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Evaluation of factors influencing the outcome of atrial tachycardia and atrial fibrillation ablation

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Nándor Szegedi

Doctoral School of Theoretical and Translational Medicine

Semmelweis University

Consultant: László Gellér, MD, Ph.D.

Official reviewers: Zoltán Pozsonyi, MD, Ph.D.
Róbert Pap, MD, Ph.D.

Complex Examination Committee:
Head: Lívia Jánoskuti, MD, PhD., med. habil.
Members: Katalin Keltai, MD, Ph.D.
Attila Borbély, MD, Ph.D.

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1. LIST OF ABBREVIATIONS

3D= three-dimensional

AAD= antiarrhythmic drug

ACT= activated clotting time

AF= atrial fibrillation

AR= arrhythmia

AT= atrial tachycardia

AV= atrioventricular

A-V= arterio-venous

AVRT= atrioventricular reentrant tachycardia

AVNRT= atrioventricular nodal reentrant tachycardia

b.p.m.= beat per minute

BRK= Brockenbrough

CAD= coronary artery disease

CF= contact force

CFSAC= contact force sensing ablation catheters

CKD= chronic kidney disease

conv.= conventional mapping

COPD= chronic obstructive pulmonary disease

Cr= crista terminalis

CS= coronary sinus

CS dist= distal coronary sinus

CT= computed tomography

DC= direct-current

DOAC= direct oral anticoagulant

EAM= electroanatomical mapping

ECG= electrocardiogram

EF= ejection fraction

EM= endocardial mapping

EP= electrophysiological

ESC= European Society of Cardiology

FAT= focal atrial tachycardia

FTI= force-time integral

h= hour

ICE= intracardiac echocardiography

IVC= inferior vena cava

L= left-sided focus

LA-LD= left atrium longitudinal diameter

LA-TD= left atrium transversal diameter

Ls= Lasso catheter

LVEF= left ventricular ejection fraction

max= maximum

MI= mitral insufficiency

min= minimum

mm= millimeter

MRAT= macro-reentrant atrial tachycardia

MR= magnetic resonance imaging

ms= milliseconds

n.d.= no data found

ns= non-significant

NCC= non-coronary cusp of the aorta

NOAC= novel oral anticoagulant

OAC= oral anticoagulants / oral anticoagulation

OR= odds ratio

p= „p" value

PSVT= paroxysmal supraventricular tachycardia

PTA= percutaneous transluminal angioplasty

PV= pulmonary vein

PVI= pulmonary vein isolation

R= right-sided focus

RAA= right atrial appendage

RAO= right anterior oblique

RF= radiofrequency

SD= standard deviation

SR= sinus rhythm

SVC= superior vena cava

SVT= supraventricular tachycardia

TEE= trans-esophageal echocardiography

TI= tricuspid insufficiency

TIA= transient ischemic attack

VKA= vitamin K antagonist

VT= ventricular tachycardia

VVI= ventricle, ventricle, inhibition

WPW= Wolff–Parkinson–White

XS= extra sharp

2. INTRODUCTION

Arrhythmias encompass a large and heterogeneous group of cardiac electrical abnormalities. Antiarrhythmic drugs were the mainstay of therapy until the late 1960's when surgical therapy was developed as an invasive treatment option. Later, this method was replaced by clinical electrophysiology (EP), which is a rapidly developing subspecialty of cardiology dealing with the invasive diagnosis and treatment of cardiac arrhythmias. Despite the fact that some decades ago, only a few simple arrhythmias were treatable with this approach, nowadays, we are able to manage even the most complex atrial and ventricular arrhythmias, as well. Electrophysiology was in the center of my interest from the beginning of my cardiology studies; even as a medical student, I started my research in this topic. Fortunately, my studies coincided with the most dynamic part of EP evolution. At the beginning of the electroanatomical mapping era where the exact value of mapping systems was not self-evident, I studied the additional benefit of the CARTO system in case of focal atrial tachycardia ablation where the fluoroscopy-based invasive treatment clearly had some limitations. At the time when this work has been finished, the additional value of electroanatomical mapping systems was recognized worldwide, and with the use of these systems, more complex arrhythmias such as atrial fibrillation (AF) were routinely treated with catheter ablation. As the efficacy of complex atrial procedures like AF ablation were acceptably good, my attention was directed to find those predictors that might propose patients to a higher risk of procedure-related adverse events.

2.1. Supraventricular tachycardias

2.1.1. Definition

Supraventricular tachycardia (SVT) literally indicates tachycardia, the mechanism of which involves tissue from the bundle of His or above: originating from the atrial musculature, atrioventricular (AV) node, the bundle of His, or using an accessory

pathway as the arrhythmia substrate. Traditionally, the term SVT has been used to describe all tachycardias apart from ventricular tachycardias (VT-s) and AF (1, 2).

2.1.2. Epidemiology

The prevalence of the SVT-s is 2.25 / 1 000 persons; incidence is 35 / 100 000 person-years. Women have a two times greater risk of developing SVT than that of men, and people aged ≥ 65 years have more than five times higher risk for developing SVT than younger persons. In specialized centers that perform catheter ablations, AV-nodal reentrant tachycardia (AVNRT) is the most frequently treated arrhythmia after AF, followed by atrial flutter and atrioventricular reentrant tachycardia (AVRT). Women are more likely to have AVNRT (ratio 70:30) than men, while the opposite is true for AVRT (ratio 45:55) (2, 3). AVNRT is more common in middle-aged persons or older, whereas in adolescents, AVRT may be even more prevalent (4). The relative frequency of tachycardias mediated by accessory pathway decreases with age. The incidence of manifest preexcitation pattern on resting electrocardiogram (ECG) tracings in the general population is between 0.1% and 0.3%. However, not all patients with manifest ventricular preexcitation suffer from accessory pathway-mediated tachycardias, and not all of the patients with AVRT have manifest preexcitation (5-7).

2.1.3. Classification

There are multiple ways to classify supraventricular arrhythmias. The current guideline of the European Society of Cardiology (ESC) recommends the classification shown in Table 1.

