Smoking	90 (57%)
LVEF, %	34 ± 11
LVEF ≤30%	74 (47%)
Percutaneous coronary intervention	93 (58%)
Coronary artery bypass grafting	39 (25%)
NYHA class	
I/II	127 (80%)
III/IV	32 (20%)
Serum creatinin, µmol/l	111 ± 56
Creatinin clearance CKD-EPI, ml/min/1.73m ²	71 ± 29
Antiarrhythmic drugs	
number	1.8 ± 0.6
beta-blocker	153 (96%)
sotalol/class I	17 (11%)
amiodarone	118 (74%)
Other cardiovascular drugs	
ACE-inhibitor/angiotensin receptor blocker	125 (79%)
mineralocorticoid receptorblocker	61 (38%)
statin	127 (80%)
Cardiac device	
ICD	146 (92%)
ICD only implanted after ablation	31/146
CRT	41 (26%)
Indication for ablation	
VT storm	86 (54%)
Appropriate ICD shock	84/115 (73%)

ACE: angiotensin-converting enzyme; CRT: cardiac resynchronization therapy;
 ICD: implantable cardioverter defibrillator; LVEF: left ventricular ejection
 fraction; NYHA: New York Heart Association; VT: ventricular tachycardia

Procedural characteristics (Table 2)

LV access was obtained by transseptal and retrograde approach in 141 (89%) and 51 (32%) patients. Dual transseptal and retrograde access was performed in 35 (22%) and percutaneous pericardial access in 46 (29%) patients. In two patients presenting with refractory VT storm requiring urgent ablation, only pericardial access was obtained due to LV thrombus.

ME mapping catheters were used in 89 (56%), 3D-EAM in 119 (75%), and RTII in 57 (36%) patients. RTII consisted of MDCT in 53 and MRI data in 23 cases (combined in 19 patients).

LAVA were identified in 146 patients (92%, endocardially n=141/157; epicardially n=36/46). In 13 patients (8%) no LAVA were mapped (4 of them with both endo- and epicardial access).

In 39 patients (25%) VT was mechanically induced during substrate mapping. In 116 of the remaining 120 patients, inducibility by programmed stimulation was tested at baseline. In 77 of them, VT was inducible. Seventy-four patients had some degree of VT mapped and in total, a mean of 1.6 ± 1.6 VTs were observed during the ablation procedure. Clinical VT was observed in 89 (56%) and non-clinical in 75 (47%) patients. A total of 39 pts had no inducible VT and in 4 patients, inducibility was not tested because of hemodynamic instability.

Table 2: Procedural data (n=159)

LV access	
Transseptal	141 (89%)
Retrograde aortic	51 (32%)
Epicardial	46 (29%)
Epicardial only	2 (1%)
Imaging	100 (63%)
CT	87 (55%)
MRI	38 (24%)
Real-time image integration	57 (36%)
Mapping and ablation	
Electroanatomic mapping system	119 (75%)
Multi-electrode mapping catheter	89 (56%)
Irrigated ablation catheter	159 (100%)
Sustained monomorphic VT during procedure	116 (73%)
Number of VT observed during procedure	1.6 ± 1.6
Clinical	89 (56%)
Non-clinical	75 (47%)
LAVA mapping	
Endocardial	141/157 (90%)
Epicardial	36/46 (78%)
No LAVA	13/159 (8%)

CT: computed tomography; LAVA: local abnormal ventricular activities; LV: left ventricular;
MRI: magnetic resonance imaging

Acute procedural outcome (Table 3)

Complete LAVA elimination was achieved in 93 of 146 patients (64%) using a mean RF time of 36±20min. In one patient with septal involvement, additional transcatheter ethanol ablation was performed during the index procedure in order to achieve complete VT/LAVA elimination. In 53 pts (36%), LAVA elimination was incomplete. In 7 cases this was due to anatomical reasons (epicardial proximity of coronary arteries in 2 and septal localization in 5), in 3 cases the procedure was shortened to due hemodynamic instability and in the remaining cases, some LAVA persisted despite extensive ablation. In 13 patients without LAVA, ablation was based on activation/entrainment mapping of induced VT (n=7), and on voltage maps combined with pace mapping if non-inducible (n=6).

Non-inducibility after ablation was achieved in 94 of 110 tested patients (85%). In 16 patients (7 with complete LAVA elimination), a non-clinical monomorphic VT (cycle length <270ms) remained inducible.

Epicardial ablation was performed in 27 of the 36 patients with epicardially mapped LAVA (in 2 patients no epicardial RF was performed due to proximity of coronary artery and in the remaining patients epicardial LAVA were eliminated after endocardial ablation).

Table 3: Procedural results (n=159)

<i>Outcome defined by LAVA elimination</i>	
Complete elimination	93/146 (64%)
Incomplete elimination	53/146 (36%)
No LAVA mapped	13/159 (8%)
<i>Outcome defined by inducibility</i>	
Inducibility tested after ablation	110/159
Non-inducibility of any VT	94/110 (85%)
Clinical VT inducible	0/110 (0%)
Only non-clinical VT inducible	16/110 (15%)
<i>Procedural parameters</i>	
Radiofrequency time, min	35.9 ± 20.4
Epicardial ablation performed, n	27
Epicardial radiofrequency time, min	9.8 ± 11.7
Fluoroscopy time, min	48.2 ± 23.7
Procedure time, min	247.9 ± 78.2

LAVA: local abnormal ventricular activities; VT: ventricular tachycardia

Adverse events

Complications were observed in 12 patients (7.5%). Nine patients experienced epicardial bleeding, of which 4 required surgical intervention. In 2 patients ablation resulted in complete AV block and 1 patient required non-invasive ventilation due to pulmonary edema shortly after the procedure. Two patients with advanced heart failure who presented with VT storm died within 24 hours following the procedure, one as a result of low-flow state and one as a result of low flow and VT storm recurrence.

Clinical outcomes (Table 4)*Arrhythmia recurrence after a single procedure:*

During a median follow-up of 47 months (IQR 33 – 82), the single procedure ventricular arrhythmia (VA)-free survival was 55%. The VA-free survival declined from 73% at 1 year to 68, 61, 55 and 49% after 2, 3, 4 and 5 years respectively (Figure 3).

Figure 3: Ventricular arrhythmia (VA)-free survival after single (A) and including repeat (B) ablation procedures.

The majority (58%) of first VA recurrence occurred during the first year (median 217 days, IQR 79-899) post-ablation, but in 25% of patients first recurrence only occurred after 2.5 years, up to 6.9 years. The proportion of patients experiencing VT storm decreased from 54% before to 10% after a single procedure. The proportion of ICD patients experiencing appropriate shocks declined from 73% to 19% after single ablation. In 74 ICD patients implanted at least one year before ablation and who survived at least one year, the VT burden was significantly reduced from a median of 20 episodes (IQR 8-58) the year before to a median of 0 (IQR 0-0) episodes during the year after ablation. In 91% of these 74 pts, the reduction in VT burden was more than 87% (Figure 4). In none of the patient, recurrent ischemia occurred prior to the first VA-recurrence. In two patients intercurrent heart failure occurred prior, but remote (5 and 7 months) to the first VA-recurrence. During follow-up, anti-arrhythmic drugs were discontinued in 52% of patients, with reduction of amiodarone use from 118 to 54 patients.

Figure 4: There were 74 patients with implantable cardioverter-defibrillator (ICD) at least 1 year prior to ablation who survived for 1 year. Each line represents an individual patient; blue lines indicate pre-ablation and orange lines post-ablation. Upper boundaries are truncated at 200 episodes. Patients are arranged by recurrences during follow-up, ranging from greatest (bottom) to least (top). In 91% of these 74 patients, the reduction in VT burden was more than 87%.

Arrhythmia recurrence including redo procedures:

Repeat procedures were performed in 29 patients (18%) (mean total procedures 1.3 ± 0.6 /patient). All repeat procedures were performed with the same strategy and procedural endpoints, except in two patients in whom repeat ablation consisted of transcatheter ethanol injection. Including repeat procedures the VA-free survival increased to 69%, and recurrence of storm decreased to 2% and appropriate shocks to 9% of ICD patients, during a median follow-up of 46 months (IQR 32 - 81). Including repeat procedures, the VA-free survival was 85, 81, 75, 68 and 62% at 1, 2, 3, 4 and 5 years respectively (Figure 3).

Overall survival

The overall survival was 91, 86, 84, 80 and 77% at 1, 2, 3, 4 and 5 years (Figure 5). During follow-up 40 patients died: 3 patients died from arrhythmia despite implanted ICD, 20 from cardiovascular morbidity (terminal heart failure), and 17 from non-cardiovascular causes. Two patients received cardiac transplant during follow-up.

Figure 5: Overall survival timed from the first ablation procedure (including repeat procedures in 18% of patients).

Table 4: Clinical outcome data (n=159)

After first procedure:	
Ventricular arrhythmia-free survival	88 (55%)
VT storm	16 (10%)
Appropriate shock in ICD patients	28/146 (19%)
Including repeat procedures:	
Ventricular arrhythmia-free survival	109 (69%)
VT storm	3 (2%)
Appropriate shock in ICD patients	13/146 (9%)
Number of procedures	
1 procedure	130 (82%)
2 procedures	20 (13%)
3 procedures	7 (4%)
4 procedures	2 (1%)
Mean number of procedures	1.3 ± 0.6
Interval between first and last procedure, days	197 (IQR 98-885)
All-cause mortality	
Arrhythmogenic cardiac death	3 (2%)
Cardiovascular death	20 (13%)
Non-cardiovascular death	17 (11%)
Heart transplant	2 (1%)
Antiarrhythmic drugs use at last follow-up	
amiodarone	54 (34%)
sotalol/class I drug	11 (7%)
beta-blocker	145 (91%)

ICD: implantable cardioverter defibrillator; VT: ventricular tachycardia

Subgroup analysis

Impact of technological evolution

The use of ME mapping catheters and real-time image integration was implemented based on availability of the technology over the study period, independently from patient characteristics. They significantly improved the VA-free survival, and with trend to improve overall survival as well (Figure 6). Use of ME mapping combined with RTII resulted in a VA-free survival of 86% at 1 and 65% at 4 years follow-up, compared to 57 and 46% with conventional mapping (p=0.043). Similarly

overall survival improved to 94% at 1 and 91% at 4 years, compared to 83 and 74% with conventional mapping ($p=0.062$).

Figure 6: Impact of different mapping technologies. Ventricular arrhythmia (VA)-free (A) and overall (B) survival rate in procedures performed without multielectrode (ME) mapping and real-time image integration (RTII) (blue, $n=35$), with ME mapping but without RTII (green, $n=53$), and with combined ME mapping and RTII (yellow, $n=47$).

LAVA elimination

Achievement of complete LAVA elimination was also associated with improved outcome. At a median follow-up of 47 months after a single procedure, VA-free survival was 63% if complete LAVA elimination was achieved, compared to 44% if LAVA elimination was incomplete or if no LAVA were mapped ($p=0.001$) (Figure 7). Further, complete LAVA elimination was associated with less recurrence of VT storm (5 vs. 17%, $p=0.030$). Recurrence of at least one ICD shock and overall mortality did not differ significantly. Including repeat procedures, the VA-free survival was 73% at median follow-up of 46 months if complete LAVA elimination was achieved after the final procedure, compared to 57% if LAVA persisted ($p=0.009$) (Figure 8).

The long-term arrhythmia-free survival of other subgroups is detailed in Table 5.

Figure 7: Ventricular arrhythmia (VA)-free survival rate in procedures with and without complete elimination of local abnormal ventricular activities (LAVA) after a *single* ablation procedure.

Figure 8: Ventricular arrhythmia (VA)-free survival rate in procedures with and without complete elimination of local abnormal ventricular activities (LAVA) after the *last* ablation procedure (*including repeat ablation procedures in 18% of patients*).

Table 5: Ventricular arrhythmia (VA)-free survival of subgroups

	Number of patients	VA-free survival* (%)	VA-free survival at				Logrank p-value
			1y	2y	3y	4y	5y
LAVA mapped at baseline	146	56	75	68	62	55	50
No LAVA mapped at baseline	13	38	62	54	46	38	38
							0.001
Complete LAVA elimination (†)	93	63	82	74	70	63	61
Incomplete LAVA elimination (†)	53	44	62	60	48	40	28
							0.001
Substrate modification only	61	49	66	60	55	50	47
Substrate modification + some activation/pace mapping	98	59	78	72	65	57	50
							0.299
Single ablation procedure	159	55	73	68	61	55	49
Multiple ablation procedures	29	69	85	81	75	68	62
							n/a

*: during median follow-up of 47 months (IQR 33 – 82)

†: patients without mapped LAVA at baseline excluded

Substrate comparison between index and repeat procedures

Twenty-seven patients underwent a repeat RF ablation procedure. In none of the patients, recurrent ischemia occurred between the index and repeat procedures. Between the index and first repeat procedure, scar areas were unchanged, but induced VTs were mostly different (Figure 9A). Only in 2 patients, 1 of the induced VTs in the repeat procedure had the same axis with similar morphology (but different cycle length) as in the index procedure. LAVA patterns in repeat procedures were mostly due to recurrence of previously successfully ablated LAVA or residual LAVA from the index procedure (Figure 9B). In 1 patient septal LAVA were de novo mapped (with the same 3D mapping system and ME mapping catheter) and ablated in the repeat procedure.

Figure 9: Comparison between index ablation and first repeat ablation procedure of (A) induced ventricular tachycardia morphologies and (B) characteristics of local abnormal ventricular activities.

Discussion

Our study is the first to report the long-term results of substrate-based catheter ablation of drug-refractory post-MI VT, targeting LAVA elimination. The main findings are:

- LAVA are successfully identified in the vast majority of patients (92%) referred for post-MI VT ablation, when using a strategy of meticulous mapping. The endpoint of LAVA elimination in addition to non-inducibility is feasible and effective for arrhythmia control.

With a single procedure, 73% of the patients are free from arrhythmia at 1 year. This success rate decreases over time, but 49% of patients are still free from any ventricular arrhythmia at 5 years. At the modest cost of repeat procedures in 18% of pts, this result is improved to 85% arrhythmia-freedom at 1 year, remaining 62% after 5 years. In addition only 9% of pts had appropriate shocks over a mean of 4 years follow-up. The reduction in VT burden was more than 87% in 91% of patients after a single procedure. This strategy allowed for a substantial discontinuation of

antiarrhythmic drugs and amiodarone use was reduced by 54%, this benefit being maintained at 5 years.

- Complete LAVA elimination, which is possible in 64% of patients, is associated with better outcome. Improved mapping by implementing modern technologies such as ME mapping catheters and integration of high-definition imaging of scar and anatomy improved both short and long-term outcome, with freedom of VA recurrence in 86% of patients at 1 year and 65% at 4 years follow-up.
- First VT recurrence occurred at median 217 days, but extended up to 6.9 years after the first procedure. In fact 25% of first VT recurrence occurred only 2.5 years after the first ablation procedure, i.e. longer than the follow-up period of most previous studies on substrate-based VT ablation.
- Albeit the all-cause mortality of this patient population was high, amounting 23% at 5 years, the incidence of arrhythmogenic death was low. Fifty percent of mortality was caused by terminal heart failure.
- In repeat VT ablation procedures, the arrhythmogenic substrate and scar remained generally unchanged. Incomplete or insufficient index substrate ablation was found in 94% of redo procedures.

