Aus dem Universitären Herzzentrum Lübeck
Medizinische Klinik II (Kardiologie, Angiologie, Intensivmedizin)
Sektion Elektrophysiologie
Universität zu Lübeck, Deutschland
Sektionsleiter: Prof. Dr. med. univ. Roland Richard Tilz

Second-generation visually guided laser balloon ablation system for pulmonary vein isolation: Learning curve, safety and efficacy

Inauguraldissertation
zur Erlangung der Doktorwürde der Universität zu Lübeck
– aus der Sektion Medizin –
vorgelegt von
Huong Lan Phan
geboren in Hanoi, Vietnam

Lübeck, 2020.

1. Berichterstatter:	Priv.-Doz. Dr. med. Christian Hendrik Heeger
2. Berichterstatter:	Priv.-Doz. Dr. med. Doreen Richardt
Tag der mündlichen Prüfung:	4. Januar 2021.

zum Druck genehmigt. Lübeck, den 4. Januar 2021.

- Promotionskomission der Sektion Medizin -

Zusammenfassung

Pulmonalvenenisolation mittels der zweiten Generation des Laserballon-Ablationssystems: Lernkurve, Sicherheit und Effektivität

Hintergrund:

Vorhofflimmern (VHF) ist die häufigste Herzrhythmusstörung weltweit, und ist mit einer deutlich erhöhten Morbidität und Mortalität assoziiert.[1, 2] Die Pulmonalvenenisolation (PVI) mit Radiofrequenzenergie (RF, oder Hochfrequenzstrom) ist der Goldstandard der katheterinterventionellen Behandlung von VHF. Diese Methode ist breit etabliert, mit guter Effektivität und Sicherheit, trotzdem handelt es sich hierbei um eine technisch komplexe Prozedur, die mit einer langen Lernkurve verbunden ist.[3-5]

Folgend kam es zur Entwicklung von ballonbasierten Kathetersystemen zur Durchführung der PVI, um diese Limitation möglicherweise zu lösen. Der Cryoballon (CB) wird heute am häufigsten als Alternative zur RF-Ablation eingesetzt. Das CB-System ist eine sichere Technologie mit vergleichbarer Effektivität, jedoch mit einer deutlich kürzeren Lernkurve.[3, 6-8]

Die zweite Generation des Laserballon-Ablationssystems (LB2, *HeartLight® Excalibur Balloon; CardioFocus Inc., Marlborough, USA*) ist eine der neuesten Entwicklungen in der Kathetertechnologie für die PVI. Der LB2 bietet die Möglichkeit einer VHF-Ablation mittels Laserenergie an, und weist gegenüber dem Laserballonkatheter (LB) der ersten Generation einen verbesserten Gewebekontakt und eine detailliertere Visualisierung auf. [9-11]

Der LB2-Katheter enthält ein integriertes Endoskop, und einen Lasergenerator innerhalb eines ultraflexiblen Ballons. Diese Eigenschaften ermöglichen es dem Untersucher eine endoskopisch gesteuerte Ablation mittels individuell titrierbaren Energieapplikationen durchzuführen.[9, 12]

Methoden und Ergebnisse:

Das Hauptziel der Dissertation ist, über die ersten Erfahrungen mit dem LB2 insbesondere bezüglich der Lernkurve, Effektivität und Sicherheit zu berichten. Insgesamt wurden 45 konsekutive Patienten mit symptomatischem VHF (89% der Patienten mit persistierendem VHF) zwischen April 2018 und Juni 2019 prospektiv eingeschlossen (MERLIN Register). Die Patienten wurden nach Reihenfolge des Einschlusses auf drei Gruppen (Gruppe T1, T2 und T3) mit jeweils 15 Patienten pro Gruppe eingeteilt.[13]

Alle Patienten erhielten eine PVI mittels des LB2 im Universitären Herzzentrum Lübeck. Die Prozeduren wurden durch zwei Untersuchern durchgeführt, die viel Erfahrung mit RF-basierten und CB-Ablationen besitzen, jedoch noch nie eine LB-Ablation vor Beginn unserer Studie durchgeführt hatten.[13]

Insgesamt wurden 175 von 177 (98%) Pulmonalvenen von 45 Patienten mittels des LB2 erfolgreich isoliert. Es konnten alle (100%**)** anatomischen Varianten der Pulmonalvenen: fünf Patienten mit einem gemeinsamen Ostium der linken Pulmonalvenen (LCPV) und zwei Patienten mit einer rechten mittleren Pulmonalvene (RMPV), erfolgreich abladiert werden.[13]

Die mediane Prozedurzeit konnte nach jeweils 15 Patienten von 132 (114, 158)* Minuten auf 119 (102, 127)* Minuten und 91 (86, 105)* Minuten (in Gruppe T1, T2 und T3) signifikant reduziert werden ($p = 0.0009$). Weiterhin konnte eine signifikante Reduktion der linksatrialen Verweildauer und Fluoroskopiezeit zwischen den Gruppen T1, T2 und T3 gezeigt werden. Die Prozedurzeiten waren mit den in randomisierten Studien beschriebenen Prozedurzeiten bei RF- und CB-basierten Ablationen vergleichbar. Die dargestellten Ergebnisse rechtfertigen die Aussage, dass der LB2 auch für Erstanwender eine technisch schnell erlernbare PVI ermöglicht. [7, 9, 13]

Periprozeduralen Komplikationen traten nur bei einer relativ geringeren Anzahl (6.7%) von den Patienten auf. Es konnte nachgewiesen werden, dass die Häufigkeit von Komplikationen mit zunehmendem Erfahrungsgrad abnahm.[13]

Schlussfolgerung

Zielsetzung der vorliegenden Arbeit war es über die ersten klinischen Erfahrungen mit dem LB2 zu berichten. Zusammenfassend lässt sich sagen, dass der LB2 eine effektive und sichere neue Methode für die PVI ist. Bereits nach 15 Prozeduren ließ sich eine relativ kurze Lernkurve bei signifikant kürzeren Prozedur-, Linksatrialen- und Fluoroskopiezeiten erkennen.[13]

***** Median (25% und 75% Perzentil)

Abkürzungen:

CB	Cryoballon, Kälteballon
LB	Laserballon
LB2	2. Generations-Laserballon
LCPV	gemeinsames Ostium der linken Pulmonalvenen
PVI	Pulmonalvenenisolation
RMPV	rechte mittlere Pulmonalvene
RF	Radiofrequenz, Hochfrequenzstrom
VHF	Vorhofflimmern

Table of Contents

Abbreviations

ABC	Atrial fibrillation Better Care (A: anticoagulation, B: better symptom control and C: cardiovascular risk factor management)
ACT	activated clotting time
AF	atrial fibrillation
AVN	atrioventricular node
CAD	coronary artery disease
CB	cryoballoon
CB1	first generation cryoballoon
CB2	second generation cryoballoon
CHA_2DS_2-VASc	Congestive heart failure, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female).
CRT	cardiac resynchronization therapy
DC	direct-current
ECG	electrogram
EP	electrophysiology, electrophysiological
EACTS	European Association for Cardio-Thoracic Surgery
EHRA	European Heart Rhythm Association
ESC	European Society of Cardiology
F	French
FAVI	first attempt vein isolated,
FAAVI	first attempt all veins isolated
FDA	U.S. Food and Drug Administration
HIFU	high intensity focused ultrasound
HFrEF	heart failure with reduced ejection fraction
HR	heart rate

ICD	implantable cardioverter defibrillator
LA	left atrium, left atrial
LB	laser balloon
LB1	first generation laser balloon
LB2	second generation laser balloon
LB3	third generation laser balloon
LCPV	left common pulmonary vein
LICU	low intensity collimated ultrasound
LIPV	left inferior pulmonary vein
LSPV	left superior pulmonary vein
LVEF	left ventricular ejection fraction
min	minute(s)
NOACs	novel oral anticoagulants
OAC	oral anticoagulation
PV	pulmonary vein
PVI	pulmonary vein isolation
RF	radiofrequency
RIPV	right inferior pulmonary vein
RMPV	right middle pulmonary vein
RSPV	right superior pulmonary vein
TIA	transient ischemic attack
TEE	transesophageal echocardiography
VGLB	visually guided laser balloon
VKA	vitamin K antagonist
vs.	versus
3D	three-dimensional

1. Introduction

1.1. Epidemiology of atrial fibrillation

Atrial fibrillation (AF) is the most common clinically significant arrhythmia, which is associated with a higher morbidity and mortality risk, and one of the main causes of stroke, heart failure and sudden cardiac death.[1, 2] AF is independently associated with a two-fold increased risk of all-cause mortality in women and a 1.5-fold increase in men.[14]

Contemporary data shows that 20–30% ischemic strokes are associated with AF, and mortality caused by AF can be significantly reduced by initiation of anticoagulation.[15, 16] Other cardiovascular mortality causes associated with AF, such as heart failure and sudden cardiac death, still stay common despite evidence based treatment.[14, 17]

The estimated number of patients with AF in the global population was 33.5 million based on the Global Burden of Disease study from 2010 (20.9 million men and 12.6 million women). There is evidence for a progressive increase of prevalence over the last decades.[18] Estimations predict that one out of four people in Europe will develop AF by the age of 55 years, with an even higher prevalence in the older population. AF occurs more frequently in men, with a male to female ratio of 1.2:1. The incidence of AF in Europe ranges between 0.21 and 0.41 per 1000 person/years.[19, 20]

AF is more common in patients with other comorbidities, such as arterial hypertension, heart failure, coronary artery disease (CAD), valvular heart disease, obesity, diabetes mellitus, or chronic kidney disease.[19, 21, 22] Screening and treatment of these comorbidities, especially cardiovascular risk factors, is a very important part of integrated management of patients with AF, and can facilitate to maintain sinus rhythm in patients undergoing rhythm control therapy.[23, 24]

The progressively increasing number of patients diagnosed with AF can probably be traced back to ageing of the population, simultaneously higher prevalence of other conditions predisposing to AF, as well as more frequent detection of silent AF. A further increase of patients with AF has been predicted, so that effective treatment of AF is foreseen to become an even more important clinical and economical issue in the near future.[1, 23-27]

1.2. Pathophysiology of atrial fibrillation

Genetic predisposition

Evidence shows an increased familial predisposition of AF, which is independent from concomitant cardiovascular conditions, that suggests a genetic factor in presentation of lone AF, especially in patients diagnosed at a young age.[26, 27] Up to one-third of AF patients carry common genetic variants associated with a predisposition of AF. At least 24 of these common gene variants, often single nucleotide polymorphisms, are known to increase the risk of AF.[28, 29] Further genomic analysis could open up individualized treatment planning options and targeted population screening in the future, though the present guidelines do not recommend a routine genetic testing of AF patients.[25, 28, 29]

Atrial remodelling

Multiple external factors, such as hypertension, diabetes mellitus, obesity, heart failure and structural heart disease, but even AF itself cause a process of structural remodelling in the atria. Major mechanisms causing atrial remodelling are stretch-induced atrial fibrosis, hypocontractility, fatty infiltration, inflammation, amyloid disposition, endothelial and microvascular remodelling, ischaemia, ion channel dysfunction and calcium-handling instability. These progressive tissue alterations cause changes in the electrical conduction of the atria and enhance both ectopy and conduction disturbances, increasing the propensity of the atria to develop or cause progression of AF.[25, 30, 31]

Structural remodelling induces electrical dissociation between muscle fibers and local conduction heterogeneities, causing re-entry and maintaining electrical mechanisms of AF. [30-33] These processes also generate a prothrombotic state, as atrial myocardial damage, expression of thrombogenic factors, as well as activation of platelets and inflammatory cells contribute to a systemic activation of the coagulation cascade.[32-34]

These complex cascades of atrial structural remodelling have a progressive nature and often occur before the onset of AF due to genetic and cardiovascular factors, while presence of AF propagates and maintains these intracellular and extracellular changes, causing a vicious circle to maintain the arrhythmia. As some stages of this remodelling e.g. atrial fibrosis and conduction abnormalities are irreversible, early initiation of treatment seems desirable.[34, 35]

1.3. Classification of atrial fibrillation

Based on the temporal pattern of AF episodes, AF can be classified as first diagnosed, paroxysmal, persistent, long-standing persistent and permanent. Approximately 50% of patients show permanent, 25% persistent and 25% paroxysmal AF. This traditional classification is commonly used, but it unfortunately does not adequately represent the clinical severity of AF, as there are multiple other factors that influence the course of management.[1, 19, 35]

A new classification scheme addressing the assessment of the severity of AF was proposed in the current ESC guidelines in 2020. The guidelines suggest the 4-S-AF scheme for a structured clinical characterization of AF, which promotes four main domains: the evaluation of **s**troke risk, **s**ymptom severity (using the European Heart Rhythm Association (EHRA) classification), **s**everity of AF burden and **s**ubstrate severity.[1, 19]

1.4. Integrated management of atrial fibrillation

The latest guidelines for management of AF were published in 2020 by the European Society of Cardiology (ESC) and were developed with the special contribution of the EHRA of the ESC in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). The guidelines propose the Atrial Fibrillation Better Care (ABC) pathway, which considers three main domains for an integrated assessment of patients presenting with AF.[1]

Implementation of the ABC pathway has been shown to significantly reduce all-cause mortality and the composite outcome of stroke, major bleeding, cardiovascular death and first hospitalization compared to usual care in the prospective randomized mAFA-II trial. It simplifies the previous five step approach from the previous guidelines from 2016 (***Figure 1)*** for better adherence in the clinical practice.[1, 36-38]

The promoted domains of the ABC pathway are:

A. **A**nticoagulation/**A**void stroke;
B. **B**etter symptom management;
C. **C**ardiovascular and Comorbidity optimization.[1, 37, 38]

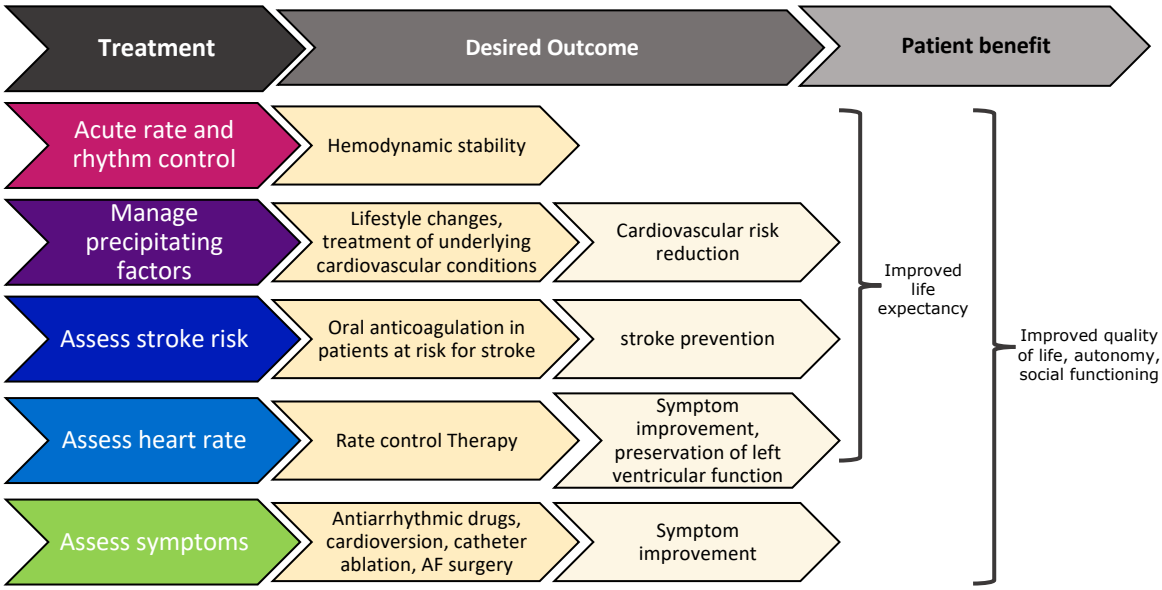

Figure 1. Acute and chronic management of atrial fibrillation patients, desired cardiovascular outcomes and patient benefits.

Adapted from the report on the 4th AFNET/EHRA consensus conference.[39] *(Figure cited from the 2016 ESC AF guidelines from of Kirchhof et al. modified by the author, H. L. Phan. © ESC 2020. All rights reserved.)* [1, 25, 39]

1.5. Stroke prevention therapy

The firs domain of the ABC pathway (A for anticoagulation) promotes the importance of stroke prevention therapy. Contemporary data shows that 20–30% ischemic strokes are associated with AF. Mortality caused by ischemic stroke can be effectively avoided by initiation of oral anticoagulation (OAC) based on the patient´s thromboembolic risk.[15, 16]

Vitamin K antagonists (VKAs) have been proven to be superior to no treatment or with a significant reduction of stroke risk by two-thirds and a mortality reduction by one-quarter. Although, there are known limitations to the use of VKAs, such as the need for frequent monitoring and dose adjustments, as well as potential food and drug interactions.[15, 16, 40]

To address these limitations, a new class of anticoagulant drugs, known as non-VKA oral anticoagulants or novel oral anticoagulants (NOACs) have been developed. There are currently four types of NOACs available: rivaroxaban, apixaban, dabigatran and edoxaban. Dabigatran works as a direct thrombin inhibitor; meanwhile apixaban, edoxaban, and rivaroxaban are factor X_a inhibitors.[40, 41]

They have been shown to have a favorable risk-benefit profile, with significant reductions in the incidence of strokes, intracranial hemorrhage and mortality, but with a slightly increased complication rate of gastrointestinal bleedings compared to VKAs. Multiple randomized trials have shown the efficacy and safety of NOACs across a wide range of patients.[40, 41]

The ESC guidelines suggest, that when OAC is initiated in a patient with AF who can be considered for a NOAC, a NOAC is recommended in preference to a VKA. AF patients already on treatment with a VKA should be considered for NOAC therapy if the therapeutic range is not well controlled, or in case of patient preference (without any contraindications).[1, 40, 41]

The ESC guidelines promote the use of the CHA_2DS_2-VASc score (demonstrated in ***Table 1***) to evaluate the risk of thromboembolic events in every patient with the diagnosis of AF. In general, patients without clinical stroke risk factors do not need antithrombotic therapy, while patients with risk factors (i.e. CHA_2DS_2-VASc score of 1 or more for men, and 2 or more for women) are likely to benefit from OAC therapy.[1, 40, 41]

By the time of initiation of OAC therapy in patients with AF, it is recommended that risk for bleeding is simultaneously evaluated as well. The most commonly used bleeding risk score in the clinical practice is the HAS-BLED score, which was initially developed for VKAs (getting one point each for hypertension, abnormal renal or liver function, stroke, history or predisposition for bleeding, labile INR, elderly – age ≥ 65 years or a known history of drug or alcohol abuse).[1]

CHA_2DS_2-VASc risk factor	Points
Congestive heart failure Signs/symptoms of heart failure or objective evidence of reduced left ventricular ejection fraction	+1
Hypertension Resting blood pressure >140/90 mmHg on at least two occasions or current antihypertensive treatment	+1
Age 75 years or older	+2
Diabetes mellitus Fasting glucose >125 mg/dl (7 mmol/l) or treatment with oral hypoglycemic agent and/or insulin	+1
Previous stroke, transient ischemic attack or thromboembolism	+2
Vascular disease Previous myocardial infarction, peripheral artery disease or aortic plaque	+1
Age 65–74 years	+1
Sex category (female)	+1

CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female).

Table 1. Clinical risk factors for stroke, transient ischemic attack (TIA) and systemic embolism in the CHA_2DS_2-VASc score.

(Table cited and modified from the 2020 ESC guidelines for the management of AF from Hindricks et al. modified by H. L. Phan. © ESC 2020. All rights reserved).[1]

1.6. Rate control therapy

Pharmacological rate control therapy

Domain B of the ABC pathway promotes symptom management for AF patients. Symptomatic AF patients mostly require heart rate (HR) control therapy in the first line. It is a key part of integrated management of AF and is often efficient to improve AF-related symptoms. Pharmacological rate control can be achieved using beta-blockers, digoxin or digitoxin, non-dihydropyridine calcium channel blockers (diltiazem and verapamil), or if necessary, a combination therapy of these agents. [1, 42]

Beta-blockers and calcium channel blockers should be preferred over digitalis (digitoxin or digoxin) in case of acute newly onset AF, because of their quick action and higher efficacy.[1, 43, 44] It should be taken into consideration that in patients with heart failure with a reduced left ventricular ejection fraction (LVEF) - or HFrEF - beta-blockers, digitalis or their combination should be preferred over diltiazem and verapamil, as they can have negative inotropic effects in patients with an LVEF under 40%.[45, 46]

Many of the antiarrhythmic drugs (amiodarone, dronedarone, sotalol and to some extent propafenone) also have HR reducing features, but they should only be administrated, when rhythm control is pursued. Intravenous amiodarone is an option in critical patients with hemodynamic instability or severely reduced LVEF. If this is not sufficient to achieve hemodynamic stability, urgent synchronized direct-current (DC) cardioversion should be considered.[1]

There is no clear evidence about what the optimal target HR should be. Randomized controlled trials that compared different rate control regimes (targeted resting HR under 80 versus 100 to 110 beat per minute) did not show beneficial effects of a strict against a lenient rate control strategy in influencing clinical outcome, severity of symptoms or quality of life. Accordingly, a lenient rate control should be targeted as an initial approach, unless symptoms call for stricter rate control. Patients, who are still severely symptomatic despite proper rate control, should be considered for further management, including rhythm control therapy.[47-49]

Atrioventricular node ablation and pacing

The “pace and ablate” strategy may be considered as an *ultima ratio* for patients when drug therapy cannot achieve rate and symptom control. This therapy option includes ablation of the atrioventricular node (AVN) or His bundle, following a previous implantation of a cardiac pacemaker. It is a relatively simple and safe procedure with low complication rates and low long-term mortality risk, and it can successfully enhance quality of life and reduce symptoms. Nonetheless, patients stay pacemaker-dependent for the rest of their lives after this procedure, that is why it should only be considered, if all other ways of rate and/or rhythm control methods fail.[50, 51]

The choice of pacing therapy between right ventricular versus (vs.) biventricular pacing with or without an implantable cardioverter defibrillator (ICD) function should be considered based on individual patient characteristics, including LVEF and the patient´s choice.[52, 53]

Despite the lack of large randomized controlled trials, experts are in favor of biventricular pacing (cardiac resynchronization therapy (CRT)) in patients with AF and HFrEF and the same indications for CRT, as for patients in sinus rhythm, provided that AVN ablation is added to enhance biventricular capture rate. For patients who already have an implanted CRT-system, AVN ablation may be performed to enhance symptoms of heart failure through enhancing biventricular pacing rate.[52, 54]

1.7. Rhythm control therapy

Rate control versus rhythm control therapy

Restoration of sinus rhythm is an integral part of AF management. Many individual factors should be considered, when a decision for rhythm control therapy is made. Alternative ways to achieve acute and long-term rhythm control are antiarrhythmic therapy, synchronized DC cardioversion and catheter ablation – or the combination of these strategies. Although many physicians believe that rhythm control therapy can improve outcome in AF patients, all trials that have compared rhythm control vs. rate control alone have not been able to show a clear benefit in outcome.[1]

Meta-analysis of randomized prospective studies (the AFFIRM[55], RACE[56], STAF[57], PIAF[58] and the HOT CAFE[59] trial) showed that AF is associated with a negative impact on quality of life that can be significantly improved through both rate and rhythm-control strategies.[60] Comparing management strategies of AF, these trials demonstrate no significant difference between a rate vs. rhythm control strategy regarding all-cause mortality.[60, 61] Recent data of the ORBIT-AF registry has shown similar results.[62]

All trials included patients with persistent AF or AF that was considered likely to be recurrent. However, it must be emphasized, that this data could be compromised by various methodologic weaknesses: different quality of life measurement methods, as well as different rate and rhythm control intervention strategies. The greatest difference is due to the variety of possible rhythm control methods. Antiarrhythmic drug therapy, synchronized DC cardioversion (with or without antiarrhythmic therapy) or catheter ablation strategies are all possible strategies, and they are very different in effectivity, complication rates and side effects. All in all, more randomized controlled trials are needed in the future to compare these different rhythm control strategies.