Table 1. Classification of supraventricular tachycardias (1)

Atrial tachycardias
Sinus tachycardia
Physiological sinus tachycardia
Inappropriate sinus tachycardia
Sinus nodal reentrant tachycardia
Focal and multifocal atrial tachycardia
Macro-reentrant atrial tachycardia (MRAT)
Cavotricuspid isthmus-dependent MRAT
Typical atrial flutter [counter-clockwise (common) or clockwise (reverse common)], lower-loop tachycardia
Non-cavotricuspid isthmus-dependent MRAT (right or left atrial)
Atrial fibrillation
AV junctional tachycardias
Atrioventricular nodal reentrant tachycardia (AVNRT)
Non-reentrant junctional tachycardia (e.g., junctional ectopic tachycardia)
Atrioventricular reentrant tachycardia (AVRT)
Orthodromic AVRT
Antidromic AVRT

Clinically, SVT may present as a narrow or a wide QRS tachycardia. Narrow QRS means a QRS width ≤ 120 milliseconds (ms), while QRS is defined wide if it is wider than 120 ms (Table 2). Narrow QRS tachycardias usually indicate supraventricular origin, except of the rare case of fascicular ventricular tachycardia. Wide QRS tachycardias might originate from the atria and ventricles, as well. The cause of QRS widening in the case of SVT is aberrant conduction, either due to preexisting or rate-dependent bundle branch block, or pre-excitation (2-4, 8, 9).

Table 2. Classification of narrow and wide QRS tachycardias (1)

Narrow QRS tachycardia (≤ 120 ms)	**Wide QRS tachycardia (> 120 ms)**
Regular	*Regular*
Sinus tachycardia (physiological, inappropriate, sinus nodal reentrant tachycardia)	Ventricular tachycardia / flutter
Focal atrial tachycardia	Paced ventricular rhythm
Atrial flutter (fixed AV-conduction)	Antidromic AVRT
AV-nodal reentrant tachycardia	SVT-s with aberrant conduction (bundle branch block, or bystander accessory pathway)
Orthodromic AV- reentrant tachycardia	SVT with QRS widening due to electrolyte disturbance or antiarrhythmic drugs
Idiopathic ventricular tachycardia	*Irregular*
Irregular	Atrial fibrillation, flutter or tachycardia with varying AV-conduction and aberrant conduction
Atrial fibrillation	Polymorphic ventricular tachycardia
Focal atrial tachycardia or flutter (varying AV-conduction)	Torsade de pointes
Multifocal atrial tachycardia	Ventricular fibrillation

2.1.4. Electrophysiological mechanisms

2.1.4.1. Non-reentrant mechanisms

Arrhythmia mechanisms are defined as “non-reentrant,” or “focal” if they result from enhanced automaticity and triggered activity.

An arrhythmia might originate from abnormal impulse initiation in a close cluster of myocytes. This can occur in non-pacemaker cells through a mechanism that is similar to

the physiological automaticity of the pacemaker cells (e.g., sinus node and AV node), and thus, it is named “abnormal” or “enhanced automaticity.” Automaticity is normally suppressed in non-pacemaking myocardial cells by hyperpolarizing membrane current that keeps diastolic potential constant. The firing of automatic myocytes is independent and, therefore, automatic rhythms are usually dissociated from the baseline rhythm, and characterized by variable coupling intervals.

An alternative form of abnormal impulse initiation involves the oscillations of membrane potential, named early or delayed “after-depolarizations.” Group set of arrhythmia mechanisms including early or delayed afterdepolarizations, are named “triggered activity” because, unlike abnormal automaticity, they are often related to a previous excitation that sets the conditions for their occurrence. Early afterdepolarization is the arrhythmia mechanism in torsade de pointes; while delayed afterdepolarization is the mechanism for arrhythmias associated to digoxin toxicity (2, 8, 9).

2.1.4.2. Reentrant mechanism

Arrhythmias can also develop when different conduction velocities and refractory periods are present. In such cases propagating impulse might fail to die out after normal activation of the heart and persists to re-excite the heart after the expiration of the refractory period. This mechanism is called “re-entry” (2, 9, 10).

This phenomenon requires the following conditions to be present:

- An area of unexcitable tissue (obstacle) that splits propagation into two fronts. The obstacle can be an “anatomical” structure (dual AV-node physiology, accessory pathways, scar tissue, etc.), or even “functional” (e.g., collision of centripetal fronts originating from the circuit).
- Conditions that prevent mutual extinction of the two wavefronts, caused by head-to-head or head-to-tail collision. “Unidirectional” conduction block in at least one part of the circuit prevents head-to-head collision; head-to-tail collision is prevented by a refractory period that is shorter than the time required by the front to reach the entrance of the obstacle.

2.1.5. Clinical presentation

SVT-s may cause a wide spectrum of symptoms. They can be asymptomatic, or might be associated with palpitations, chest discomfort, dyspnea, fatigue, light-headedness, but in some cases may even lead to hemodynamic instability and loss of consciousness. The duration of symptoms and patient's age at onset are of high importance, e.g., teenagers or younger persons are less likely to have atrial tachycardia or AF while the likelihood of AV-reentrant tachycardia is higher (2, 9). Clinical signs and symptoms of heart failure might occur when the patient develops tachycardia-induced cardiomyopathy, usually due to long-lasting tachycardia (e.g., incessant focal atrial tachycardia) (11-14). Presyncope and syncope are less common and tend to be more frequent in older individuals. In the elderly, symptoms may be more extreme – with dizziness, presyncope, or even syncope – as a result of the less-accommodating characteristics of the circulation (15). SVT-s are relatively benign arrhythmias, but in specific situations, e.g., in patients with Wolff-Parkinson-White (WPW) syndrome and AF may even lead to sudden cardiac death (16). Abrupt onset and termination occur more often in AVNRT or AVRT, although an atrial tachycardia (AT) may also present in this way. Characteristics in terms of regularity or irregularity are also helpful. The duration of the individual episodes may help in terms of differentiation. Reentrant tachycardias usually last longer than AT episodes, which commonly occur in a series of shorter repetitive runs (17). Pounding in the neck (so-called "frog sign") would point to the possible competing atrial and ventricular contraction on the atrioventricular valves, and to AVNRT as the most likely cause (8, 9, 11). SVT-s may be underdiagnosed at initial medical evaluation as the clinical characteristics can mimic panic disorder (18).

2.1.6. Diagnostic evaluation

The diagnostic evaluation of patients with palpitations should include a detailed history taking, physical examination, and resting 12-lead electrocardiography. An ECG recorded during tachycardia is desirable to diagnose the arrhythmia and to start the specific treatment; thus, patients should be encouraged to seek medical assistance to record an ECG during arrhythmia episode.

The history should include the patient's age at the onset of palpitations. The patient should give a detailed description of the symptoms, e.g., the rate and degree of regularity of the palpitation. Rapid and regular rhythms might indicate paroxysmal supraventricular tachycardia (PSVT) episodes, atrial flutter with fixed AV-conduction or ventricular tachycardia. Fast and irregular rhythms suggest atrial fibrillation, atrial flutter, or atrial tachycardia with variable AV-conduction. The mode of onset and termination of the arrhythmia sometimes may indicate its cause. Patients are often able to terminate their palpitations with vagal maneuvers, such as the Valsalva maneuver. This mode of termination is more suggestive of supraventricular tachycardias, particularly AVNRT or AVRT (2, 3, 8, 9, 11).