Activation and entrainment mapping vs. substrate modification

Initial strategies for ablation of post-MI VT predominantly used activation and/or entrainment mapping to identify the critical isthmus as the ideal target for RF delivery.⁹ Limited linear ablation transecting these isthmuses would interrupt reentry, terminate the mapped VT and render the targeted VT non-inducible. This strategy and the endpoint of non-inducibility are hampered by several limitations, such as baseline inducibility, sustainability and hemodynamic tolerance of the VT, reproducibility of inducibility, etc... Despite all these limitations, non-inducibility has been reported as an interesting endpoint, correlated with improved clinical outcomes, with non-inducibility of both clinical and non-clinical VT being superior to non-inducibility of clinical VT only.² Inducible non-clinical VTs observed after such ablation suggests the persistence of a substrate able to sustain VT and likely to be clinically relevant in the future, as shown by superior outcomes when ablated. In the only randomized trial comparing extensive substrate-based ablation to a strategy only targeting clinical and stable VTs in patients with ICMP, the substrate-based approach resulted in a superior VT-free survival at 1 year follow-up (84.5% vs. 51.7%).¹⁰ For these reasons a substrate-based ablation strategy, has gained prominence in the current era of VT ablation. Several different methods of substrate modification have been described, such as elimination of LAVA,⁷ late potential abolition,⁶ scar de-channeling,¹¹ scar core isolation¹² and scar homogenization.^{10,13}

Differences in substrate modification techniques

Several groups have tried to modify potentially arrhythmogenic surviving myocardial tissue by targeting late potentials in scar regions.¹⁴⁻¹⁶ In routine clinical practice, electroanatomic mapping is typically performed in sinus rhythm or during right ventricular pacing. However it has recently been demonstrated that the activation direction of the wavefront impacts the voltage amplitude.¹⁷ Tung et al performed voltage maps with at least two different activation wavefronts and found that 18% of critical VT isthmuses were within low-voltage areas during 1 wavefront, but were within normal amplitude ($>1.5\text{mV}$) during another activation wavefront.¹⁷ The timing of near-field signals from poorly coupled surviving bundles is also dependent on the activation wavefront, and sometimes ventricular (and decremental) pacing is needed to unmask them.¹⁴ Hence substrate-based ablation targeting solely late potentials or confined to voltage-defined scar might miss part of the arrhythmogenic substrate. The LAVA approach aims to overcome these limitations, by not being limited to late potentials (occurring after the QRS) or confined to low-voltage regions. In fact earlier coupled LAVA are targeted first in our approach and can result in elimination of later LAVA using limited RF delivery, as they may indicate a channel entrance to the scar.

Comparison with other outcome studies

Data on outcomes of VT ablation beyond 24 months of follow-up are scarce. Our study compared favorably to 2 recently published studies reporting long-term outcomes of VT ablation in ICMP patients, predominantly guided by *activation and entrainment mapping* of inducible and hemodynamically tolerated VTs.²⁻³ In the largest study, Kumar et al presented a single center retrospective series of 358 patients with ICMP undergoing VT ablation.² Including repeat ablation in 25% of pts (mean 1.3 ± 0.6 procedures/pt), the VA-free and overall survival were around 54 and 77% respectively at 5 years FU, compared to 62 and 77% in our study. The prospective multicenter Post-Approval THERMOCOOL VT trial, reported follow-up up to 3 years after EAM-system-guided VT ablation in 249 patients with coronary artery disease (85.4% with previous MI).³ While acute procedural success, defined as non-inducibility of the targeted VT, was achieved in 75.9%, the single-procedure freedom from arrhythmia was considerably lower when compared to our study amounting only 41% after 3 years (with possible underreporting of asymptomatic VT episodes due to recall bias). The overall survival was 75% 3 years post-ablation. The HELP-VT study reported medium-term outcomes 164 patients undergoing VT ablation predominantly guided by activation/entrainment mapping.¹⁸ VT-free survival amounted 57% at 12 months and 43% at a mean follow-up of 27 (16-37) months.

Outcomes from *substrate-based* VT ablation studies have only been reported with limited follow-up.^{4-6,10,12-13} Silberbauer et al reported 160 patients undergoing substrate modification (20% epicardial mapping) targeting *late potential abolition* combined with non-inducibility for post-MI VT.⁶ Sixty-

five percent had baseline LP, of which 77% underwent successful abolition. After a mean follow-up time of 18.8 (12.2–29.0) months, VT-free survival was 68%. Proietti et al reported outcomes of 87 patients with ICMP undergoing EAM-guide substrate-based VT ablation targeting LP in scar regions and regions in the scar-border zone with good pace-map correlation to clinical VTs.⁵ Non-inducibility of any VT was achieved in 69% of patients after a mean RF time of 96±51 minutes, but in 21% of patients clinical VT remained inducible at the end of the procedure. After a mean follow-up of 21±10 months, the VA-free survival was 74% with overall survival of 91%.

Better short-term results were reported after more extensive substrate modification targeting not only delayed but all abnormal potentials within and around scar (“scar homogenization”). Di Biase et al reported outcomes of endo- and epicardial scar homogenization in 43 patients with ICMP and electrical storm.¹⁰ Epicardial access was obtained in all of them, but epicardial ablation was only performed in 33% if abnormal potentials remained after endocardial ablation. The acute procedural endpoint of non-inducibility of any VT was achieved in 100%. At a mean follow-up of 21 months the VT-free survival was 81%. Despite extensive ablation (mean RF time 74±21min) and systematic pericardial access, no major complications were reported. The results of this ablation approach were confirmed in the VISTA Randomized Multicenter Trial, in which 58 patients underwent extensive ablation of all abnormal electrograms in endocardial scar, but epicardial access was limited to 10% of patients in whom VT remained inducible after endocardial ablation.¹³ After a mean RF time of 86±21min, all abnormal potentials within scar were successfully eliminated in 84% of cases. At 12 months follow-up, the VT-free survival was 84.5% and the overall-survival 88.1%. Both the scar homogenization and LAVA elimination strategy aim to modify the substrate more comprehensively, although the LAVA strategy may allow for less extensive ablation (36±20 vs. 74±21 and 86±21min), especially if earlier coupled LAVAs are targeted first. Short-term freedom from arrhythmia was however >80% with the scar homogenization strategy, compared to 73 and 68% at 1 and 2 years follow-up after a single procedure in our patient series.

Impact of strategy variants

In our approach, identification of the substrate is contingent on the detectability of LAVA by the mapping catheters used. Our group previously demonstrated that the use of ME mapping catheters is associated with increased LAVA detection due to reduction of the far-field signal and magnification of the near-field component.¹⁹ In our study, ME mapping catheters were used in only 56% of patients. Of note, ME catheters were not used in any of the above-mentioned studies of substrate based VT ablation.

Our research group also reported the added value of real-time integration of preprocedural imaging with DE-MRI or MDCT in post-MI VT ablation.²⁰ Both DE on MRI as well as wall thinning on MDCT correlate well with low voltage areas on EAM and the presence of LAVA.²¹⁻²² After substrate

mapping, real-time integration of image-derived substrate has been shown to motivate the operator to perform additional mapping in the majority of cases with extra LAVA detection in all of them. In addition, in some patients, pre-procedural imaging influenced the decision to perform epicardial access and RTII modified epicardial ablation strategy due to proximity of coronary arteries or phrenic nerve.²⁰

In our most recent approach of LAVA ablation, RTII and ME mapping catheters are therefore consistently implemented and resulted in significantly improved outcomes with a VA-free survival of 86% at 1 year, remaining 65% at 4 years of follow-up and overall survival of 94 and 91% at 1 and 4 years respectively. With the contemporary LAVA-strategy, (short-term) results comparable to the scar homogenization strategy are achieved, but with more limited RF delivery.^{10,13} Given these results, a randomized, head-to-head comparison of the contemporary LAVA elimination approach and the scar homogenization approach could be of interest.

Reasons for VA recurrence

Potential reasons for VA recurrence are 1. inadequate mapping of the substrate, 2. inadequate ablation with lesion regression and reconnection of critical isthmuses, 3. inadequate ablation due to anatomic limitations (mid-myocardial substrate, substrate in vicinity of the coronary arteries or phrenic nerve), 4. progression of the substrate, and 5. progression of neurohormonal and autonomic remodeling.²³ While inadequate mapping can be improved by triple (both retrograde and transseptal endocardial, and epicardial) LV access and use of ME mapping catheters and RTII, intramyocardial infusion-needle and bipolar irrigated RF catheter ablation may offer benefit when conventional RF ablation lesions are of insufficient depth to reach a mid-myocardial substrate.^{24,25} Comparable to previously published series in post-MI VT ablation²⁶, recurrent VTs had new morphologies in our study. During repeat ablation, ≥ 1 VT with different morphology from the index procedure was induced in all evaluable patients and only in a minority, a VT with a same exit as during the index procedure was induced. Despite different VT morphologies, the arrhythmogenic substrate generally remained unchanged between index and repeat procedures. In redo procedures, LAVA were generally located in the same area as during the index ablation, either due to recurrence of previously ablated LAVA or residual, unablated LAVA from the index procedure (in several cases possibly missed by mapping with the ablation catheter in the index, but detected by ME mapping in the redo procedure). The recurrence of previously ablated LAVA advocates the importance of effective and durable RF lesions. Without recurrent ischemia, substrate progression in post-MI VT appears to be the exception, as scar areas were unchanged between index and repeat procedures and ‘new’ LAVA in repeat procedures were very rare.

Limitations

Our study is a single-center, non-randomized study and represents the experience of skilled operators. Outcomes may therefore not be generalized to lower volume centers. Although the endpoint of the

ablation procedure remained unchanged, additional mapping technologies were implemented based upon availability over the study period resulting in improved outcomes. Therefore, the outcomes of the entire study cohort were hampered by the procedures performed at the beginning of the study period, but this was clarified by providing subgroup analysis. The discontinuation of antiarrhythmic drugs was not part of a study protocol and therefore up to the discretion of the treating physician. As antiarrhythmic drugs were not systematically discontinued at the first follow-up consultation, outcomes of ablation have to be interpreted as adjunct to medical therapy, but reflect the real-world clinical setting.

Conclusions

In this mono-centric study, substrate modification by LAVA elimination for post-MI VT resulted in a substantial reduction of VT storm, VT burden and need for ICD shocks. Both short- and long-term outcomes were improved by repeat ablation in a limited number of patients. Complete LAVA elimination was associated with improved VA-free survival. When combined with ME mapping and RTII, LAVA ablation was very successful at one year, with an annual 5% attrition rate.

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Supplemental Table: Predictors for VA-free and overall survival after first ablation procedure.

VA-free survival						
	Univariable analysis		Multivariable analysis			
	p-value	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)		
Clinical characteristics						
Gender (male)	0.250	2.28 (0.56-9.39)	0.002	0.29 (0.13-0.62)		
Age, y	0.920	1.00 (0.98-1.02)				
LVEF ≤30%	0.069	0.65 (0.41-1.04)				
renal clearance ≤30ml/min/1.73m ²	0.000	0.24 (0.11-0.52)				
Storm	0.236	0.75 (0.47-1.21)				
Amiodarone	0.538	0.84 (0.47-1.48)				
CRT	0.078	0.64 (0.39-1.05)				
NYHA class III/IV	0.121	0.64 (0.37-1.12)				
Procedural techniques						
Epicardial access	0.907	1.03 (0.63-1.70)	0.009	1.94 (1.18-3.20)		
ME mapping	0.393	1.23 (0.77-1.96)				
3D mapping system	0.788	1.07 (0.64-1.80)				
RTII	0.076	1.62 (0.95-2.75)				
Procedural endpoints						
Complete LAVA elimination	0.001	2.21 (1.38-3.54)				
RF time, min	0.042	1.01 (1.00-1.04)				

Overall survival				
	Univariable analysis		Multivariable analysis	
	p-value	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)
Clinical characteristics				
Gender (male)	0.478	0.49 (0.07-3.55)	0.007	0.29 (0.12-0.71)
Age, y	0.003	1.05 (1.02-1.09)		
LVEF ≤30%	0.015	0.45 (0.24-0.85)		
renal clearance ≤30ml/min/1.73m ²	0.000	0.20 (0.09-0.46)		
Storm	0.195	0.65 (0.34-1.25)		
Amiodarone	0.220	0.51 (0.24-1.39)		
CRT	0.005	0.40 (0.21-0.75)		
NYHA class III/IV	0.002	0.34 (0.17-0.66)		
Procedural techniques				
Epicardial access	0.199	1.58 (0.79-3.18)	0.046	2.00 (1.01-3.85)
ME mapping	0.035	1.98 (1.05-3.74)		
3D-mapping system	0.865	1.06 (0.54-2.10)		
RTII	0.218	1.65 (0.74-3.65)		
Procedural endpoints				
Complete LAVA elimination	0.267	1.42 (0.76-2.65)		
RF time, min	0.824	1.00 (0.99-1.02)		

CI: confidence interval; CRT: cardiac resynchronization therapy; LAVA: local abnormal ventricular activities; LVEF: left ventricular ejection fraction; ME: multi-electrode; NYHA: New York Heart Association; RF: radiofrequency; RTII: real-time image integration

III

Part III

12

Chapter 12

General discussion and summary

ABLATION OF ATRIAL FIBRILLATION

Scope of the problem and rationale for ablation

Atrial fibrillation (AF) is a serious public health problem because of its increasing incidence and prevalence in the aging population¹ and its association with elevated risks of cardiovascular events and death.²⁻⁷ In addition AF causes a wide variety of symptoms, including fatigue and reduced exercise tolerance, and significantly impairs quality of life.⁸ The morbidity and mortality associated with AF provide a rationale to maintain sinus rhythm. Yet to date, rhythm control strategy has failed to demonstrate a beneficial effect on hard endpoints such as a reduction in stroke or mortality rate.⁹⁻¹¹ Ablation of atrial fibrillation has proven to reduce symptoms and improve quality of life, and is superior to antiarrhythmic drugs in obtaining rhythm control.¹¹⁻¹³ Therefore according to current guidelines AF ablation is indicated in symptomatic patients as a second-line treatment after failure of a class I or III antiarrhythmic drug (Class I indication (level of evidence A) in paroxysmal AF, a class IIa indication (level of evidence B) in persistent AF and a class IIb indication (level of evidence C) in long-standing persistent AF).¹⁴ Given that catheter ablation of AF as a first-line treatment is associated with a higher freedom from atrial fibrillation compared with drug therapy,¹⁵⁻¹⁸ current guidelines also state that catheter ablation of AF as a first-line treatment (without a trial of class I or III antiarrhythmic drugs) is indicated in symptomatic paroxysmal (Class IIa – level of evidence B) and persistent AF patients (Class IIa – level of evidence C; and Class IIb – level of evidence C in case of long-standing persistent AF).¹⁴

Principle of pulmonary vein isolation

Since Haïssaguerre et al identified the triggers initiating AF to arise predominantly from the muscular sleeves within the pulmonary veins,¹⁹ electrical isolation of the pulmonary veins has become the cornerstone of catheter ablation of AF.¹⁴ Ablation strategies to achieve PV isolation evolved from a segmental ablation at the PV ostium near the earliest activation of the PV muscular sleeves,²⁰ to a wider continuous circumferential lesion set around left and right vein pairs, usually guided by a 3D anatomical mapping system.²¹⁻²³ In a recent randomized trial a complete contiguous circumferential ablation lesion around the PVs was found superior with respect to AF recurrence compared to an incomplete ablation circle.²⁴

Despite the ability to achieve acute procedural PVI in >99% of cases with standard irrigated catheters, permanent, durable isolation of the PVs is only achieved in the minority of cases. Indeed, in studies that performed a repeat procedure irrespective of the clinical outcome after the index PVI, reconduction of at least one PV was observed in 62 to 90% of cases.²⁴⁻²⁶ Studies that performed a repeat ablation procedure because of AF recurrence after index PVI, observed PV reconduction of at least one PV in >80% of patients.²⁶⁻³⁰ This coincides with a suboptimal clinical outcome with AF recurrence in up to 50% of patients after a single intervention.^{13,16,17,31}

This is because of insufficient quality of the initial ablation lesion set resulting in parts with latently non-conduction tissue that is still viable and at high risk of restored conduction. Of interest, reconnection of a PV pair after circumferential point-by-point RF PVI could even be attributed to a single ineffective ablation point (principle of the weakest link). It was observed that electrical PV reconnection often occurs fast, with one third of reconnections occurring within 30 minutes after initial isolation.³²⁻³⁴ For this reason, one proposed technique in order to reduce the chance of PV reconnection is to install a waiting time of 20 – 30 minutes following initial PV isolation (Class IIa – level of evidence B¹⁴). In one prospective randomized trial the benefit of a 30 minute waiting period with ‘bonus’ lesions was shown.³⁵ Another technique aiding to differentiate a durable PVI lesion set with permanent conduction block from a suboptimal lesion set at risk of early reconnection was to administer intravenous adenosine (class IIb indication – level of evidence B¹⁴).^{36,37} Intravenous adenosine or adenosine triphosphate is able to transiently restore cellular excitability and unmask so-called ‘dormant’ conduction (viable but latently non-conducting tissue). Not only was it demonstrated that the presence of dormant PV conduction was associated with a higher risk of AF recurrence, but additional adenosine-guided targeted ablation eliminating dormant PV conduction significantly reduced arrhythmia recurrence.³⁶⁻³⁷ The downside of incorporating a waiting phase and adenosine testing into the procedure however, is the prolongation of the left atrial dwell time (increased thromboembolic risk) and procedure time, as well as an increase in cost.