Pharmacological versus electrical cardioversion

Acute restoration of sinus rhythm can be achieved by synchronized DC electrical cardioversion or by administration of specific antiarrhythmic drug therapy with the goal to achieve conversion to sinus rhythm.[42, 63, 64]

Conversion of AF by oral or intravenous administration of antiarrhythmic drugs is called a pharmacological cardioversion. Many antiarrhythmic drugs, such as amiodarone[65, 66], flecainide[63, 67, 68], propafenone[67, 69], ibutilide[68, 70] or vernakalant[71] have been shown to be effective compared to placebo in conversion of recent onset AF to sinus rhythm without the need for sedation.[64]

In selected patients with symptomatic episodes of paroxysmal AF, oral administration of high-dose flecainide (200–300 mg) or propafenone (450–600 mg) can be self-administered as a '*pill in the pocket'* strategy to restore sinus rhythm. This way of treatment can also be managed in an outpatient setting, it was shown to be effective in over 90% of cases with a low rate of adverse events and a significant reduction of emergency room visits and hospital admissions.[63, 67, 69]

Synchronized direct current electrical cardioversion is a quick and effective method to restore sinus rhythm and is the method of choice in severely hemodynamically compromised patients with newly onset AF.[72] Previous treatment of antiarrhythmic drugs can facilitate the success rate of conversion to sinus rhythm[73].

The RHYTHM-AF international registry compared acute and long-term arrhythmia outcomes of pharmacological and electrical cardioversion. Electrical cardioversion was shown to have a higher success rate and a shorter conversion time than pharmacological cardioversion, especially in persistent AF, but it requires deep sedation. Pharmacological cardioversion is only effective in approximately 70% of patients with recent-onset AF, compared to a success rate of around 90% when an electrical cardioversion is performed. Complication and AF-recurrence rates were similar in both strategies. Amiodarone is the most often administered drug, although class I C antiarrhythmic agents (propafenone, flecainide) seem to be more potent for pharmacological cardioversion than amiodarone. [74-76]

Antiarrhythmic drug therapy

Antiarrhythmic agents are traditionally divided to five main classes, based on the Vaughan Williams classification, that was introduced in 1970 by Miles Vaughan Williams, according to their cellular electrophysiological working mechanisms, summarized in ***Table 2.***[77-80]

The goal of long-term antiarrhythmic drug therapy is reduction of AF-related symptoms, through suppression of arrhythmia burden. Antiarrhythmic agents are moderately effective in maintaining sinus rhythm, with an effectivity around 20-50%. Several class I A (disopyramide, quinidine), class I C (flecainide, propafenone) and class III agents (amiodarone, dronedarone, sotalol) were shown to significantly reduce AF burden, including beta-blockers (e.g. metoprolol). Amiodarone appears to be the most effective in long-term prevention of AF recurrence.[73, 81, 82]

There is a great selection of antiarrhythmic agents with different efficacy-safety profiles, but some of them need monitoring as they might increase adverse events, including pro-arrhythmia. Some of these drugs (e.g. disopyramide, quinidine and sotalol) might even be associated with higher incidence of all-cause mortality, based on results of a meta-analysis.[82]

When antiarrhythmic therapy is initiated, possible adverse drug reactions, and patient preferences should be carefully considered. Generally, safety considerations should primarily be guiding the choice of the antiarrhythmic drug.[73, 81-83]

Dronedarone, flecainide, propafenone or sotalol can only be initiated, if there are no or only minimal signs of structural heart disease, as they increase the risk of ventricular arrhythmia in these patients. In case of coronary artery disease, significant valvular heart disease or significant left ventricular hypertrophy drug therapy options for AF are limited to dronedarone, sotalol or amiodarone. [1, 25, 84, 85]

Amiodarone is recommended in patients with AF and heart failure. Extracardiac toxic effects during long-term amiodarone therapy are common and increase with duration of therapy, so that for this reason, other agents should be considered first if possible.[1, 25, 85, 86]

	Mechanism	**Agents**
Class I A	Sodium and Potassium channel blockers	Quinidine, Ajmaline, Procainamide, Disopyramide
Class I B	Sodium channel blockers (fast association/dissociation)	Lidocaine, Phenytoin, Mexiletine, Tocainide
Class I B	Sodium channel blockers (slow association/dissociation)	Encainide, Flecainide, Propafenone, Moricizine
Class II	Betablockers	Carvedilol, Propranolol, Esmolol, Timolol, Metoprolol, Atenolol, Bisoprolol, Nebivolol
Class III	Potassium channel blockers	Amiodarone (also Class I-II-IV activity), Sotalol (also Betablocker), Ibutilide, Dofetilide, Dronedarone, Vernakalant
Class IV	Calcium channel blockers	Verapamil, Diltiazem
Class V	Unknown mechanism, direct nodal inhibition	Adenosine, Digoxin, Magnesium Sulfate

Table 2. *The Vaughan Williams classification of antiarrhythmic drugs based on their electrophysiological working mechanisms*
(Table cited from Rang et al. modified by H. L. Phan)[79]

Short-term antiarrhythmic drug treatment seems to be desirable to avoid the risk of long-term side effects. Although short-term flecainide therapy after electrical cardioversion has been shown to be less effective compared to long-term treatment, it was still able to prevent most recurrences of AF. Persistent AF recurrence rate is 46% versus 39% under of short versus long-term antiarrhythmic drug treatment after cardioversion.[73]

Recurrence rates after only short-term amiodarone therapy were also significantly higher than in patients with a continuous amiodaron therapy after electric cardioversion (80 % vs. 54 % under short- versus long-term therapy). On the other hand, all-cause mortality and cardiovascular hospitalizations were also higher among patients receiving episodic amiodaron therapy (53% vs. 34%).[87]

1.8. Hybrid rhythm control therapy

Combining antiarrhythmic drugs and catheter ablation

It is common practice to treat patients with antiarrhythmic medication a few months after catheter ablation of AF in the so-called "*blanking period*", since patients often experience recurrent arrhythmias within in the healing phase. To suppress these early recurrence episodes, antiarrhythmic drug therapy is usually recommended for this short period of time to reduce symptoms. The most commonly used agents are flecainide and amiodarone.[88]

There is not much data supporting this practice, though meta-analysis of the available evidence suggests slightly better prevention of AF recurrence in patients undergoing catheter ablation if they are treated with antiarrhythmic drugs.[89] A small randomized controlled trial showed that short-term post-ablation treatment with amiodarone can reduce the early recurrence rate by half compared with placebo.[90]

Combining antiarrhythmic drug therapy and pacemaker therapy

Pacemaker and antiarrhythmic drug therapy as a combination may be relevant in two main clinical scenarios. The first one is in case of selected patients with sick sinus syndrome with intermittent bradycardia and intermittent AF with fast ventricular response (or so called tachy-brady syndrome) requiring rate control therapy. Pacemaker implantation not only optimizes rate control but may also help to achieve rhythm control.[91, 92]

Another indication for this approach may be when antiarrhythmic drug treatment leads to sinus node dysfunction and consecutive bradycardia. In this case pacing therapy may allow higher dosage of the antiarrhythmic drug therapy to prevent AF. These strategies may be chosen in very individual indications and have only been studied in small and highly selected populations.[93]

1.9. Catheter ablation

Triggers in the pulmonary veins (PVs) that provoke paroxysmal AF were first described in 1998 by *Haissaguerre et al.*[94] Since this discovery, electric isolation of the PVs by catheter ablation became the cornerstone of interventional treatment of AF, and is a well-established, effective and safe therapy option for symptomatic, drug refractory AF patients today. Pulmonary vein isolation (PVI) is proven to be more effective compared to antiarrhythmic drug therapy in maintaining sinus rhythm, and the periprocedural complication rates are comparable to the complication rates for antiarrhythmic drug therapy, although still not irrelevant.[1, 95, 96]

Current recommendations based on the ESC guidelines suggest, that PVI should be indicated in patients with symptomatic AF, who are refractory or intolerant to at least one antiarrhythmic medication - especially for paroxysmal AF and may be considered for persistent and long-standing persistent AF. It could also be indicated prior to initiation of an antiarrhythmic drug therapy for paroxysmal AF and may be considered for persistent and for long-standing persistent AF. Catheter ablation may be more successful in patients with paroxysmal AF rather than persistent atrial fibrillation.[1, 97]

1.9.1. Catheter ablation versus antiarrhythmic drug therapy

The first randomized trial comparing clinical outcomes of catheter ablation vs. rate-control or rhythm-control drug therapy in patients with symptomatic AF was the highly awaited CABANA trial, which enrolled over 2200 patients. The results of the trial were finally published in 2018, and have been intensively discussed ever since. The protocol of the trial was designed to randomize patients with symptomatic AF to medical therapy (rate or rhythm control) vs. catheter ablation. The trial did not show significant difference in all-cause mortality or in the composite primary endpoint of death, disabling stroke, serious bleeding or cardiac arrest – making the analysis based on the randomization protocols (intention-to-treat analysis). The secondary endpoint of time to first AF recurrence was significantly reduced by 47% in the ablation group ($p< 0.0001$) compared to the drug therapy group.[98]

The trial was criticized for its several limitations, such as significant differences in the intention-to-treat analysis compared to the treatment-received and per-protocol analysis. Based on this fact, alternative interpretations emphasize the relevance of the high rate of cross-over between the randomized arms, as 27.5% of patients from the group assigned to medical drug therapy eventually underwent catheter ablation. In the treatment-received analysis, catheter ablation of AF showed a significant advantage over drug therapy with a 33% risk reduction for the primary endpoint among patients who actually did receive the assigned therapy.[98]

For many observers, the trial's subgroup analysis provided new insights about which patients with AF might mostly benefit from an invasive approach. Patients younger than 65 years seemed to benefit more from an ablation therapy, while patients older than 75 years showed less advantage of a PVI. Patients with heart failure seemed to particularly benefit from the procedure, supporting the results of the CASTLE-AF trial, which showed a mortality benefit of PVI vs. medical therapy in patients with heart failure.[98, 99]

The CABANA trial also showed in its secondary end point investigations, that catheter ablation was favorable compared to medical therapy, regarding improvement of quality of life, death or cardiovascular hospitalization, as well as in significant reduction of time to AF recurrence.[98]

Complication rates were relatively low in both therapy arms. The most common serious periprocedural complication in the PVI group was cardiac tamponade (0.8%). The most common adverse events in the ablation group included the occurrence of minor groin hematoma (2.3%) and pseudoaneurysms (1.1%). In the drug therapy arm, hyper- or hypothyroid disorders were reported in 1.6%, proarrhythmic events in 0.8% of patients. Other studies reported about similar investigation results.[98]

1.9.2. Outcome and complications of catheter ablation

Efficacy, safety and clinical outcomes of PVI may vary based on various individual factors: from the experience of the center or the operator, the ablation strategy to the duration and frequency of AF, and it generally can be quite difficult to predict. What we also know is that many patients may require multiple procedures to achieve freedom of AF related symptoms, in average approximately 1.7 times. The main reason for recurrence of AF after catheter ablation is PV reconnection in 97 % of the cases. The optimal re-ablation strategy remains unclear for patients with AF recurrence after PVI and persistently isolated PVs.[4, 89, 100-102]

Clear influential parameters for high efficacy of AF ablation are the duration and frequency of AF episodes, as PVI in patients with paroxysmal vs. persistent, and persistent vs. long-term persistent AF can be performed with a significantly higher success rate. Recurrence rate has been shown to be higher in patients with heart failure, with a reduced LVEF and structural heart disease. The overall success rate of PVI lies around 80% after multiple procedures, and 50% after a single procedure, but may vary based on the individual risk factors, and the experience of the operator and the EP center, where PVI is performed.[4, 89, 100, 102]

Catheter ablation of AF is a safe procedure with an overall low periprocedural complication rate, although some of the possible complications are not negligible and might be potentially life threatening in some cases, even though they are very rare. The most serious periprocedural complications are death, cardiac tamponade, esophageal injury (atrio-esophageal fistula or perforation) and stroke. The most frequent possible complications of PVI and their incidence rates are summarized in ***Table 3***.[4, 102-104]

PVI is increasingly being offered to patients as a treatment option, with the tendency of treating more multimorbid and older patients. An overall reduction of complication rates has been observed over the last decades, showing the increasing experience and quality of catheter ablation over the world. In most centers, PVI is a well-established, routinely performed procedure nowadays.[4, 102-104]

Complication severity	Complication type	Rate[110]
Life-threatening	Periprocedural death	<0.1%
	Esophageal injury (perforation/fistula)	<0.5%
	Periprocedural thromboembolic event	<1%
	Cardiac tamponade	~1%
Severe complications	Pulmonary vein stenosis	<1%
	Persistent phrenic nerve palsy	<1%
	Vascular complications	2-4%
	Other severe complications	≈1%
Moderate or minor complications	Various	1-2%
Unknown significance	Asymptomatic cerebral embolism	5-15%

Table 3. Complications related to catheter ablation of atrial fibrillation.[1, 105]

(Table modified from the 2020 ESC guidelines for the management of AF guidelines from Hindricks et al., modified by the author, H. L. Phan. © ESC 2020. All rights reserved)[1]

1.9.3. Radiofrequency ablation

Various technologies using different energy sources have been developed for catheter ablation. The first established and most widely used technology to achieve PVI is based on radiofrequency (RF) energy. RF based PVI is considered to be the "*gold standard*" method for PVI. RF energy is the most often used energy source in all types of catheter ablation procedures, it is traditionally used e.g. for the ablation of supraventricular tachycardia, atrial flutter or ventricular tachycardia.[4, 5, 97]

During ablation using RF energy as an energy source, energy is transmitted from a single point of a thin endocardial catheter's tip, so that ablation needs to be performed in a "point-by-point" fashion. RF energy generated from the catheter tip causes tissue scarring through the heat generated from the RF waves, which is conducted to the deeper layers of the connective tissue, generating scar formation, or so-called myocardial ablation (***Figure 2, Panel B***).[4, 5, 97]

The main goal of the procedure is to create a transmural lesion, which is the key for durable tissue ablation. Multiple factors influence the size and depth of a lesion created by RF energy: power, impedance, temperature, duration and contact force. Ablation quality markers, such as contact force or force-time integral[106, 107], as well as ablation index[108, 109] have been developed to provide objective reference parameters during catheter ablation. Ablation index incorporates contact force, time and power in a weighted formula to provide accurate information about lesion formation achieve durable ablation lesions.[97]

Generally, high-power delivery and good catheter-tissue contact leads to creation of larger transmural lesions, which supports higher procedural efficacy. However, this usually requires very high temperatures and overheating of the catheter tip over 100 C° may result in boiling and coagulation of blood tissue and proteins, causing steam expansion at the end of the catheter, causing generation of a so-called "*steam pop*", that may possibly cause tissue injury and endo- or epicardial perforation.[97, 110, 111]

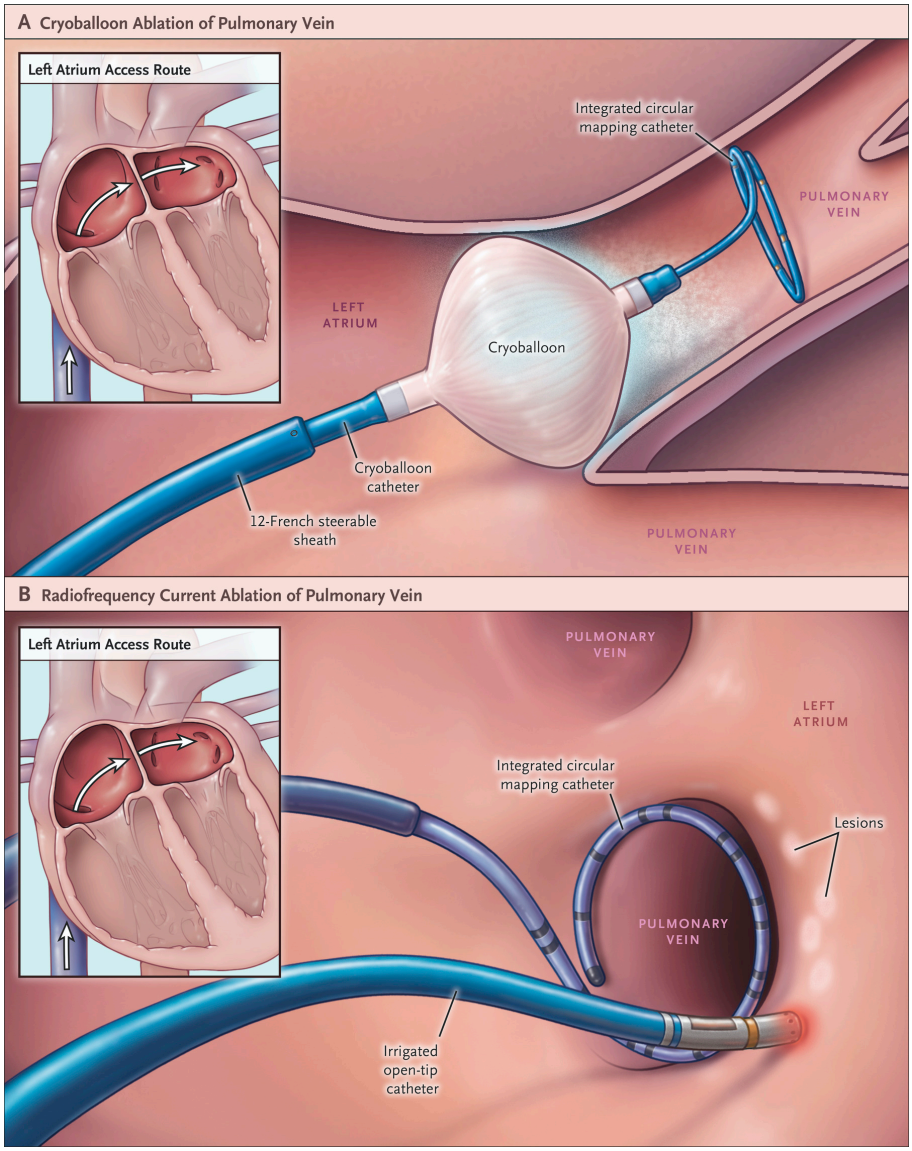

Figure 2. Catheter ablation methods.

Panel A *shows the cryoballoon system, a single-step approach in which a balloon delivers subzero temperatures to the pulmonary-vein.*

Panel B *shows the radiofrequency catheter ablation system, which uses heat-energy transfer to tissue and delivers a series of point-by-point connected lesions with assistance from a three-dimensional navigational system.*

(Figure published in the FIRE and ICE trial by the New England Journal of Medicine. Figure cited with permission from Kuck et al. Copyright Massachusetts Medical Society©)[8]

Prevention of overheating and creation of "*steam pops*" are crucial to avoid most complications of RF PVI. Therefore, RF ablation is now usually performed with special catheters with the feature of catheter tip irrigation, where active cooling of the tip-electrode helps to achieve higher power delivery, greater lesion depth, width, and volume. Active open-loop tip-electrode cooling might also reduce the risk for thrombus and char formation.[110-112]

Catheters are usually made of a material with a high electrical conductivity e.g. gold, so that passive cooling would be as fast as possible. Higher complication rates of RF PVI compared to ablation of other arrhythmias is probably due to the greater ablation surfaces, and localization of the procedure with possible injury of connecting anatomical structures as the esophagus, phrenic nerve or PV, as well as left-atrial thromboembolic complications.[97, 110, 111]

Histology of RF lesions shortly after ablation demonstrate coagulation necrosis and edema, which transform to lesions showing an inflammation process with infiltration of inflammatory cells 2 to 7 days post-ablation. About 4 weeks after ablation transformation to granulation tissue can be observed microscopically. Tissue exposed to high temperature (over 50° C) over several seconds will go through coagulative necrosis which generate non-conducting myocardial scars. In case of AF, circular ablation of the PVs is performed to achieve electric isolation, giving the procedure the name pulmonary vein isolation or PVI.[97, 110, 111]

Achieving optimal catheter-tissue contact requires high operator skills and experience. RF PVI is usually performed under visualization with a three-dimensional (3D) electroanatomical mapping system to assist the creation of linear circumferential lesions around the antra of the PVs. Overall, it is a relatively complex procedure and demands a long learning curve, and multiple procedures are often required to achieve durable PVI.[97, 110, 111]

RF ablation has been shown to result in favorable clinical outcome, and has been proven to be more effective than antiarrhythmic drug therapy. Major complications of RF PVI occur in about 5 % of patients. In comparison, adverse events for antiarrhythmic drug therapy are generally more common (30% vs. 5%) but are usually less severe.[89, 113, 114]

1.9.4. Cryoballoon ablation

Cryothermal energy has been used for surgical ablation of arrhythmias for decades. The first balloon-based transvenous cryoablation systems have been introduced in the 2000s to possibly solve limitations of the RF AF ablation system, making PVI a technically easier procedure in order to optimize the learning curve, procedure time and increase safety, efficacy and reproducibility.[6, 8, 25, 97]

The first generation cryoballoon (CB1) ablation system (Arctic Front™, Medtronic, Inc., USA) was introduced as a tool for a single-shot anatomical based PVI. The cryoballoon (CB) was designed to be advanced to the antrum of the targeted pulmonary vein, until total occlusion is achieved and ablation along the balloon equator can be performed. This technology utilizes cryothermal energy (or cryo-energy) to achieve circumferential ablation of the PVs by cooling the tissue surface to subzero temperatures (up to -80°C) using dinitrogen monoxide (N_2O) infused in the wall of the balloon-catheter.[6, 7, 97]

The CB1 system uses a non-compliant balloon catheter which is available in two sizes: with a diameter of 23 or 28 mm. A special advantage of the CB1 ablation vs. the RF ablation system is that as the catheter surface cools down, the surface of the catheter freezes to the endocardium, which gives greater stability for the operator - which may also shorten the procedure time (***Figure 2, Panel A***). Thanks to its effectivity, safety and simplicity to use in comparison with an RF PVI, the CB technology became very popular in a short period of time.[6, 7, 97]

In 2012, the second-generation CB (CB2, Arctic Front Advance™, Medtronic, Inc., USA), was introduced. An improved balloon catheter promised even faster and technically easier procedures. Some of the biggest improvements of the new system is a larger surface area of coolant distribution, which encompasses the complete distal hemisphere of the balloon, opposed to the CB1, which only distributes the cooling material at the equatorial belt of the balloon surface. Evidence showed a much faster lesion generation without affecting the safety profile.[101, 115-120]

In summary, multiple randomized trials have shown feasibility, short-term and long-term efficacy of CB ablation. The biggest multicentric prospective randomized control trial comparing CB to RF ablation was the FIRE AND ICE trial published by *Kuck et al.*[7] This study showed non-inferiority in efficacy and safety of CB versus RF ablation in symptomatic patients with paroxysmal AF. The trial supported evidence for the previous ESC guidelines for the management of AF from 2016, which proposed CB ablation with the same level of evidence as RF ablation.[7, 8, 25]

The FIRE and ICE trial demonstrated statistically significant and clinically relevant advantages of the CB ablation in terms of necessary repeat ablation and electric cardioversion procedures, all-cause rehospitalization and cardiovascular hospitalization rates. Both groups showed significant improvement in quality of life after PVI.[7, 8]

CB ablation appears to require a shorter learning curve, and shorter procedural times – especially when using the CB2. The median fluoroscopy time is similar using both ablation techniques. CB procedures seem to be more reproducible and less operator-dependent than RF ablation. Major complication rates are generally low, and similar with both methods, except for a uniquely higher incidence of phrenic nerve palsy (PNP) with the CB. However, the majority of PNP cases are asymptomatic and resolve by the time of one-year follow-up. Because of its many advantages, CB ablation has become a highly popular technique for PVI for patients with symptomatic AF in many different patient collectives.[7, 102, 121-126]

1.9.5. Novel innovative technologies for pulmonary vein isolation

Ultrasound-based ablation systems

The field of EP shows rapid development of new technologies as a response to the high demand, as number of catheter ablations are rapidly increasing every year. There are many novel balloon-based technologies showing similar advantages as described about the CB catheter ablation system.