Although physicians rarely have an opportunity to examine the patient during an arrhythmia episode, the physical examination is useful in establishing potential cardiovascular abnormalities that could serve as a substrate for arrhythmias, e.g., signs of congestive heart failure, murmurs suggesting valvular heart disease (2, 9, 11, 17).

In a patient with normal sinus rhythm, baseline 12-lead ECG is helpful in the differential diagnosis of palpitations. The presence of a short PR interval and delta waves indicates ventricular preexcitation, thus presenting the substrate for supraventricular tachycardia. Marked left ventricular hypertrophy with deep septal Q waves in I, aVL, II, III, aVF, and $V_{4\text{-}6}$ leads, together with the presence of T-wave insertion suggests hypertrophic cardiomyopathy which may be a cause of atrial fibrillation. The presence of Q-waves characteristic of prior myocardial infarction warrants a search for ischemic substrate and ventricular tachycardia (2, 9, 11, 17).

Resting echocardiography is helpful in the evaluation of underlying structural heart disease, e.g., prior myocardial infarction, left ventricular hypertrophy, heart valve abnormalities (2, 9, 11, 17).

Ambulatory electrocardiographic monitoring devices are helpful tools for the diagnosis of paroxysmal arrhythmias. The chosen tool should be in concordance with the frequency of palpitation symptoms (Holter-ECG monitor for 24-72 hours, trans-telephonic ECG monitoring, mobile recording devices, novel technologies such as smartwatch, implantable loop recorder) (2, 3, 8, 9, 11).

The electrophysiological study can diagnose specific arrhythmias, and catheter ablation can be conducted within the same procedure. Catheter ablation is the most effective treatment method for supraventricular tachycardias (8, 9).

2.1.7. Treatment of supraventricular tachycardias

2.1.7.1. Acute treatment of supraventricular tachycardias

In the case of hemodynamic instability, immediate direct-current (DC) cardioversion is the first choice of treatment. If the patient is hemodynamically stable, a less aggressive approach is recommended starting with non-drug-based actions. In such cases, a 12-lead ECG should be obtained to have the possibility of differential diagnosis. The principle behind non-pharmacologic methods is to increase vagal tone to slow conduction through the AV node, which is the part of the re-entry circuit in many of these arrhythmias. Vagal maneuvers include different techniques used to stimulate the receptors in the internal carotid arteries, e.g., blowing into a syringe. The efficacy in terminating AV node dependent tachycardias, such as AVNRT or AVRT, varies between 19 and 54% (8, 9, 19, 20). Carotid sinus massage has similar efficacy; however, this technique should be avoided in patients with previous transient ischemic attack or stroke, and in patients with carotid bruits (8, 21).

When the aforementioned non-pharmacological therapy fails to terminate the PSVT episode, it is appropriate to administer drugs. The preferred initial agents are intravenous (i.v.) verapamil, adenosine, or beta-blockers. PSVT termination after adenosine administration might indicate AVNRT or AVRT as the most likely PSVT mechanism (6, 8, 9). However, unifocal AT might also respond with cessation to adenosine, especially in cases when the focus is located in the proximal coronary sinus and the septal region (meaning about 7-18% of all FAT-s) (14, 22-24). Adenosine should not be used in patients with Wolff–Parkinson–White syndrome and atrial fibrillation as it shortens the refractory period of the accessory pathway, resulting in rapid conduction to the ventricles, causing a potentially life-threatening arrhythmia (25, 26). Clinically significant bronchoconstriction has been rarely reported in patients receiving i.v. adenosine, thus, other drugs should be considered in individuals with severe asthma (27). In case of

uncertain diagnosis, administration of i.v. adenosine has an additional value in terms of differential diagnosis.

2.1.7.2. Long-term treatment of supraventricular tachycardias

Calcium channel blockers and beta-blockers improve symptoms in 60 to 80% of patients with PSVT. In some cases, e.g., focal atrial tachycardia, specific antiarrhythmic agents such as propafenone, sotalol, or amiodarone can also be administered. However, these antiarrhythmic drugs expose the patient to the risk of proarrhythmia over the long term, in addition to other non-cardiac side effects (3, 8, 9).

Given the high success rate and favorable safety profile of diagnostic electrophysiology study followed by catheter ablation, this is the preferred pathway of treatment for many patients. Current guidelines recommend catheter ablation for patients who have recurrent PSVT episodes, considering the high success rates of these procedures (3, 8, 9, 28-30).

2.2. Electroanatomical mapping and catheter ablation

2.2.1. Electroanatomical mapping

Single-channel evaluation of intracardiac electrograms has given way to simultaneous multichannel mapping, resulting in a more detailed temporal and spatial characterization of specific arrhythmias. It has thereby become more challenging to keep track of an increasing number of channels of electrograms and analyze them within the context of their particular anatomic locations. This limitation has provided the intention for the development of computer-based electroanatomical mapping systems (31).

An electroanatomical mapping system should be able to:

- accurately replicate the cardiac anatomy
- provide a plausible representation of activation of the mapped cardiac chamber
- intelligibly display other details of physiology, and
- catalog the site of interventions.

The system displays three-dimensional (3D) structures on a monitor screen in two-dimensional views. The ability to show multiple views simultaneously is essential to give the 3D perspective. The addition of virtual endoscopic views might also be helpful. There is the possibility to tag anatomically important structures that should be treated or avoided (e.g., phrenic nerve, see Figure 1) (32). The system can determine the position of the catheters with a resolution of less than 1 mm (33). Many points at a sufficient density are required to resolve more and more complex arrhythmia mechanisms. The acquisition of a huge amount of points (containing both electrograms and corresponding anatomical sites) is possible with recent advanced computational capabilities and automatic annotation. The system can intelligibly display the electrograms in multiple ways, e.g., resulting in a voltage map or activation map. Scar map stands for an electroanatomical map that depicts the local voltage amplitudes of the acquired points: low voltage areas represent damaged myocardium, whereas high voltage areas indicate healthy tissue. The optimal cutoff values differ in unipolar and bipolar voltage maps, and also different values apply for atria and ventricles (34-38). The activation map depicts the timing of local electrograms compared to a selected reference electrogram for the generation of a color-coded three-dimensional map (see Figure 2) (33). Arrhythmia mechanism (focal vs. macro-reentrant) and localization of arrhythmogenic substrate (e.g., localization of focus or re-entry circuit) can be understood with this technique (31, 39-43). Here we briefly describe the basics of the two mapping systems that are most frequently used in our Center (CARTO, Biosense Webster, Inc., Diamond Bar, CA, USA; and EnSite, St. Jude Medical, Inc., MN, USA).