Technological advances to improve the outcome of PVI: contact force sensing

The likelihood of obtaining permanent PVI is related to the quality of ablation energy delivery and lesion formation. With RF energy the important factors that influence lesion size and transmuralty are catheter stability, contact force (CF), RF power, RF duration and temperature.

For point-by-point RF, irrigated-tip catheters are used to avoid excessive tissue heating with subsequent char formation. This allows higher RF power delivery, resulting in increased lesion size, but also increases safety by reducing the risk for steam pops.

The electrode tip – tissue CF is one of the key determinants of lesion size. Without adequate CF, no effective lesions can be generated. Prior to the development of direct CF-sensing catheters, surrogate markers for tip-tissue contact, such as impedance, intracardiac electrogram amplitude, the catheter movement on fluoroscopy and tactile feedback, were used but they proved unreliable to predict actual tip-tissue contact.³⁸⁻⁴¹ Ablation catheters using two different technologies have been developed to measure precisely real-time catheter–tissue CF: 1) use of three optical fibres to measure the microdeformation of a deformable body in the catheter tip (TactiCath, St. Jude Medical, Inc.), 2) use of a small spring between the tip electrode and the catheter shaft, with a magnetic transmitter in the tip and magnetic sensors proximal to the tip to measure microdeflection of the spring (ThermoCool SmartTouch, Biosense Webster, Inc.), both corresponding to CF. Even though several clinical studies have shown benefit of CF catheters over non-CF sensing catheters in terms of procedural parameters

and clinical outcome (lower adenosine-induced dormant conduction and AF recurrence), the two large randomized trial performed were negative, both in terms of (long-term) arrhythmia free survival and rate of complications.^{42,43}

One could speculate on theories on why these randomized trials did not prove superiority of CF-guided PVI, while operators perceived they have clearly improved outcomes in daily practice. In the UK Multicenter trial, CF-guided PVI was compared to non-CF guided PVI using the identical ablation catheter (SmartTouchTM, Biosense Webster) with blinding of the online CF-value.⁴² In this study protocol a 60-minute waiting time (+ adenosine) was used to assess acute PV reconnection. Even though CF-guided ablation did result in less acute reconnection (22% vs. 32%, $p = 0.03$), no difference in 1-year arrhythmia-free survival (49 vs. 52%, $p = 0.90$) was observed. One could speculate that if shorter waiting times (e.g. 20 minutes) were applied, which is more in line with reality of the daily clinical practice, less acute reconnections and subsequent re-isolations would have occurred. Therefore the benefit of CF-guided PVI might have been offset by the very long waiting time and higher rate of re-isolation in the non-CF guided PVI group. In the Toccstar Study, CF-guided PVI was performed with the TactiCathTM catheter and EnSiteTM NavXTM mapping system (St. Jude Medical), while in the control group non-CF-guided PVI was performed with the Thermocool Navistar and Carto mapping system (Biosense Webster). Use of different mapping systems might have accounted for lack of superiority of CF-guided PVI (operators were less experienced with the EnSite system). Also during this trial, the target values for CF were not yet established at the onset of this trial.

Despite the absence of prospective, randomized trials proving the superiority of online CF feedback in efficacy and safety, operators worldwide have quickly adopted CF catheters in their routine clinical practice, because they believe that CF monitoring provides important biomechanical feedback to improve effective lesion formation, durability of PVI and clinical outcomes.¹⁴ Indeed, both acute adenosine-proof PV isolation and one-year freedom of AF increased to 72-88%.⁴⁴⁻⁴⁶

In **Chapter 2** we studied if an extensive ‘learning period’ with CF catheters with online CF feedback improved the operator’s ability to perform PVI when returning to ablation catheters without CF measurement. In September 2013 the Thermocool[®] SmartTouchTM catheter was temporarily withdrawn worldwide from clinical use due to technical defaults leading to safety concerns in a small number of catheters. In this transient recall period, the experienced operator involved in the current study returned to the use of the irrigated-tip ablation catheter without CF measurement technology (NaviStar[®] Thermocool[®] ablation catheter). Procedural outcome parameters of consecutive PVI procedures performed without CF measurements during the recall period to a control group undergoing PVI with CF measurement technology were prospectively compared and shown in Table 1 below.

Table 1:

Procedural outcomes of PVI performed with and without online CF feedback beyond the learning period

	CF- group (n=12)	CF+ group (n=24)	P-value
Number of PV pairs without first-pass isolation (n, %)	7/24 (29.2)	2/48 (4.2)	0.005
Number of patients without first-pass isolation (n, %)	7/12 (58.3)	2/24 (8.3)	0.002
Number of adenosine-induced reconnected PV pairs (n, %)	1/24 (4.2)	0/48 (0)	0.333
Total procedure time (min)	167.8 ± 26.0	151.8 ± 24.8	0.075
Total left atrial time (min)	134.1 ± 25.3	117.9 ± 23.3	0.033
RF time (min)	31.8 ± 7.0	31.5 ± 7.1	0.919
Fluoroscopy time (min)	11.0 ± 5.8	11.8 ± 5.6	0.708

Data are presented as mean ± standard deviation or absolute number (n) + percentage (%)

CF-: group in which CPVI is performed with the NaviStar[®] Thermocool[®] ablation catheter; CF+: control group in which CPVI is performed with the Thermocool[®] SmartTouch[™] catheter; PV: pulmonary vein;

RF: radiofrequency

Acknowledging the limitations of this relatively small-sized, non-randomized and single-center, single-operator study design, our results suggest that after gaining experience with CF-measuring catheters, procedural PVI parameters (most importantly first-pass PV isolation) remained superior with this technology when compared to non-CF guided PVI procedures. An extensive training period with real-time direct CF-feedback was not a substitute for real-time direct CF measurement to maintain this advantage.

A new protocol aiming to optimize radiofrequency pulmonary vein isolation.

In addition to CF, the lesions depth and quality are also determined by the ablation power and application time. Whereas minimal CF (>10 to 20g) and force-time integral (FTI) (>400gs) previously have shown to predict durable PVI with high sensitivity and durability,^{47,48} both parameters have severe limitations: it is impossible to achieve minimal CF values of >10 – 20g at each RF site; targeting CF >20g can lead to catheter dislocation during ablation as well as tissue compression and increase complications (e.g. protrusion of the posterior left atrial wall towards the esophagus). FTI has 2 severe limitations: first, FTI (calculated as the product of force by application time) suggests a linear lesion formation during ablation, whereas it is known that lesion volume growth describes a monoexponential curve.⁴⁹ Second, FTI ignores the important and evident role of power delivery in lesion creation. Therefore the lesion volume of 400 gs FTI applications highly differs depending on

the power used. This could be one of the reasons why the use of CF feedback and aiming for minimal CF/FTI targets did not prove to be superior in randomized trials.^{42,43}

The Force-Power-Time Index or Ablation Index (AI) incorporates CF, ablation power and application time in a logarithmic function, taking into account the greater contribution of power (over CF) and of the initial time of ablation and, unlike mere CF, was found to predict lesion depth in the canine ventricle with high accuracy.^{50,51} The AI is both a reliable and useful parameters to target durable PVI for the following reasons: 1) lesion quality is expected to be similar at a certain AI value (despite differences in power, force, and time of application required to reach that value), and 2) AI targets can be reached readily at each site within the circle (eg, by increasing power at sites with low but stable contact). However the AI does not take into account lesion contiguity. Logically in order to obtain block across a lesion set, not only the lesion depth of single applications is of importance but also the lesion width ensuring that neighbouring applications are in fact histologically ‘contiguous’. Therefore the distance between neighbouring applications is an important parameter to consider, when analysing ablation application effectiveness characteristics.^{48,52}

In **part IB** of this thesis we developed and tested a specific new protocol aiming to improve the point-by-point RF PVI technique by combining strict criteria for both RF application contiguity and quality.

In **Chapter 3** we retrospectively analysed 42 CF-guided PVI procedures to define optimal target criteria for RF application quality and contiguity. For each RF tag within the circle, we collected RF characteristics reflecting lesion depth/quality (Ablation Index [AI]) and contiguity (automated interlesion distance [ILD]). To combine both depth (AI) and contiguity (ILD) in one single criterion we developed in Matlab (Mathworks, Natick, MA) a new algorithm to assess ablation line contiguity index (ALCI). ALCI is defined as the ratio of the estimated width of 2 neighboring lesions (i and j) over their interlesion distance (ILD_{ij}) and calculated as follows:

$$ALCI_{ij} = \frac{OC \times Conv \times \left(\frac{AI_i + AI_j}{2} \right)}{ILD_{ij}}$$

The width of a lesion is defined as the multiplication of estimated lesion depth (AI) and the conversion factor (Conv). The conversion factor is used because experimental studies have shown that maximal lesion width exceeds depth by a factor ranging from 1.5 to 2.0 (ellipsoid nature of RF lesions). In the present study, Conv was 1.5 for the anterior wall (thick tissue) and 2.0 for the posterior wall (thin tissue) lesions. To assure contiguity, we hypothesized that lesions should overlap by 25%. Therefore,

an overlapping coefficient (OC) of 0.75 was used. This overlap also corrects for the fact that lesion width at the tip–tissue interface is smaller than its maximal width.

In all procedures RF applications were depicted on the anatomical map with automated tagging technology (Carto VisiTag™, Biosense Webster Inc.) with predefined settings of catheter stability and CF. This automated tagging is a crucial part of this analysis, because 1) it allows to precisely collect the RF characteristics of each tag, and 2) it accurately (i.e. reproducibly) localizes the center of each RF tag, allowing to objectively determine the inter-tag distance (center-to-center). PV circle segments with acute (adenosine or waiting time) and late (at repeat procedures) pulmonary vein reconnections ($n = 44$) were compared to segments without reconnection ($n = 758$). For each segment, we determined its weakest link by annotating minimal RF time, power, impedance drop, CF, force-time integral (FTI), AI and maximal ILD and minimal ALCI. Segments with reconnections were characterized by comparable $\text{power}_{\min}$ (20 versus 22 W; $P=0.877$) and $\Delta\text{-Imp}_{\min}$ (4.8 versus 7.4 Ω ; $P=0.08$). In contrast, those segments showed significantly lower $\text{time}_{\min}$ (33 versus 35 s; $P=0.025$), $\text{CF}_{\min}$ (8.5 versus 11.8 g; $P=0.006$), $\text{FTI}_{\min}$ (351 versus 473 gs; $P<0.001$), and $\text{AI}_{\min}$ (367 versus 408 au; $P<0.001$). Furthermore, segments with reconnection were characterized by higher $\text{ILD}_{\max}$ (6.8 versus 5.5 mm; $P=0.001$). Also, minimal ALCI per segment was significantly lower in segments with reconnection (74 versus 104%; $P<0.001$). In multivariable analysis, $\text{FTI}_{\min}$, $\text{AI}_{\min}$, and $\text{ILD}_{\max}$ remained significantly different between segments with and without reconnection. Overall, ROC curve analysis for all segments together showed the highest diagnostic accuracy for ALCI (area under the curve, $\text{AUC}=0.73$), compared to ILD (0.70), FTI (0.69), CF (0.68), AI (0.67), and $\Delta\text{-Imp}$ (0.64).

AI and ILD were independently associated with durable lesions, as is illustrated in Figure 1. In those selected segments characterized by the presence of RF tags, all with an $\text{ILD}_{\max} < 5$ mm (an $\text{ILD}_{\max}$ of < 5 mm was associated with a specificity of 90% to discriminate durable segments), $\text{AI}_{\min}$ discriminated between segments with gaps and no gaps ($P=0.009$, left). Conversely, in those selected segments characterized by the presence of RF tags, all with an optimal AI (defined as $\text{AI}_{\min} > 550$ au on the anterior wall and > 417 on the posterior wall, both associated with a specificity of 90%), $\text{ILD}_{\max}$ discriminated between segments with gaps and no gaps ($P<0.001$, right). The difference in AI target between the anterior and posterior wall reflects the difference in wall thickness.

Combining both ILD and AI in a single index, the ALCI (target $\approx 100\%$) had the highest accuracy to predict durable PVI. We therefore hypothesize that combined ILD- and AI-guided ablation would increase freedom from AF after PVI procedures.

Figure 1: Left, Difference in minimal ablation index (AI_{min}) for segments with maximum automated interlesion distance (ILD_{max}) ≤ 5 mm. Right, Difference in ILD_{max} for segments with AI_{min} > 550 mm (anterior) and > 417 mm (posterior). Red scatter markers represent anterior segments. Pink scatter markers represent posterior segments. PVR indicates pulmonary vein reconnection.

Prospective evaluation of the 'CLOSE' protocol: acute and 1-year efficacy outcome

The analysed targets for RF application quality and contiguity (Chapter 3) were incorporated in a new PVI protocol, aiming at delivering stable, relatively high-power, short-duration RF applications relatively close to the left atrial (LA)-PV junction.

This 'CLOSE' (Contiguous Lesion Optimized pre-Specified Encircling) protocol consisted of the following principles:

1. Detailed mapping of the PV junction (performed with the Thermocool SmartTouch catheter). Applying a prespecified nephroid shaped circle around left and right PV pairs relatively close to the LA-PV junction prior to onset of ablation, based on CF/stability (identification of carina and ridge).
2. Automated RF tagging using Visitag module, after respiratory gating, with specific settings for lesion stability (3mm for 8s) and minimal CF (30% of time >4g). Stability was ensured before onset of RF in order to avoid dislocation before reaching the AI target (to avoid edema and ineffective lesions).
3. Contiguity of optimized RF applications:

- AI ≥ 550 au on the anterior wall and ≥ 400 au on the posterior wall/roof (300au in case of esophageal temperature rise $>38.5^{\circ}\text{C}$ or excessive pain in awake patients)
 - Maximum ILD ≤ 6 mm (center-to-center) with strict ruling
 - In case of dislocation a new application reaching the AI target was applied
4. RF power was delivered in a power-controlled mode (without ramping) at 35 Watts. RF power is only reduced in case of catheter tip temperature rise $>43^{\circ}\text{C}$ or in case of high CF (≥ 20 g) that might lead to overshoot of the AI target.
 5. Combined endpoint of ALCI $>100\%$ (except if lower AI due to esophageal temperature rise) on top of electrical PVI.