One of these innovative alternative catheter methods is using ultrasound energy. The high intensity focused ultrasound balloon (HIFU, Atrionix, Inc.) has the ability to precisely focus ultrasound waves in a specific area with a high energy density. The HIFU balloon catheter is able to create linear lesions to achieve PVI. Long-term results showed comparable efficacy of the HIFU balloon to RF ablation. Despite its promising results though, at present, this technology has been withdrawn from clinical use due to an unacceptably high complication rate in terms of incidence of persistent phrenic nerve palsy and atrioesophageal fistula, as the latter is one of the most serious and possibly lethal complications of PVI.[127-130]

There have been recent developments of another ultrasound-based technology, the so-called low intensity collimated ultrasound (LICU) based ablation system (VytronUS, Inc., Sunnyvale, California). This method uses a low intensity ultrasound-equipped catheter tip to automatically recreate a 3D-map of the endocardial geometry of the left atrium (LA) and the PVs with the help of a graphical software. After mapping the LA, individual geometry lesions can be defined through the software, as desired by the operator. Lesion generation is automatized and can be individually optimized based on the detected wall thickness, to achieve transmural lesions with minimizing the risk of complications. Preclinical studies in a porcine model and initial clinical phase data on the first human patients have been published recently with promising results, but obviously more studies are needed to prove feasibility, safety and efficacy of this system.[131, 132]

Radiofrequency-based balloon systems

Toray-Satake Radiofrequency Hot Balloon

Recent efforts of multiple research groups set the goal to create a balloon that uses RF energy. The so-called RF "*hot balloon*" or Toray-Satake balloon (Hayama Arrhythmia Institute, Kanagawa, Japan) was recently introduced. The "*hot balloon*" has an inner lumen and a J-tip guidewire that can be inflated from 26 to 33 mm in each PV ostium, where RF-based balloon-based ablation can be performed after PV occlusion. During ablation with the Toray-Satake hot balloon, RF current of 1.8 MHz is applied between a coil electrode inside the balloon and four cutaneous electrode patches, that are placed on the back of the patient to induce capacitive-type heating of the balloon with a target internal balloon temperature of 70°C. Further clinical experience is needed to prove feasibility of this system.[133-135]

Luminize radiofrequency balloon

Another development of a RF based balloon is the Luminize RF balloon ablation system (Boston Scientific, Marlborough, MA, USA; formerly, Apama Medical). The Luminize RF balloon is built of a steerable 28 mm compliant balloon catheter, a steerable sheath, and a multichannel generator. The Luminize RF balloon is wrapped with 12 equatorial and 6 forward-facing irrigated electrodes, which can not only ablate, but are also microelectrodes that can sense and pace. The system also incorporates built-in cameras with LED lightning for real-time visualization of tissue-electrode contact. The recently published first feasibility trial has demonstrated a high rate of acute efficacy with no serious short-term adverse events.[136]

The Heliostar radiofrequency balloon

The Heliostar RF balloon ablation system (Biosense Webster, Irvine, CA, USA) consists of a 28 mm compliant balloon catheter with 10 irrigated, flexible, gold-plated electrodes, and a circular mapping catheter, a steerable sheath, and a multichannel generator. All electrodes have the ability to ablate, sense, and pace. The sensors are also compatible with the established CARTO® (Biosense Webster, Irvine, CA, USA) 3D anatomical mapping system.[137, 138]

Clinical data using the previously mentioned RF-based balloon catheter systems (the Toray-Satake, the Luminize or the Heliostar RF balloon) are scarce, and long-term data is still lacking. Currently, none of these systems have been granted a CE mark or approval by the U.S. Food and Drug Administration (FDA) yet.[137, 138]

The "Globe" multi-electrode contact mapping and ablation system

Another interesting and innovative technology on the market is the "Globe" multi-electrode contact mapping and ablation system (Globe; Kardium Inc., Burnaby, BC, Canada). The multielectrode Globe array combines the feature of a single-tip catheter in the form of a golden balloon. The balloon consists of 16 flat ribs with 122 gold-plated electrodes. Each electrode can record ECGs, ablate, pace and can measure tissue contact and temperature. Single-shot pulmonary vein isolation (PVI) is possible with up to 24 electrodes simultaneously with individual power control of every electrode. The first report of the first 60 clinical cases has just been published in 2019. The system has recently received a CE mark approval in July 2020.[139, 140]

Visually guided laser-balloon system

One of the new promising innovative balloon-based catheter ablation technologies for PVI is the visually guided laser balloon system (VGLB, *HeartLight®* CardioFocus Inc.). There are currently three generations of the VGLB system available. The main focus of this dissertation and our investigation - the MERLIN registry - is the first clinical experience with this novel catheter ablation system. The VGLB is utilizing a laser beam for PVI, with the unique possibility of direct visualization through an endoscopic fiber optic within the balloon.[13, 97, 141, 142]

The VGLB system has three defining parts: a laser balloon (LB), a lesion generator and an endoscope. Laser energy is created by a 980 nm diode laser generator, which creates light waves in the infrared spectrum, that convert to heat energy when they are absorbed, which generates the ablation lesions. The balloon is filled with deuterium-oxide (D_2O) which is an inert medium that does not absorb the energy of the laser beam, so that it can be let through without relevant energy loss.[13, 97, 141, 142]

The laser requires minimal power to generate energy. The power used for ablation with the VGLB can be manually and individually titrated between 5.5 to 12 W lasting from 20 to 30 seconds, based on the quality of tissue contact. This wide range of possibilities of energy titration makes this system more individual than other balloon-based technologies. The endoscope provides real-time direct visualization of the pulmonary veins and contact of the balloon during ablation. Lower power is preferred in contact with the posterior LA wall or when blood can be seen in the field of view. (***Figure 3***).[13, 97, 141, 142]

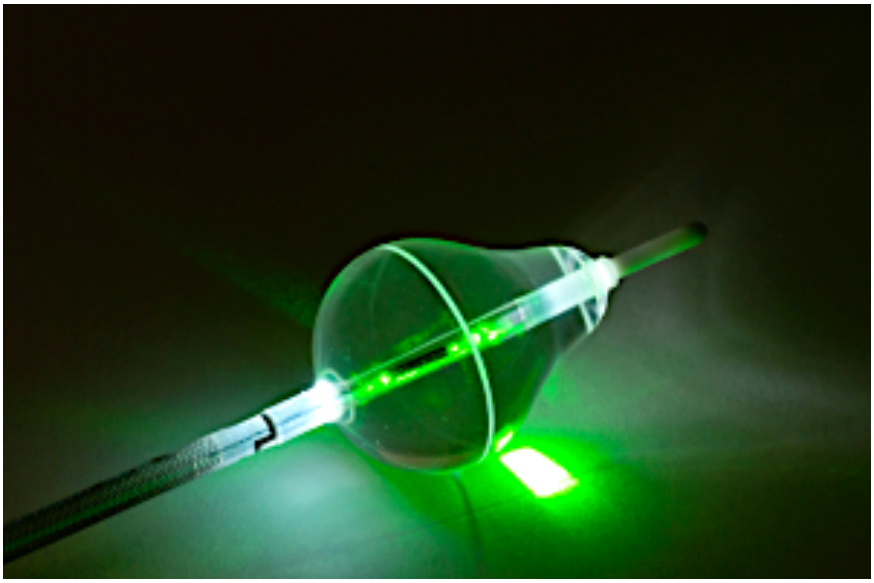

Figure 3. Second-generation laser balloon (LB2, HeartLight® Excalibur Balloon; CardioFocus Inc.) (All rights reserved)

The VGLB ablation system has three current generations available. The first (LB1), second (LB2) and third generation LB system (LB3) have been approved in the countries of the European Union, including Germany, and they have also been approved by the U.S FDA. The first clinical studies in 2009 showed comparable efficacy and safety of the LB1 with other AF ablation systems, but more multicentre prospective randomized studies, and long-term data in comparison with other available ablation methods are required, especially for the LB2 and LB3.[11, 97, 141, 142]

After the introduction and European Union CE approval of the LB1 in 2009, followed by the U.S. FDA approval in 2016, a new, optimized version of the VGLB, the LB2 (HeartLight® Excalibur Balloon, CardioFocus, Inc.) was introduced in 2017 ***(Figure 3)***.[143] The new developments of the LB2 compared to the LB1 offer greater compliance of the balloon, improved tissue contact, better PV occlusion and visibility during ablation. Another new feature is the Dynamic Response™ technology, which is a remote-control unit, that helps the operator to easily adjust the balloon size in a continuous way up to 38 mm in diameter during ablation.[11, 97, 141, 142]

As another new innovation, the Arc Marks™ were added on the catheter shaft in the LB2 system, as a helping tool to support orientation during generator rotation to achieve optimal lesion overlap, when the aiming beam is not in view. It should also support physicians, who choose to ablate behind the catheter shaft (*blind spot*) (***Figure 4***).[11, 97, 141, 142]

The new system has many advantages, but on the other hand, it also has its shortcomings. Performing PVI with the LB1 and LB2 a point-by-point ablation is still needed, which is more complex and time-consuming in comparison to single-shot devices, such as the CB. The VGLB system also does not provide EP recordings during ablation, which means that the operator cannot know real time, if the vein is isolated. [11, 97, 141, 142]

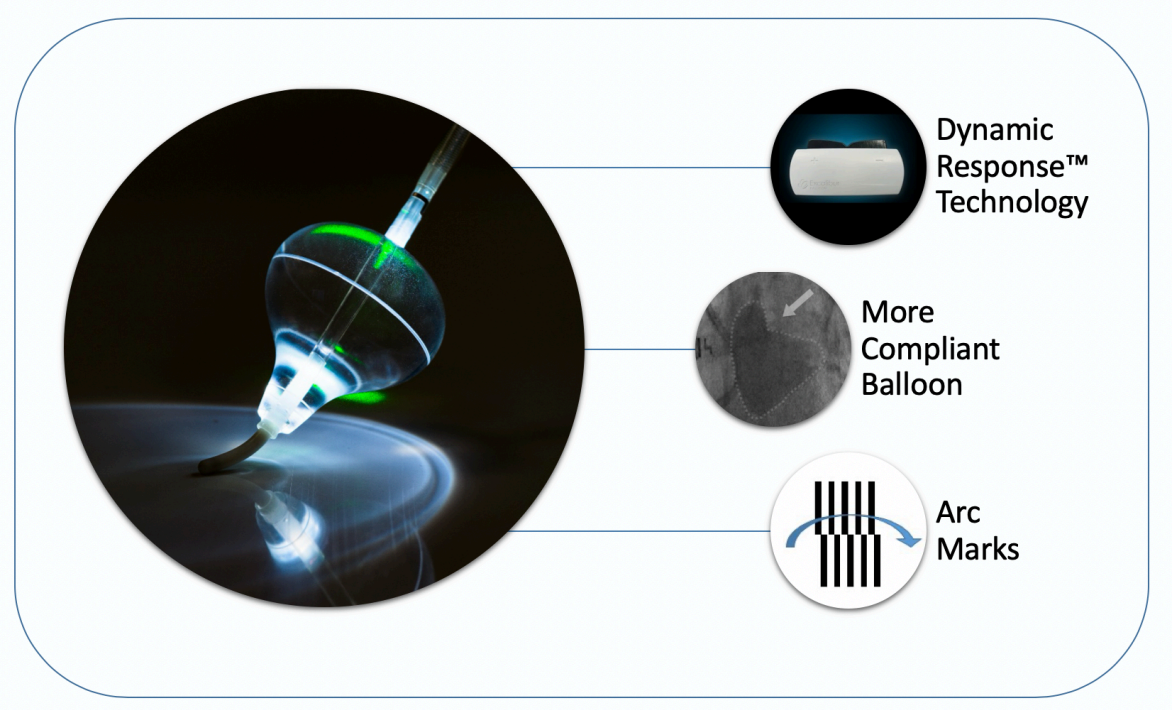

Figure 4. New features of the second-generation laser balloon (LB2, HeartLight® Excalibur Balloon; CardioFocus,).

(*Figure cited with permission from the 21-4610 HeartLight Excalibur laser balloon messaging presentation of CardioFocus, Inc. All rights reserved).*

The learning process of using a new catheter ablation system is both clinically and economically important due to rapid innovation of cardiac electrophysiology (EP) and the increasing number of EP centers, operators and ablation procedures in the last and presumably in the coming years as well. Since the learning curve effects of a new technique cannot be avoided, an ideally steep learning curve has key importance in the clinical practice, when a new technology is introduced.[144-146]

The VGLB system is quite different compared to the RF or the CB ablation systems, which are the technologies mainly used for PVI. It is very unique that catheter ablation can and needs to be performed under direct visualization through an endoscope. The LB also has a much greater compliance, but its wall is also much thinner compared to the CB so that the danger of balloon perforation, or so-called "*pinholes*" is higher. Additionally, choosing optimal energy titration when using the system for the first couple of times may be difficult, when the operator does not have previous experience with it.[144-146]

As with every novel technology, an individual learning process is needed at the beginning, as operators acquire the skills to perform the procedure safely and effectively. As the procedure is performed on patients, it is very imported that new procedures can be adopted to routine clinical practice in a safe way. The beginning of the learning curve is inevitably associated with longer procedure and fluoroscopy times, higher complication rates, and less favorable acute as well as long-term clinical results.[144-146]

1.10. Atrial fibrillation surgery

Concomitant atrial fibrillation surgery in patients undergoing cardiac surgery (e.g. coronary artery bypass graft surgery or valve replacement) has been shown to reduce incidence of AF, atrial flutter and atrial tachycardia. It is not associated with higher perioperative mortality or complication, but it increases the risk of a permanent pacemaker implantation. Traditionally the Cox maze procedure is performed, which creates complex lesions in both atria, but different variations of this surgery are possible. The ESC AF guidelines suggest that an AF Heart Team should inform the patient about the option of additional AF surgery, and it should be performed based on the patient´s choice when another open heart procedure is planned.[147, 148]

2. Methodology

2.1. Research objectives

RF based PVI is already a well-established and is considered to be the "*gold-standard*" strategy for invasive treatment for symptomatic AF. It has been proven to deliver results of favorable clinical outcome and safety. However, it demands complex technical skills, considerable clinical experience in EP and a long learning curve for physicians to master the procedure.[1, 4, 5, 97]

Balloon-based ablation systems for PVI using different energy sources have been developed to possibly solve these limitations. The CB ablation system has already become a well-approved method and has been shown to have a good efficacy and safety profile, as well as a faster learning curve compared to RF PVI. CB ablation is currently recommended by the ESC with the same level of recommendation as RF PVI for treatment of patients with symptomatic AF.[1, 7, 8, 97, 124]

The novel VGLB system has been introduced as a new balloon-based modality utilizing laser-energy, as previously described. The LB1 (HeartLight®, CardioFocus Inc.) has already showed high efficacy, durability and safety for PVI in patients with symptomatic paroxysmal and persistent AF.[149-152]

The objective of our study, the MERLIN registry (Second-generation VGLB system for PVI: Learning curve, safety and efficacy) was to prospectively investigate safety, acute efficacy and learning curve effects in the first 45 procedures of performing PVI using the LB2 in the University Heart Center of Lübeck (Germany).[13]

All procedures were performed by two experienced EP physicians, who had broad experience in RF and CB ablation procedures but had previously never used any generations of the VGLB system (neither LB1 nor LB2). The MERLIN registry is the first prospective study reporting on clinical experience using the LB2.[13]

2.2. Patient population

This study prospectively included 45 consecutive patients with symptomatic drug-refractory paroxysmal or persistent AF, who presented for PVI using the LB2 at the University Heart Center of Lübeck, Germany between April 2018 and June 2019. Exclusion criteria were prior left atrial (LA) ablation (PVI or ablation of atrial tachycardia), an LA-diameter over 60 mm or severe valvular heart disease.[13]

All patients gave written informed consent to the procedure. Our study (the MERLIN registry) was part of the prospective Lübeck ablation registry and was approved by the local ethic's board and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.[13, 153]

2.3. Pre-procedural management

Transesophageal echocardiography (TEE) was performed prior to PVI to investigate LA diameter and LA volume, and most importantly to rule out intracardiac thrombi. In case of detection of an intracardiac thrombus prior to ablation, PVI was not performed. TEE also provider further additional information, such as detection of pre-existing atrial septal defects, persistent foramen ovale, pericardial effusion, impaired LVEF or significant valve disease. Besides TEE, no other pre-procedural imaging was performed.[13]

Regarding pre- and periprocedural oral anticoagulation, in patients on VKAs, anticoagulation was continued throughout the procedure aiming at an INR value of 2 to 3. In patients taking NOACs, the anticoagulation was discontinued 12-24 hours prior to the procedure and re-initiated six hours after the ablation was performed with half of the regular dosage and was continued at full dose on the first post-procedural day after catheter ablation.[13, 97, 154]

2.4. Ablation protocol

All ablation procedures with the LB2 were performed under deep sedation and analgesia by intravenous administration of midazolam, fentanyl and continuous infusion of propofol, under continuous monitoring of ECG, noninvasive blood pressure and oxygen saturation.[13, 155, 156]

A ten-pole diagnostic catheter (Webster® CS Uni-Directional, Biosense Webster Inc., CA, USA) was introduced via the right femoral vein and positioned within the coronary sinus. A double transseptal puncture was performed via the right femoral vein under fluoroscopic guidance, using a modified Brockenbrough technique, and an 8.5 French (F) transseptal sheath. Heparin was administered after transseptal puncture to maintain an activated clotting time (ACT) of ≥300 seconds. One transseptal sheath was exchanged over a guidewire for a 12 F steerable sheath (CardioFocus Inc.), and the LB2 was advanced into the LA (***Figure 5***).[3, 13]

A 15 mm circular mapping catheter (Lasso®, Biosense Webster Inc., CA, USA) was introduced via the second transseptal sheath and placed at each of the individual PV ostia to detect intracardiac electrograms (ECGs) from the PVs using a computerized EP-system. Selective PV angiography was performed after injection of contrast medium in order to identify the ostia of all PVs for balloon placement.[13]

The LB2 is filled and continuously flushed with deuterium-oxide (D_2O), which is a medium that lets through the laser beam without relevant energy loss. Once the balloon is inflated, a 2 F fiber optic endoscope is positioned within the central catheter shaft, which enables direct visualization of the PV antrum. A diode laser generator delivers energy at a wavelength of 980 nm via a second fiber. After positioning the balloon in the targeted PV, the LB2 was inflated at the antrum of PV and the balloon was expanded (from 9 to 35 mm) until optimal PV occlusion and 360° visibility was achieved by utilizing the remote-control unit (***Figure 3, 4 and 5)***.[12, 13, 142, 143, 145]

The LB2 system enables individual optimization of laser energy delivery. Power delivery was titrated from 5.5 W to 12 W.[141, 152] The energy level was targeted to a minimum of 8.5 W.[152] Anterior parts of the PVs were treated with a maximum of 12 W of laser energy, whereas a maximum of 10 W was delivered at the posterior aspects. Laser energy of 5.5 W or 7 W was only used if it was required to perform energy titration in areas near blood due to poor PV occlusion.[12, 13, 142, 143, 145]

Ablation was performed in a point-by-point fashion by manual rotation of the catheter under visual guidance provided by the endoscope, overlapping each lesion by 30–50% (***Figure 6***).[141, 142] The endoscope provides real-time direct visualization of the pulmonary veins and contact of the balloon during ablation. Lower power is preferred in contact with the posterior LA wall or when blood can be seen in the field of view (***Figure 5***).[12, 13, 142, 143, 145]

Our goal was to perform circumferential PVI without rotating the LB2, if possible (*zero-rotation*). Therefore, we were set to perform ablation behind the catheter shaft (i.e. *blind spot*) if possible. For performing a safe, effective and continuous ablation line in the area behind the blind spot, complete PV occlusion was confirmed pulling the lesion generator to a proximal position, with utilization of the Arc Marks for creating overlapping lesions (***Figure 5*** and ***Figure 6***). If complete PV occlusion was not possible rotation of the LB2 was performed.[12, 13, 142, 143, 145]

After completion of circular ablation, PVs were re-mapped using a circular mapping catheter. If PV potentials were still present, additional laser balloon ablation was performed with guidance of a circumferential mapping catheter. If PVI could not be achieved by the LB2, RF touch-up ablation was performed. All PVs were checked by the circular mapping catheter to confirm acute electrical PVI at the end of the procedure.[13]

In all procedures, an esophageal temperature probe (Sensitherm^{TM}, St Jude Medical, Inc., MN, USA or CIRCA S-CATH^{TM}, CIRCA Scientific, Inc., USA) was inserted and positioned in the patients according to the individual LB2 position to facilitate esophageal temperature monitoring during energy delivery in order to prevent thermal esophageal injury. The intraluminal esophageal temperature cut-off was set at 40.5 °C. If esophageal temperature exceeded the cut-off, energy delivery was paused, and catheter ablation was continued using reduced energy and/or at a more proximal or distal location.[13, 97]

During ablation of the right superior PV (RSPV) and the right inferior PV (RIPV) phrenic-nerve stimulation (with 12 V and 2.9 ms) via a diagnostic catheter placed in the vena cava superior was performed. A loss or weakening of the capture signal resulted in instant termination of energy delivery in order to prevent permanent phrenic nerve injury.[13, 97]

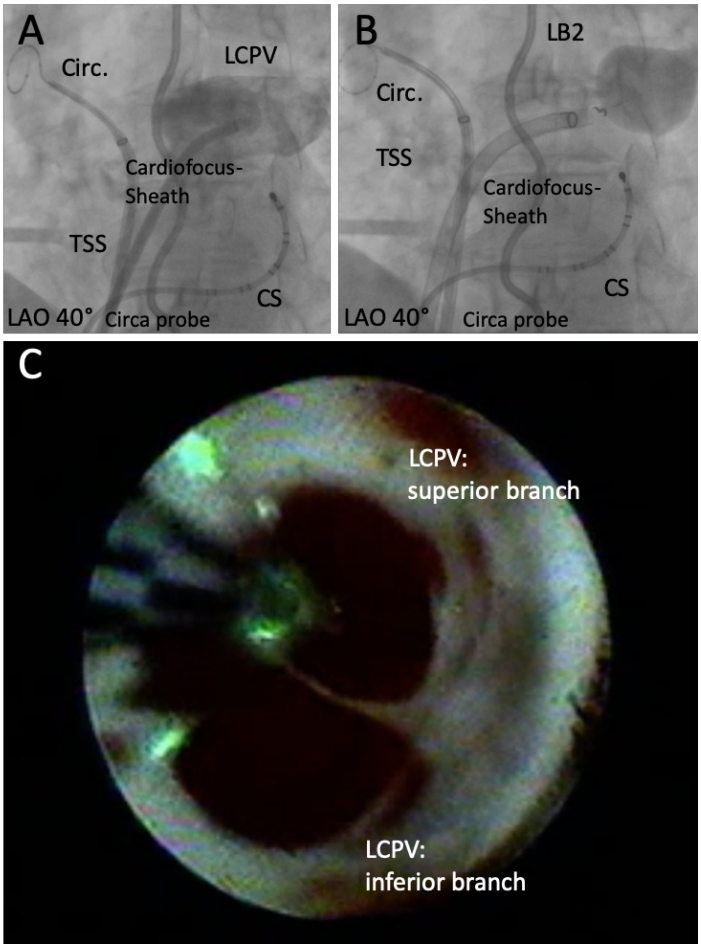

Figure 5. 69-year-old female patient with persistent atrial fibrillation and left common pulmonary vein (LCPV) with 35 mm diameter.