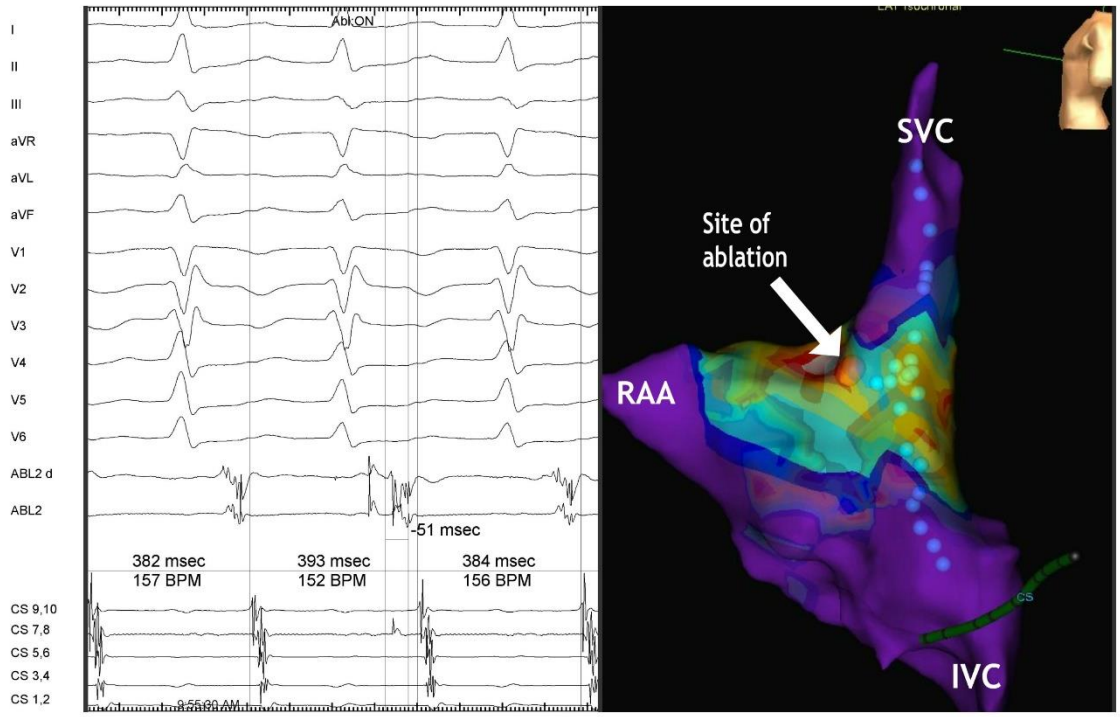

Figure 1. Left side: 12 lead surface ECG (registration speed 100 mm/s) and intracardiac ECG (ablation catheter and coronary sinus catheter) during ongoing focal atrial tachycardia. Tachycardia cycle length shows a beat to beat change. The local activation time recorded on the ablation catheter (ABL2d and ABL2 electrodes) precedes the beginning of surface P wave with 51 ms, indicating that this is the site of arrhythmia origin (red dot on the right side). Right side: activation map of the right atrium during ongoing focal atrial tachycardia (left lateral view, EnSite system). Small blue dots show the location of the phrenic nerve; the big red dot shows the successful ablation site. Abbreviations: IVC= inferior vena cava, RAA= right atrial appendage, SVC= superior vena cava. Electrophysiology Laboratory, Heart and Vascular Center, Semmelweis University (32).

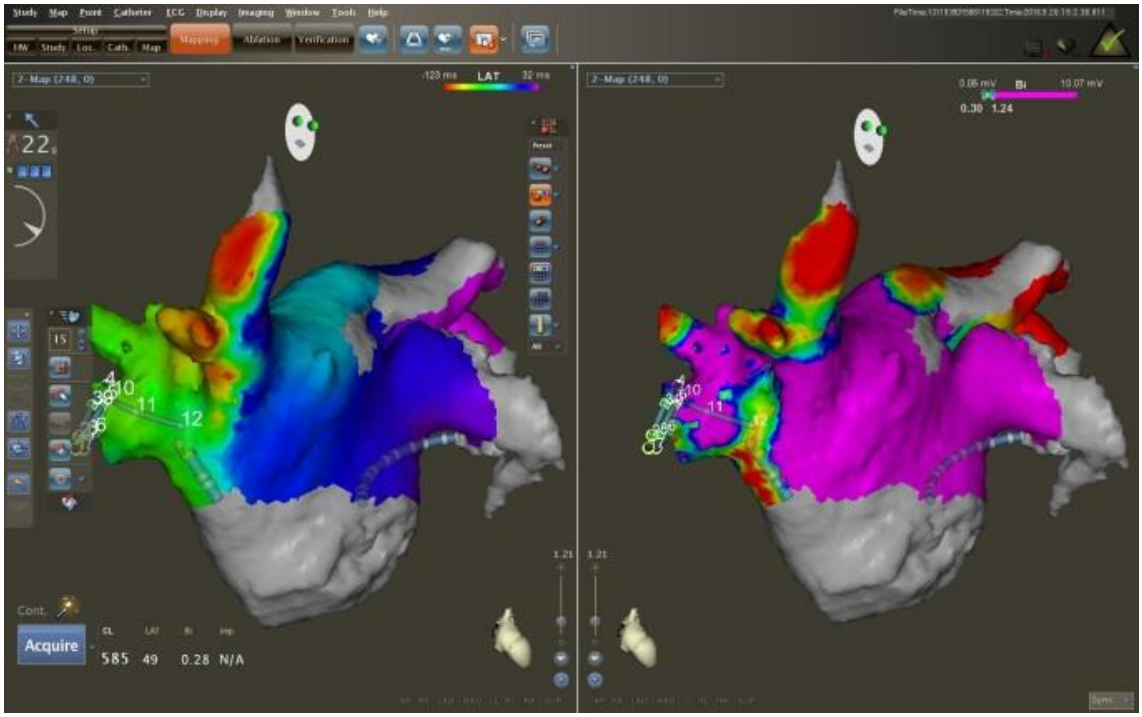

Figure 2. Atrial tachycardia after previous pulmonary vein isolation. Electroanatomical activation map (left side) and voltage map (right side) of the left atrium, performed with the CARTO system and CT-Merge. The AT originates from the right superior pulmonary vein; the site of reconnection is at the infero-anterior part of the vein. Electrophysiology Laboratory, Heart and Vascular Center, Semmelweis University.