CLOSE guided PVI

Figure 2: illustration of the CLOSE protocol

In **Chapter 4** we provided comparative data on the efficiency, safety, and efficacy of ‘CLOSE-PVI’ to a historical control group of conventional CF-guided PVI for paroxysmal AF. We analysed the first 50 cases performed according to the ‘CLOSE’-protocol and compared results to the last 50 consecutive cases performed with conventional CF-guided PVI. In the CF-guided group the operator was blinded to the AI, and no formal ILD criterion was put forward. CF target was >10 g and RF power was delivered at 25 W (30 s) at the posterior wall / roof, and at 35 W (60 s) at the anterior wall.

Figure 3: comparison of the deployed circle in CF guided PVI and CLOSE-PVI.

In the CLOSE-PVI group, procedure time was found shorter (149 ± 33 min vs. 192 ± 42 min, $P < 0.0001$), as well as RF time (17 ± 3 min vs. 29 ± 8 min, $P < 0.0001$ for the right circles, 19 ± 4 min vs. 26 ± 6 min, $P < 0.001$ for the left circles). Also in CLOSE-PVI, first pass-isolation (98% vs. 54%, $P < 0.0001$) and waiting time/adenosine-proof isolation (97% vs. 82%, $P < 0.001$) were higher compared to conventional CF-guided PVI. The shorter procedure time in the CLOSE-PVI group was explained by the absence of PV reconnections (no time spent chasing gaps) and a reduction in RF time. The shorter RF time was explained by the markedly shorter applications (use of AI allowing delivery of higher power) and a trend towards fewer applications.

Holter-ECG was performed at 3 months (24 h), 6 months (24 h), and 12 months (7 day) or in case of symptoms. At the end of the blanking period (3 months), 23 patients continued antiarrhythmic drugs (ADT) in the conventional CF-guided group (46%) vs. 18 patients in the CLOSE-PVI group (36%). Overall, single-procedure 12 month-freedom from AF, atrial flutter (AFL) or atrial tachycardia (AT) was 94% in CLOSE-PVI compared to 80% in conventional CF-guided PVI ($P < 0.05$). Both in patients with and without ADT, 'CLOSE' was associated with a higher freedom from AF/AT/AFL. No clinical complications occurred in the CLOSE-PVI group.

Figure 4: Comparison of procedural outcomes between CLOSE-PVI and conventional CF-guided PVI.

Figure 5: Freedom from atrial fibrillation/tachycardia/flutter after 90 days blanking period in CLOSE PVI (50 patients) versus conventional CF-guided PVI (50 patients).

Following these promising results, in **Chapter 5** we investigated the safety, the acute and 1-year outcome of CLOSE-PVI in a larger patient cohort of 130 consecutive paroxysmal AF patients. Also in this study, the follow-up consisted of Holter-ECGs performed at 3 months (24 h), 6 months (24 h), and 12 months (7 day) or in case of symptoms. The procedure time was 155 ± 28 min, with RF time 17 ± 5 min per PV circle. Also in this larger cohort, CLOSE-PVI was associated with high incidence of first-pass isolation (98% per circle) and waiting time/adenosine-proof isolation (98% per circle). Overall, the single-procedure 12-month freedom from AF/AT/AFL was 92.3%, confirming the efficacy of CLOSE-PVI. Throughout the course of the study, 26 patients were on antiarrhythmic drug therapy (ADT). ADT was not systematically stopped and those patients had continued taking ADT after the 3-month blanking period. However importantly, no patient was taking ADT to treat a recurrence documented while being off ADT. In those 26 patients on ADT, freedom from AF/AT/AFL was 96.2%. In those 104 patients off ADT, freedom from AF/AT/AFL was 91.3%. Aside from one transient ischemic attack that occurred 8 days after the ablation, no adverse events occurred.

Figure 6: Procedural results of 130 consecutive CLOSE-PVI procedures: (A) Procedure time. (B) Radiofrequency (RF) time per circle. (C) Perimeter of the deployed circle. (D) Number of RF tags within the circle. (E) Obtained minimal ablation index (AI_{min}) per circle. (F) Obtained maximal ILD. (G) Incidence of first-pass isolation (per circle). (H) Incidence of waiting time/adenosine-proof isolation (per circle)

Figure 7: 1-year freedom from recurrence of AF/AFL/AT after a 3-month blanking period in 130 CLOSE-PVI procedures for paroxysmal AF.

Figure 8: Kaplan-Meier curves depicting time to first recurrence of AF, AFL, or AT in patients undergoing CLOSE-PVI ablation for subgroups of patients not taking antiarrhythmic drug therapy (ADT) (left) and taking ADT (right).

In 72 of 130 patients CLOSE-PVI was performed under general anaesthesia and in 58 patients under conscious sedation. The 1-year arrhythmia-free survival was comparable between groups (90.3% with general anesthesia, and 94.8% with conscious sedation ($p = 0.511$), demonstrating the effectiveness of the CLOSE protocol irrespective of the sedation used. However use of conscious sedation comes at the expense of a longer (skin-to-skin) procedure time (164 ± 31 min, compared to 147 ± 22 min, $p = 0.01$), fluoroscopy time (17 ± 8 min, compared to 16 ± 7 min, $p = 0.725$) and RF time (for the right circle 18 ± 4 min vs. 15 ± 3 min, $p < 0.001$; for the left circle 21 ± 7 min vs. 16 ± 4 min, $p < 0.001$).

Safety evaluation of the CLOSE protocol.

Atrio-esophageal fistula (AEF) is a very rare but often fatal and therefore one of the most feared complications of AF ablation. In order to minimize the risk of AEF, operators often reduce the RF power (20 – 25 W) on the posterior wall of the left atrium (or at least over the trajectory of the esophagus).¹⁴ This comes at the expense of the efficacy and efficiency of PVI procedures, because a lower RF power might result in non-transmural first-pass RF lesions with the need for touch-up applications, and consequently an increased RF and procedure time and suboptimal long-term PVI. Even despite this precaution, the reported incidence of AEF remains 0.02 to 0.11%.¹⁴ The CLOSE protocol however uses relatively high-power (35 W) applications to target the prespecified AI, also on the posterior wall. Using higher power is attractive because it allows reaching the target AI faster and therefore reduces RF and procedure time directly but also indirectly by reducing the risk for dislocation prior to reaching the AI target and the need for a second application. Using a higher power along the posterior wall in CLOSE-PVI was assumed not to increase the risk of esophageal injury because at a specific AI value (e.g. 400au on the posterior wall) the lesion depth is expected to be similar despite differences in power (higher power is offset by a shorter RF time). For safety reasons the target AI is decreased to ≥ 300 au in case of intra-esophageal temperature rise (ITR) $>38.5^{\circ}\text{C}$ (in anesthetized patients with an esophageal temperature probe) or excessive pain in awake patients.

Figure 9: example of CLOSE-PVI: in six applications on the posterior wall of the left circle that resulted in intra-esophageal temperature rise $>38.5^{\circ}\text{C}$, the ablation index target was reduced to ≥ 300 au (pink Visitags).

In **Chapter 6** we evaluated the safety of the CLOSE protocol with regard to esophageal injury. Whereas the incidence of AEF itself is low (0.02 to 0.11%),¹⁴ there is a high (2 to 30%) incidence of subclinical esophageal or peri-esophageal injury on endoscopy performed within 7 days after AF ablation.^{14,53,54} Halbfass et al showed that the only risk factor associated with the occurrence of esophageal injury or ulcer is ITR.⁵³ Furthermore they found that an esophageal ulcer is a necessary precursor for AEF.⁵³ Therefore, to assess the incidence of esophageal injury (and potential risk of AEF) of the CLOSE protocol, we performed echo-endoscopy in 85 patients revealing ITR>38.5°C (max ITR per patient was 39.9°C ([IQR 39.2-41.2°C], with range 38.6-50.0°C). Additional endoscopic ultrasound evaluation was performed in the first 38 patients. Of interest, with optimal positioning of the esophageal temperature probe, ITR>38.5°C can be observed in 72% of CLOSE-PVI cases. Endoscopy was performed after mean 9±4 days after PVI. In none of the 85 patients an esophageal ulcer was detected. In one patient we observed two erythematous lesions at day 4 after ablation. In none of the 38 patients undergoing additional sonographic evaluation, we observed direct signs of injury to the esophageal wall. In addition, during a median follow-up of 8.9 months [IQR 7.1-11.1] no complications of esophageal fistula, stroke or death were noted.

Figure 10: Results of endoscopic evaluation in 85 patients undergoing CLOSE-PVI with intra-esophageal temperature rise > 38.5 °C. Below two examples of esophageal lesions during endoscopy.

We found that the incidence of esophageal injury on endoscopy after CLOSE-PVI is low (1.2%), despite significant ITR during the procedure. We hypothesized this was due to the specific characteristics of the CLOSE protocol:

1. Due to the automated ablation tag, stability and contiguity criteria (resulting in limited dislocations and high incidence of first-pass isolation), there is a minimal amount of applications required to isolate the PVs. On average 10 applications per circle cross the posterior wall and only 5 of those are associated with ITR.
2. To reach the pre-specified AI targets at 35 W, RF applications at the posterior wall can be as short as 10s (mean 18s) for AI 400au and as short as 8s (mean 14s) for AI 300au. It has been hypothesized that short duration-high power (SD-HP) applications favor the balance in resistive to convective heating thus preventing the risk of collateral damage.⁵⁵ At least in experimental models, SD-HP applications result in more shallow lesions.^{56,57}
3. Also inherent to CLOSE-PVI is the concept of striving for high stability rather than high CF. Excessive CF by the ablation catheter (applied in non-CF guided procedures or in earlier CF studies) might result in inadvertent displacement of the posterior wall towards the esophagus.⁵⁸
4. Finally CLOSE-PVI is characterized by ablation at the LA-PV junction. Avoiding a wider encirclement reduces potential overlap with the esophagus and limits the number of procedures in which ITR is observed during both the left and right circle.

It seems unlikely that esophageal injury (and more specifically ulcer) was missed due to the relatively late timing of endoscopy (9±4 days). In those patients with endoscopy within 7 days we also did not observe any ulceration. Moreover, also in the study by Halbfass et al, reporting 18% of injury, endoscopy was performed up to 7 days after ablation.⁵³ Finally in that latter study, 47 patients with documented esophageal injury underwent a control endoscopy at 12.3±8.9 days. Whereas in those patients with initial erythema/erosion, the site of injury was still detectable in 21% of patients, in those patients with initial ulcer the site of injury was still apparent in 83% of patients. As such it is unlikely that ulceration was missed in the present study. This hypothesis is further supported by the absence of esophageal or peri-esophageal wall injury on ultrasound.

The absence of esophageal ulceration and lack of changes on ultrasound in our study suggest that the CLOSE protocol is safe with regard to esophageal injury. These findings do require confirmation in a larger patient cohort.

Efficacy evaluation: PV isolation status at repeat procedure

In Chapter 4 and 5 we demonstrated that CLOSE-PVI was associated with a very high rate of first-pass and adenosine-proof isolation and a high single-procedure arrhythmia-free survival at 1 year, suggesting durable PV isolation. In **Chapter 7** we further evaluated the effectiveness of CLOSE-PVI by determining the prevalence of patients presenting with 4 isolated veins at repeat ablation for AF recurrence after CLOSE-PVI. Out of 326 patients who had received a first CLOSE-PVI for paroxysmal AF, 45 patients underwent repeat ablation because of AF recurrence (ablation occurring at

7 ± 7 months after the index procedure). Four isolated veins were found in 28 of those 45 patients (62%). In patients with PV reconnection (n = 17) the mean number of reconnected veins was 2 ± 1 with no predilection sites of PV reconnection.

Figure 11: (Left) Localization of gaps in the ablation circles among patients (17 patients, 27 gaps) with atrial fibrillation recurrence and pulmonary vein (PV) reconnection. No predilection sites of PV reconnection could be identified. (Right) Circles with gaps showed similar lesion quality compared with circles with durable PV isolation.

Patients revealing 4 isolated veins at repeat ablation had similar clinical characteristics as patients with PV reconnection. Also, the arrhythmic profile of the initial paroxysmal AF was not different, with similar AF burden, both in terms of frequency and duration of AF episodes. Compared with patients with PV reconnection, patients revealing 4 isolated veins had also similar first procedural and RF characteristics.

Table 2: Characteristics of the first PVI procedure in patients revealing 4 isolated veins at repeat

	All repeat patients (n=44)	Patients with 4 isolated veins (n=27)	Patients with reconnected veins (n=17)	p value
Procedure characteristics				
General anesthesia, n (%)	29(66)	20(74)	9(53)	0.198
Common pulmonary vein, n (%)	4(9)	2(7)	2(12)	0.634
Procedure duration (min)	162±37	158±42	168±29	0.443
N of RF applications (points)	71±13	69±13	75±13	0.148
Total time of RF energy (min)	33±7	32±6	35±7	0.076
Fluoroscopy time (min)	15±8	13±6	17±9	0.211
RF circle characteristics				
Time _{Med} (s)	29[26:32]	29[26:33]	28[27:31]	0.365
Ablation index _{Med} (au)	486[478:494]	484[478:496]	487[479:494]	0.689
Force time integral _{Med} (gs)	426[379:484]	426[370:501]	426[386:451]	0.567
Inter lesion distance _{Med} (mm)	3.9[3.7:4.4]	4.1[3.7:4.4]	3.9[3.7:4.3]	0.907
Contact force _{Med} (g)	15[13:18]	15[13:18]	16[14:18]	0.716
Δ Impedance _{Med} (ohm)	12[11:13]	12[11:14]	12[11:13]	0.772

Previously, paroxysmal AF recurrence after PVI was invariably assumed to be caused by reconnection of 1 or more PVs. This was based on numerous prior studies reporting a low incidence of a status of complete vein isolation at repeat ablation for AF recurrence.^{27-29,59-66} Moreover the good outcome after re-isolation of reconnected veins with repeat ablation supports the theory of PV reconnection as the main pathophysiological mechanism of AF recurrence.

In the earlier years (using non-irrigated or irrigated non-CF RF to isolate the veins) the likelihood of complete isolation was as low as 0% and certainly not exceeding 20%. Although CF-guided ablation is associated with higher percentage of complete isolation in study patients undergoing invasive re-evaluation at 3 months regardless of symptoms,^{47,67} more recent data on CF-guided RF PVI still show high reconnection rates at repeat procedure for AF recurrence.^{64,65} Shah et al. showed that the incidence of isolated veins in patients with late AF recurrence (>36 months after first PVI) was 19%.⁶⁵ Buist et al. reported a low incidence of finding 4 veins isolated at repeat for CF-guided RF (only 3%).⁶⁴ Finally, a recent meta-analysis by Nery et al. reported an overall 14% likelihood of finding 4 isolated veins in case of a clinically indicated repeat ablation after PVI.⁶⁸

Figure 12: Overview of studies assessing the likelihood of finding 4 isolated veins after single PVI. After CLOSE-guided PVI, AF recurrence no longer implies PV reconnection. (CB: cryoballoon)

The present observation that 62% of clinically indicated repeat patients reveal a status of complete isolation confirms that CLOSE-PVI, by avoiding weak links in the ablation chain, is associated with durable isolation. This finding is in line with our prior data of favorable acute and 1-year outcome after CLOSE-PVI. Of course, the likelihood of finding 4 isolated veins is expected to be higher when evaluating all CLOSE-PVI patients (i.e. also those without AF recurrence).

This implies that AF recurrence after CLOSE-PVI is more likely to point to non-PV mediated AF. Whereas in the past repeat ablation for paroxysmal AF was straightforward, there are now several issues to consider. Repeat procedures after non-CF or conventional CF-guided PVI were generally shorter than the index procedure, because closing one or more gaps was usually faster than a complete first circumferential lesion set. In addition the clinical outcome of re-isolation of reconnection veins was favorable. In case of AF recurrence with status of four isolated veins, the procedure time can be highly variable (with practical planning issues), the preferred ablation strategy is unknown (unless there is an overt non-PV trigger during the procedure), and the outcome is worse irrespective of which ablation strategy is chosen as we also demonstrated in our patient cohort. Indeed, patients with 4 isolated veins, compared with patients treated for PV reconnection, showed a lower 12-month freedom from AF after repeat ablation (61% vs. 88%, $p = 0.045$).