A: Angiography of LCPV, B: Second-generation laser balloon (LB2) advanced to the LCPV. C: Endoscopic view with superior and inferior branches of the LCPV. LCPV: left common pulmonary vein, TSS: transseptal sheath, CS: coronary sinus catheter, LB2 = second-generation laser balloon. Circ. = Circular mapping catheter.
(Figure cited from Heeger C.H. and Phan. H L. et al., Circulation Journal, 2019.)[13]

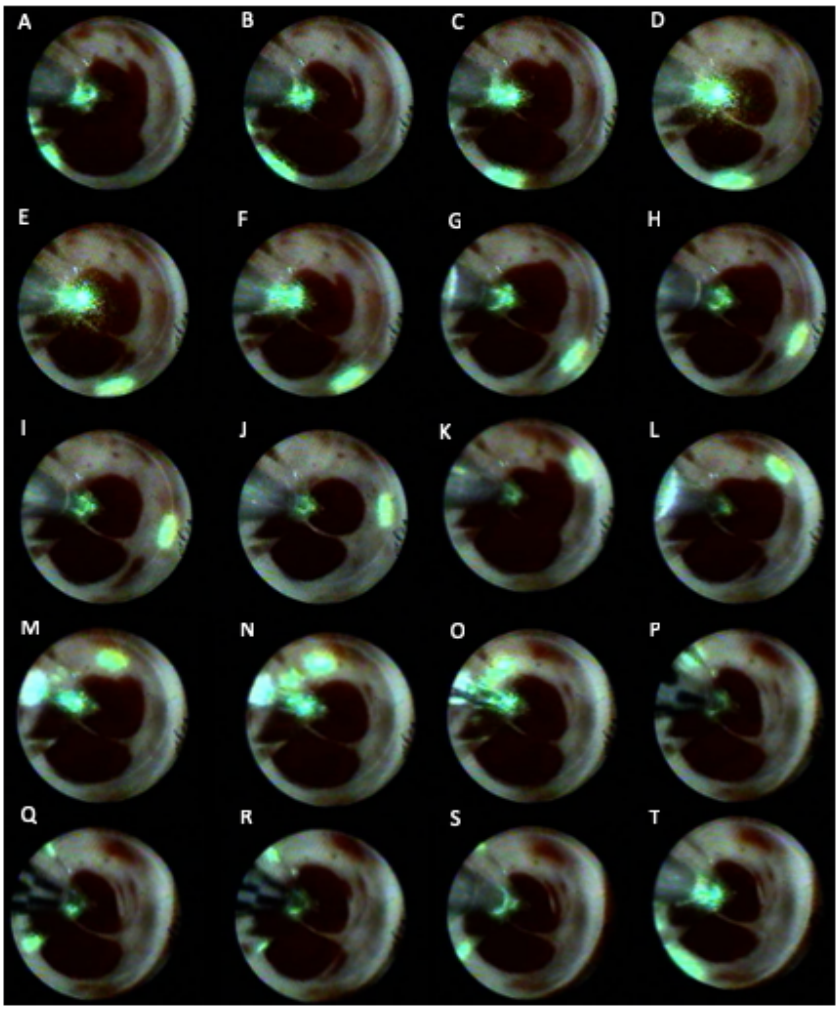

Figure 6. Endoscopic view of the second-generation laser balloon based PVI in a patient with a LCPV.

Complete circumferential 30-50% overlapping applications of laser-energy (from picture A to T) and utilization of arc marcs (O-P) to ablate at the blind spot behind the catheter shaft without balloon rotation (zero rotational maneuver). After 20 laser-applications a successful isolation of LCPV was observed.

PVI = pulmonary vein isolation, LCPV = left common pulmonary vein.

(Figure cited from Heeger C.H. and Phan. H L. et al., Circulation Journal, 2019.)[13]

2.5. Postprocedural management

After the ablation procedure, all patients underwent transthoracic echocardiography to rule out pericardial effusion 4 to 6 hours after the procedure and on the first postoperative day. Low molecular-weight heparin was administered in patients on VKAs in case of an INR under 2.0 until a therapeutic INR of 2.0 to 3.0 was achieved. NOACs were re-initiated 6 hours post ablation. Anticoagulation therapy was recommended for at least 3 months, independent from CHA_2DS_2-VASc score and thereafter according to the individual CHA_2DS_2-VASc score.[1, 13, 97]

Antiarrhythmic drug therapy was recommended for 3 months post ablation in the so-called blanking period to prevent early recurrences during the healing phase. All patients were treated with prophylactic proton pump inhibitors for 6 weeks after the procedure to prevent esophageal complications, following current recommendations.[1, 13, 97]

2.6. Statistical analysis

Continuous data were summarized as means ± standard deviations or as medians (25th and 75th percentiles) as appropriate. Categorical data were presented as N (%). Differences in procedural data between the groups were compared with an unpaired t-test or the Wilcoxon-Mann-Whitney test, chosen as appropriate. Differences in complications between the groups were analyzed using the Chi-squared test. All p-values were two-sided and a p-value <0.05 was considered as significant. All calculations were performed with the statistical analysis software R (R Core Team, 2018).[13]

3. Results

3.1. Patient characteristics

A total of 45 consecutive patients were prospectively enrolled. All patients presented with symptomatic AF and agreed to undergo PVI using the LB2 at the University Heart Center of Lübeck, Germany. Patients were divided into three groups, with 15 patients in each group, based on the time of enrolment: the first 15 patients divided to group T1, the second 15 patients to group T2, and the last 15 patients to group T3. All patients underwent LB2 PVI procedures, which were performed between April 2018 and June 2019 at the University Heart Center of Lübeck, Germany.[13]

The patient characteristics are summarized in ***Table 4***. Continuous data are summarized as medians (25^{th} and 75^{th} percentiles), categorical data are presented as values (percentage %). The median age of the patients was 68 (61, 78) years. Our youngest patient was 44, the oldest was 83 years old. Our patient population was dominantly of male gender (69%). A total of 40 of 45 patients (89%) suffered from persistent AF, the rest of the patients (11%) had paroxysmal AF. The median AF duration was 18 months.[13]

The majority (71%) of patients had a history of hypertension, other cardiovascular comorbidities were relatively rare, with a rate under 25 %. Only 11% of patients were diabetic, 24% of the patient population had coronary heart disease, and only 9% of patients suffered from congestive heart failure. The median LVEF was 60% (55%, 60%). 13% of the patients undergoing LB2 ablation had a prior TIA or stroke in the medical history, with a median CHA_2DS_2-VASc score of 3 (1, 4), as presented in ***Table 4.***[13]

Patients in group T2 were more likely to have hypertension compared to other groups ($p=0.018$), which we interpret as an accidental finding due to a relative low number of the patient population. Besides that, no further differences in patients baseline characteristics were observed. There was no significant difference in the incidence of CAD, congestive heart failure, diabetes mellitus, prior TIA or stroke, age, gender or CHA_2DS_2-VASc score.[13]

	All	T1	T2	T3	p
Number of patients	45	15	15	15	
Age (years)	68 (61, 76)	67 (62, 72)	70 (67, 78)	65 (58, 72)	0.191
LA volume index (ml/m^2)	25 (20, 35)	20 (20, 31)	20 (20, 39)	30 (20, 35)	0.959
Persistent AF	40 (89)	10 (67)	15 (100)	15 (100)	0.067
Duration of AF (month)	18 (3, 38)	18 (7, 38)	6 (4, 43)	24 (1, 36)	0.639
Female gender	17 (31)	8 (53)	6 (40)	3 (20)	0.166
Arterial hypertension	32 (71)	11 (73)	14 (93)	7 (47)	0.018
Coronary artery disease	11 (24)	5 (33)	4 (27)	2 (13)	0.431
Congestive heart failure	4 (9)	2 (13)	2 (13)	0 (0)	0.799
Diabetes mellitus type II	5 (11)	1 (7)	4 (27)	0 (0)	0.177
Prior TIA/stroke	6 (13)	2 (13)	3 (20)	1 (7)	0.561
CHA_2DS_2-VASc score	3 (1, 4)	3 (2, 4)	3 (3, 5)	2 (1, 4)	0.234

Table 4. Baseline characteristics.

Continuous data are summarized as medians [25th and 75th percentiles]. Categorical data are presented as N (%). AF = atrial fibrillation, LA = left atrial, p = p-value, TIA = transient ischemic attack.

(Figure cited from Heeger C.H. and Phan. H L. et al., Circulation Journal, 2019.) [13]

3.2. Acute procedural efficacy

A total of 177 PVs were identified in a total of 45 patients undergoing PVI. 174 out of 177 PVs (98%) were successfully isolated utilizing the LB2 (***Table 5 B***). In one patient, which was the second patient of the population, additional irrigated RF current catheter touch-up was needed to achieve complete isolation of the RSPV and RIPV, because of a pinhole rupture of the balloon. In one other patient the RSPV was not isolated due to periprocedural occurrence of pericardial tamponade. In this case the procedure was stopped immediately, as cardiopulmonary stabilization through pericardial drainage was prioritized, and for this reason PVI was not completed.[13]

The median number of laser applications to achieve PVI per PV significantly decreased from group T1 to group T3 for LSPV (p=0.035), RIPV (p=0.019) and RSPV (p=0.012). For LIPV no significant difference, but a trend towards a lower number of applications that were needed was observed (p=0.102). RF catheter touch-up was only necessary in two PVs of the second patient in group T1, after that case no further patient needed additional RF application to achieve PVI in group T2 or T3. (***Table 5 B***).[13]

162 of 177 PVs (92 %) could be successfully isolated with the LB2 after the first application of a circular lesion around the PVs (first attempt vein isolated, FAVI). No differences were observed between the groups (T1 vs. T2 vs. T3). The rate of successful PVI after the initial circular ablation (i.e. FAVI) was not significantly different between group T1, T2 or T3 for individual PVs. Nevertheless, a trend towards higher rates of successful PVI after the initial circular ablation was observed [FAVI in 49 (83%) vs. 57 (97%) vs. 56 (95%) in group T1 vs. T2 vs. T3] (***Table 5 B***).[13]

Successful isolation of all PVs after the initial circular ablation (first attempt all veins isolated, FAAVI) was achieved in 33 out of 45 (73%) patients, with no significant difference, but a higher tendency between the group T1 and T2 [FAAVI in 9 (60%) vs. 13 (87%) vs. 11 (73%) in group T1 vs. T2 vs. T3, p =0.209] (***Table 5 A***). All anatomic variants, including five left common pulmonary veins (LCPVs) and two right middle pulmonary veins (RMPVs) were successfully isolated with the first attempt of circular ablation (FAVI), which is quite remarkable, as these are technically more difficult to isolate (***Table 5 A and 5 B***).[13]

3.3. Zero rotational maneuvers

Zero rotational maneuvers utilizing the Arc Marks™ significantly increased with growing experience over time for isolation of the LSPV [3 (7%) vs. 4 (33%) vs. 9 (64%) in group T1 vs. T2 vs. T3, p=0.005] and LIPV [1 (2%) vs. 4 (33%) vs. 8 (57%) in group T1 vs. T2 vs. T3, p=0.026]. Although the difference was not significant, a tendency of higher rates of zero rotation PVI could be observed for RSPV [1 (2%) vs. 5 (33%) vs. 5 (33%) in group T1 vs. T2 vs. T3, p=0.220] and RIPV [0 (0%) vs. 3 (20%) vs. 4 (27%) in group T1 vs. T2 vs. T3, p=0.132] (***Table 5 B***).[13]

Zero rotational maneuvers were successfully performed during isolation of 4 out of 5 (80%) LCPVs, and 5 out of 5 (100%) LCPVs after the initial circular ablation (first attempt vein isolated: FAVI) (***Table 5 B***). In 5 out of 5 (100%) cases, the antral ostium of the LCPV was completely occluded by inflating the LB2 up to a diameter of 38mm. Neither sequential isolation, nor RF touch-up of superior and inferior branches was necessary to achieve isolation of the LCPVs (***Figure 5 and 6)***.[13]

3.4. Procedure times

The total procedure time significantly declined from 132 (114, 158) minutes (min) to 119 (102, 127) min and 91 (86, 105) min between group T1, T2 and T3, respectively (p = 0.0009) (***Table 5 A and Figure 7 A***). Similarly, significant decrease of the median LA dwelling time was observed between the groups over time [85 (71, 102) min vs. 85 /72, 102) min vs. 72 (62, 84) min in group T1 vs. T2 vs. T3, respectively, p=0.021] (***Table 5 A, Figure 7 B***). The same observation could be made about the median fluoroscopy time [22 (17, 27) min vs. 21 (16, 24) min vs. 13 (10, 17) min in group T1 vs. T2 vs. T3, respectively, p=0.045] ***(Table 5 A, Figure 7 C***). This demonstrates a quick learning curve of the procedure.[13]

Table 5 A. Procedural data per patient					
	All	**T1**	**T2**	**T3**	**p**
Number of patients	45	15	15	15	
RF ablation touch-up	2 (4.4)	2 (13.3)	0 (0)	0 (0)	0.129
1st attempt all veins isolated	33 (73)	9 (60)	13 (87)	11 (73)	0.209
Left common pulmonary vein	5 (11)	1 (7)	3 (20)	1 (7)	0.407
Right middle pulmonary vein	2 (4)	0 (0)	2 (13)	0 (0)	0.129
Procedure duration (min)	110 (100,132)	132 (114, 158)	119 (102, 127)	91 (86, 105)	0.0009
Fluoroscopy time (min)	18 (15, 24)	22 (17, 27)	21 (16, 24)	13 (10, 17)	0.045
LA dwelling time (min)	85 (71, 102)	100 (90, 124)	85 (72, 102)	72 (62, 84)	0.021
Contrast medium (ml)	50 (40, 50)	50 (40, 50)	50 (50, 50)	50 (30, 50)	0.329
Pinhole balloon ruptures	11	7	3	1	0.034

Table 5 A. Procedural data per patient.

Continuous data are summarized as medians [25th and 75th percentiles]. Categorical data are presented as N (%). LA = left atrial, p = p-value, RF = radiofrequency (Figure cited from Heeger C.H. and Phan. H L. et al., Circulation Journal, 2019.)[13]

Table 5 B. Procedural data per pulmonary vein					
	All	**T1**	**T2**	**T3**	**p**
Number of PVs	177	59	59	59	
Number of isolated PVs	174/177 (98)	56/59 (99)	59/59 (100)	59/59 (100)	0.999
Number of applications (LSPV)	26 (23, 28)	28 (26, 32)	23 (22, 25)	24 (22, 27)	0.035
Number of applications (LIPV)	24 (22, 29)	27 (24, 31)	24 (22, 26)	22 (20, 26)	0.102
Number of applications (RIPV)	25 (23, 35)	35 (24, 41)	24 (23, 29)	23 (22, 25)	0.019
Number of applications (RSPV)	28 (22, 35)	33 (31, 41)	25 (21, 34)	25 (19, 32)	0.012
Number of applications (LCPV)	35 (31, 35)	35 (35, 35)	35 (33, 35)	30 (30, 30)	-
Number of applications (RMPV)	47 (41, 53)		47 (41, 53)		-
RF ablation touch-up	2 (1)	2 (3)	0 (0)	0 (0)	0.129
Zero rotation (LSPV)	14 (35)	3 (7)	4 (33)	9 (64)	0.005
Zero rotation (LIPV)	13 (33)	1 (2)	4 (33)	8 (57)	0.026
Zero rotation (RSPV)	11 (28)	1 (2)	5 (33)	5 (33)	0.220
Zero rotation (RIPV)	7 (18)	0 (0)	3 (20)	4 (27)	0.132
Zero rotation (LCPV)	4 (80)	1 (100)	3 (100)	0 (0)	-
Zero rotation (RMPV)	0 (0)	0 (0)	0 (0)	0 (0)	-
1st attempt vein isolated (LSPV)	38 (95)	12 (86)	12 (100)	14 (100)	0.149
1st attempt vein isolated (LIPV)	38 (95)	12 (86)	12 (100)	14 (100)	0.149
1st attempt vein isolated (RSPV)	40 (89)	11 (73)	14 (93)	15 (100)	0.129
1st attempt vein isolated (RIPV)	39 (89)	13 (87)	14 (93)	12 (80)	0.449
1st attempt vein isolated (LCPV)	5 (100)	1 (100)	3 (100)	1 (100)	-
1st attempt vein isolated (RMPV)	2 (100)	0	2 (100)	0	-

Table 5 B. Procedural data per pulmonary vein.

Continuous data are summarized as medians [25th and 75th percentiles]. Categorical data are presented as N (%). p = p-value, PV = pulmonary vein. LSPV = left superior PV, LIPV = left inferior PV, RSPV = right superior PV, RIPV = right inferior PV, LCPV = left common PV, RMPV = right middle PV.

(Table modified from Heeger C.H. and Phan. H L. et al., Circulation Journal, 2019.)[13]

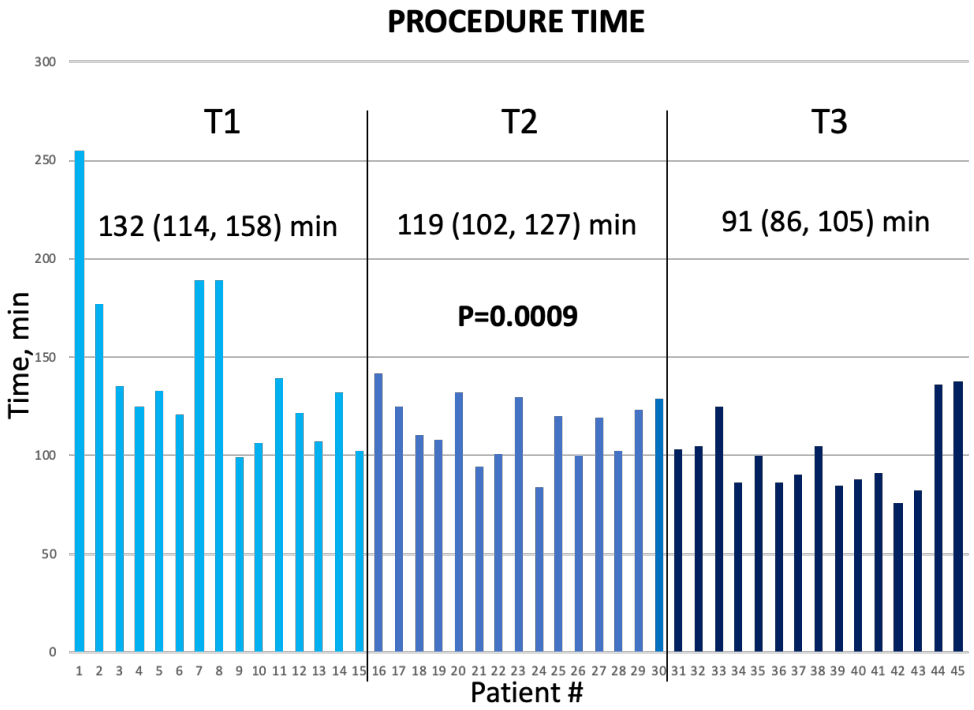

Figure 7 A. Learning curve of procedure time.
Data are summarized as medians [25th and 75th percentiles], p = p-value.
(Figure modified from Heeger C.H. and Phan. H L. et al., Circulation Journal, 2019.)[13]

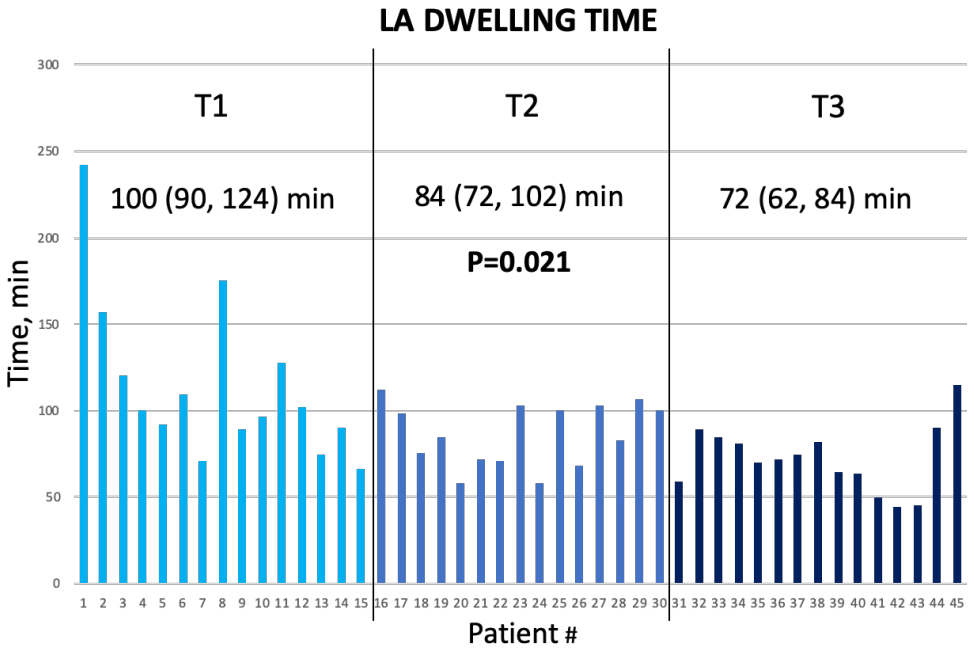

Figure 7 B. Learning curve of left atrial dwelling time.
Data are summarized as medians [25th and 75th percentiles], p = p-value.
(Figure modified from Heeger C.H. and Phan. H L. et al., Circulation Journal, 2019.)[13]

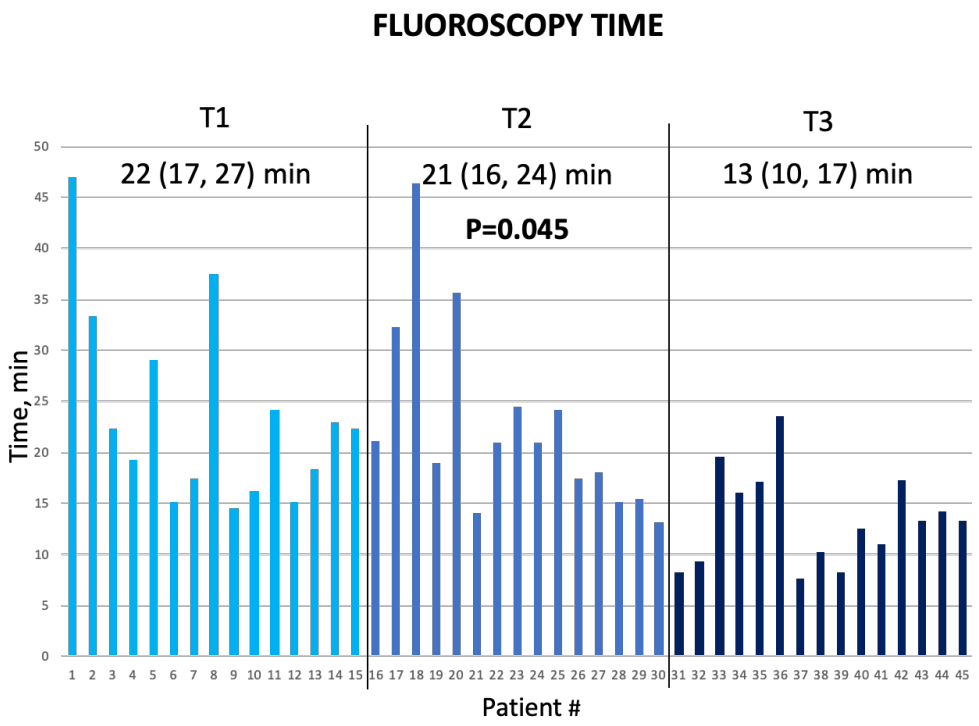

Figure 7 C. Learning curve of fluoroscopy time.
Data are summarized as medians [25th and 75th percentiles], p = p-value.
(Figure modified from Heeger C.H. and Phan. H L. et al., Circulation Journal, 2019.) [13]