2.2.1.1. CARTO electroanatomical mapping system

The patient is positioned over a tripod emitting three electromagnetic waves at unique frequencies, thus generating an electromagnetic field around the patient's chest. Each beam is registered by one of the three specifically tuned coils embedded in the distal end of the deflectable 8 French mapping catheter. Proximal to the tip electrode lies the location sensor, embedded within the catheter. The sensor gives information about the actual position (x, y, and z axes) of the catheter. With these features, the catheter tip's location can be specified in 3D space, compared to an anatomical reference. The direction of the catheter tip, along with its pitch, yaw, and roll attitude creates an orientation vector, which is also displayed on the screen. Thereby, the information necessary to resolve the exact location and orientation of the sensor is provided in 6 degrees of freedom. The tip of the catheter includes the tip electrode and one additional proximal ring electrode, which enables the recording of unipolar and bipolar signals. The local electrogram recorded at

a specific site is then archived with its positional context. Multiple mapping and ablation catheters can be visualized, however only those which are produced by a certain company (31, 44).

2.2.1.2. EnSite system

This system is based on currents across the thorax, which has been developed originally in the LocaLisa system. This basic technology has undergone substantial development in the EnSite iteration. Briefly, low-level high-frequency alternating currents are conducted from three orthogonal electrode pairs positioned on the body surface. The specific position of a catheter tip within the cardiac chambers can be established based on the three resulting potentials measured in the recording tip with respect to a reference electrode seen over the distance from each patch set to that recording tip. This system permits the visualization of catheters independent of the manufacturer (31).

2.2.2. Catheter ablation

The purpose of catheter ablation is to destroy myocardial tissue by delivery of energy through electrodes on a catheter, placed at the area of the arrhythmogenic substrate. Ablation by radiofrequency- (RF) or cryo-energy is important curative treatment modalities for cardiac arrhythmias. Other energy types, such as laser, ultrasound, microwave-based ablation, and stereotactic irradiation approaches, were also investigated; however, those did not become part of the everyday practice (45-47).

2.2.2.1. Radiofrequency ablation

Lesion size is affected by several parameters, such as electrode size, contact force, time of application, power, blood flow, the presence of irrigation.

During an RF ablation, medium frequency (350 – 500 kHz) alternating current is applied, which flows through the ablation catheter’s tip to reach the target tissue. Even if an electrode touches the myocardial tissue, only some part of the tip will contact the tissue itself, while other parts of the tip will contact the blood. Thus, some proportion of the

delivered power will be lost in the blood pool, as blood is a better conductor than the tissue. After leaving the electrode-blood-tissue interface, the current flows through the chest to the indifferent electrode (48).

Tissue destruction caused by heating occurs partly due to direct resistive heating and partly because of conductive heating. Resistive heating is generated when the electrical current flows through a material that has a particular electrical resistance. When the delivered power dissipates in the material, heat will be generated. About 90% of the delivered energy is absorbed immediately (1–1.5 mm) underneath the electrode surface. Other parts of the ablated tissue will be warmed by conductive heating. In contrast to resistive heating, which starts immediately as the RF power is delivered, conductive heating depends much more on the time of the RF application (49, 50).

A potential problem might be the coagulation of blood on the tip of the ablation catheter. The use of temperature control mode may prevent coagulum formation; however, this still does not lead to the total elimination of clot formation. Thus, there are important safety measures during left-sided ablations, such as limiting the RF power level, or the use of an irrigated ablation catheter (48, 49).

Electrode temperature is a weak reflection of the tissue temperature. The main reason behind this fact is that the electrode is not heated directly by the RF energy, but it warms up due to the heat of the contacted myocardium. Another cause of the temperature difference between the electrode and tissue is that electrode is cooled by the blood flow (50-53).

The impedance monitoring during RF applications may also have a significant role. Several studies have shown that there is a good correlation between the drop in impedance and the lesion size during RF applications (54, 55). On the other hand, a sudden rise in impedance may indicate excessively high contact forces, while gradual impedance rise might be associated with char formation on the electrode surface (56).

The size of the catheter tip electrode also affects lesion formation. Larger electrodes (e.g., 8-mm tip) require more power to achieve the same tissue temperatures and lesion sizes, compared to smaller (e.g., 4-mm tip) electrodes. Thus, with the same energy, lesions with a larger electrode will be smaller than with a smaller electrode (49, 57, 58).

One additional problem during ablation might be thrombus or char formation on the catheter surface and inadequate lesion formation in low-blood-flow areas. Both of these can be avoided with the active cooling of the catheter tip. Open irrigation means the flushing of saline through pores of the catheter tip. Saline irrigation cools both the electrode and its environment. Irrigation alone does not increase lesion size; actually, cooling may minimally reduce lesion size by cooling the tissue surface (59, 60). Thus, the maximum lesion diameter is slightly deeper in the tissue in the case of irrigated electrodes. The mechanism which results in larger lesion diameters and depth is that irrigation facilitates the delivery of higher RF powers by providing environmental cooling, even in areas with low blood flow (48).

An increase in contact force leads to higher power delivery, as it improves efficient power delivery to the tissue. Thus, higher tissue temperature and lesion size may be reached with lower power levels. There are numerous data regarding the effect of contact force on the lesion dimensions (61-64). These days, more complex lesion predicting parameters are available such as lesion size index for EnSite-guided procedures or ablation index for CARTO-guided procedures. Both of these parameters are derived from the contact force, time, and power, using specific mathematical formulas (65-67).

2.2.2.2. Cryoablation

Cryoablation – where the catheter tip is cooled with the help of liquid nitrogen – represents a valuable alternative of RF ablation. Cooling the tissue to -50 − -80 °C causes intra- and extracellular formation of ice crystals, finally resulting in a dense and circumscribed scar. The characteristics of tissue injury from freezing are generally arising from two major mechanisms: direct damage to cells caused by ice crystal formation and a microcirculatory failure, the latter occurs during the thawing period. The cryogenic lesion is characterized by central uniform coagulation necrosis, surrounded by a peripheral zone (where the tissue temperature was only 0 – 20 °C) in which only partial cell death occurs. The extent of necrosis becomes definite in about two days (68).