Figure 13: Kaplan-Meier curves depicting time to AF recurrence after repeat ablation for patients with (n=17) and without (n=28) PV reconnection at repeat ablation. Patients with all 4 veins being isolated (treated with either empirical trigger ablation or linear substrate ablation) showed worse outcome.

Unfortunately there are no distinct characteristics (neither clinical (e.g. age, sex, LA size) nor in phenotype of paroxysmal AF (e.g. duration and frequency of AF episodes)) that predict the likelihood of finding four isolated veins after AF recurrence. We did observe that in patients with AF recurrence and 4 isolated veins, the incidence of low voltage was significantly higher (57% vs. 17% in reconnected patients, $p = 0.033$) and the area of low voltage was significantly larger (median: 4.6 [IQR: 2.3, 7.9] cm² vs. 0.0 [IQR: 0.0, 0.0] cm² in reconnected patients, $p = 0.049$). Those low voltage areas are suggestive for atrial fibrosis either as a manifestation of structural heart disease or as a result of an intrinsic fibrotic atrial cardiomyopathy.^{69,70} Our findings are in line with prior studies reporting worse single procedure outcome after first PVI in patient presenting with fibrosis or low voltage areas in the LA.^{71,72} The association of low voltage with less favorable outcome after empirical ablation suggests that a patient-specific set-up of repeat ablation might be required to optimize outcome in patients presenting with complete vein isolation.

Efficacy evaluation: arrhythmia-free survival after CLOSE-PVI evaluated with insertable cardiac monitors.

In Chapter 5 we demonstrated that CLOSE-PVI in a cohort of 130 patients with paroxysmal AF was associated with favourable single-procedure, 1-year arrhythmia-free survival, evaluated by intermittent holter monitoring. With intermittent Holter recordings arrhythmia-free survival depends on the extent of monitoring and will always be overestimated as (asymptomatic) recurrences between Holters will be missed. Yet the time-to-first recurrence is an objective outcome parameter, well suited to compare 2 techniques, but does not reflect the most important/relevant clinical efficacy endpoint. The “atrial tachyarrhythmia (ATA) burden” (defined as the % of time spent in AF/AT/AFL) after an index

ablation is not limited to the first event, but – more relevantly – it reflects the amount and duration of all recurring events. To illustrate, both a patient with an isolated recurrence and a patient with frequent recurrences are equally deemed clinical trial failures by time-to-first event analysis, yet the impact of failure is completely different from the clinical point of view. Indeed, prior studies suggested a dose-effect relation between ATA burden and symptoms, heart failure and stroke.⁷³⁻⁷⁷

In **Chapter 8**, we evaluated the 2-year efficacy of CLOSE-PVI in 105 patients with paroxysmal AF using continuous monitoring with insertable cardiac monitors (ICM) and also evaluated its effect on the ATA burden. To reliably quantify the effect on the ATA burden, all patients were implanted with an ICM at least 2 months before PVI. Within the two-year follow-up period, 0 patients received ADT or cardioversion, 14 patients received a repeat procedure at 150 [100-513] days after PVI.

Even using continuous rhythm monitoring, the single-procedure, off-ADT freedom from any 2-min ATA was very favourable and amounted 87% after 1 year and 78% after 2 years.

Figure 14: Kaplan-Meier curves depicting time to first recurrence of any ATA during the first 2 years after PVI (blue curve: entire study population; red curve: 84 patients with ILR-documented ATA within 2 months before ablation).

After CLOSE-PVI (1.13 ± 0.39 procedure per patient throughout the 2-year follow-up), the ATA burden decreased from $2.68 [0.09-15.02]$ % at baseline to $0 [0-0]$ % during the first year (reduction in

ATA burden 100 [100-100] %, $p < 0.001$) and 0 [0-0] % during the second 2-year (reduction in ATA burden 100 [100-100] %, $p < 0.001$). Results for the subset of 84 patients with documented ATA during the 2-month monitoring period prior to ablation were similar. The proportion of patients with >95% reduction in ATA burden was 94% and 96% at 1 and 2-y FU. Finally, throughout the first and second year after ablation, only 5 (6%) and 1 (1%) had a residual ATA burden >0.5%. These results show that CLOSE-PVI (with a low number or repeat procedures and without ADT) results in a major overall reduction in ATA burden and this effect is maintained at longer-term follow-up. These results confirm the efficacy of CLOSE-PVI.

Figure 15: Plots showing the % of time spent in ATA during the first and second year compared to baseline in the entire population (upper panels) and subpopulation (lower panels). Each line represents an individual patient. Patients are arranged by recurrences during follow-up, ranging from greatest (bottom) to fewest (top).

The CLOSE protocol: conclusion and future perspectives

Over the past 20 years, there has been a constant effort to improve the PVI technique and achieve durable PV isolation in order to improve the outcome of AF ablation. In this thesis we developed a new PVI protocol after analysing optimal target criteria for lesion quality and contiguity. In single-center experience, this CLOSE protocol has demonstrated superior efficacy, even when using

continuous monitoring to detect AF recurrence, compared to previously published outcomes of PVI performed with either RF or cryo-energy.

Evaluation of a new ablation protocol/technique in a single arm design and comparing its outcome to historical results of older techniques has however inherent pitfalls and limitations. A blinded, randomized controlled trial comparing CLOSE-PVI to conventional CF-guided PVI would be needed to prove the true superiority of the CLOSE protocol. However, after gaining extensive experience with CLOSE-PVI, the principles of RF application quality and contiguity have become so accustomed to the operator, conventional CF-guided PVI results would always be influenced by the gained knowledge and experience and such randomized trial would therefore probably be futile. However, the favourable results on outcome and safety need to be confirmed in larger studies. As such, the multicenter VISTAX study was designed to assess the reproducibility of CLOSE-PVI across 17 European centers and evaluate the outcome in a larger group of 340 paroxysmal AF patients.

Over the last years, PVI with cryo-energy has gained much popularity. This is largely due to two of the major advantages of the Cryoballoon over RF, i.e. the shorter procedure time and the faster learning curve. In the landmark FIRE and ICE trial, non-inferiority of these two treatment modalities was demonstrated, but the results and conclusion were hampered by the use of both non-CF and CF sensing catheters in the RF-arm, and both second and first generation Cryoballoon in the cryo-arm.⁷⁸ However recently the CIRCA-DOSE study evaluating Cryoballoon vs. CF-guided RF PVI for paroxysmal AF confirmed no difference in one-year efficacy assessed by continuous cardiac rhythm monitoring, neither in time-to-first-recurrence nor in reduction of the atrial tachyarrhythmia burden.⁷⁹ Undeniably, the Cryoballoon does have two disadvantages over point-by-point RF. First, the incidence of phrenic nerve palsy is up to 2.7% with cryo compared to ~0% with RF.^{78,79} Even if most phrenic nerve palsies recover over time, any (transient) intra-procedural phrenic nerve palsy will limit the applied cryo-application time and rarely even result in omission of an attempt to achieve isolation of the right (superior) PV. Second, the fixed balloon shape is not adaptable to individual anatomical configurations of the left atrial-PV junction. In some cases this results in suboptimal freeze temperatures, too distal PV isolation and rarely incomplete procedural PV isolation. In contrast, with point-by-point RF, the CLOSE protocol targets can be achieved in nearly any anatomical variant. In order to investigate if the CLOSE protocol will finally be able to tip the balance in favour of point-by-point RF when compared to Cryoballoon PVI, a randomized, multicenter trial would be needed.

The CLOSE protocol has markedly reduced procedure times compared to non-CF en CF guided PVI. Because of the 98% adenosine and waiting time proof isolation, CLOSE-PVI has allowed omission of the adenosine testing and the 20-minute waiting-time in our institutional ablation protocol. After a learning period, and with general anaesthesia, dislocations during application have become rare, and skin-to-skin procedure times are reproducible around 100 minutes. However in our striving to

optimize PVI results there is growing interest in increasing the ablation power (high-power, short-duration applications) in order to further decrease the procedure time while maintaining/increasing safety. Given that the lesion depth is similar at a specific AI value (irrespective of the power) using a higher ablation power (45-50 W) is expected to be feasible. The POWER-AF trial was designed to investigate the efficacy and safety of the CLOSE protocol while using 45 W applications.

Even when point-by-point ablation is meticulously performed according to the strict established criteria, the CLOSE protocol is still not able to ensure durable PV isolation in 100% of cases. Indeed, at repeat ablation due to arrhythmia recurrence, we found that 38% of patients still had at least one reconnected vein. This could be due to variables that are not taken into account, such as the tissue thickness or tissue composition. A patient-tailored strategy with adapted ablation characteristics based on pre- or intra-procedural imaging (e.g. with computed tomography or intra-cardiac echo) as well as intra-procedural lesion verification (e.g. with magnetic resonance imaging) might be the next step to improve CLOSE-PVI results.

Optimizing left atrial linear ablation

Left atrial (LA) linear lesions are one of the main techniques described for additional ablation in persistent AF and are also frequently performed for left atrial macroreentrant tachycardia. Roof and mitral isthmus (MI) lines are the most commonly performed LA linear lesions. Even though achieving bidirectional conduction block is challenging⁸⁰⁻⁸⁴ (reported block across roof lines of 81 to 95%^{81,84,85} and for the MI line between 57 to 92%^{80-82, 86-87}), it is well known that incomplete bidirectional conduction block has been associated with an increase in subsequent arrhythmia during follow-up.⁸¹⁻⁸² On the other hand, increased success in completing linear block is often associated with an increased complication rate from higher ablation power and a higher risk of steam pop, perforation, and tamponade.⁸⁸

In **Chapter 9** we applied the same ablation principles of the *CLOSE* protocol, to assess the efficacy of optimized point-by-point linear RF lesions at the roof and posterior mitral isthmus (MI) in 41 patients.

Figure 16: Single anatomical linear lesions at roof and posterior mitral isthmus of contiguous applications with a maximum interlesion distance $\leq 6\text{mm}$ (center-to-center) and Ablation Index (AI) ≥ 550 (red VisiTags).

By only using criteria for contiguity (interlesion distance $\leq 6\text{mm}$) and Ablation Index (≥ 550), we achieved complete block in the roof line in 93% of patients after a single linear lesion set, but only in 23% at the MI line (without ablation in the coronary sinus) confirming the difference for both lines when applying RF catheter ablation.

Figure 17: Results of first-pass and final roof and mitral isthmus block.

The very high success rate of first-pass block on the roof in our study (93%) can probably be explained by the favorable and uniform anatomy of the roof, which renders the roof quite suitable for a strategy aiming at transmural and contiguous of RF lesions. This was emphasized by the low number of dislocations before reaching Ablation Index target value (0 [IQR 0 – 1] per patient). In the case of absence of block after the first-pass roof line and during the redo procedures, all conduction gaps were located in the middle of the roof or near the right PVs (never at the left side of the roof). These locations are characterized by lower stability during RF delivery and also by thicker tissue with interatrial muscular bridges.⁸⁹

Conversely, the success rate for achieving bidirectional conduction block after a first pass linear lesion at the MI was low (23%). This can probably be explained by the complex 3D anatomical characteristics of the MI region: 1) Post mortem anatomical and *in vivo* studies have shown that the atrial myocardium at the left mitral line has a wall thickness of up to 10mm at the ostium of the left inferior PV.⁹⁰ In comparison, the LA roof is thinner with a range between 3.5 and 6mm.⁸⁹ The distance between the endocardium and the overlying inner surface of the coronary sinus (CS) is even larger than the MI thickness, due to the adipose tissue overlaying the CS along the mitral valve, sometimes with interlaying circumflex artery branches.^{86,91} 2) Numerous recesses and cavities along the left mitral isthmus have also been reported¹⁸ as well as epicardial muscular connections.^{80,91-92} 3) Blood flow in the CS and circumflex artery may also act as a ‘heat sink’ and reduce the efficacy of radiofrequency ablation.⁹¹

These anatomical characteristics of the MI region necessitate additional ablation within the CS in the majority of patients (reported in 60 to 84% of cases^{80,86-87}, and to 54% in our patient cohort) in order to achieve conduction block.

Recovery of conduction has been reported to occur in up to 90% of MI line and 79% of the roof lines during repeat evaluation for atrial arrhythmia recurrence^{93,94}. In 12 patients conduction recovery was evaluated at repeat ablation for recurrence of atrial tachycardia. For the roof, there was persistent block in 8 out of 12 (67%) evaluated lines. Of the 12 re-evaluated MI lines, 2 were not blocked during the index procedure and were still conducting. Of the remaining 10 evaluated lines, 5 MI lines showed persistent block (50%) while 5 had re-conduction. Limited RF delivery was necessary to achieve conduction block and was successful in all re-ablated patients for both lines. The different results in durability of achieved block between roof and MI lines was probably again attributable to the differences in anatomy.

As such, anatomical ablation using contiguous and optimized RF lesions appeared very effective for the roof line but not for the MI line. Unlike in CLOSE-PVI, the criteria for Ablation Index and interlesion distance were not based on retrospective analysis, but were arbitrarily chosen for both lines. The chosen criteria were based on previously acquired local experience, and in order to minimize the risk of complications and dislocation (during longer RF applications) which could have impacted the interpretation of the data. In the future, higher Ablation Index or shorter interlesion distance should be evaluated for the MI line given the low amount of first pass block. Also pre-evaluation with imaging technologies might also improve the results by allowing adaptation of the criteria depending on individual anatomical variations and helping avoid RF under- and overshooting. Although no safety-related issues were observed, larger studies are necessary to evaluate the safety and efficacy of this protocol for linear LA lesions.