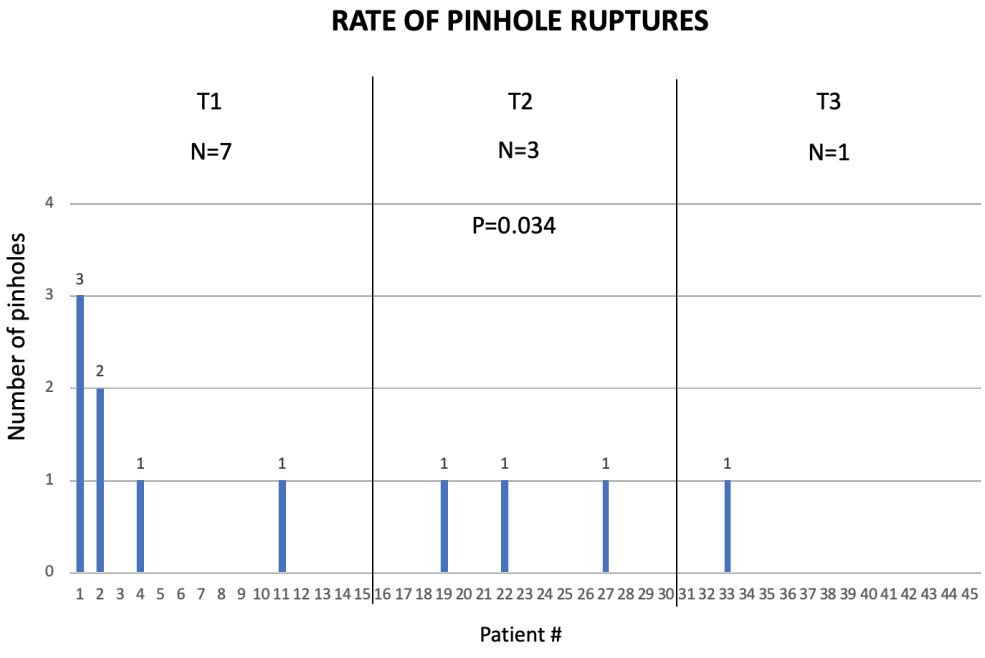

Figure 8. Rate of pinhole balloon ruptures.

p = p-value. (Figure from Heeger C.H. and Phan. H L. et al., Circulation Journal, 2019.)[13]

3.5. Pinhole balloon ruptures

A total of eleven pinhole balloon ruptures occurred during the procedures. A pinhole leads to loss of balloon pressure and decreased view, which therefore requires a change of the complete LB2. A total of 6 out of 11 (55%) pinholes occurred during the first four procedures. Three pinholes occurred during the first case and two pinholes occurred in the second case (***Table 5 A***).[13]

Pinhole ruptures were categorized into three groups (mechanical pinholes, hot pinholes and unknown pinholes). We observed pinhole ruptures due to pulling an incompletely deflated LB2 into the sheath in two cases (*mechanical pinholes*). In two cases pinhole ruptures occurred due to laser applications on blood filled folds of the balloon surface which arose from incomplete inflated LB2. In three cases energy applications from 10 to12 W were utilized despite imperfect view of the PV, which lead to laser applications on blood instead of LA tissue (*hot pinholes*). In four cases, the reason for development of the pinholes could not be identified (*unknown pinholes*).[13]

After implementing pinhole prevention strategies and gaining more experience with the LB2 ablation system, the rate of pinhole ruptures decreased significantly over time [7 vs. 3 vs. 1 pinholes in group T1 vs. T2 vs. T3, p=0034] ***(Table 5 A, Figure 8***). Further reduction of the rate of pinhole ruptures may be achieved after the learning curve of using the LB2.[13]

3.6. Periprocedural complications

All periprocedural complications are presented in ***Table 6***. The total rate of major periprocedural complications was 6.7% (3 out of 45 patients). The rate of complications was slightly, but not significantly higher in group T1 and T2. No periprocedural complications occurred in group T3. In group T1, one (2.2%) pericardial tamponade requiring pericardiocentesis happened as a complication, that was not related to the utilization of the LB2. The pericardial effusion was drained by percutaneous puncture. No surgical operation was necessary in this case, and the patient recovered without any sequelae.[13]

Additionally, one (2.2%) case of periprocedural contrast-induced encephalopathy occurred in group T1 We evaluated this case as a transient ischemic attack (TIA). Cranial computer tomography showed evidence of minimal brain edema, without signs of an ischemic lesion. The symptoms completely resolved during the hospital stay after further observation in the stroke unit. This is considered to be a rare complication of administration of injectable intravascular contrast media.[13, 157, 158]

In one patient of group T3, phrenic nerve palsy (PNP) occurred during ablation of the RSPV. The patient did not present any symptoms and it did not require any treatment, so this was not counted as a major complication. During the three-months follow-up after the procedure, PNP was still detected by fluoroscopy, but the patient remained asymptomatic.[13]

A vascular complication occurred in only one (2.2%) patient of group T2. The patient developed a severe groin hematoma, which required blood transfusion. No surgical intervention was necessary in this case.[13]

Periprocedural complications	All	T1	T2	T3	p
Major complications	3 (6.7)	2 (13.3)	1 (6.7)	0 (0)	0.359
Phrenic nerve palsy	1 (2.2)	0 (0)	0 (0)	1 (6.7)	0.376
Severe hematoma	1 (2.2)	0 (0)	1 (6.7)	0 (0)	0.376
Pericardial tamponade	1 (2.2)	1 (6.7)	0 (0)	0 (0)	0.376
Periprocedural Stroke/TIA	1* (2.2)	1* (6.7)	0 (0)	0 (0)	0.376

Table 6. Periprocedural complications.

Continuous data are summarized as medians [25th and 75th percentiles]. Categorical data are presented as N (%). P = p value,
PV = pulmonary vein. LSPV = left superior PV, LIPV = left inferior PV, RSPV = right superior PV, RIPV = right inferior PV, LCPV = left common PV, RMPV = right middle PV.[13]
** This was a case of contrast-induced encephalopathy.*[13]

4. Discussion

An increasing number of EP procedures and EP centers is observed every year in Germany as well as in Europe. A total of over 49000 catheter ablation procedures were reported in Germany in 2015, which showed a 44% increase compared to 2010. Almost every second ablation was performed to treat AF, which was the most commonly treated arrhythmia by catheter ablation in 2015. This significant rise of PVIs demonstrates how it became a well-established, routine EP procedure to treat symptomatic AF over the last decades.[159, 160]

New EP technologies and ablation systems have been developed with the main goal to be able to perform durable and safe PVI requiring simple techniques that can be mastered promptly. It is desirable, that procedures show a high reproducibility to be able to adapt to the upcoming demands, but on the other hand, physicians still need to perform procedures on a standard high level of quality with a steep learning curve. All new technologies share the design of a balloon catheter, which enables easier navigation and antral PVI without greater difficulties. In 2015, RF ablation (62%) and cryoablation (33%) were the mostly preferred ablation strategies in Germany, but there are numerous innovative technologies that appeared in the past years to compete with these strategies.[159, 160]

The VGLB system is one of the most promising novel balloon-based technology for PVI. The LB system utilizes laser energy, and its features promise an endoscopic, visually guided balloon-based anatomical AF ablation, which can be performed safely and effectively with a steep learning curve. The MERLIN registry is the first prospective study reporting on the safety, efficacy, and learning curve effects of the implementation of the LB2 into an EP center's clinical practice.[13]

Preclinical studies

The first animal study using an endoscopic VGLB system was presented by *Reddy et al.* in 2004 in a canine model using open thoracotomy.[161, 162] These initial experimental studies were followed by the first human investigations published by *Themistoclakis et al.* in 2006, that demonstrated that an endoscopic catheter balloon could successfully occlude the PVs without complications in five patients. Complementary help of intracardiac echocardiography was used in this experiment, and no ablation was attempted yet.[162, 163]

The first experimental preclinical feasibility trial, which reported about the first catheter ablations performed by an endoscopic catheter balloon system was published in 2009 by *Reddy et al*. using a canine model. In this experiment, a non-compliant LB was used, provided in fixed diameters and a laser arc from 90 to 360°. The data confirmed the possibility of antral lesions by the system, but a high rate of pulmonary stenosis was reported. Further investigations revealed a mismatch between balloon size and PV diameter, which resulted in distal ablation, which caused the high rate of PV stenosis. These observations lead to further developments in the design of the LB: creating a more compliant balloon with a narrower laser arc of 30°.[162, 164]

In 2010, a repeat study in a porcine model by *Dukkipati et al.* revealed acute and long-term efficacy of the enhanced version of the VGLB without any occurrence of PV stenosis. Histological analysis of the PVs showed evidence of transmural lesions in 98% of the cases. After the success of the preclinical phase, the first human visually guided ablations were performed.[162, 165]

Clinical studies

The first in-human-trial was a multicentric report published with the initial preclinical results by the research group of *Reddy et al*., which presented the first 30 human patients with paroxysmal AF undergoing PVI performed by the first generation non-compliant VGLB. Data showed a promising acute success with a rate of 91% of veins effectively isolated by the balloon. Success rate at the 12-month follow-up was at 67% after a single procedure with an incidence of only three major complications (one case of stroke, one cardiac tamponade and one PNP). After learning from the lessons of the preclinical phase considering the choice of balloon size, no PV stenosis was reported from the clinical phase.[162, 164]

As described earlier, after the first experiences, a newly designed VGLB system was developed: with greater compliance and a narrower laser arc of the balloon. The first human trial which reported on the first 27 catheter ablations with the new generation of the LB showed acute success and durability of PVI with a clear improvement of the safety profile - with no major complications reported by *Dukkipati et al.* in 2010.[162, 165]

In 2010, *Schmidt et. al* made further investigations considering feasibility, safety and learning curve of performing PVI of 30 patients with paroxysmal AF using the improved VGLB system. 98% of the PVs could be successfully isolated. Gap mapping of the lesions showed a similar pattern as of cryothermal balloon procedures. The system was demonstrated to be feasible with a complication rate comparable to other established approaches. Post-procedural endoscopy showed esophageal injury in 15% of patients emphasizing consequent procedural esophagus temperature monitoring during LB ablation. Procedure times showed a fast learning curve with a significant acceleration after only 10 procedures.[9]

Further investigations followed these initial trials, published by *Metzner, Schmidt* and *Dukkipati et al*. amongst others, broadening the experience with this novel ablation system, supporting data of acute efficacy, safety and comparable short-term and long-term durability of PVI using the first generation VGLB system in patients with paroxysmal AF.[145, 149, 166]

The results of the first multicenter, prospective, randomized clinical trial of the first generation VGLB system (LB1, HeartLight®, CardioFocus Inc.) were published in 2013 by *Dukkipati et al.*, and showed high efficacy, durability and safety for PVI in patients with symptomatic drug refractory paroxysmal AF. This pivotal trial demonstrated non-inferiority of the LB1 system compared to irrigated RF balloon ablation with a similar one-year success rate (61.1% with the LB1 vs. 61.7% with RF ablation).[167]

After the pivotal trial, the LB1 was soon approved by FDA in the USA, as well as in multiple European countries. PVI with the VGLB system is performed globally today. A worldwide registry of over 406 procedures of 19 medical centers was presented at the Heart Rhythm Society´s annual symposium in 2012. It summarized the first clinical experiences with the VGLB technology among experts, which was a groundbreaking milestone for introducing this novel ablation system.[168]

The research group of *Dukkipati et al.* reported about the first 200 patients treated by the LB1 in 2013, the procedures were performed in 15 EP centers from all over the world. 98.8% of targeted PVs were isolated successfully. No cases of stroke, TIA, atrio-esophageal fistulas, or significant PV stenosis were reported. There was a 2% incidence of cardiac tamponade and a 2.5% incidence of PNP. At one-year follow-up, freedom from AF or other atrial arrhythmias after one or two procedures was at 60.2%.[10]

A meta-analysis published in 2018 by *Reynolds et al.* presented a summarized data of 17 selected studies including 1188 patients (range of 20 to 194 patients each study) from around 40 centers from 8 countries performing PVI with the LB1. All but one of the studies reported on procedures using the first generation LB ablation system. Overall, in this report 80% of the patients had paroxysmal AF. Procedural and safety data demonstrated that the LB1 is highly effective at achieving PVI, with a comparable12-month efficacy of 74.3% in patients with paroxysmal AF and 72.9% of all patients. The system showed a good procedural safety profile with no periprocedural deaths or atrioesophageal fistulae reported.[169]

Experience with the VGLB system is definitely growing, but high-volume randomized multicenter studies with long-term results - especially with the LB2 - are still sparse. Available data today dominantly presents about the experiences with the LB1 treating patients mainly with paroxysmal AF. Our registry is showing an insight to our first clinical experience with the LB2 in a patient population with dominantly persistent AF.[13, 169]

4.1. Patient population

Our patient population represents a mixed entity of AF, but mostly patients with persistent AF. A total of 89% of our patient population suffered from persistent AF, which is quite unique in comparison to most of the available data that has been published about the VGLB ablation system. Patients presented with a median AF duration of 18 months, which demonstrates patients in a rather progressed stadium of AF. It is known, that acute and long-term efficacy results are worse in patients with persistent AF, than in patients with paroxysmal AF.[4, 167, 169, 170]

Age and comorbidities of our patient population represents average characteristics of patients who are generally presenting for elective AF ablation with a generally relatively low rate of cardiovascular comorbidities. Groups of T1, T2 and T3 had a similar incidence of comorbidities, besides a probably just coincidental higher rate of hypertension in group T2. Only 24% of the patient population had CAD, 9% of the patients had a history of congestive heart failure, with a median LVEF of 60%. (***Table 4)***.[13]

4.2. Main findings

Balloon-based ablation systems, applying either cryothermal or laser energy, have been developed to possibly reduce complexity and improve safety and efficacy of 3D mapping system guided RF-based ablation.[8, 150, 171] The VGLB system allows precise PVI under direct endoscopic control. The LB1 has shown clinical efficacy comparable to 3D mapping guided RF based PVI.[13, 150, 151]

Recently, the next generation of this system (LB2*, HeartLight® Excalibur Balloon; CardioFocus Inc.*) was introduced to clinical practice. Some features to optimize the procedure were implemented. Compared to the LB1 a recent study demonstrated that the optimized LB2 provides better PV occlusion and a higher rate of zero rotational maneuvers, which was not translated to other procedural parameters, including the rate of successful PVI, procedure time, fluoroscopic time and complications though.[143] All in all, procedural data of the new generation of this promising system is still sparse and no learning curve effects has been evaluated up to date.[13]

In summary, our main findings were that 175 out of 177 (98%) PVs could be successfully isolated with the LB2. It was effective even for operators without any previous experience in VGLB procedures. Procedure time, LA dwelling time and fluoroscopy time significantly decreased along the learning curve, after only 15 procedures. A procedure time of under two hours was achieved after the first 15 cases, which is comparable to RF and CB procedures. Therefore, we demonstrated that the LB2 may allow a quick learning curve for beginners in VGLB ablation.[13, 143]

The rate of periprocedural major complications was relatively low (6.7%). As other balloon-based ablations systems, the LB2 offers the opportunity of an antral lesion formation to achieve PVI in patients with a LCPV. Pinhole balloon ruptures occurred mainly in the beginning of the learning curve and could be significantly reduced after implementing prevention strategies and gaining more experience with the LB2.[13]

4.3. Acute procedural efficacy

Our patient population consists mainly of persistent AF patients (89%). The optimal ablation strategy for patients with persistent AF has been investigated during the last years, yet ablation strategies beyond PVI did not lead to improved outcomes.[172] Recent data suggested that balloon based PVI procedures with the CB may also successfully be used to treat patients with persistent AF.[13, 118, 151]

Acute procedural data showed that a very high rate, 174 out of 177 PVs (98%) could be successfully isolated utilizing the LB2 in our registry.[13] A recently published meta-analysis of almost 1200 patients undergoing PVI with the LB1 showed similar results of an acute PVI rate of 98.8%.[13, 169]

The VGLB offers a PVI by a purely visually guided circular ablation. Previous studies found acute PVI in 68 to 85% of cases after the first circular ablation (FAVI) utilizing the LB1, and 80% utilizing the LB2.[10, 144, 173] In our registry, with the rate of 91% of PVs, we found a comparable and even slightly higher rate of PVI after the first circular ablation (FAVI) with the LB2. This fact is reflecting on the promising excellent characteristics of the LB2, considering better PV occlusion, visualization and the possibility to use zero rotational maneuvers during ablation.[13, 143]

The research group of *Schmidt et al.* have looked for factors that influence acute procedural success of PVI with the LB1. They determined that the degree of PV occlusion by the balloon, which provides the quality of visualization, as well as the quantity of catheter repositioning are predictors of successful acute PVI. Total ablation energy or the number of laser applications did not influence acute procedural success in this trial. Conduction gaps of the PVs were detected at sites with suboptimal occlusion, as well as places where elevation of esophageal temperature limited further energy applications. We set the goal of possibly performing PVI with zero rotational maneuvers, which might have been advantageous in our study and could have been a reason for a higher acute efficacy rate in our procedures.[174]

Energy titration

The LB2 system enables individual titration of each laser energy delivery. Power delivery can be titrated from a range from 5.5 W to 12 W for a duration of 20 to 30 seconds depending on the operator´s choice. *Metzner et. al* published the first study examining the effectivity and safety profile of different energy titration settings, comparing three groups: using 5.5 and 7.0 W (group A), 7.0 and 8.5 W (group B), and 8.5 and 10.0 W (group C) for the isolation of each PVI respectively. The use of higher energy dosage increased the acute efficacy of PVI: after placing one circular lesion in the PVs with the described settings, successful isolation could be achieved in 69% vs. 73% vs. 90% of the PVs in group A vs. group B vs. group C.[141]

In all patients, esophagogastroduodenoscopy was performed 2 days after the ablation for detection of thermal lesions. No sign of thermal esophageal injury was found in group A, and only a single case of a thermal ulceration was found in group B, and one superficial thermal lesion was detected in group C. No cases of atrio-esophageal fistulas, pericardial tamponade, PNP or stroke was observed. In summary, higher energy settings with careful esophageal temperature monitoring seemed to increase acute efficacy without compromising safety.[141]

Bordignon et al. was also investigating the role of energy titration further in the role of acute PVI. VGLB ablation was carried out after obtaining optimal tissue contact with an energy dose of 5.5 to 8.5 W (low-dose group) or >8.5 W (high-dose group). Acute PVI after a single endoscopically guided circular lesion was achieved in a significantly higher rate using higher energy dosages (89 vs. 69% in the high vs. low-dose group respectively, $p = 0.0004$). In 70% vs. 39% of all patients in the high-dose vs. low-dose group could all PVs be isolated after a single ablation circle respectively (FAAVI; first attempt all veins isolated; $p = 0.009$).[152]

Higher energy dosage was associated with significantly less applications (31.6±8 vs. 35.2±15 applications per PV, $p=0.03$) leading to shorter procedure times. The Kaplan–Meier estimate of AF-free survival considering long-term results of PVI were significantly in favor of the high-dose group. One case of PNP was observed in each group, and besides that no other major complications were observed. Two steam pops and one balloon perforation were observed in the high-dose group without any sequelae.[152]

According to the results of these previous investigations, energy level was targeted to a minimum of 8.5 W in our procedures, as far as it was possible. Anterior parts of the PVs were treated with a maximum of 12 W of laser energy, whereas a maximum of 10 W was delivered at the posterior aspects. Laser energy of 5.5 W or 7 W was only used if it was required to perform energy delivery in areas near blood due to poor PV occlusion.[143, 152]

4.4. Procedure times

The recorded procedural data of the MERLIN registry showed a mean fluoroscopy time of 18 (15, 24) min, and a mean procedure time of 110 (100, 132) min. Procedure time, LA dwelling time and fluoroscopy time were significantly reduced along the learning curve (***Table 5 A, Figure 7 A, 7 B and 7 C***). An acceptable median procedure time of under 2 hours was achieved after 15 cases which could be reduced further to a median of around 90 min after 15 additional cases.[13]

A multicentric analysis of the first 200 patients undergoing PVI with the first generation VGLB presented by *Dukkipati et al.* reported on a mean fluoroscopy time of 31 min, and a mean procedure time of 200 min respectively, which improved with operator experience.[10] A meta-analysis by *Reynolds et al.* reported on similar times (183 min of procedure time and 28 mins of fluoroscopy time).[169] Our procedure and fluoroscopy times with LB2 were significantly shorter than the ones reported on the LB1. This showcases advantages of the further developments and new features of the LB2, that make the balloon easier to manipulate, and help operators achieve better visualization und tissue contact, which definitely leads to shorter procedure time and better results.[10, 13]

A short learning curve is essential for implementing novel technologies to clinical practice. Shortening has The LB2 offers a relatively short learning curve and seems to be a favorable system for physicians, especially beginners in VGLB based PVI procedures. A quick learning curve with significant reduction of procedure times even after 10 patients has similarly been reported using the LB1 by other authors.[142]

Procedure time, left atrial dwelling time and fluoroscopy time of ablation procedures using the LB2 was approximately at 110 min, 85 min and 15 min (***Table 5 A*** *and* ***Figure 7 A, 7 B*** and ***7 C***).[13] Procedure time, left atrial dwelling time and fluoroscopy times of RF procedures were reported at around 140 min, 110 min and 17 min; while those of CB procedures are around 120-140 min, 90-100 min, 20-27 min (CB2 vs CB1) (based on the data of the FIRE and ICE study).[7, 8] Comparing these data, PVI with the LB2 can be performed faster than an average RF PVI procedure and is comparable to procedure times of a CB PVI with the CB2.

4.5. Circular ablation of left common pulmonary veins

Anatomical variants of the PVs may pose technical challenges during AF-ablation.[119] The incidence of a LCPV in patients scheduled for PVI has been reported at 13-29%.[119, 175] In our cohort a LCPV was assessed in 11% of patients and thus in a considerably high proportion of patients. For RF procedures, anatomic variants such as LCPV were reported to be associated with procedural challenges, thus resulting in compromised lesion formation and lesion quality as well as impaired clinical outcomes.[175-177]

For CB based PVI the findings in patients with LCPV are controversial.[119, 154, 178] However, the CB is available at only two different balloon sizes (23 mm and 28 mm), therefore, its adaptability to variations of the PV-anatomy is limited. The LB2 offers the opportunity to adjust the balloon size in a continuous way up to 38 mm in diameter, which is the biggest possible balloon size by any energy source.