An important advantage of this energy source is the possibility of “cryomapping,” during which the targeted structure is cooled down to -30 °C. At this temperature, a reversible cryothermal lesion is created when a temporary loss of electrical conduction of the ablated

structure occurs, and thus this procedure grants improved safety of ablation (69, 70). It is especially useful when ablation is performed near to electrically essential structures such as AV-node (71, 72). Cryoenergy is also very popular for pulmonary vein isolation (PVI) using the cryoballoon that we will discuss in detail below in chapter 4.4.4.3.

2.3. Focal atrial tachycardia

2.3.1. Definition, epidemiology, localization of foci

Focal atrial tachycardia (FAT) indicates an organized atrial rhythm ≥100 b.p.m. originating from a discrete ectopic (non- sinus node origin) point of the left or right atrium and spreading over the atria in a centrifugal pattern. The atrial rate is usually between 120 and 250 b.p.m., while the ventricular rate depends on the AV nodal conduction (2, 14, 73). The arrhythmia may be asymptomatic; the estimated prevalence of asymptomatic FAT has been reported to be about 0.34%. The prevalence of symptomatic FAT is 0.46% (74).

The origin of FAT theoretically can be anywhere in the atria, but usually it tends to be located to certain anatomical structures. Most common right-sided foci are terminal crest, the orifice of the coronary sinus, superior vena cava; whilst left-sided FAT-s frequently originate from the pulmonary veins, distal portion of coronary sinus, left atrial appendage, or ligament of Marshall (14, 73, 75-80). High septal foci might be in close relationship with the bundle of His and the non-coronary cusp of the aorta (81, 82).

2.3.2. Arrhythmia mechanisms

Focal AT presents a wide range of electrophysiologic characteristics. Potential mechanisms of FAT include micro-re-entry, abnormal automaticity, and triggered activity. The majority of histological analyses of AT foci have shown normal myocardium at the AT focus; however, abnormal myocardium (e.g., fibrosis,

hypertrophy, or islets of fatty tissue) has also been observed (14). The method of successful initiation and termination might be predictive for the arrhythmia mechanism. FAT caused by abnormal automaticity can usually be initiated with an infusion of isoprenaline; however, it cannot be induced via programmed extrastimulation. It might be terminated with beta-blockers; however, it does not respond to Valsalva maneuver, adenosine or verapamil. In case of triggered activity, induction and termination can be usually reached with atrial extrastimulus test, and it usually responds to Valsalva maneuvers, adenosine, and carotid sinus massage. The micro-reentrant mechanism is characterized by reproducible inducibility with programmed extrastimulation. Termination is possible via adenosine, verapamil, and programmed extrastimulus. In real life there is an overlap in the electrophysiologic characteristics of focal AT-s, e.g., both triggered activity and micro-re-entry can be initiated and terminated with programmed stimulation. The analysis found that the mechanism of FAT did not predict successful ablation or recurrence of AT (14, 83).

2.3.3. Etiology

Focal atrial tachycardia might be present without any underlying disease. However, paroxysmal FAT might be associated with structural heart diseases, such as coronary artery stenosis, myocardial infarction, valvular heart disease, congenital anomalies, and heart failure. Most frequent extracardiac causes are electrolyte imbalance (especially hypopotassemia), chronic pulmonary diseases (e.g., COPD, asthma bronchiale), hypoxia, digoxin toxicity, and theophylline (3, 8, 73, 84).

2.3.4. ECG characteristics

The identification of P-wave on the 12 lead ECG recording during tachycardia is critical. Depending on the AV conduction and AT rate, the P waves may be hidden in the QRS or T waves. The P waves are monomorphic; the cycle length is usually more the less stable. In case of uncertainty, intravenous injection of adenosine can help in terms of identification of P waves and differentiating from other SVT-s. The identification of discrete P waves with intervening isoelectric intervals should suggest a focal AT.

However, the presence of an isoelectric line does not rule out a macro-reentrant mechanism, particularly in the presence of atrial scar tissue. In a structurally normal heart and the absence of a previous ablation, the usual ECG localization rules apply. A negative P wave in lead I and aVL suggests left atrial origin. If P waves in V1 are negative, the arrhythmia source is in the right atrium, while septal (see Figure 3) right or left atrial origins show biphasic or positive P waves. Negative P waves in the inferior leads indicate caudal origin, whereas positive P waves in those leads favor a superior location. Wide P-waves might indicate lateral origin, while narrow P-waves are usually associated with septal foci (14, 77, 85-89).

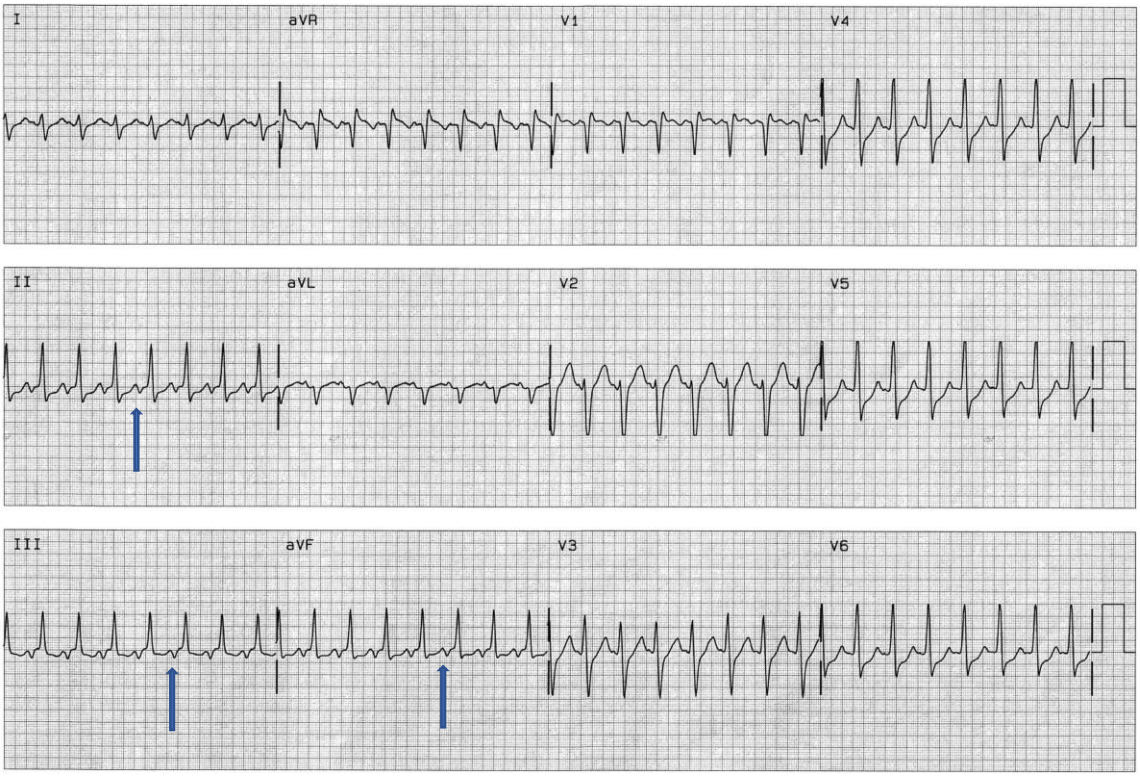

Figure 3. Twelve-lead ECG recording of a focal atrial tachycardia, paper speed 25 mm/s. The ratio of atrioventricular conduction is 1:1; the RP interval is long. Narrow P-waves (arrows) indicate septal origin (Cardiology Department of Military Hospital, Budapest).