Mapping of drivers in persistent atrial fibrillation

Despite the advances in technology and our insight in the molecular, ionic, and physiological fundamentals of cardiac electrophysiology, the exact mechanism of AF is still not completely elucidated. Mechanisms how AF is initiated and sustained may differ from patient to patient, and in various AF types (paroxysmal, persistent or permanent). The following concepts have competed trying to explain the pathophysiology of AF: 1) the multiple wavelets hypothesis (Moe⁹⁵ and Allesie⁹⁶), 2) rapidly discharging automatic foci (Waldo⁹⁷), 3) anatomical localized reentry (Fedorov⁹⁸) and 4) functional reentry or rotors (Jalife⁹⁹). Aside from the technical limitations in delivering qualitative ablation lesions, our limited understanding of the mechanisms that initiate and sustain AF withholds us from being able to cure this arrhythmia. While the outcome of AF ablation in paroxysmal AF is favorable and ensues from elimination of the triggering firing sources that arise predominantly from the pulmonary veins, the results of PVI are inferior in persistent AF. It is therefore perceived that in these patients (additional) ablation targeting the sustaining atrial substrate is necessary in order to improve ablation outcome. The benefit of non-specific ablation strategies (such as linear ablation or ablation of non-specific complex fragmented atrial electrograms)¹⁰⁰⁻¹⁰¹ has proven modest and therefore research is focusing on patient-tailored substrate ablation that is selectively targeting either the patient's specific anatomical substrate (e.g. fibrosis¹⁰²) or patient specific mechanistic AF drivers. Indeed intra-procedural identification of focal and reentrant AF drivers could pose attractive and patient-specific targets for AF ablation. In the last few years, there has been progress in mapping AF sources and mechanisms, mostly using phase-based analysis of epicardial or endocardial potentials.¹⁰³⁻¹⁰⁹ However, *phase mapping* has limitations as it is known to generate false rotational activities, particularly in cases of low voltage, variable contact and when far-field signals are present.¹¹⁰⁻¹¹¹ Recently, some studies created AF propagation maps based on *direct contact mapping* (without phase transformation) using dedicated software (CARTOFINDERTM, Biosense Webster) and a multi-electrode basket catheter and were able to reliably and reproducibly identify repetitive activation patterns in the majority of patients.¹¹²⁻¹¹⁵ However, as the basket catheter has issues of long interelectrode distance and obtaining stable contact with the atrial wall in some regions leading to underdetection of AF drivers, in **Chapter 10** we sought to evaluate the Cartofinder software for automated detection of AF drivers with a new mapping technique using a regional high-density contact mapping catheter (PentaRayTM, Biosense Webster) in sequential positions that overlap the previous recording position with the radius of the PentaRay until the whole biatrial surface is covered. In 14 patients with persistent AF, we characterized repetitive atrial activation patterns (RAAPs), with either focal or rotational activity, during ongoing AF based upon the automated annotation of directly obtained unipolar electrograms. This technique of sequential biatrial mapping proved feasible: a mean of 35.6±7.6 PentaRay recording per patient were performed during 44±6 min. of mapping with 6±3 min radiation exposure. The number of PentaRay recordings displaying RAAP was 9.8±3.1 per patient (range 3-15), of which 2.4±2.4 RAAP_{rotational} (range 0-7) and 7.4±4.4 RAAP_{focal} (range 1-13). 77% of

RAAPs portrayed focal firing. RAAPs were observed both in the RA (35%) and LA (65%), with the majority being near the left PVs/appendage (35% of all RAAPs) and the SVC/right appendage (23% of all RAAPs). Our study showed that direct endocardial high-density contact mapping EGM analysis during ongoing AF allows identification of RAAPs in all persistent AF patients (predominantly focal firing sources in our study). Our technique of sequential high-density mapping may detect a greater number of RAAPs due to better coverage and mapping density in comparison with basket catheter. The automated annotation software has the potential to provide on-line detection of potential bi-atrial AF drivers annotated on the 3D-geometric bi-atrial shell, making patient-tailored substrate ablation possible. However the effect of ablation of RAAP was not investigated in our study and further studies are needed to investigate if ablation of RAAPs as detected by the system would improve clinical outcome.

Evolutions in ablation of ventricular tachycardia and impact on long-term outcome results.

Catheter ablation for sustained monomorphic ventricular tachycardia (VT) has emerged as an effective tool for the control of VT recurrence. Ablation strategies have shifted from using activation and entrainment mapping of inducible and hemodynamically tolerated VTs¹¹⁶⁻¹¹⁷ to alternative strategies predominantly based on straightforward substrate modification, such as elimination of LAVA (local abnormal ventricular activities),¹¹⁸ late potential abolition,¹¹⁹ scar de-channeling,¹²⁰ scar core isolation¹²¹ and scar homogenization.^{122,123} These strategies not only have the advantage of identifying targets for ablation in patients in whom VT is not inducible or not tolerated, but they may also provide a more comprehensive treatment of the substrate for present but also future VT, as they are not limited to inducible or “clinical” types of VT.

Several groups have tried to modify potentially arrhythmogenic surviving myocardial tissue by targeting late potentials in scar regions.¹²⁴⁻¹²⁶ However both the voltage amplitude¹²⁷ and the timing of near-field signals from poorly coupled surviving bundles¹²⁴ are dependent on the activation wavefront, and consequently substrate-based ablation targeting solely late potentials or confined to voltage-defined scar might miss part of the arrhythmogenic substrate. The LAVA approach¹¹⁸ aims to overcome these limitations, by not being limited to late potentials (occurring after the QRS) or confined to low-voltage regions.

In **Chapter 11** we report long-term outcomes after single and multiple ablation procedures with elimination of LAVA in 159 patients (65±11y, 92% ICDs, 54% storms and 73% appropriate shocks) with post-myocardial infarction VT. We also investigated the effect of implementation of evolutionary techniques such as multi-electrode mapping and/or use of real-time image integration on ablation outcomes.

We demonstrated that LAVA can be successfully identified in the vast majority of patients (92%) referred for post-MI VT ablation, when using a strategy of meticulous mapping. The endpoint of LAVA elimination in addition to non-inducibility is feasible and effective for arrhythmia control. With a single procedure, 73% of the patients are free from arrhythmia at 1 year. This success rate decreases over time, but 49% of patients are still free from any ventricular arrhythmia at 5 years. At the modest cost of repeat procedures in 18% of patients, this result is improved to 85% arrhythmia-freedom at 1 year, remaining 62% after 5 years.

Figure 18: Ventricular arrhythmia (VA)-free survival after single (A) and including repeat (B) ablation procedures in 18% of patients (1.3 ± 0.6 ablations/patient).

In addition only 9% of patients had appropriate shocks over a mean of 4 years follow-up. The reduction in VT burden was more than 87% in 91% of patients after a single procedure (Figure 19). This strategy allowed for a substantial discontinuation of antiarrhythmic drugs and amiodarone use was reduced by 54%, this benefit being maintained at 5 years. In accordance with previous reports, complete LAVA elimination, which was achieved in 64% of patients in our cohort, was associated with better outcome.

Figure 19: There were 74 patients with implantable cardioverter-defibrillator (ICD) at least 1 year prior to ablation who survived for 1 year. Each line represents an individual patient; blue lines indicate pre-ablation and orange lines post-ablation. Upper boundaries are truncated at 200 episodes. Patients are arranged by recurrences during follow-up, ranging from greatest (bottom) to least (top). In 91% of these 74 patients, the reduction in VT burden was more than 87%.

Comparison with other outcome studies

These results are favorable when compared to reported long-term outcomes of VT ablation in ischemic cardiomyopathy patients, predominantly guided by *activation and entrainment mapping* of inducible and hemodynamically tolerated VTs.^{116,117} In a single center retrospective series of 358 patients (including repeat ablation in 25% of patients) the VA-free survival was around 54% at 5 years FU, compared to 62% in our study.¹¹⁶ Also in the prospective multicenter Post-Approval THERMOCOOL VT trial (249 patients) the single-procedure freedom from arrhythmia was considerably lower when compared to our study amounting only 41% after 3 years.¹¹⁷

Outcomes from *substrate-based* VT ablation studies have only been reported with limited follow-up.^{119,120,122,123,128,129} Silberbauer et al reported a VT-free survival of 68% at 19 months after substrate modification (160 pts, 20% epicardial mapping) targeting *late potential abolition* combined with non-inducibility.¹¹⁹ Proietti et al reported a VA-free survival of 74% after a mean follow-up of 21±10 months in 87 patients undergoing substrate-based VT ablation targeting late potentials in scar regions and regions in the scar-border zone with good pace-map correlation to clinical VTs.¹²⁹ Better short-term results were reported after more extensive substrate modification targeting not only delayed but all abnormal potentials within and around scar ("*scar homogenization*"). Di Biase et al reported outcomes of endo- and epicardial scar homogenization in 43 patients with idiopathic dilated cardiomyopathy and electrical storm.¹²² Epicardial access was obtained in all of them, but epicardial ablation was only performed in 33% if abnormal potentials remained after endocardial ablation. At a mean follow-up of 21 months the VT-free survival was 81%. The results of this ablation approach were confirmed in the VISTA Randomized Multicenter Trial, in which 58 patients underwent extensive ablation of all abnormal electrograms in endocardial scar, but epicardial access was limited to 10% of patients in whom VT remained inducible after endocardial ablation.¹²³ At 12 months follow-up, the VT-free survival was 84.5%. Both the scar homogenization and LAVA elimination strategy aim to modify the substrate more comprehensively, although the LAVA strategy may allow for less extensive ablation (36±20 vs. 74±21 and 86±21min). Short-term freedom from arrhythmia was however >80% with the scar homogenization strategy, compared to 73 and 68% at 1 and 2 years follow-up after a single procedure in our patient series.

Impact of technological evolution

In our approach, identification of the substrate is contingent on the detectability of LAVA by the mapping catheters used. It was previously demonstrated that the use of multi-electrode (ME) mapping catheters is associated with increased LAVA detection due to reduction of the far-field signal and magnification of the near-field component.¹³⁰ In our study, ME mapping catheters were used in 56% of patients. Also the added value of real-time integration of preprocedural imaging with DE-MRI or MDCT in post-MI VT ablation was previously reported.¹³¹ Both DE on MRI as well as wall thinning on MDCT correlate well with low voltage areas on electroanatomic mapping and the presence of

LAVA.^{132,133} After substrate mapping, real-time integration of image-derived substrate has been shown to motivate the operator to perform additional mapping in the majority of cases with extra LAVA detection in all of them. In addition, in some patients, pre-procedural imaging influenced the decision to perform epicardial access and RTII modified epicardial ablation strategy due to proximity of coronary arteries or phrenic nerve.¹³¹ In our most recent approach of LAVA ablation, RTII and ME mapping catheters are therefore consistently implemented and resulted in significantly improved outcomes with a VA-free survival of 86% at 1 year, remaining 65% at 4 years of follow-up and overall survival of 94 and 91% at 1 and 4 years respectively.

Figure 20: Impact of different mapping technologies. Ventricular arrhythmia (VA)-free (A) and overall (B) survival rate in procedures performed without multi-electrode (ME) mapping and real-time image integration (RTII) (blue, n=35), with ME mapping but without RTII (green, n=53), and with combined ME mapping and RTII (yellow, n=47).

With the contemporary LAVA-strategy, (short-term) results comparable to the scar homogenization strategy are achieved, but with more limited RF delivery.^{122,123} Given these results, a randomized, head-to-head comparison of the contemporary LAVA elimination approach and the scar homogenization approach could be of interest.

Reasons for VA recurrence

Potential reasons for VA recurrence are 1. inadequate mapping of the substrate, 2. inadequate ablation with lesion regression and reconnection of critical isthmuses, 3. inadequate ablation due to anatomic limitations (mid-myocardial substrate, substrate in vicinity of the coronary arteries or phrenic nerve), 4. progression of the substrate, and 5. progression of neurohormonal and autonomic remodeling.¹³⁴ While inadequate mapping can be improved by triple (both retrograde and transseptal endocardial, and epicardial) LV access and use of ME mapping catheters and RTII, intramyocardial infusion-needle and

bipolar irrigated RF catheter ablation may offer benefit when conventional RF ablation lesions are of insufficient depth to reach a mid-myocardial substrate.^{135,136} Comparable to previously published series in post-MI VT ablation¹³⁷, recurrent VTs had new morphologies in our study. During repeat ablation, ≥ 1 VT with different morphology from the index procedure was induced in all evaluable patients and only in a minority, a VT with a same exit as during the index procedure was induced. Despite different VT morphologies, the arrhythmogenic substrate generally remained unchanged between index and repeat procedures. In redo procedures, LAVA were generally (94%) located in the same area as during the index ablation, either due to recurrence of previously ablated LAVA or residual, unablated LAVA from the index procedure (in several cases possibly missed by mapping with the ablation catheter in the index, but detected by ME mapping in the redo procedure). Without recurrent ischemia, substrate progression in post-MI VT appears to be the exception, as scar areas were unchanged between index and repeat procedures and ‘new’ LAVA in repeat procedures were very rare.

Figure 21: Comparison between index ablation and first repeat ablation procedure of (A) induced ventricular tachycardia morphologies and (B) characteristics of local abnormal ventricular activities.

Conclusion and future clinical perspectives

Substrate modification by LAVA elimination for post-MI VT resulted in a substantial reduction of VT storm, VT burden and need for ICD shocks. Both short- and long-term outcomes were improved by repeat ablation in a limited number of patients. Implementation of modern mapping technologies such as ME mapping and RTII significantly improved outcomes. However, the recurrence of previously ablated LAVA advocates the importance of effective and durable RF lesions. Therefore, in order to improve outcomes of VT ablation, further research should aim to develop criteria and/or tools for effective RF lesion creation in the ventricle. Secondly, while elimination of all LAVA was associated with a better outcome, many LAVA might be innocent bystanders and are not involved in channels responsible for current or future clinical VTs. Identification of potential VT channels on imaging

studies (MRI or CT) might significantly reduce the amount of RF delivery, procedures times, avoid unnecessary myocardial destruction and improve arrhythmia-free survival.

Final conclusion

Outcomes of ablation of complex atrial and ventricular arrhythmias have significantly improved over the last decade. This can be attributed to technological advances that have resulted in both improved radiofrequency lesion creation and identification of the arrhythmogenic substrate, in combination with robust and innovative clinical ablation strategies based on the pathophysiology of these arrhythmias.

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Addenda

Summary – Samenvatting
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Acknowledgement – Dankwoord
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SUMMARY

This thesis addresses recent evolutions in ablation of complex atrial and ventricular arrhythmias, and how technological advances applied in pathophysiology-based ablation strategies have aided to improve these procedures and their outcome results.

In **PART I** we aimed to improve outcome results of ablation of atrial fibrillation (AF) and atrial tachycardia. In **PART IA** (Chapter 2) we investigated and demonstrated that also after having gained extensive experience with online contact force (CF)-measuring catheters, procedural outcomes of pulmonary vein isolation (PVI) remained superior with this technology when compared to non-CF guided PVI. **PART IB** of this thesis addresses the development of a protocol aiming to improve the point-by-point radiofrequency PVI technique by combining strict criteria for both radiofrequency application contiguity and quality. In **Chapter 3** we analysed optimal cut-off criteria for maximum distance ($\leq 6\text{mm}$) between neighbouring radiofrequency applications and minimum *ablation index* targets ($\geq 400\text{au}$ posterior/roof and $\geq 550\text{au}$ anterior) associated with durable PVI. These criteria were incorporated into the ‘*CLOSE*’ protocol. In **Chapter 4 and 5** we investigated the feasibility of *CLOSE*-PVI in paroxysmal AF patients and observed shorter procedure times, significant improvement in acute PVI durability and high single-procedure arrhythmia-free survival at 1 year, when compared to conventional CF-guided PVI. In **Chapter 6** we investigated and demonstrated the safety profile of *CLOSE*-PVI concerning oesophageal injury. We performed echo-endoscopy in those patients revealing intra-oesophageal temperature rise during *CLOSE*-PVI and found complete absence of esophageal ulceration in all evaluated patients. These findings suggest safety of *CLOSE*-PVI concerning esophageal injury. The efficacy of *CLOSE*-PVI was further investigated in Chapters 7 and 8. In **Chapter 7** we evaluated the durability of PVI in patients undergoing repeat ablation for AF recurrence after undergoing an index *CLOSE*-PVI procedure. Durable PV isolation was found in 62% - higher than previously reported - supporting the efficacy and favorable clinical results of *CLOSE*-PVI in paroxysmal AF. In **Chapter 8** we studied the impact of *CLOSE*-PVI on AF burden during the first two years after *CLOSE*-PVI using insertable cardiac monitors. Even when using continuous cardiac monitoring to detect arrhythmia recurrence, the outcome results of *CLOSE*-PVI for paroxysmal AF remained excellent: the single-procedure freedom of atrial arrhythmia without use of anti-arrhythmic drugs amounted 87% after 1 year and 78% after 2 years, with a median atrial arrhythmia burden of 0 [IQR 0-0] % in the first two years after ablation.

In **PART IC** (Chapter 9) we focused on the optimization of left atrial linear ablation by applying the same principles of the ‘*CLOSE*’ protocol. This strategy of delivering contiguous and optimized radiofrequency lesions applied to linear ablation appeared very effective for the left atrial roof, but not for the (posterior) mitral isthmus, because of its specific anatomical properties.