Using the LB2 resulted in a 100% antral LCPV occlusion rate and a 100% isolation rate after the initial circular ablation and 80% with zero rotational maneuvers. Therefore, no distal ablation of superior and inferior branches was necessary to achieve successful PVI which might be an advantage favoring the LB2 compared to fixed sizes of current and upcoming balloon devices (***Table 5 B, Figure 4 and 5***).[13] Remarkably, similar results were reported previously about successful ablation of LCPVs with the LB1.[9]

4.6. Safety

The rate of complications was relatively low in our study, major complications only occurred in 3 (6.7%) cases. No significant difference was observed between the groups (T1-T3), but with two periprocedural complications in group T1, one periprocedural complication in group T2 and no incidence of periprocedural complications in T3, a trend towards reduction of complications along the learning curve was found in our study (***Table 6***).[13]

Right phrenic nerve injury is reported as the most common complication of VGLB ablation, and is known to be characteristic complication of balloon-based procedures.[169, 179] For CB procedures reported rates are between 3.5 and 5.8%[123, 179], while for LB1 the reported rates are between 1.4 and 3,9%.[143, 144, 151, 169, 180] In our study, PNP occurred during only one (2.2%) procedure among the patient population. This case was unresolved at the 3-months follow-up, but the patient presented without any symptoms.[13]

The adaptability of the LB2 potentially allows a more proximal energy delivery, which may reduce the risk for nerve damage. Balloon catheters were suggested to have a reduced risk for cardiac tamponades by cardiac perforation due to larger surface area compared to single-tip ablations catheters.[143, 144, 151, 169, 180] In our population, one (2.2%) case of pericardial tamponade, which was not related to the LB2 occurred and was successfully treated by epicardial puncture and drainage. The patient recovered without any sequalae, and no surgical intervention was needed.[13]

Generally, incidence of periprocedural stroke or TIA using the LB1 were reported at a very low rate at around 1%, which is comparable to those occurring during RF or CB procedures (0.5%).[13] The incidence of so-called transient neurological complications in the FIRE AND ICE study were at 0.8% in the RF group, and at 0.3% in the CB group.[7, 8] In our population one (2.2%) case of periprocedural contrast-induced encephalopathy occurred. The symptoms completely resolved during the hospital stay. This complication is generally considered to be rather rare after administration of contrast media.[7, 8, 169]

A vascular complication occurred in only one (2.2%) patient of group T2. The patient developed a severe groin hematoma, which required blood transfusion.[13] No surgical intervention was necessary in this case, which is relatively low and also comparable to procedural data of the LB1, RF and CB ablation systems.[7, 8, 169]

All in all, based on our results, it may be concluded that performing PVI with the LB2 can be considered as a safe procedure with a low complication rate, which showed a tendency towards reduction of complications along the learning curve. It is important to emphasize though, that our registry presents procedural data of only one center and a relatively low number of procedures, and that all procedures were performed by operators who never used a VGLB system before but had great experience in RF and CB based procedures before.[13]

Pinhole ruptures

Incidence of pinhole ruptures decreased significantly over time, and 5 out of 7 pinholes in the first group (T1) happened in the first two cases, which demonstrates the learning curve effect very well. The operator needs to acquire and develop new technical skills and adopt refinements, while learning to use a new catheter ablation system. The MERLIN registry could show that the learning curve of the LB2 can already display a significant improvement over experience of 15 cases even with operators who had no previous experience using a LVGLB-based system before.[13]

To prevent mechanical pinholes the operators learned that they need to completely deflate the LB2 before pulling it into the sheath, preventing small injuries of the balloon. It is also key to achieve sufficient inflation of the LB2 to eliminate folds, and that no laser applications are performed on spots with blood if possible, or that in case of an imperfect view, power adjustment are implemented to 5.5-7 W sufficiently prevented hot pinholes.[13]

4.7. Limitations

The number of patients included in this study was relatively small and was only reflecting experience of a single center. The collection of long-term data is still ongoing. The MERLIN registry is only an observational study, and it mainly focused on the acute procedural data and safety of the LB2 for PVI. Further data assessment of multiple centers and investigation of a higher number of procedures with a longer observation period is required to assess the long-term efficacy and safety of PVI with the LB2. Our study also did not compare data of catheter ablation with the LB2 with other more established technologies, such as RF or CB PVI. Multicentric randomized controlled trials are needed to compare this technology with other ablation modalities for PVI.[13]

5. Conclusions and future prospects

The goal of the MERLIN registry was to report on the first clinical experience using the LB2 for PVI in patients with symptomatic AF. The ablation system was used by operators who had great experience in other EP procedures using RF and cryothermal energy but have never performed PVI with a LB before.[13]

We reported on procedural and clinical data about the first, second and third 15 patients undergoing PVI with the LB2. We have shown that he LB2 was effective for PVI even for operators without any previous experience in VGLB ablation procedures. Procedure time, LA dwelling time and fluoroscopy time significantly decreased along the learning curve. A high rate of successfully isolated PVs without balloon reposition was observed by utilizing the Arc Marks™ even in patients with LCPVs.[13]

Although the increased compliance of the system may improve visibility during the procedures, a relatively high rate of pinhole ruptures has been observed, especially in the beginning of the learning curve. By implementing pinhole prevention strategies, the rate of pinholes significantly decreased. Incidence of other conventional complications of PVI were relatively low, and comparable to RF and CB PVI. All in all, further investigations of a higher number of patients is necessary to draw final conclusions and to judge on safety and efficacy of this new promising system.[8, 13]

As this technology is new, long term clinical experience as well as high-volume prospective randomized multicenter trials are still sparse. The MERLIN registry was only a single center analysis examining a limited number of patients, and procedures were only performed by two operators. Follow-up data of our patients to see long-term results of PVI with the LB2 is still being collected, and we aim to report on these results in the near future.[13]

During our data collection for the MERLIN registry, a new generation of the LB has been introduced in 2019. The LB3 promises even faster and more efficient procedures due to a new RAPID™ mode (CardioFocus) feature which enables automatized continuous circular isolation of the PVs.[181-183]

In summary, the VGLB system is a promising new catheter technology, and PVI using the LB2 showed good acute efficacy and safety according to our results. It provides a fast learning curve with significantly improved procedural results (procedures times and complications) even after 15 patients.[13]

The currently popular technologies for PVI are ablation with RF and the CB. The great question regarding this new technology is, if the VGLB can compete with these modalities in the future, and what this new method can offer in comparison. The LB2 definitely seems to have an advantage in terms of balloon compliance, and the possibility of individualization of energy delivery matching each vein. This is especially advantageous in AF ablation procedures in patients with a LCPV or other anatomic PV variations.[13]

The LB2 system promises easier navigation and a simpler, more reproducible technique to learn in comparison to RF ablation procedures with a fast learning curve. Procedures with the LB1 were more time-consuming than RF or CB procedures, but our data using the LB2 shows comparable procedure times even during the first 45 procedures without no previous experience with VGLB systems.[13]

This disadvantage has been addressed further in the new generation of LB, where circumferential ablation can be performed by an automatic rotation of the laser beam. The new LB3 system seems to incorporate exciting developments in comparison to the LB2, which could enhance the popularity of the system even more. All in all, further investigation is necessary to draw final conclusions and to judge the safety and long-term efficacy of this promising new system.[13, 183]

6. References

1. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan G-A, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau J-P, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL and Group ESD. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *European Heart Journal*. 2020:1-125.

2. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB and Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998;98:946-52.

3. Calkins H, Hindricks G, Cappato R, Kim Y-H, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, Chen P-S, Chen S-A, Chung MK, Nielsen JC, Curtis AB, Davies DW, Day JD, D'Avila A, De Groot NMS, Di Biase L, Duytschaever M, Edgerton JR, Ellenbogen KA, Ellinor PT, Ernst S, Fenelon G, Gerstenfeld EP, Haines DE, Haissaguerre M, Helm RH, Hylek E, Jackman WM, Jalife J, Kalman JM, Kautzner J, Kottkamp H, Kuck KH, Kumagai K, Lee R, Lewalter T, Lindsay BD, Macle L, Mansour M, Marchlinski FE, Michaud GF, Nakagawa H, Natale A, Nattel S, Okumura K, Packer D, Pokushalov E, Reynolds MR, Sanders P, Scanavacca M, Schilling R, Tondo C, Tsao H-M, Verma A, Wilber DJ and Yamane T. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: Executive summary. *Heart Rhythm*. 2017;14:445-494.

4. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, Kim YH, Klein G, Natale A, Packer D, Skanes A, Ambrogi F and Biganzoli E. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2010;3:32-8.

5. Arora PK, Hansen JC, Price AD, Koblish J and Avitall B. An Update on the Energy Sources and Catheter Technology for the Ablation of Atrial Fibrillation. *J Atr Fibrillation*.

2010;2:233.

6. Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG, Dubuc M, Reddy V, Nelson L, Holcomb RG, Lehmann JW and Ruskin JN. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. *J Am Coll Cardiol*. 2013;61:1713-23.

7. Kuck KH, Brugada J, Fürnkranz A, Metzner A, Ouyang F, Chun KR, Elvan A, Arentz T, Bestehorn K, Pocock SJ, Albenque JP and Tondo C. Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. *N Engl J Med*. 2016;374:2235-45.

8. Kuck KH, Furnkranz A, Chun KR, Metzner A, Ouyang F, Schluter M, Elvan A, Lim HW, Kueffer FJ, Arentz T, Albenque JP, Tondo C, Kuhne M, Sticherling C and Brugada J. Cryoballoon or radiofrequency ablation for symptomatic paroxysmal atrial fibrillation: reintervention, rehospitalization, and quality-of-life outcomes in the FIRE AND ICE trial. *Eur Heart J*. 2016;37:2858-2865.

9. Schmidt B, Metzner A, Chun KR, Leftheriotis D, Yoshiga Y, Fuernkranz A, Neven K, Tilz RR, Wissner E, Ouyang F and Kuck KH. Feasibility of circumferential pulmonary vein isolation using a novel endoscopic ablation system. *Circ Arrhythm Electrophysiol*. 2010;3:481-488.

10. Dukkipati SR, Kuck KH, Neuzil P, Woollett I, Kautzner J, McElderry HT, Schmidt B, Gerstenfeld EP, Doshi SK, Horton R, Metzner A, d'Avila A, Ruskin JN, Natale A and Reddy VY. Pulmonary vein isolation using a visually guided laser balloon catheter: the first 200-patient multicenter clinical experience. *Circ Arrhythm Electrophysiol*. 2013;6:467-72.

11. Gerstenberg EP. How to Perform Pulmonary Vein Isolation Using Laser Catheter Ablation. In: A. Al-Ahmad, D. J. Callans, H. H. Hsia, A. Natale and P. J. Wang, eds. *Hands-On Ablation: The Experts' Approach, 2nd Edition* Minneapolis, Minnesota, USA: Cardiotext Publishing LCC.; 2017: 173-180.

12. Perrotta L, Bordignon S, Dugo D, Furnkranz A, Chun KJ and Schmidt B. How to learn pulmonary vein isolation with a novel ablation device: learning curve effects using the endoscopic ablation system. *J Cardiovasc Electrophysiol*. 2014;25:1293-1298.

13. Heeger CH, Phan HL, Meyer-Saraei R, Fink T, Sciacca V, Liosis S, Brüggemann B, Große N, Fahimi B, Sano M, Kuck KH, Ouyang F, Vogler J, Eitel C and Tilz RR. Second-Generation Visually Guided Laser Balloon Ablation System for Pulmonary Vein Isolation: Learning Curve, Safety and Efficacy - The MERLIN Registry. *Circ J*. 2019;83:2443-2451.

14. Stewart S, Hart CL, Hole DJ and McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med*. 2002;113:359-64.

15. Henriksson KM, Farahmand B, Asberg S, Edvardsson N and Terent A. Comparison of cardiovascular risk factors and survival in patients with ischemic or hemorrhagic stroke. *Int J Stroke*. 2012;7:276-81.

16. Grond M, Jauss M, Hamann G, Stark E, Veltkamp R, Nabavi D, Horn M, Weimar C, Kohrmann M, Wachter R, Rosin L and Kirchhof P. Improved detection of silent atrial fibrillation using 72-hour Holter ECG in patients with ischemic stroke: a prospective multicenter cohort study. *Stroke*. 2013;44:3357-64.

17. Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, Lip GY, Coats AJ, Andersson B, Kirchhof P, von Lueder TG, Wedel H, Rosano G, Shibata MC, Rigby A and Flather MD. Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. *Lancet*. 2014;384:2235-43.

18. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH, Jr., Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M and Murray CJ. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation*. 2014;129:837-47.

19. Zoni-Berisso M, Lercari F, Carazza T and Domenicucci S. Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol*. 2014;6:213-20.

20. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, Stijnen T, Lip GY and Witteman JC. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J*. 2006;27:949-53.

21. Kannel WB, Wolf PA, Benjamin EJ and Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol*.

1998;82:2n-9n.

22. Chiang CE, Naditch-Brule L, Murin J, Goethals M, Inoue H, O'Neill J, Silva-Cardoso J, Zharinov O, Gamra H, Alam S, Ponikowski P, Lewalter T, Rosenqvist M and Steg PG. Distribution and risk profile of paroxysmal, persistent, and permanent atrial fibrillation in routine clinical practice: insight from the real-life global survey evaluating patients with atrial fibrillation international registry. *Circ Arrhythm Electrophysiol*. 2012;5:632-9.

23. Abed HS, Wittert GA, Leong DP, Shirazi MG, Bahrami B, Middeldorp ME, Lorimer MF, Lau DH, Antic NA, Brooks AG, Abhayaratna WP, Kalman JM and Sanders P. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. *Jama*. 2013;310:2050-60.

24. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, Alasady M, Hanley L, Antic NA, McEvoy RD, Kalman JM, Abhayaratna WP and Sanders P. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol*. 2014;64:2222-31.

25. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Alexandru Popescu B, Schotten U, Van Putte B and Vardas P. 2016 ESC Guidelines for the Management of Atrial Fibrillation Developed in Collaboration With EACTS. *Rev Esp Cardiol (Engl Ed)*. 2017;70:50.

26. Kishore A, Vail A, Majid A, Dawson J, Lees KR, Tyrrell PJ and Smith CJ. Detection of atrial fibrillation after ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. *Stroke*. 2014;45:520-6.

27. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, Rymer MM, Thijs V, Rogers T, Beckers F, Lindborg K and Brachmann J. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med*. 2014;370:2478-86.

28. Olesen MS, Nielsen MW, Haunso S and Svendsen JH. Atrial fibrillation: the role of common and rare genetic variants. *Eur J Hum Genet*. 2014;22:297-306.

29. Sinner MF, Tucker NR, Lunetta KL, Ozaki K, Smith JG, Trompet S, Bis JC, Lin H, Chung MK, Nielsen JB, Lubitz SA, Krijthe BP, Magnani JW, Ye J, Gollob MH, Tsunoda T, Muller-Nurasyid M, Lichtner P, Peters A, Dolmatova E, Kubo M, Smith JD, Psaty BM, Smith NL, Jukema JW, Chasman DI, Albert CM, Ebana Y, Furukawa T, Macfarlane PW, Harris TB, Darbar D, Dorr M, Holst AG, Svendsen JH, Hofman A, Uitterlinden AG, Gudnason V, Isobe M, Malik R, Dichgans M, Rosand J, Van Wagoner DR, Benjamin EJ, Milan DJ, Melander O, Heckbert SR, Ford I, Liu Y, Barnard J, Olesen MS, Stricker BH, Tanaka T, Kaab S and Ellinor PT. Integrating genetic, transcriptional, and functional analyses to identify 5 novel genes for atrial fibrillation. *Circulation*. 2014;130:1225-35.

30. Nguyen BL, Fishbein MC, Chen LS, Chen PS and Masroor S. Histopathological substrate for chronic atrial fibrillation in humans. *Heart Rhythm*. 2009;6:454-60.

31. Chimenti C, Russo MA, Carpi A and Frustaci A. Histological substrate of human atrial fibrillation. *Biomed Pharmacother*. 2010;64:177-83.

32. Spach MS and Josephson ME. Initiating reentry: the role of nonuniform anisotropy in small circuits. *J Cardiovasc Electrophysiol*. 1994;5:182-209.

33. Allessie MA, de Groot NM, Houben RP, Schotten U, Boersma E, Smeets JL and Crijns HJ. Electropathological substrate of long-standing persistent atrial fibrillation in patients with structural heart disease: longitudinal dissociation. *Circ Arrhythm Electrophysiol*. 2010;3:606-15.

34. Lim HS, Willoughby SR, Schultz C, Gan C, Alasady M, Lau DH, Leong DP, Brooks AG, Young GD, Kistler PM, Kalman JM, Worthley MI and Sanders P. Effect of atrial fibrillation on atrial thrombogenesis in humans: impact of rate and rhythm. *J Am Coll Cardiol*. 2013;61:852-60.

35. Shinagawa K, Shi YF, Tardif JC, Leung TK and Nattel S. Dynamic nature of atrial fibrillation substrate during development and reversal of heart failure in dogs. *Circulation*. 2002;105:2672-8.

37. Lip GYH. The ABC pathway: an integrated approach to improve AF management. *Nat Rev Cardiol*. 2017;14:627-628.

38. Yang P-S, Sung J-H, Jang E, Yu HT, Kim T-H, Lip GYH and Joung B. Application

of the simple atrial fibrillation better care pathway for integrated care management in frail patients with atrial fibrillation: A nationwide cohort study. *Journal of arrhythmia*. 2020;36:668-677.

39. Kirchhof P, Breithardt G, Aliot E, Al Khatib S, Apostolakis S, Auricchio A, Bailleul C, Bax J, Benninger G, Blomstrom-Lundqvist C, Boersma L, Boriani G, Brandes A, Brown H, Brueckmann M, Calkins H, Casadei B, Clemens A, Crijns H, Derwand R, Dobrev D, Ezekowitz M, Fetsch T, Gerth A, Gillis A, Gulizia M, Hack G, Haegeli L, Hatem S, Häusler KG, Heidbüchel H, Hernandez-Brichis J, Jais P, Kappenberger L, Kautzner J, Kim S, Kuck KH, Lane D, Leute A, Lewalter T, Meyer R, Mont L, Moses G, Mueller M, Münzel F, Näbauer M, Nielsen JC, Oeff M, Oto A, Pieske B, Pisters R, Potpara T, Rasmussen L, Ravens U, Reiffel J, Richard-Lordereau I, Schäfer H, Schotten U, Stegink W, Stein K, Steinbeck G, Szumowski L, Tavazzi L, Themistoclakis S, Thomitzek K, Van Gelder IC, von Stritzky B, Vincent A, Werring D, Willems S, Lip GY and Camm AJ. Personalized management of atrial fibrillation: Proceedings from the fourth Atrial Fibrillation competence NETwork/European Heart Rhythm Association consensus conference. *Europace*. 2013;15:1540-56.

40. Hart RG, Pearce LA and Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146:857-67.

41. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T and Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383:955-62.

42. Al-Khatib SM, Allen LaPointe NM, Chatterjee R, Crowley MJ, Dupre ME, Kong DF, Lopes RD, Povsic TJ, Raju SS, Shah B, Kosinski AS, McBroom AJ and Sanders GD. Rate- and rhythm-control therapies in patients with atrial fibrillation: a systematic review. *Ann Intern Med*. 2014;160:760-73.

43. Siu CW, Lau CP, Lee WL, Lam KF and Tse HF. Intravenous diltiazem is superior to intravenous amiodarone or digoxin for achieving ventricular rate control in patients with acute uncomplicated atrial fibrillation. *Crit Care Med*. 2009;37:2174-9.

44. Scheuermeyer FX, Grafstein E, Stenstrom R, Christenson J, Heslop C, Heilbron B, McGrath L and Innes G. Safety and efficiency of calcium channel blockers versus beta-blockers for rate control in patients with atrial fibrillation and no acute underlying medical illness. *Acad Emerg Med*. 2013;20:222-30.

45. Goldstein RE, Boccuzzi SJ, Cruess D and Nattel S. Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. The Adverse Experience Committee; and the Multicenter Diltiazem Postinfarction Research Group. *Circulation*. 1991;83:52-60.

46. Elkayam U. Calcium channel blockers in heart failure. *Cardiology*. 1998;89 Suppl 1:38-46.

47. Van Gelder IC, Wyse DG, Chandler ML, Cooper HA, Olshansky B, Hagens VE and Crijns HJ. Does intensity of rate-control influence outcome in atrial fibrillation? An analysis of pooled data from the RACE and AFFIRM studies. *Europace*. 2006;8:935-42.

48. Van Gelder IC, Groenveld HF, Crijns HJ, Tuininga YS, Tijssen JG, Alings AM, Hillege HL, Bergsma-Kadijk JA, Cornel JH, Kamp O, Tukkie R, Bosker HA, Van Veldhuisen DJ and Van den Berg MP. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med*. 2010;362:1363-73.

49. Groenveld HF, Crijns HJ, Van den Berg MP, Van Sonderen E, Alings AM, Tijssen JG, Hillege HL, Tuininga YS, Van Veldhuisen DJ, Ranchor AV and Van Gelder IC. The effect of rate control on quality of life in patients with permanent atrial fibrillation: data from the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation II) study. *J Am Coll Cardiol*. 2011;58:1795-803.

50. Queiroga A, Marshall HJ, Clune M and Gammage MD. Ablate and pace revisited: long term survival and predictors of permanent atrial fibrillation. *Heart*. 2003;89:1035-8.

51. Lim KT, Davis MJ, Powell A, Arnolda L, Moulden K, Bulsara M and Weerasooriya R. Ablate and pace strategy for atrial fibrillation: long-term outcome of AIRCRAFT trial. *Europace*. 2007;9:498-505.

52. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde

C, Mont L, Padeletti L, Sutton R, Vardas PE, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Kirchhof P, Blomstrom-Lundqvist C, Badano LP, Aliyev F, Bansch D, Baumgartner H, Bsata W, Buser P, Charron P, Daubert JC, Dobreanu D, Faerestrand S, Hasdai D, Hoes AW, Le Heuzey JY, Mavrakis H, McDonagh T, Merino JL, Nawar MM, Nielsen JC, Pieske B, Poposka L, Ruschitzka F, Tendera M, Van Gelder IC and Wilson CM. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J*. 2013;34:2281-329.

53. Chatterjee NA, Upadhyay GA, Ellenbogen KA, Hayes DL and Singh JP. Atrioventricular nodal ablation in atrial fibrillation: a meta-analysis of biventricular vs. right ventricular pacing mode. *Eur J Heart Fail*. 2012;14:661-7.

54. Ganesan AN, Brooks AG, Roberts-Thomson KC, Lau DH, Kalman JM and Sanders P. Role of AV nodal ablation in cardiac resynchronization in patients with coexistent atrial fibrillation and heart failure a systematic review. *J Am Coll Cardiol*. 2012;59:719-26.

55. Jenkins LS, Brodsky M, Schron E, Chung M, Rocco T, Jr., Lader E, Constantine M, Sheppard R, Holmes D, Mateski D, Floden L, Prasun M, Greene HL and Shemanski L. Quality of life in atrial fibrillation: the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Am Heart J*. 2005;149:112-20.

56. Hagens VE, Ranchor AV, Van Sonderen E, Bosker HA, Kamp O, Tijssen JG, Kingma JH, Crijns HJ and Van Gelder IC. Effect of rate or rhythm control on quality of life in persistent atrial fibrillation. Results from the Rate Control Versus Electrical Cardioversion (RACE) Study. *J Am Coll Cardiol*. 2004;43:241-7.

57. Carlsson J, Miketic S, Windeler J, Cuneo A, Haun S, Micus S, Walter S and Tebbe U. Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. *J Am Coll Cardiol*. 2003;41:1690-6.

58. Gronefeld GC, Lilienthal J, Kuck KH and Hohnloser SH. Impact of rate versus rhythm control on quality of life in patients with persistent atrial fibrillation. Results from a prospective randomized study. *Eur Heart J*. 2003;24:1430-6.

59. Opolski G, Torbicki A, Kosior DA, Szulc M, Wozakowska-Kaplon B, Kolodziej P and Achremczyk P. Rate control vs rhythm control in patients with nonvalvular persistent atrial fibrillation: the results of the Polish How to Treat Chronic Atrial Fibrillation (HOT CAFE) Study. *Chest*. 2004;126:476-86.

60. Thrall G, Lane D, Carroll D and Lip GY. Quality of life in patients with atrial fibrillation: a systematic review. *Am J Med*. 2006;119:448.e1-19.

61. de Denus S, Sanoski CA, Carlsson J, Opolski G and Spinler SA. Rate vs rhythm control in patients with atrial fibrillation: a meta-analysis. *Arch Intern Med*. 2005;165:258-62.

62. Noheria A, Shrader P, Piccini JP, Fonarow GC, Kowey PR, Mahaffey KW, Naccarelli G, Noseworthy PA, Reiffel JA, Steinberg BA, Thomas LE, Peterson ED and Gersh BJ. Rhythm Control Versus Rate Control and Clinical Outcomes in Patients With Atrial Fibrillation: Results From the ORBIT-AF Registry. *JACC Clin Electrophysiol*. 2016;2:221-229.

63. Khan IA. Oral loading single dose flecainide for pharmacological cardioversion of recent-onset atrial fibrillation. *Int J Cardiol*. 2003;87:121-8.