2.3.5. Clinical presentation

Focal AT-s may present a broad spectrum of symptoms. Those may include palpitations, chest pain, shortness of breath, and rarely presyncope or syncope. Sometimes it may even be asymptomatic. The arrhythmia can be sustained or incessant. Paroxysmal forms may be frequent with recurrent interruptions and re-initiations. Incessant form of FAT is relatively rare; however, it may have important consequences: the high heart rate that is present for many weeks or months may lead to the impairment of left ventricular ejection fraction, thus causing "tachycardia-induced cardiomyopathy" or "tachycardiomyopathy". This type of arrhythmia occurs more often in children (90, 91). The most optimal treatment, namely catheter ablation, is inevitable in such cases as cardiac function usually improves after the restoration of sinus rhythm (3, 9, 12, 13, 29, 73, 90, 92).

2.3.6. Treatment

2.3.6.1. Acute therapy

If the diagnosis of the regular narrow QRS tachycardia is uncertain, acute therapy can be initiated with adenosine, which will help the differential diagnosis, as well. It terminates AV-node dependent arrhythmias such as AVRT or AVNRT. In the case of FAT, the response for adenosine is usually transient AV-block with persisting tachycardia on the atrial level; however, in 7-18% of cases, it also might terminate the FAT (2, 3, 8, 9, 22-24, 29, 73, 93). The next step can be the administration of beta-blockers or calcium channel blockers, which can potentially terminate FAT-s or at least slow the ventricular rate. Class IA, IC, and III drugs may also be useful, by prolonging tissue refractoriness or suppressing automaticity. DC cardioversion is usually effective in acute termination of the tachycardia, irrespective of the mechanism. However, in incessant forms due to enhanced automaticity, the arrhythmia instantly re-initiates after the cardioversion. In such cases, repeated DC shocks are not appropriate (2, 3, 8, 9, 29, 73).

2.3.6.2. Chronic treatment with drugs

Studies investigating chronic drug therapy are limited, and thus reliable conclusions cannot be drawn. Beta-blockers and calcium channel blockers may be useful, and the risk

of side effects is low. Class IC drugs and amiodarone may also be effective; however, the long-term side effects should be taken into account (3, 8, 9, 29, 73).

2.3.6.3. Catheter ablation

Catheter ablation is the treatment of choice for recurrent symptomatic paroxysmal focal AT-s, especially if those are refractory for antiarrhythmic drug treatment (2, 3, 8, 9, 29, 73). The indication is even much more robust for the incessant form of FAT, as this might be the only way to reverse left ventricular dysfunction (2, 8, 9, 12).

Distinguishing macro-reentrant tachycardias from focal AT-s is essential to find the optimal ablation strategy. In order to differentiate between these two mechanisms, there are many aspects to consider: past medical history (e.g., previous heart surgery or ablation), presence of isoelectric line on surface ECG, inducibility during the electrophysiology study, tachycardia cycle length, the variation of cycle length during tachycardia, biatrial activation time and its relation to cycle length (8, 9, 94, 95). Focal AT-s display a centrifugal activation pattern that spreads throughout both atria. Mapping and ablation of focal AT-s are based on determining the earliest activation site in the atria, which can be found with conventional mapping methods and with the help of electroanatomical mapping systems (see Figure 4) (31, 33, 41-44, 96-103). The only exception might be the PV-related AT, where focal ablation might be considered, but electrical isolation of both the culprit PV along with other PV-s should be preferred (104).

Catheter ablation is reported to have a 75 - 100% acute and long-term success rate with a very low complication rate. A significant amount of data is available regarding the success rate and complication rate of FAT ablation with both conventional mapping and electroanatomical mapping (2, 8, 9, 12, 29, 30, 42, 73, 75, 77, 78, 80, 81, 83, 91, 92, 96, 97, 99, 101, 103-114). However, no other working groups compared the two mapping strategies apart from ours so far.