While the subject of the previous chapters was optimization of *ablation*, in **PART ID** (Chapter 10) we aimed to improve our understanding of the *pathophysiology* of persistent AF. We sought to evaluate a new mapping method to identify and characterize AF drivers (in casu *repetitive atrial activation*

patterns) obtained by sequential overlapping recordings with a regional high-density contact mapping catheter (Pentaray) covering the entire bi-atrial endocardial surface, and automatically analyzed with new software (Cartofinder). This mapping method demonstrated the presence of repetitive activation patterns during persistent AF in all patients. In our series, focal firing was the most frequently observed pattern.

The second part of this thesis (**PART II**) focused on the evolution and technological advances in ablation of ventricular tachycardia (VT), more specifically in the setting post-myocardial infarction. In **Chapter 11** we reported long-term outcomes after single and multiple ablation procedures targeting elimination of *local abnormal ventricular activities* (LAVA). We also investigated the added value of multi-electrode mapping catheters and of real-time integration of pre-procedural imaging with delayed enhancement-magnetic resonance imaging or multi-detector computed tomography. In our study, this ablation strategy resulted in a substantial reduction of VT storm, VT burden and need for ICD shocks. Both short- and long-term outcomes were improved by repeat ablation in a limited number of patients. Complete LAVA elimination, multi-electrode mapping and real-time image integration were associated with improved ventricular arrhythmia-free survival.

The conclusion of this thesis is that outcomes of ablation of complex atrial and ventricular arrhythmias have significantly improved over the last decade. This can be attributed to technological advances that have resulted in both improved radiofrequency lesion creation and identification of the arrhythmogenic substrate, in combination with robust and innovative clinical ablation strategies based on the pathophysiology of these arrhythmias.

A

SAMENVATTING

Deze thesis richt zich op recente evoluties in de ablatie van complexe atriale en ventriculaire ritmestoornissen, en hoe technologische vooruitgang gekoppeld aan pathofysiologische principes deze invasieve therapeutische procedures veiliger en effectiever gemaakt hebben.

DEEL I van deze thesis is gericht op de verbetering van de resultaten van ablatie van atriale fibrillatie (AF) en atriale tachycardie. In **DEEL IA** (Hoofdstuk 2) onderzochten en toonden we aan dat ook na uitgebreide ervaring te hebben opgebouwd met katheters met online contact force (CF)-feedback, de procedurele resultaten van pulmonale venen isolatie (PVI) met deze technologie superieur blijven in vergelijking met PVI zonder CF-meting. In **DEEL IB** ontwikkelden we een protocol met als doel de punt-per-punt radiofrequentie PVI techniek te optimaliseren, dit door combinatie van strikte criteria voor zowel contiguiteit als kwaliteit van de radiofrequentie applicaties. In **Hoofdstuk 3** analyseerden we optimale cutoff criteria voor maximale afstand ($\leq 6\text{mm}$) tussen naburige radiofrequentie applicaties en voor minimale *ablatie index* waarden ($\geq 400\text{au}$ posterior/dak en $\geq 550\text{au}$ anterior), die geassocieerd waren met duurzame PVI. Deze criteria werden geïncorporeerd in het 'CLOSE' protocol. In **Hoofdstuk 4 en 5** onderzochten we de haalbaarheid van CLOSE-PVI bij paroxismale AF patiënten en observeerden we een kortere proceduretijd, een significante verbetering in acute PVI duurzaamheid, en een hoge aritmievrije overleving na 1 jaar na een enkele ablatieprocedure, wanneer vergeleken met conventionele CF-geleide PVI. In **Hoofdstuk 6** onderzochten en toonden we het veiligheidsprofiel van CLOSE-PVI aan met betrekking tot slokdarmschade. We voerden endo-echoscopie uit in die patiënten die tijdens CLOSE-PVI een stijging van de intra-oesofagiale temperatuur vertoonden en stelden een volledige afwezigheid van slokdarmulceratie in alle onderzochte patiënten vast. Deze bevindingen suggereren dat CLOSE-PVI veilig is voor wat slokdarmschade betreft. De effectiviteit van CLOSE-PVI werd verder onderzocht in Hoofdstukken 7 en 8. In **Hoofdstuk 7** evalueerden we de duurzaamheid van PVI in patiënten die een redo-ablatie ondergingen omwille van herval van AF na index CLOSE-PVI te hebben ondergaan. Duurzaamheid van alle vier longvenen werd vastgesteld bij 62% van deze patiënten – i.e. hoger dan ooit eerder gepubliceerd – wat de effectiviteit en gunstige klinische resultaten van CLOSE-PVI voor paroxismale AF ondersteunt.

In **Hoofdstuk 8** bestudeerden we de impact van CLOSE-PVI op de AF burden gedurende de eerste 2 jaar a CLOSE-PVI door gebruik te maken van implanteerbare cardiale monitoren. Zelfs bij gebruik van continue cardiale monitoring om herval van aritmie te detecteren, bleef de uitkomst van CLOSE-PVI bij paroxismale AF excellent: de aritmie-vrije overleving na 1 ablatieprocedure, zonder gebruik van antiaritmica bedroeg 87% na 1 jaar en 78% na 2 jaar, met een mediane atriale aritmie burden van 0 [IQR 0-0] % gedurende de eerste 2 jaar na ablatie.

In **DEEL IC** (Hoofdstuk 9) legden we ons toe op de optimalisatie van lineaire ablatie in het linker atrium door dezelfde principes van het 'CLOSE' protocol toe te passen. Deze strategie van aaneensluitende en geoptimaliseerde radiofrequentie applicaties bleek tevens zeer effectief wanneer

toegepast voor lineaire ablatie ter hoogte van het dak van het linker atrium, maar niet voor de (posterior) mitraalisthmus, omwille van de specifieke anatomische eigenschappen van deze laatste.

Daar waar optimalisatie van *ablatie* het onderwerp van de voorgaande hoofdstukken was, legden we ons in **DEEL ID** (Hoofdstuk 10) toe op het verwerven van meer inzicht in de *pathofysiologie* van persistente AF. We evalueerden een nieuwe mapping techniek voor de identificatie en typering van AF drivers (in casu *repetitieve atriale activatiepatronen*), die gedetecteerd werden door sequentiële overlappende registraties met een regionale high-density mapping katheter (Pentaray) die het hele bi-atriale oppervlak overspannen en automatisch geanalyseerd werden met nieuwe software (Cartofinder). Deze mappingmethode demonstreerde in alle patiënten de aanwezigheid van repetitieve atriale activaties tijdens persistente AF. In onze reeks werden focale afvurende bronnen het meest frequent geobserveerd.

Het tweede deel van deze thesis (**DEEL II**) spitst zich toe op de evolutie en technologische vooruitgang in de ablatie van ventrikeltachycardie (VT), meer specifiek bij het substraat na doorgemaakt myocardinfarct. In **Hoofdstuk 11** rapporteerden we de lange-termijnsresultaten na enkelvoudige en meervoudige ablatieprocedures gericht op eliminatie van *lokale abnormale ventriculaire activiteit* (LAVA). We onderzochten tevens de toegevoegde waarde van multi-elektrode mapping katheters en van real-time integratie van pre-procedurele beelden bekomen door middel van magnetische resonantie of multi-detector computertomografie. In onze studie resulteerde deze ablatiestrategie in een substantiële reductie aan VT storm, VT burden en aantal ICD shocks. Het resultaat op zowel korte als lange termijn werd verder verbeterd door additionele ablatieprocedures in een beperkt aantal patiënten. Complete LAVA-eliminatie, multi-elektrode mapping en integratie van real-time beeldvorming was geassocieerd met betere ventriculaire aritmie-vrije overleving.

De conclusie van deze thesis is dat het resultaat van katheterablatie van complexe atriale en ventriculaire aritmie tijdens de laatste decade significant verbeterd is. Dit is deels te danken aan technologische vooruitgang die heeft geleid tot verbetering van radiofrequentie laesie-vorming en identificatie van het aritmogene substraat, en ook aan toepassing van deze nieuwe technologie in innovatieve klinische ablatie strategieën die gebaseerd werden op de pathofysiologie van deze aritmieën.

VALORIZATION

Scope, rationale and socio-economic relevance

The findings presented in this thesis will boost a significant improvement in the clinical efficacy of catheter ablation for complex arrhythmias such as atrial fibrillation (AF) and ventricular tachycardia (VT). As a consequence more patients may be treated effectively with fewer procedures per patient, thus improving the cost-effectiveness of this costly intervention. The revenue of our strategic physiological application of new ablation technology is even broader: it may not only lead to improved cost-effectiveness, but also it has already formed a firm stepping stone for follow-up observational and randomized controlled studies, enhancing on one hand the spread of our findings across centres in Europe (and the rest of the world), and on the other it generated new data to further enhance efficacy and safety of arrhythmia ablation, and formed a trigger for new technological developments as well.

The scope of atrial fibrillation

AF is the most common sustained arrhythmia. In 2010, the estimated worldwide prevalence was 33.5 million.^{1,2} Estimates suggest an overall prevalence of approximately 3% in adults aged >20 years³ and its incidence keeps rising due to better detection of silent AF⁴⁻⁶, alongside increasing age and conditions predisposing to AF.⁷ By 2030, 14–17 million AF patients are anticipated in the European Union, with 120 000–215 000 newly diagnosed patients per year.^{3,8,9} AF is a serious public health problem because of its increasing incidence and prevalence in the aging population¹⁰ and its association with elevated risks of cardiovascular events and death.^{4,11-15} The direct costs of AF already amount to approximately 1% of total healthcare spending in the UK, and between 6.0–26.0 billion US dollars in the US for 2008,^{16,17} driven by AF-related complications (e.g. stroke) and treatment costs (e.g. hospitalizations). These costs will increase dramatically unless AF is prevented and treated in a timely and effective manner. In addition, AF causes a wide variety of symptoms, including fatigue and reduced exercise tolerance, and significantly impairs quality of life.¹⁸ The morbidity and mortality associated with AF provide a rationale to maintain sinus rhythm. Yet to date, rhythm control strategy has failed to demonstrate a beneficial effect on hard endpoints such as a reduction in stroke or mortality rate.¹⁹⁻²⁰ Ablation of atrial fibrillation has proven to reduce symptoms and improve quality of life, and is superior to antiarrhythmic drugs in obtaining rhythm control.²¹⁻²³ Therefore according to current guidelines AF ablation is indicated in symptomatic patients as a second-line treatment after failure of a class I or III antiarrhythmic drug (Class I indication (level of evidence A) in paroxysmal AF, A class IIa indication (level of evidence B) in persistent AF and a class IIb indication (level of evidence C) in long-standing persistent AF.²⁴ Given that catheter ablation of AF as a first-line treatment is associated with a higher freedom from AF compared with drug therapy,²⁵⁻²⁷ current guidelines also state that catheter ablation of AF as a first-line treatment (without a trial of class I or III antiarrhythmic drugs) is indicated in symptomatic paroxysmal (Class IIa – level of evidence B) and

persistent AF patients (Class IIa – level of evidence C; and Class IIb – level of evidence C in case of long-standing persistent AF).²⁴

Pulmonary vein isolation

Since the initial description of triggers in the pulmonary veins that initiate paroxysmal AF, pulmonary vein isolation (PVI) has become the cornerstone of catheter ablation of AF.²⁴ Over the past 20 years, the development of AF ablation technologies has been a constant effort to improve the PVI technique. The goal has been to improve patient outcomes, reducing the need for repeat procedures, to reduce procedure times and to increase the safety of the procedure. However, despite these advances and two decades of experience, long-term procedural success rates at curing AF are still suboptimal and may require repeat procedures or hybrid therapy with antiarrhythmic drugs to improve outcome. The reason for these suboptimal results is twofold; on one side the pathophysiological mechanism of AF is still not completely elucidated, and on the other side the ablation tools and techniques still fail to deliver durable and transmural ablation lesions. The cornerstone of ablation of AF is to achieve *durable* electrical isolation of the pulmonary veins.²⁴ Radiofrequency ablation, the most established ablation technique, aims to achieve PVI by applying circumferential contiguous and transmural point-by-point ablation lesions.²⁹ Despite achieving nearly always acute procedural PVI, early and late pulmonary vein reconnections are frequent and are associated with increased AF recurrences and the need for repeat ablation procedures.

Mapping drivers in persistent atrial fibrillation

Despite the advances in technology and our insight in the molecular, ionic, and physiological fundamentals of cardiac electrophysiology, the exact mechanism of AF is still not completely elucidated. Mechanisms in how AF is initiated and sustained may differ from patient to patient, and in various AF types (paroxysmal, persistent or permanent). Aside from the technical limitations in delivering qualitative ablation lesions, our limited understanding of the mechanisms that initiate and sustain AF withholds us from being able to cure this arrhythmia. While the outcome of AF ablation in paroxysmal AF is favorable and ensues from elimination of the triggering firing sources that arise predominantly from the pulmonary veins, the results of PVI are inferior in persistent AF. It is therefore perceived that in these patients (additional) ablation targeting the sustaining atrial substrate is necessary in order to improve ablation outcome. The benefit of non-specific ablation strategies (such as linear ablation or ablation of non-specific complex fragmented atrial electrograms)³⁰⁻³¹ has proven modest and therefore research is focusing on patient-tailored substrate ablation that is selectively targeting either the patient's specific anatomical substrate (e.g. fibrosis³²) or patient specific mechanistic AF drivers. Indeed intra-procedural identification of focal and reentrant AF drivers could pose attractive and patient-specific targets for AF ablation.

Ablation of post-myocardial infarction ventricular tachycardia

For ischemic heart disease patients presenting with VT despite antiarrhythmic drug (AAD) therapy, which often results in ICD therapies (shocks or antitachycardia pacing), therapeutic options include escalating AAD therapy by increasing the dose, changing the drug, adding a new drug, and catheter ablation. In the recent VANISH trial, catheter ablation proved superior to increasing the dose of amiodarone or adding mexiletine.³³ In addition, in 3 large, prospective, multicenter cohort studies, VT ablation in patients with ischemic heart disease and recurrent VT despite AAD treatment ablation resulted in a consistent reduction of VT episodes.³⁴⁻³⁶ Based on these results VT ablation in ischemic heart disease has become a Class I indication for patients with recurrence of (symptomatic) monomorphic VT despite AAD treatment.³⁷ Recently few studies have reported long-term follow-up data of VT ablation, guided predominantly by activation and entrainment mapping,^{36,38} but long-term results of alternative strategies such as substrate modification have not been reported.

The novelty of our research and clinical perspectives

In PART I we aimed to contribute to the improvement of catheter ablation of AF. In PART IA we were the first to investigate if the benefits on contact force-sensing catheters maintained after acquiring extensive tip-tissue feedback with these advanced catheters. We found that an extensive learning-period still was no substitute for online contact force sensing.

In PART IB we developed a new protocol to optimize the results of pulmonary vein isolation, termed CLOSE-PVI. CLOSE-PVI proved to be associated with a very high single-procedure freedom from atrial arrhythmia recurrence, even when assessed with continuous cardiac monitoring; with more durable isolation at repeat studies; and without compromising safety. Using this novel ablation concept, efficacy is superior compared to previously published outcomes of PVI performed with either radiofrequency or cryo-energy. However, our favourable results on outcome and safety need to be confirmed in larger studies. As such, our multicenter VISTAX study was designed to assess the reproducibility of CLOSE-PVI across 17 European centers and evaluate the outcome in a larger group of 340 paroxysmal AF patients.³⁹

In our striving to optimize PVI results there is growing interest in increasing the ablation power (high-power, short-duration applications) in order to further decrease the procedure time while maintaining/increasing safety. Given that the lesion depth is similar at a specific *ablation index* value (irrespective of the power) using a higher ablation power (45-50 W) is expected to be feasible. The POWER-AF trial was designed to investigate the efficacy and safety of the 'CLOSE' protocol while using 45 W applications.