64. Chevalier P, Durand-Dubief A, Burri H, Cucherat M, Kirkorian G and Touboul P. Amiodarone versus placebo and class Ic drugs for cardioversion of recent-onset atrial fibrillation: a meta-analysis. *J Am Coll Cardiol*. 2003;41:255-62.

65. Khan IA, Mehta NJ and Gowda RM. Amiodarone for pharmacological cardioversion of recent-onset atrial fibrillation. *Int J Cardiol*. 2003;89:239-48.

66. Letelier LM, Udol K, Ena J, Weaver B and Guyatt GH. Effectiveness of amiodarone for conversion of atrial fibrillation to sinus rhythm: a meta-analysis. *Arch Intern Med*. 2003;163:777-85.

67. Alboni P, Botto GL, Baldi N, Luzi M, Russo V, Gianfranchi L, Marchi P, Calzolari

M, Solano A, Baroffio R and Gaggioli G. Outpatient treatment of recent-onset atrial fibrillation with the "pill-in-the-pocket" approach. *N Engl J Med*. 2004;351:2384-91.

68. Reisinger J, Gatterer E, Lang W, Vanicek T, Eisserer G, Bachleitner T, Niemeth C, Aicher F, Grander W, Heinze G, Kuhn P and Siostrzonek P. Flecainide versus ibutilide for immediate cardioversion of atrial fibrillation of recent onset. *Eur Heart J*. 2004;25:1318-24.

69. Khan IA. Single oral loading dose of propafenone for pharmacological cardioversion of recent-onset atrial fibrillation. *J Am Coll Cardiol*. 2001;37:542-7.

70. Stambler BS, Wood MA, Ellenbogen KA, Perry KT, Wakefield LK and VanderLugt JT. Efficacy and safety of repeated intravenous doses of ibutilide for rapid conversion of atrial flutter or fibrillation. Ibutilide Repeat Dose Study Investigators. *Circulation*. 1996;94:1613-21.

71. Savelieva I, Graydon R and Camm AJ. Pharmacological cardioversion of atrial fibrillation with vernakalant: evidence in support of the ESC Guidelines. *Europace*. 2014;16:162-73.

72. Kirchhof P, Monnig G, Wasmer K, Heinecke A, Breithardt G, Eckardt L and Bocker D. A trial of self-adhesive patch electrodes and hand-held paddle electrodes for external cardioversion of atrial fibrillation (MOBIPAPA). *Eur Heart J*. 2005;26:1292-7.

73. Kirchhof P, Andresen D, Bosch R, Borggrefe M, Meinertz T, Parade U, Ravens U, Samol A, Steinbeck G, Treszl A, Wegscheider K and Breithardt G. Short-term versus long-term antiarrhythmic drug treatment after cardioversion of atrial fibrillation (Flec-SL): a prospective, randomised, open-label, blinded endpoint assessment trial. *Lancet*. 2012;380:238-46.

74. Chen WS, Gao BR, Chen WQ, Li ZZ, Xu ZY, Zhang YH, Yang K and Guan XQ. Comparison of pharmacological and electrical cardioversion in permanent atrial fibrillation after prosthetic cardiac valve replacement: a prospective randomized trial. *J Int Med Res*. 2013;41:1067-73.

75. Gitt AK, Smolka W, Michailov G, Bernhardt A, Pittrow D and Lewalter T. Types and outcomes of cardioversion in patients admitted to hospital for atrial fibrillation: results of the German RHYTHM-AF Study. *Clin Res Cardiol*. 2013;102:713-23.

76. Crijns HJ, Weijs B, Fairley AM, Lewalter T, Maggioni AP, Martin A, Ponikowski P, Rosenqvist M, Sanders P, Scanavacca M, Bash LD, Chazelle F, Bernhardt A, Gitt AK, Lip GY and Le Heuzey JY. Contemporary real life cardioversion of atrial fibrillation: Results from the multinational RHYTHM-AF study. *Int J Cardiol*. 2014;172:588-94.

77. Williams EV. Symposium on Cardiac Arrhythmias. 1970.

78. Vaughan Williams EM. Classification of Antiarrhythmic Actions. In: E. M. Vaughan Williams, ed. *Antiarrhythmic Drugs* Berlin, Heidelberg: Springer Berlin Heidelberg; 1989: 45-67.

79. Rang HPR, James M.; Flower, Rod J.; Henderson, Graeme Rang and Dale's pharmacology (7th ed.): Elsevier; 2012: 255.

80. Lei M, Wu L, Terrar DA and Huang CL. Modernized Classification of Cardiac Antiarrhythmic Drugs. *Circulation*. 2018;138:1879-1896.

81. Roy D, Talajic M, Dorian P, Connolly S, Eisenberg MJ, Green M, Kus T, Lambert J, Dubuc M, Gagne P, Nattel S and Thibault B. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. *N Engl J Med*. 2000;342:913-20.

82. Lafuente-Lafuente C, Longas-Tejero MA, Bergmann JF and Belmin J. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. *Cochrane Database Syst Rev*. 2012:Cd005049.

83. Valembois L, Audureau E, Takeda A, Jarzebowski W, Belmin J and Lafuente-Lafuente C. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. *Cochrane Database of Systematic Reviews*. 2019.

84. Investigators TCASTC. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med*. 1989;321:406-12.

85. Freemantle N, Lafuente-Lafuente C, Mitchell S, Eckert L and Reynolds M. Mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation. *Europace*. 2011;13:329-45.

86. Goldschlager N, Epstein AE, Naccarelli GV, Olshansky B, Singh B, Collard HR and Murphy E. A practical guide for clinicians who treat patients with amiodarone: 2007. *Heart Rhythm*. 2007;4:1250-9.

87. Ahmed S, Rienstra M, Crijns HJ, Links TP, Wiesfeld AC, Hillege HL, Bosker HA, Lok DJ, Van Veldhuisen DJ and Van Gelder IC. Continuous vs episodic prophylactic treatment with amiodarone for the prevention of atrial fibrillation: a randomized trial. *Jama*. 2008;300:1784-92.

88. Arbelo E, Brugada J, Hindricks G, Maggioni AP, Tavazzi L, Vardas P, Laroche C, Anselme F, Inama G, Jais P, Kalarus Z, Kautzner J, Lewalter T, Mairesse GH, Perez-Villacastin J, Riahi S, Taborsky M, Theodorakis G and Trines SA. The atrial fibrillation ablation pilot study: a European Survey on Methodology and results of catheter ablation for atrial fibrillation conducted by the European Heart Rhythm Association. *Eur Heart J*. 2014;35:1466-78.

89. Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, Williams CJ and Sledge I. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. *Circ Arrhythm Electrophysiol*. 2009;2:349-61.

90. Darkner S, Chen X, Hansen J, Pehrson S, Johannessen A, Nielsen JB and Svendsen JH. Recurrence of arrhythmia following short-term oral AMIOdarone after CATheter ablation for atrial fibrillation: a double-blind, randomized, placebo-controlled study (AMIO-CAT trial). *Eur Heart J*. 2014;35:3356-64.

91. Andersen HR, Nielsen JC, Thomsen PE, Thuesen L, Mortensen PT, Vesterlund T and Pedersen AK. Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinus syndrome. *Lancet*. 1997;350:1210-6.

92. Connolly SJ, Kerr CR, Gent M, Roberts RS, Yusuf S, Gillis AM, Sami MH, Talajic M, Tang AS, Klein GJ, Lau C and Newman DM. Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. Canadian Trial of Physiologic Pacing Investigators. *N Engl J Med*. 2000;342:1385-91.

93. Saksena S, Prakash A, Ziegler P, Hummel JD, Friedman P, Plumb VJ, Wyse DG, Johnson E, Fitts S and Mehra R. Improved suppression of recurrent atrial fibrillation with

dual-site right atrial pacing and antiarrhythmic drug therapy. *J Am Coll Cardiol*. 2002;40:1140-50; discussion 1151-2.

94. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Metayer P and Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med*. 1998;339:659-66.

95. Cosedis Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Kongstad O, Pehrson S, Englund A, Hartikainen J, Mortensen LS and Hansen PS. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. *N Engl J Med*. 2012;367:1587-95.

96. Mont L, Bisbal F, Hernandez-Madrid A, Perez-Castellano N, Vinolas X, Arenal A, Arribas F, Fernandez-Lozano I, Bodegas A, Cobos A, Matia R, Perez-Villacastin J, Guerra JM, Avila P, Lopez-Gil M, Castro V, Arana JI and Brugada J. Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). *Eur Heart J*. 2014;35:501-7.

97. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, Chen PS, Chen SA, Chung MK, Nielsen JC, Curtis AB, Davies DW, Day JD, d'Avila A, de Groot N, Di Biase L, Duytschaever M, Edgerton JR, Ellenbogen KA, Ellinor PT, Ernst S, Fenelon G, Gerstenfeld EP, Haines DE, Haissaguerre M, Helm RH, Hylek E, Jackman WM, Jalife J, Kalman JM, Kautzner J, Kottkamp H, Kuck KH, Kumagai K, Lee R, Lewalter T, Lindsay BD, Macle L, Mansour M, Marchlinski FE, Michaud GF, Nakagawa H, Natale A, Nattel S, Okumura K, Packer D, Pokushalov E, Reynolds MR, Sanders P, Scanavacca M, Schilling R, Tondo C, Tsao HM, Verma A, Wilber DJ and Yamane T. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm*. 2017;14:e275-e444.

98. Mark DB, Anstrom KJ, Sheng S, Piccini JP, Baloch KN, Monahan KH, Daniels MR, Bahnson TD, Poole JE, Rosenberg Y, Lee KL and Packer DL. Effect of Catheter Ablation vs Medical Therapy on Quality of Life Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. *Jama*. 2019;321:1275-1285.

99. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L,

Merkely B, Pokushalov E, Sanders P, Proff J, Schunkert H, Christ H, Vogt J and Bänsch D. Catheter Ablation for Atrial Fibrillation with Heart Failure. *New England Journal of Medicine*. 2018;378:417-427.

100. Ganesan AN, Shipp NJ, Brooks AG, Kuklik P, Lau DH, Lim HS, Sullivan T, Roberts-Thomson KC and Sanders P. Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *J Am Heart Assoc*. 2013;2:e004549.

101. Heeger CH, Wissner E, Knoll M, Knoop B, Reissmann B, Mathew S, Sohns C, Lemes C, Maurer T, Santoro F, Riedl J, Inaba O, Fink T, Rottner L, Wohlmuth P, Goldmann B, Ouyang F, Kuck KH and Metzner A. Three-Year Clinical Outcome After 2nd-Generation Cryoballoon-Based Pulmonary Vein Isolation for the Treatment of Paroxysmal and Persistent Atrial Fibrillation- A 2-Center Experience. *Circ J*. 2017;81:974-980.

102. Tilz RR, Heeger C-H, Wick A, Saguner AM, Metzner A, Rillig A, Wohlmuth P, Reissmann B, Lemeš C, Maurer T, Santoro F, Riedl J, Sohns C, Mathew S, Kuck K-H and Ouyang F. Ten-Year Clinical Outcome After Circumferential Pulmonary Vein Isolation Utilizing the Hamburg Approach in Patients With Symptomatic Drug-Refractory Paroxysmal Atrial Fibrillation. *Circulation: Arrhythmia and Electrophysiology*. 2018;11:e005250.

103. Lee G, Sparks PB, Morton JB, Kistler PM, Vohra JK, Medi C, Rosso R, Teh A, Halloran K and Kalman JM. Low risk of major complications associated with pulmonary vein antral isolation for atrial fibrillation: results of 500 consecutive ablation procedures in patients with low prevalence of structural heart disease from a single center. *J Cardiovasc Electrophysiol*. 2011;22:163-8.

104. Gupta A, Perera T, Ganesan A, Sullivan T, Lau DH, Roberts-Thomson KC, Brooks AG and Sanders P. Complications of catheter ablation of atrial fibrillation: a systematic review. *Circ Arrhythm Electrophysiol*. 2013;6:1082-8.

105. Berger WR, Meulendijks ER, Limpens J, van den Berg NWE, Neefs J, Driessen AHG, Krul SPJ, van Boven WJP and de Groot JR. Persistent atrial fibrillation: A systematic review and meta-analysis of invasive strategies. *Int J Cardiol*. 2019;278:137-143.

106. Neuzil P, Reddy VY, Kautzner J, Petru J, Wichterle D, Shah D, Lambert H, Yulzari A, Wissner E and Kuck KH. Electrical reconnection after pulmonary vein isolation is

contingent on contact force during initial treatment: results from the EFFICAS I study. *Circ Arrhythm Electrophysiol*. 2013;6:327-33.

107. Kautzner J, Neuzil P, Lambert H, Peichl P, Petru J, Cihak R, Skoda J, Wichterle D, Wissner E, Yulzari A and Kuck KH. EFFICAS II: optimization of catheter contact force improves outcome of pulmonary vein isolation for paroxysmal atrial fibrillation. *Europace*. 2015;17:1229-35.

108. Nakagawa H, Ikeda A, Govari A, Papaioannou T, Constantine G, Bar-Tal M, Silberschein E, Saba-Keren E, Rubissa A, Sharma T, Pitha JV, Lazzara R and Jackman WM. Abstract 12104: Prospective Study Using a New Formula Incorporating Contact Force, Radiofrequency Power and Application Time (Force-Power-Time Index) for Quantifying Lesion Formation to Guide Long Continuous Atrial lesions in the Beating Canine Heart. *Circulation*. 2013;128:A12104-A12104.

109. Das M, Loveday JJ, Wynn GJ, Gomes S, Saeed Y, Bonnett LJ, Waktare JEP, Todd DM, Hall MCS, Snowdon RL, Modi S and Gupta D. Ablation index, a novel marker of ablation lesion quality: prediction of pulmonary vein reconnection at repeat electrophysiology study and regional differences in target values. *Europace*. 2017;19:775-783.

110. Haines DE. Biophysics and Pathophysiology of Lesion Formation by Transcatheter Radiofrequency Ablation *Catheter Ablation of Cardiac Arrhythmias*; 2007: 20-34.

111. Haines DE, Strunk AR, Novichenok A, Kirchhof N and Stewart M. The Biophysics of Passive Convective Cooling During Catheter Ablation with Gold versus Platinum Electrodes and Multielectrode Phased Radiofrequency Energy Delivery. *J Cardiovasc Electrophysiol*. 2015;26:1257-1261.

112. Nakagawa H, Yamanashi WS, Pitha JV, Arruda M, Wang X, Ohtomo K, Beckman KJ, McClelland JH, Lazzara R and Jackman WM. Comparison of In Vivo Tissue Temperature Profile and Lesion Geometry for Radiofrequency Ablation With a Saline-Irrigated Electrode Versus Temperature Control in a Canine Thigh Muscle Preparation. *Circulation*. 1995;91:2264-2273.

113. Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, Macle L, Morillo CA, Haverkamp W, Weerasooriya R, Albenque JP, Nardi S, Menardi E, Novak P and

Sanders P. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med*. 2015;372:1812-22.

114. Mont L, Bisbal F, Hernández-Madrid A, Pérez-Castellano N, Viñolas X, Arenal A, Arribas F, Fernández-Lozano I, Bodegas A, Cobos A, Matía R, Pérez-Villacastín J, Guerra JM, Ávila P, López-Gil M, Castro V, Arana JI and Brugada J. Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). *Eur Heart J*. 2014;35:501-7.

115. Straube F, Dorwarth U, Schmidt M, Wankerl M, Ebersberger U and Hoffmann E. Comparison of the first and second cryoballoon: high-volume single-center safety and efficacy analysis. *Circ Arrhythm Electrophysiol*. 2014;7:293-9.

116. Fürnkranz A, Bordignon S, Dugo D, Perotta L, Gunawardene M, Schulte-Hahn B, Nowak B, Schmidt B and Chun JKR. Improved 1-year clinical success rate of pulmonary vein isolation with the second-generation cryoballoon in patients with paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol*. 2014;25:840-844.

117. Ciconte G, Baltogiannis G, de Asmundis C, Sieira J, Conte G, Di Giovanni G, Saitoh Y, Irfan G, Mugnai G, Hunuk B, Chierchia GB and Brugada P. Circumferential pulmonary vein isolation as index procedure for persistent atrial fibrillation: a comparison between radiofrequency catheter ablation and second-generation cryoballoon ablation. *Europace*. 2015;17:559-65.

118. Ciconte G, Ottaviano L, de Asmundis C, Baltogiannis G, Conte G, Sieira J, Di Giovanni G, Saitoh Y, Irfan G, Mugnai G, Storti C, Montenero AS, Chierchia GB and Brugada P. Pulmonary vein isolation as index procedure for persistent atrial fibrillation: One-year clinical outcome after ablation using the second-generation cryoballoon. *Heart Rhythm*. 2015;12:60-6.

119. Heeger CH, Tscholl V, Wissner E, Fink T, Rottner L, Wohlmuth P, Bellmann B, Roser M, Mathew S, Sohns C, Reissmann B, Lemes C, Maurer T, Santoro F, Riedl J, Goldmann B, Landmesser U, Ouyang F, Kuck KH, Rillig A and Metzner A. Acute efficacy, safety, and long-term clinical outcomes using the second-generation cryoballoon for pulmonary vein isolation in patients with a left common pulmonary vein: A multicenter study. *Heart rhythm : the official journal of the Heart Rhythm Society*. 2017;14:1111-1118.

120. Brito VG, N V, L T, Jj J, I M, L B, S O, S R, G A, A G and F S. Second Generation Cryoballoon vs. Radiofrequency Ablation in Paroxysmal Atrial Fibrillation: Outcomes Beyond One-Year Follow-up. *J Atr Fibrillation*. 2019;11:2147.

121. Mugnai G, Chierchia GB, de Asmundis C, Sieira-Moret J, Conte G, Capulzini L, Wauters K, Rodriguez-Mañero M, Di Giovanni G, Baltogiannis G, Ciconte G, Saitoh Y, Juliá J and Brugada P. Comparison of pulmonary vein isolation using cryoballoon versus conventional radiofrequency for paroxysmal atrial fibrillation. *Am J Cardiol*. 2014;113:1509-13.

122. Aryana A, Bowers MR and O'Neill PG. Outcomes Of Cryoballoon Ablation Of Atrial Fibrillation: A Comprehensive Review. *J Atr Fibrillation*. 2015;8:1231.

123. Luik A, Radzewitz A, Kieser M, Walter M, Bramlage P, Hormann P, Schmidt K, Horn N, Brinkmeier-Theofanopoulou M, Kunzmann K, Riexinger T, Schymik G, Merkel M and Schmitt C. Cryoballoon Versus Open Irrigated Radiofrequency Ablation in Patients With Paroxysmal Atrial Fibrillation: The Prospective, Randomized, Controlled, Noninferiority FreezeAF Study. *Circulation*. 2015;132:1311-9.

124. Providencia R, Defaye P, Lambiase PD, Pavin D, Cebron J-P, Halimi F, Anselme F, Srinivasan N, Albenque J-P and Boveda S. Results from a multicentre comparison of cryoballoon vs. radiofrequency ablation for paroxysmal atrial fibrillation: is cryoablation more reproducible? *EP Europace*. 2016;19:48-57.

125. Heeger CH, Abdin A, Mathew S, Reissmann B, Yalin K, Liosis S, Fink T, Proietti R, Eitel C, Vogler J, Lemes C, Maurer T, Rillig A, Meyer-Saraei R, Graf T, Wohlmuth P, Goldmann B, Ouyang F, Kuck KH, Metzner A and Tilz RR. Efficacy and Safety of Cryoballoon Ablation in Patients With Heart Failure and Reduced Left Ventricular Ejection Fraction- A Multicenter Study. *Circ J*. 2019;83:1653-1659.

126. Murray MI, Arnold A, Younis M, Varghese S and Zeiher AM. Cryoballoon versus radiofrequency ablation for paroxysmal atrial fibrillation: a meta-analysis of randomized controlled trials. *Clin Res Cardiol*. 2018;107:658-669.

127. Schmidt B, Chun KR, Kuck KH and Antz M. Pulmonary vein isolation by high intensity focused ultrasound. *Indian Pacing Electrophysiol J*. 2007;7:126-33.

128. Schmidt B, Antz M, Ernst S, Ouyang F, Falk P, Chun JK and Kuck KH. Pulmonary vein isolation by high-intensity focused ultrasound: first-in-man study with a steerable balloon catheter. *Heart Rhythm*. 2007;4:575-84.

129. Borchert B, Lawrenz T, Hansky B and Stellbrink C. Lethal atrioesophageal fistula after pulmonary vein isolation using high-intensity focused ultrasound (HIFU). *Heart Rhythm*. 2008;5:145-8.

130. Metzner A, Chun KR, Neven K, Fuernkranz A, Ouyang F, Antz M, Tilz R, Zerm T, Koektuerk B, Wissner E, Koester I, Ernst S, Boczor S, Kuck KH and Schmidt B. Long-term clinical outcome following pulmonary vein isolation with high-intensity focused ultrasound balloon catheters in patients with paroxysmal atrial fibrillation. *Europace*. 2010;12:188-93.

131. Koruth JS, Schneider C, Avitall B, Ribeiro L, Dukkipati S, Walcott GP, Phillips P, McElderry HT and Reddy VY. Pre-Clinical Investigation of a Low-Intensity Collimated Ultrasound System for Pulmonary Vein Isolation in a Porcine Model. *JACC: Clinical Electrophysiology*. 2015;1:306-314.

132. Turagam MK, Petru J, Neuzil P, Kakita K, Kralovec S, Harari D, Phillips P, Piazza D, Whang W, Dukkipati SR and Reddy VY. Automated Noncontact Ultrasound Imaging and Ablation System for the Treatment of Atrial Fibrillation. *Circulation: Arrhythmia and Electrophysiology*. 2020;13:e007917.

133. Sohara H, Satake S, Takeda H, Yamaguchi Y, Toyama H, Kumagai K, Kuwahara T, Takahashi A and Ohe T. Radiofrequency hot balloon catheter ablation for the treatment of atrial fibrillation: A 3-center study in Japan. *Journal of Arrhythmia*. 2013;29:20-27.

134. Nagashima K, Okumura Y, Watanabe I, Nakahara S, Hori Y, Iso K, Watanabe R, Arai M, Wakamatsu Y, Kurokawa S, Mano H, Nakai T, Ohkubo K and Hirayama A. Hot Balloon Versus Cryoballoon Ablation for Atrial Fibrillation: Lesion Characteristics and Middle-Term Outcomes. *Circ Arrhythm Electrophysiol*. 2018;11:e005861.

135. Wakamatsu Y, Nagashima K, Nakahara S, Iso K, Watanabe R, Arai M, Otsuka N, Yagyu S, Kurokawa S, Ohkubo K, Nakai T and Okumura Y. Electrophysiologic and anatomic factors predictive of a need for touch-up radiofrequency application for complete pulmonary vein isolation: Comparison between hot balloon- and cryoballoon-based ablation. *J Cardiovasc Electrophysiol*. 2019;30:1261-1269.

136. Al-Ahmad A, Aidietis A and Daly M, et al. . Assessment of the safety and performance of a novel RF balloon catheter system to isolate pulmonary veins: results of the multicenter AF-FICIENT Trial. Paper presented at: EuropeanHeart Rhythm Association Scientific Sessions; 2019; Lisbon, Portugal.

137. Dhillon GS, Honarbakhsh S, Di Monaco A, Coling AE, Lenka K, Pizzamiglio F, Hunter RJ, Horton R, Mansour M, Natale A, Reddy V, Grimaldi M, Neuzil P, Tondo C and Schilling RJ. Use of a multi-electrode radiofrequency balloon catheter to achieve pulmonary vein isolation in patients with paroxysmal atrial fibrillation: 12-Month outcomes of the RADIANCE study. *J Cardiovasc Electrophysiol*. 2020;31:1259-1269.

138. Reddy VY, Schilling R, Grimaldi M, Horton R, Natale A, Riva S, Tondo C, Kuck KH, Neuzil P, McInnis K, Bishara M, Zhang B, Govari A, Abdelaal A and Mansour M. Pulmonary Vein Isolation With a Novel Multielectrode Radiofrequency Balloon Catheter That Allows Directionally Tailored Energy Delivery: Short-Term Outcomes From a Multicenter First-in-Human Study (RADIANCE). *Circ Arrhythm Electrophysiol*. 2019;12:e007541.

139. Kottkamp H, Moser F, Rieger A, Schreiber D, Pönisch C and Trofin M. Global multielectrode contact mapping plus ablation with a single catheter: Preclinical and preliminary experience in humans with atrial fibrillation. *J Cardiovasc Electrophysiol*. 2017;28:1247-1256.

140. Mounsey JP. A novel multielectrode combined mapping and ablation basket catheter: A future player in the atrial fibrillation ablation space? *J Cardiovasc Electrophysiol*. 2017;28:1257-1258.

141. Metzner A, Wissner E, Schoonderwoerd B, Burchard A, Tilz R, Furnkranz A, Rillig A, Mathew S, Ouyang F and Kuck KH. The influence of varying energy settings on efficacy and safety of endoscopic pulmonary vein isolation. *Heart rhythm : the official journal of the Heart Rhythm Society*. 2012;9:1380-5.

142. Schmidt B, Metzner A, Chun KR, Leftheriotis D, Yoshiga Y, Fuernkranz A, Neven K, Tilz RR, Wissner E, Ouyang F and Kuck KH. Feasibility of circumferential pulmonary vein isolation using a novel endoscopic ablation system. *Circulation Arrhythmia and electrophysiology*. 2010;3:481-8.

143. Nagase T, Bordignon S, Perrotta L, Bologna F, Tsianakas N, Chen S, Konstantinou A, Chun JKR and Schmidt B. Analysis of procedural data of pulmonary vein isolation for atrial fibrillation with the second-generation laser balloon. *Pacing and clinical electrophysiology : PACE*. 2019;42:837-845.

144. Perrotta L, Bordignon S, Dugo D, Furnkranz A, Chun KJ and Schmidt B. How to learn pulmonary vein isolation with a novel ablation device: learning curve effects using the endoscopic ablation system. *Journal of cardiovascular electrophysiology*. 2014;25:1293-8.

145. Schmidt B, Gunawardene M, Urban V, Kulikoglu M, Schulte-Hahn B, Nowak B, Bordignon S and Chun KJ. Visually guided sequential pulmonary vein isolation: insights into techniques and predictors of acute success. *J Cardiovasc Electrophysiol*. 2012;23:576-582.

146. Deshmukh A, Patel NJ, Pant S, Shah N, Chothani A, Mehta K, Grover P, Singh V, Vallurupalli S, Savani GT, Badheka A, Tuliani T, Dabhadkar K, Dibu G, Reddy YM, Sewani A, Kowalski M, Mitrani R, Paydak H and Viles-Gonzalez JF. In-hospital complications associated with catheter ablation of atrial fibrillation in the United States between 2000 and 2010: analysis of 93 801 procedures. *Circulation*. 2013;128:2104-12.

147. Cox JL, Boineau JP, Schuessler RB, Ferguson TB, Jr., Cain ME, Lindsay BD, Corr PB, Kater KM and Lappas DG. Successful surgical treatment of atrial fibrillation. Review and clinical update. *Jama*. 1991;266:1976-80.

148. Huffman MD, Karmali KN, Berendsen MA, Andrei AC, Kruse J, McCarthy PM and Malaisrie SC. Concomitant atrial fibrillation surgery for people undergoing cardiac surgery. *Cochrane Database Syst Rev*. 2016:Cd011814.

149. Dukkipati SR, Neuzil P, Kautzner J, Petru J, Wichterle D, Skoda J, Cihak R, Peichl P, Dello Russo A, Pelargonio G, Tondo C, Natale A and Reddy VY. The durability of pulmonary vein isolation using the visually guided laser balloon catheter: multicenter results of pulmonary vein remapping studies. *Heart rhythm : the official journal of the Heart Rhythm Society*. 2012;9:919-25.

150. Dukkipati SR, Cuoco F, Kutinsky I, Aryana A, Bahnson TD, Lakkireddy D, Woollett I, Issa ZF, Natale A, Reddy VY and HeartLight Study I. Pulmonary Vein Isolation Using the Visually Guided Laser Balloon: A Prospective, Multicenter, and Randomized

Comparison to Standard Radiofrequency Ablation. *Journal of the American College of Cardiology*. 2015;66:1350-60.

151. Schmidt B, Neuzil P, Luik A, Osca Asensi J, Schrickel JW, Deneke T, Bordignon S, Petru J, Merkel M, Sediva L, Klostermann A, Perrotta L, Cano O and Chun KRJ. Laser Balloon or Wide-Area Circumferential Irrigated Radiofrequency Ablation for Persistent Atrial Fibrillation: A Multicenter Prospective Randomized Study. *Circulation Arrhythmia and electrophysiology*. 2017;10.

152. Bordignon S, Chun KR, Gunawardene M, Urban V, Kulikoglu M, Miehm K, Brzank B, Schulte-Hahn B, Nowak B and Schmidt B. Energy titration strategies with the endoscopic ablation system: lessons from the high-dose vs. low-dose laser ablation study. *Europace*. 2013;15:685-9.

153. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *Jama*. 2013;310:2191-4.

154. Yalin K, Abdin A, Lyan E, Sawan N, Liosis S, Elsner C, Jobs A, Bruggemann B, Koester J, Eitel I, Eitel C and Tilz RR. Safety and efficacy of persistent atrial fibrillation ablation using the second-generation cryoballoon. *Clinical research in cardiology : official journal of the German Cardiac Society*. 2018;107:570-577.

155. Tilz RR, Chun KRJ, Deneke T, Kelm M, Piorkowski C, Sommer P, Stellbrink C and Steven D. Positionspapier der Deutschen Gesellschaft für Kardiologie zur Kardioanalgosedierung. *Der Kardiologe*. 2017;11:369-382.

156. Calkins H, Hindricks G, Cappato R, Kim Y-H, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, Chen P-S, Chen S-A, Chung MK, Nielsen JC, Curtis AB, Davies DW, Day JD, D'Avila A, De Groot NMS, Di Biase L, Duytschaever M, Edgerton JR, Ellenbogen KA, Ellinor PT, Ernst S, Fenelon G, Gerstenfeld EP, Haines DE, Haissaguerre M, Helm RH, Hylek E, Jackman WM, Jalife J, Kalman JM, Kautzner J, Kottkamp H, Kuck KH, Kumagai K, Lee R, Lewalter T, Lindsay BD, Macle L, Mansour M, Marchlinski FE, Michaud GF, Nakagawa H, Natale A, Nattel S, Okumura K, Packer D, Pokushalov E, Reynolds MR, Sanders P, Scanavacca M, Schilling R, Tondo C, Tsao H-M, Verma A, Wilber DJ and Yamane T. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: Executive

summary. *Heart Rhythm*. 2017;14:e445-e494.

157. Dattani A, Au L, Tay KH and Davey P. Contrast-Induced Encephalopathy following Coronary Angiography with No Radiological Features: A Case Report and Literature Review. *Cardiology*. 2018;139:197-201.

158. Hamra M, Bakhit Y, Khan M and Moore R. Case report and literature review on contrast-induced encephalopathy. *Future Cardiol*. 2017;13:331-335.

159. Eckardt L, Frommeyer G, Sommer P, Steven D, Deneke T, Estner HL, Kriatselis C, Kuniss M, Busch S, Tilz RR, Bonnemeier H, von Bary C, Voss F, Meyer C, Thomas D and Neuberger H-R. Updated Survey on Interventional Electrophysiology: 5-Year Follow-Up of Infrastructure, Procedures, and Training Positions in Germany. *JACC: Clinical Electrophysiology*. 2018;4:820-827.

160. Raatikainen MJ, Arnar DO, Merkely B, Camm AJ and Hindricks G. Access to and clinical use of cardiac implantable electronic devices and interventional electrophysiological procedures in the European Society of Cardiology Countries: 2016 Report from the European Heart Rhythm Association. *Europace*. 2016;18 Suppl 3:iii1-iii79.

161. Reddy VY, Houghtaling C, Fallon J, Fischer G, Farr N, Clarke J, McIntyre J, Sinofsky E, Ruskin JN and Keane D. Use of a diode laser balloon ablation catheter to generate circumferential pulmonary venous lesions in an open-thoracotomy caprine model. *Pacing Clin Electrophysiol*. 2004;27:52-7.

162. Bordignon S, Chun KR, Gunawardene M, Schulte-Hahn B, Nowak B, Fuernkranz A and Schmidt B. Endoscopic ablation systems. *Expert Rev Med Devices*. 2013;10:177-83.

163. Themistoclakis S, Wazni OM, Saliba W, Schweikert RA, Bonso A, Rossillo A, Gordon M, Melsky J, Raviele A and Natale A. Endoscopic fiberoptic assessment of balloon occlusion of the pulmonary vein ostium in humans: comparison with phased-array intracardiac echocardiography. *Heart Rhythm*. 2006;3:44-9.

164. Reddy VY, Neuzil P, Themistoclakis S, Danik SB, Bonso A, Rossillo A, Raviele A, Schweikert R, Ernst S, Kuck KH and Natale A. Visually-guided balloon catheter ablation of atrial fibrillation: experimental feasibility and first-in-human multicenter clinical outcome. *Circulation*. 2009;120:12-20.

165. Dukkipati SR, Neuzil P, Skoda J, Petru J, d'Avila A, Doshi SK and Reddy VY. Visual balloon-guided point-by-point ablation: reliable, reproducible, and persistent pulmonary vein isolation. *Circ Arrhythm Electrophysiol*. 2010;3:266-73.

166. Metzner A, Schmidt B, Fuernkranz A, Wissner E, Tilz RR, Chun KR, Neven K, Konstantinidou M, Rillig A, Yoshiga Y, Mathew S, Koester I, Ouyang F and Kuck KH. One-year clinical outcome after pulmonary vein isolation using the novel endoscopic ablation system in patients with paroxysmal atrial fibrillation. *Heart Rhythm*. 2011;8:988-693.

167. Dukkipati SR, Kuck K-H, Neuzil P, Woollett I, Kautzner J, McElderry HT, Schmidt B, Gerstenfeld EP, Doshi SK, Horton R, Metzner A, d'Avila A, Ruskin JN, Natale A and Reddy VY. Pulmonary Vein Isolation Using a Visually Guided Laser Balloon Catheter. *Circulation: Arrhythmia and Electrophysiology*. 2013;6:467-472.

168. Schmidt B, Metzner A and Reddy V. Worldwide experience using the endoscopic ablation system for ablation of atrial fibrillation. *Heart Rhythm*. 2012;9:S475-S495.

169. Reynolds MR, Zheng Q and Doros G. Laser balloon ablation for AF: A systematic review and meta-analysis. *J Cardiovasc Electrophysiol*. 2018;29:1363-1370.

170. Oral H, Knight BP, Tada H, Ozaydin M, Chugh A, Hassan S, Scharf C, Lai SW, Greenstein R, Pelosi F, Jr., Strickberger SA and Morady F. Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. *Circulation*. 2002;105:1077-81.

171. Kuck KH, Brugada J, Furnkranz A, Metzner A, Ouyang F, Chun KR, Elvan A, Arentz T, Bestehorn K, Pocock SJ, Albenque JP, Tondo C, Fire and Investigators ICE. Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. *The New England journal of medicine*. 2016;374:2235-45.

172. Verma A JC, Betts TR, Chen J, Deisenhofer I, Mantovan R, Macle L, Morillo CA, Haverkamp W, Weerasooriya R, Albenque JP, Nardi S, Menardi E, Novak P, Sanders P; STAR AF II Investigators. Approaches to catheter ablation for persistent atrial fibrillation. *The New England journal of medicine*. 7;372:1812-1822.

173. Metzner A, Schmidt B, Fuernkranz A, Wissner E, Tilz RR, Chun KR, Neven K, Konstantinidou M, Rillig A, Yoshiga Y, Mathew S, Koester I, Ouyang F and Kuck KH.

One-year clinical outcome after pulmonary vein isolation using the novel endoscopic ablation system in patients with paroxysmal atrial fibrillation. *Heart rhythm : the official journal of the Heart Rhythm Society*. 2011;8:988-93.

174. Schmidt B, Gunawardene M, Urban V, Kulikoglu M, Schulte-Hahn B, Nowak B, Bordignon S and Chun KJ. Visually guided sequential pulmonary vein isolation: insights into techniques and predictors of acute success. *J Cardiovasc Electrophysiol*. 2012;23:576-82.

175. Sohns C, Sohns JM, Bergau L, Sossalla S, Vollmann D, Luthje L, Staab W, Dorenkamp M, Harrison JL, O'Neill MD, Lotz J and Zabel M. Pulmonary vein anatomy predicts freedom from atrial fibrillation using remote magnetic navigation for circumferential pulmonary vein ablation. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. 2013;15:1136-42.

176. Kubala M, Hermida JS, Nadji G, Quenum S, Traulle S and Jarry G. Normal pulmonary veins anatomy is associated with better AF-free survival after cryoablation as compared to atypical anatomy with common left pulmonary vein. *Pacing and clinical electrophysiology : PACE*. 2011;34:837-43.

177. Ahmed J, Sohal S, Malchano ZJ, Holmvang G, Ruskin JN and Reddy VY. Three-dimensional analysis of pulmonary venous ostial and antral anatomy: implications for balloon catheter-based pulmonary vein isolation. *Journal of cardiovascular electrophysiology*. 2006;17:251-5.

178. Stroker E, Takarada K, de Asmundis C, Abugattas JP, Mugnai G, Velagic V, de Regibus V, Coutino HE, Choudhury R, Iacopino S, De Greef Y, Tanaka K, Brugada P and Chierchia GB. Second-generation cryoballoon ablation in the setting of left common pulmonary veins: Procedural findings and clinical outcome. *Heart rhythm : the official journal of the Heart Rhythm Society*. 2017;14:1311-1318.

179. Metzner A, Rausch P, Lemes C, Reissmann B, Bardyszewski A, Tilz R, Rillig A, Mathew S, Deiss S, Kamioka M, Toennis T, Lin T, Ouyang F, Kuck KH and Wissner E. The incidence of phrenic nerve injury during pulmonary vein isolation using the second-

generation 28 mm cryoballoon. *Journal of cardiovascular electrophysiology*. 2014;25:466-70.

180. Reissmann B, Budelmann T, Wissner E, Schluter M, Heeger CH, Mathew S, Maurer T, Lemes C, Fink T, Rillig A, Santoro F, Riedl J, Ouyang F, Kuck KH and Metzner A. Five-year clinical outcomes of visually guided laser balloon pulmonary vein isolation for the treatment of paroxysmal atrial fibrillation. *Clinical research in cardiology : official journal of the German Cardiac Society*. 2018;107:405-412.

181. Tohoku S, Bordignon S, Chen S, Trolese L, Bologna F, Zanchi S, Bianchini L, Cho D, Julian Chun KR and Schmidt B. From point by point to single shot: evolution of visually guided pulmonary vein isolation using the third-generation laser balloon catheter. *J Cardiovasc Electrophysiol*. 2020.

182. Neužil P, Schmidt B and Chun J. Performance of a 3rd Generation Visually-Guided Laser Balloon Catheter for Pulmonary Vein Isolation: Results of the X3 Study. Excluding 30 minute wait period with operators out of the learning curve. Paper presented at: HRS 2019; 2019; San Fransisco.

183. Heeger C-H, Tiemeyer CM, Phan H-L, Meyer-Saraei R, Fink T, Sciacca V, Liosis S, Brüggemann B, Große N, Fahimi B, Reincke S, Kuck K-H, Ouyang F, Vogler J, Eitel C and Tilz RR. Rapid pulmonary vein isolation utilizing the third-generation laserballoon – The PhoeniX registry. *IJC Heart & Vasculature*. 2020;29:100576.

Acknowledgements

I would like to thank my supervisors PD Dr. med. Christian-Hendrik Heeger and Prof. Dr. med. univ. Roland Richard Tilz for their consistent support and guidance during the running of this project and writing of this dissertation. Furthermore, I would like to thank the rest of the electrophysiology research team of the Heart Center Lübeck, Germany for their collaborative efforts.

I would also like to express how grateful I am for the encouragement of my friends, colleagues and my family, for their love, patience and support during the whole project. This achievement would have never been possible without them.

Lebenslauf

Vorname:	Huong Lan
Nachname:	Phan
geboren:	am 01.04.1990 in Hanoi (Vietnam)
E-Mail-Adresse:	huonglan.phan@uksh.de

Ausbildung

seit 04/2018	**Assistenzärztin der Sektion für Elektrophysiologie (Herzzentrum Lübeck)**
seit 01/2015	**Assistenzärztin für Kardiologie** Medizinische Klinik II (Kardiologie, Angiologie, Intensivmedizin) Universitäres Herzzentrum Lübeck, UKSH
2008 – 2014	**Medizinische Fakultät der Semmelweis Universität Budapest** Abschluss: Juni 2014 Bewertung: summa cum laude (ausgezeichnet) Diplomarbeit: Untersuchung der Mitralklappengeometrie mit 3D-Echokardiographie in verschiedenen ätiologischen Formen der Mitralklappeninsuffizienz; Bewertung: ausgezeichnet
03/2013 – 07/2013	**Medizinische Fakultät der Universität Leipzig** Auslandssemester im Rahmen des ERASMUS-Programms
2002 – 2008	**Radnóti Miklós Gymnasium der Eötvös Loránd Universität** (Budapest, Ungarn), Schwerpunkt: Chemie und Biologie

Praktika im Ausland

2013 – 2014	**Im Rahmen des Praktischen Jahres:**
Herzchirurgie (2014)	Herzzentrum Dresden, Klinik für Herzchirurgie (Dresden)
Gynäkologie (2013)	Zentrales Universitätskrankenhaus in Asturias (Oviedo, Spanien) im Rahmen des IFMSA-Programms
Kinderheilkunde (2013)	Klinik und Poliklinik für Kinder- und Jugendmedizin, Universität Leipzig (Leipzig)
Kardiologie (2011)	CCM, Charité Centrum 11 für Herz-, Kreislauf- und Gefäßmedizin Charité - Universitätsmedizin Berlin (Berlin)

Wissenschaftliche Tätigkeiten

- Als Assistenzärztin der Medizinische Klinik II, Herzzentrum Lübeck, UKSH:

2019 – 2020 Promotion	Sektion der Medizin der Universität zu Lübeck Thema: "Second-generation visually guided laser balloon ablation system for pulmonary vein isolation: Learning curve, safety and efficacy“ Doktorvater: PD Dr. med. Christian-Hendrik Heeger

- Als Mitglied der Stiftung für Studentenforschung (TDK) der Semmelweis Universität:

02/2011 – 02/014	**Herzzentrum der Semmelweis Universität Budapest Abteilung für Kardiologie** Thema: Untersuchung der Mitralklappengeometrie mit 3D-Echokardiographie in verschiedenen ätiologischen Formen der Mitralklappeninsuffizienz; Doktormutter: Dr. med. Astrid Apor, assistant professor Wissenschaftliche Studentenkonferenz in Budapest (2013): 3. Preis
09/2011 – 09/2013	**II. Institut für Pathologie der Semmelweis Universität Budapest** Thema: Histopathologische und klinikopathologische Karakteristika von Mammakarzinom im jungen Alter und während der Schwangerschaft Wissenschaftliche Studentenkonferenz in Budapest (2013): 1. Preis, und Nominierung für die Nationale Wissenschaftliche Studentenkonferenz in Szeged, Ungarn (2013)
2010/09 – 2011/09	**Medizinische Klinik I für Innere Medizin, Kardiologie** Semmelweis Universität Budapest Thema: Herzfrequenzvariabilität, periphere und autonome Neuropathie in Diabetes mellitus
2010/09 – 2011/02 Tätigkeit als Lehrassistent	Anatomisches, Histologisches und Embryologisches Institut **der Semmelweis Universität** (Budapest) Thema: ABC-Transporter der Blut-Hirn-Schranke

Mitgliedschaften

- Deutsche Gesellschaft für Kardiologie (DGK)
  - Arbeitsgruppe Elektrophysiologie (AGEP)
- European Society of Cardiology (ESC)
- European Heart Rhythm Association (EHRA)

Sachkunden

- DGK Sachkunde Herzschrittmacher-Therapie (2018)
- DGK Sachkunde ICD-Therapie (2018), DGK Sachkunde CRT-Therapie (2019)

Sprachkenntnisse

- **Ungarisch, Vietnamesisch** – Muttersprachen
- **Englisch** – fließend, IELTS 7.5, staatliche Oberstufenprüfung C1
- **Deutsch** – fließend, Goethe Zertifikat Deutsch C1

Publikationsliste

1. Phan HL, Tilz RR, Schlüter M and Kuck KH. New ESC Guidelines for the Management of Supraventricular Tachycardia. Journal of Cardiology Research. 2020;3(1):31-3.

2. Heeger C-H, Tiemeyer CM, Phan H-L, Meyer-Saraei R, Fink T, Sciacca V, Liosis S, Brüggemann B, Große N, Fahimi B, Reincke S, Kuck K-H, Ouyang F, Vogler J, Eitel C and Tilz RR. Rapid pulmonary vein isolation utilizing the third-generation laserballoon – The PhoeniX registry. IJC Heart & Vasculature. 2020;29:100576.

3. Abdin A, Heeger C-H, Yalin K, Santoro F, Brunetti ND, Fink T, Liosis S, Brueggemann B, Keelani A and Phan H-L. Safety and Efficacy of Cryoballoon Ablation for the Treatment of Atrial Fibrillation in Diabetic Patients. JAFIB: Journal of Atrial Fibrillation. 2020;12(6):2285.

4. Sano M, Heeger C-H, Sciacca V, Große N, Keelani A, Fahimi BHH, Phan HL, Reincke S, Brüggemann B, Fink T, Liosis S, Vogler J, Eitel C and Tilz RR. Evaluation of predictive scores for late and very late recurrence after cryoballoon-based ablation of atrial fibrillation. Journal of Interventional Cardiac Electrophysiology. 2020; Advance online publication. doi:10.1007/s10840-020-00778-y.

5. Heeger CH, Phan HL, Meyer-Saraei R, Fink T, Sciacca V, Liosis S, Brüggemann B, Große N, Fahimi B, Sano M, Kuck KH, Ouyang F, Vogler J, Eitel C and Tilz RR. Second-Generation Visually Guided Laser Balloon Ablation System for Pulmonary Vein Isolation: Learning Curve, Safety and Efficacy - The MERLIN Registry. Circ J. 2019;83:2443-2451.

6. Kuck KH, Phan HL and Tilz RR. [New ESC guidelines 2019 for the treatment of supraventricular tachycardia]. Herz. 2019;44:701-711.

7. Madaras L, Baranyák Z, Kulka J, Szász AM, Kovács A, Phan HL, Székely B, Dank M, Nagy T, Kiss O, Harsányi L, Barbai T, Kenessey I and Tőkés AM. Retrospective analysis of clinicopathological characteristics and family history data of early-onset breast cancer: a single-institutional study of Hungarian patients. Pathol Oncol Res. 2013;19:723-9.

Poster und Vorträge

- DGK-Herztage 2018

“The next generation visually guided laser balloon ablation system for pulmonary vein isolation: First Clinical Experience - The MERLIN Registry” Poster, 10. Oktober 2018, Berlin.

- DGK-Herztage 2019

“The next generation visually guided laser balloon ablation system for pulmonary vein isolation: First Clinical Experience - The MERLIN Registry” Poster, 11. Oktober 2019, Berlin.

- 30. Rhythmologisches Expertengespräch in Berlin 2019

"CRT bei Vorhofflimmern: zusätzlich Pulmonalvenenisolation oder AV-Knoten-Ablation? Vortrag, 13.12.2019, Berlin, 2. Preis.

01.10.2020, Lübeck