Even when point-by-point ablation is meticulously performed according to the strict established criteria, the 'CLOSE' protocol is still not able to ensure durable PV isolation in 100% of cases. Indeed,

at repeat ablation due to arrhythmia recurrence, we found that 38% of patients still had at least one reconnected vein. This could be due to variables that are not taken into account, such as the tissue thickness or tissue composition. A patient-tailored strategy with adapted ablation characteristics based on pre- or intra-procedural imaging (e.g. with computed tomography or intra-cardiac echo) as well as intra-procedural lesion verification (e.g. with magnetic resonance imaging) might be the next step to improve CLOSE-PVI results.

After optimized index-PVI, even the majority of patients with clinical AF recurrence now present with four isolated pulmonary veins (PVs) during a repeat invasive procedure. On one hand this is the signature of our improvement in achieving durable, effective PVI. On the other hand, this poses several issues. Whereas in the past, repeat ablation for paroxysmal AF generally was straightforward, consisted of closing one or more gaps, had a favorable clinical result and had a shorter, predictable procedure duration. Now, in case of four isolated veins, the preferred ablation strategy is unknown (unless there is an overt non-PV trigger during the procedure), the outcome is worse irrespective of which ablation strategy is chosen, and the procedure time is highly variable (with practical planning issues). Therefore knowing prior to a repeat invasive procedure which patients have a status of four isolated veins is much desired and might – at this time – even lead to deferment of a repeat invasive procedure until all conservative treatment options have been exhausted. Unfortunately there are no distinct non-invasive characteristics that predict the likelihood of finding four isolated veins after AF recurrence. A randomized trial comparing a strategy of detailed invasive evaluation of the atrial substrate (such as high-density voltage mapping, localization/documentation of non-PV atrial extrasystole, ...) during index-PVI vs. index-PVI without these invasive diagnostics would therefore be of interest.

In PART IC we applied the same principles of the ‘CLOSE’ protocol to left atrial linear ablation, and demonstrated that this ablation strategy is also effective at the roof. The applicability of this ablation strategy could therefore be expanded to linear ablation in order to treat macro-reentrant atrial tachycardia or to isolate arrhythmogenic atrial areas. Only at the posterior mitral isthmus this ablation strategy proved unsuccessful, due to its specific anatomical configuration often necessitating epicardial ablation in order to achieve block. Other strategies, such as a combination with alcoholization of the Vein of Marshall, might increase our success in achieving mitral isthmus block.

In PART ID we investigated a new mapping technique with a high yield of online detection of potential bi-atrial drivers in persistent AF. These potential AF drivers can be automatically analyzed and annotated on a 3D-geometric bi-atrial shell, allowing patient-tailored substrate ablation. However the effect of ablation of was not investigated in our study and further studies are needed to investigate if ablation of these *repetitive atrial activation sequences* would indeed improve clinical outcome.

In PART II we aimed to contribute to the improvement of catheter ablation of ventricular tachycardia (VT) in ischemic heart disease. Our research was the first to publish long-term outcomes of single and multiple ablation procedures targeting modification of the arrhythmogenic substrate (in casu elimination of all *local abnormal ventricular activities* (LAVA)). This technique resulted in a substantial reduction of VT storm, VT burden and need for ICD shocks. Outcomes were improved by implementation of modern mapping technologies such as multi-electrode mapping and integration of pre-procedural imaging. However, the recurrence of previously ablated *LAVA* advocates the importance of effective and durable radiofrequency lesions. Therefore, in order to improve outcomes of VT ablation, further research should aim to develop criteria and/or tools for effective radiofrequency lesion creation in the ventricle. Secondly, while elimination of all *LAVA* was associated with a better outcome, many *LAVA* might be innocent bystanders and are not involved in channels responsible for current or future clinical VTs. Identification of potential VT channels on imaging studies (computed tomography or magnetic resonance imaging) might significantly reduce the amount of radiofrequency delivery, procedures times, avoid unnecessary myocardial destruction and improve arrhythmia-free survival.

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A

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CURRICULUM VITAE

LIST OF PUBLICATIONS

CURRICULUM VITAE

Michael Wolf was born on January 13th 1983 in Lier (Antwerp, Belgium). He obtained his high school diploma at Onze-Lieve-Vrouw-van-Lourdescollege Edegem in 2001. He became Doctor in Medicine summa cum laude at the University of Antwerp in 2008. After cardiology fellowships in ZNA Middelheim and the Antwerp University Hospital, he became a certified cardiologist in 2014. Thereafter, he undertook additional fellowship training in interventional cardiac electrophysiology with professor Mattias Duytschaever in AZ Sint-Jan Bruges (2014–2016) and a fellowship in advanced electrophysiology and ablation of complex arrhythmias with professor Michel Haïssaguerre at Hôpital Cardiologique du Haut-Lévêque – CHU de Bordeaux (2016–2017). During these fellowships, he obtained full accreditation by the European Heart Rhythm Association in interventional electrophysiology and cardiac device therapy (pacing, ICDs and cardiac resynchronization). In addition, he has obtained certification in sports medicine, diving medicine and intensive care medicine. In 2018, he graduated with the first batch of the DASCAM programme (the Diploma of Advanced Studies in Cardiac Arrhythmia Management), at Maastricht University and the European Heart Academy (European Society of Cardiology). As from June 2018, he joined the staff of the Hartcentrum ZNA in Antwerp as a full-time cardiologist-electrophysiologist.

Michael's particular clinical and research interests in the treatment of complex cardiac arrhythmias, such as atrial fibrillation, atrial tachycardia and ventricular tachycardia have resulted in over 50 publications in both national and international peer-reviewed scientific journals, contribution to a book chapter, and several presentations at national and international congresses. In 2016 and 2017, he received the award for best poster presentation at the annual Belgian Heart Rhythm Meeting, and in 2018 the Young EP Best Clinical Case award at the European Heart Rhythm Association congress.

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54. Takigawa M, Derval N, Martin CA, Vlachos K, Denis A, Nakatani Y, Kitamura T, Cheniti G, Bourrier F, Lam A, Martin R, Frontera A, Thompson N, Massoulié G, **Wolf Michael**, Escande W, André C, Zeng LJ, Roux JR, Duchateau J, Pambrun T, Sacher F, Cochet H, Hocini M, Haïssaguerre M, Jaïs P. Mechanism of Recurrence of Atrial Tachycardia: Comparison Between First Versus Redo Procedures in a High-Resolution Mapping System. *Circulation: Arrhythmia & Electrophysiology*; 2020; 13(1): e007273.

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57. Takigawa M, Vlachos K, Martin C, Bourier F, Denis A, Kitamura T, Cheniti G, Lam A, Martin R, Frontera A, Thompson N, Massoulié G, **Wolf Michael**, Escande W, André C, Zeng L, Nakatani Y, Nakashima T, Ramirez D, Duchateau J, Pambrun T, Sacher F, Cochet H, Hocini M, Haïssaguerre M, Jaïs P, Derval, N. Does epicardial Marshall Vein Ethanol infusion add benefit over conventional endocardial radiofrequency ablation in perimitral flutter? (*submitted*)

ORAL PRESENTATIONS AT NATIONAL AND INTERNATIONAL CONFERENCES

1. The evolution of hypertension treatment in Belgium. *2011 scientific meeting of the Belgian Hypertension Committee*, Liège (8/10/2011)
2. PCI and atrial fibrillation: combination antithrombotic treatment in practice. *Cardiology seminar update atrial fibrillation*, Antwerp University Hospital (9/10/2012)
3. Paroxysmal AF ablation: Substrate for PV reconnection. *State of the art in electrical management of cardiac diseases - Alliance Program*, Bordeaux (7–8/3/2017)
4. Comparison of procedural endpoints for ablation of post-myocardial infarction ventricular tachycardia. *EHRA Europace – Cardioslim 2017*, Vienna (18–22/6/2017)
5. Challenges with post-ablation flutter. *17th Atrial Fibrillation Symposium – 10th Practical Session*, Prague (7–9/2/2018)
6. Vein-of-Marshall mediated complex atrial tachycardia. *EHRA congress*, Barcelona (18–20/3/2018) (**Young EP Best Clinical Case award**)

ABSTRACTS AT NATIONAL AND INTERNATIONAL CONGRESSES

1. **Wolf Michael**, et al. Unexpected autoimmune response caused by Castleman's disease in a patient with spondylarthropathy. *14th Belgian Congress on Rheumatology*, Luxembourg (22–24/9/2010)
2. **Wolf Michael**, et al. The evolution of hypertension treatment in Belgium. *EuroDURG (European Drug Utilization Research Group): joint educational course and scientific meeting*, Antwerp (30/11–3/12/2011)
3. **Wolf Michael**, et al. Percutaneous left atrial appendage closure with Amplatzer cardiac plug for stroke prevention in atrial fibrillation patients with contraindication for oral anticoagulation: feasibility, safety and initial results. *Belgian Society of Cardiology: 31st Annual Scientific Meeting*, Brussels (2–3/2/2012)
4. **Wolf Michael**, et al. Superior efficacy of pulmonary vein isolation with online contact force measurement persists after the learning period: a prospective case control study. *EHRA Europace – Cardioslim congress 2015*, Milan (21–24/6/2015); *ESC congress 2015*, London (29/8–2/9/2015)
5. **Wolf Michael**, et al. Incidence of "First Pass" Block after 'CLOSE' guided Linear Ablation at the Roof and Mitral Isthmus. *Heart Rhythm, 37th annual scientific sessions*, San Francisco (4–7/5/2016); *10th Belgian Heart Rhythm Meeting*, Brussels (6–7/10/2016) (**moderated poster – Best Poster award**)
6. **Wolf Michael**, et al. Management of Electrical Storm in Idiopathic Ventricular Fibrillation. *8th Euro VT/VF Meeting 2016*, Berlin (2–3/12/2016)
7. Coeman M, et al. Time Course of Changes in Unipolar and Bipolar Electrogram Amplitude and Morphology during Contact Force-guided Pulmonary Vein Isolation. *Heart Rhythm, 38th annual scientific sessions*, Chicago (10–13/5/2017)
8. Kitamura T, et al. Validation of body surface mapping of atrial tachycardia by novel high-density mapping. *Heart Rhythm, 38th annual scientific sessions*, Chicago (10–13/5/2017)
9. Haïssaguerre M, et al. Characterization of drivers maintaining ventricular fibrillation in early repolarization syndrome. *Heart Rhythm, 38th annual scientific sessions*, Chicago (10–13/5/2017)
10. Haïssaguerre M, et al. Subclinical arrhythmogenic substrate as a cause of unexplained cardiac death. *Heart Rhythm, 38th annual scientific sessions*, Chicago (10–13/5/2017)
11. Derval N, et al. Anatomical and electrophysiological characteristics of complex atrial tachycardia: insight from high-resolution mapping. *Heart Rhythm, 38th annual scientific sessions*, Chicago (10–13/5/2017)
12. Martin R, et al. High-density mapping of conduction barriers in ventricular tachycardia. *Heart Rhythm, 38th annual scientific sessions*, Chicago (10–13/5/2017)

13. Martin R, et al. Surface ECG confirmation of isthmus block in Tetralogy of Fallot VT ablation. *Heart Rhythm*, 38th annual scientific sessions, Chicago (10–13/5/2017)
14. Denis A, et al. High density mapping of atrial reentrant tachycardia in patients without previous AF catheter ablation or cardiac surgery. *Heart Rhythm*, 38th annual scientific sessions, Chicago (10–13/5/2017)
15. Cheniti G, et al. The right ventricle underlies failed electrical cardioversion in human VF. *Heart Rhythm*, 38th annual scientific sessions, Chicago (10–13/5/2017)
16. Cheniti G, et al. Spontaneous termination of induced ventricular fibrillation: dominant role of left ventricular drivers. *Heart Rhythm*, 38th annual scientific sessions, Chicago (10–13/5/2017)
17. Frontera A, et al. Relationship between scar and atrial tachycardia mechanisms: insight from registered magnetic resonance and ultra-high density mapping system. *Heart Rhythm*, 38th annual scientific sessions, Chicago (10–13/5/2017)
18. Frontera A, et al. EGM fractionation in apparently healthy tissue: time to redefine the voltage threshold for diseased atrium? *Heart Rhythm*, 38th annual scientific sessions, Chicago (10–13/5/2017)
19. Massoulié G, et al. High concentration of sodium-bicarbonate as treatment for ventricular fibrillation storm related to Brugada syndrome. *Heart Rhythm*, 38th annual scientific sessions, Chicago (10–13/5/2017)
20. Fedida J, et al. Efficacy of advanced pace mapping technology for idiopathic PVC ablation. *EHRA Europace – Cardioslim 2017*, Vienna (18–22/6/2017)
21. **Wolf Michael**, et al. Pattern and timing of coronary sinus activation in complex atrial tachycardia. *EHRA Europace – Cardioslim 2017*, Vienna (18–22/6/2017)
22. Frontera A, et al. Characterization of slow conduction areas in scar-related atrial tachycardia. Insights from high-density mapping system. *EHRA Europace – Cardioslim 2017*, Vienna (18–22/6/2017)
23. Frontera A, et al. Relationship of voltage and EGM duration at sites of fractionation during atrial tachycardias and paced rhythms. *EHRA Europace – Cardioslim 2017*, Vienna (18–22/6/2017)
24. Takigawa M, et al. Precise circuit of dual-loop reentry and the characteristics of common isthmus in post AF ablation left atrial tachycardia. *EHRA Europace – Cardioslim 2017*, Vienna (18–22/6/2017)
25. **Wolf Michael**, et al. Long-term Outcome of LAVA Elimination in Ablation of Post-Myocardial Infarction Ventricular Tachycardia. *Heart Rhythm*, 38th annual scientific sessions, Chicago (10–13/05/2016); *EHRA Europace – Cardioslim 2017*, Vienna (18–22/06/2017) (**moderated poster**); *11th Belgian Heart Rhythm Meeting*, Brussels (5–6/10/2017) (**moderated poster – Best Poster award**)
26. Duytschaever M, et al. Paroxysmal AF burden measured by continuous monitoring before and after ‘CLOSE-guided’ PV isolation: preliminary results from the prospective patient-controlled CLOSE-TO-CURE study. *Heart Rhythm*, 39th annual scientific sessions, Boston (9–12/5/2018)
27. Martin C, et al. Multi-center study of ultra-high density activation mapping to aid isthmus identification of atrial tachycardias in congenital heart disease. *Heart Rhythm*, 39th annual scientific sessions, Boston (9–12/5/2018)
28. Lam A, et al. Are recurrences of post-myocardial infarction ventricular tachycardia due to substrate progression or insufficient index ablation? A 4 years follow-up study. *Heart Rhythm*, 39th annual scientific sessions, Boston (9–12/5/2018); *EHRA – Europace*, Barcelona (18–20/3/2018)
29. Kitamura T, et al. Does ventricular tachycardia ablation reduce ventricular fibrillation incidence? *Heart Rhythm*, 39th annual scientific sessions, Boston (9–12/5/2018)
30. Cheniti G, et al. Fat deposition in patients with post-myocardial infarction ventricular tachycardia has distinctive electrophysiological characteristics. *Heart Rhythm*, 39th annual scientific sessions, Boston (9–12/5/2018)
31. De Pooter J, et al. Predictors of long-term outcome in a large group of patients undergoing a first repeat ablation consisting solely of re-isolation of reconnected pulmonary veins. *12th Belgian Heart Rhythm Meeting*, Brussels (4–5/10/2018)
32. De Greef Y, et al. Influence of pulmonary vein isolation on autonomic function in patients with paroxysmal atrial fibrillation. *12th Belgian Heart Rhythm Meeting*, Brussels (4–5/10/2018)

33. Strisciuglio T, et al. Clinical, echocardiographic and electro-anatomical determinants of the duration of paroxysmal AF episodes. *12th Belgian Heart Rhythm Meeting*, Brussels (4–5/10/2018)
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