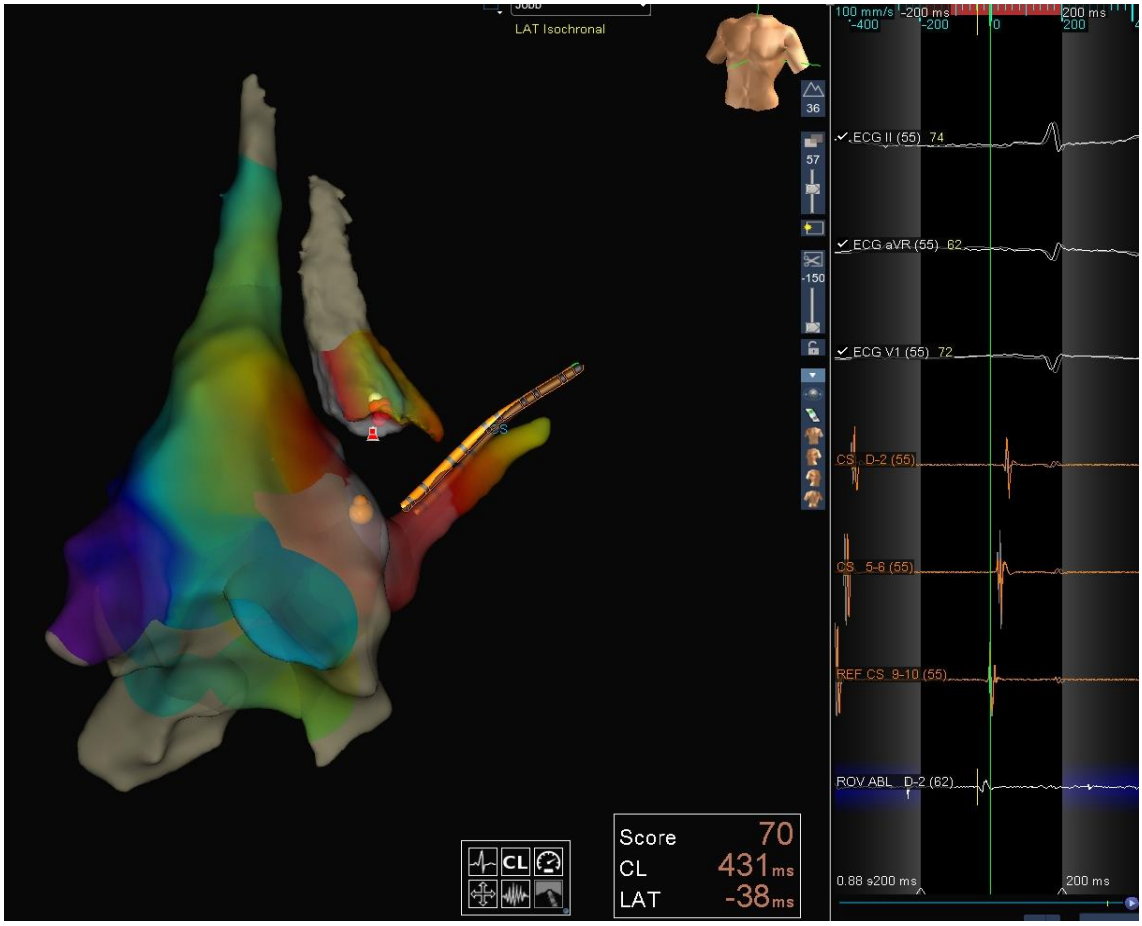

Figure 4. Electroanatomical activation map (EnSite system) of a focal atrial tachycardia arising from the non-coronary cusp (NCC) of the aorta. A decapolar catheter is visible in the coronary sinus. The right atrial map shows that the earliest activation is in the para-Hisian region (location of His signal is tagged with a yellow dot). The earliest signal registered in the NCC is shown on the right side of the image that precedes the reference signal with 38 ms. Ablation at that site successfully eliminated the tachycardia. Electrophysiology Laboratory, Heart and Vascular Center, Semmelweis University.

2.4. Atrial fibrillation

2.4.1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. AF – as an independent risk factor – is associated with higher mortality compared to the general population (115, 116). Diagnosis is based on documentation of a > 30 seconds long arrhythmia with AF pattern (absolutely irregular R-R intervals and no noticeable, distinct P waves), using an ECG. It is one of the major causes of stroke, heart failure, sudden death, and cardiovascular morbidity in the world (116). Thus, appropriate management of this arrhythmia and the underlying diseases is essential. Besides stroke prevention with therapeutic anticoagulation, the rate control or rhythm control treatment is the basis of AF management.

2.4.2. Epidemiology

The estimated prevalence of AF is approximately 3% in adults with higher prevalence in older persons and patients with predisposing factors such as hypertension, coronary artery disease (CAD), heart failure, diabetes mellitus, valvular heart disease, obesity, or chronic kidney disease (CKD) (116-119).

2.4.3. Classification

Based on the presentation, duration, and termination of AF episodes, five types are distinguished: first diagnosed, paroxysmal, persistent, long-standing persistent, and permanent AF. Usually, AF progresses from short, infrequent episodes to more prolonged and more frequent attacks. Over time, many patients will develop more sustained forms of AF. The mechanism behind this behavior is the progressive structural remodeling of the atria, caused by many cardiac and extracardiac factors, such as structural heart disease, hypertension, and the AF itself even precipitates it. Structural remodeling leads to

electrical dissociation between muscle bundles and local conduction heterogeneities, favoring re-entry, and perpetuation of the arrhythmia (116, 120, 121).

2.4.4. Management

The management of atrial fibrillation requires complex patient care which has several essential components:

- lifestyle changes (weight loss, regular physical activity, reduction of alcohol consumption, avoidance of high-volume food intake, etc.)
- diagnosis and adequate treatment of underlying diseases (obstructive sleep apnea, valvular heart disease, uncontrolled hypertension, thyroid dysfunction, etc.)
- anticoagulation based on CHA_2DS_2-VASc score
- treatment of arrhythmia: rate control and/or rhythm control

2.4.4.1. Oral anticoagulation (OAC)

The CHA_2DS_2-VASc score is generally accepted and widely used for thromboembolic risk stratification of patients with non-valvular AF. Patients without stroke risk factors do not need anticoagulant therapy. In patients with one risk factor (except female gender), anticoagulation should be considered; however, there is not a strict recommendation for this patient group. Thus the initiation should be based on discussion with the patients after informing them about the risks and benefits of OAC therapy. Patients with a higher CHA_2DS_2-VASc score (≥ 2 for men and ≥ 3 for women) anticoagulation is recommended, preferably with novel oral anticoagulants (NOAC-s). The only patient group where NOAC-s should not be used is valvular atrial fibrillation (patients with a mechanical heart valve, or moderate/severe mitral stenosis) (116, 122).

2.4.4.2. Pharmacological rate and rhythm control treatment of atrial fibrillation

2.4.4.2.1. Pharmacological rate control

Rate control is an integral part of AF management, and it is often sufficient to improve AF-related symptoms. Pharmacological rate control of the tachyarrhythmia can be achieved with beta-blockers, calcium channel blockers, digoxin, or combination therapy (116, 123, 124). Lenient (resting heart rate < 110 b.p.m.) and strict (resting heart rate < 80 b.p.m.) rate control are similarly effective; thus, a more permissive rate control might be sufficient for patients with persistent or permanent AF (125).

2.4.4.2.2. Pharmacological rhythm control

Rhythm control means those activities of AF management that aim to restore and maintain sinus rhythm. It can be usually achieved with class IA, IC, or class III antiarrhythmic agents. Antiarrhythmic drugs approximately double the chance of sinus rhythm compared to placebo; thus, those can slightly decrease the risk of AF-related hospitalization. However, there is no apparent effect of these drugs on mortality and cardiovascular complications (123, 124, 126).

2.4.4.3. Non-pharmacological rate and rhythm control treatment of atrial fibrillation

2.4.4.3.1. Non-pharmacological rate control

Ablation of the AV node after implantation of a pacemaker can control the high ventricular rate when pharmacological rate control fails. AV nodal ablation renders patients pacemaker-dependent permanently; thus, AV nodal ablation and pacing should be limited to patients whose symptoms cannot be managed by rate-controlling drugs or by rhythm control interventions. In the case of bradyarrhythmia, the rate should also be controlled but with increasing the heart rate to the normal range with pacemaker implantation (116).

2.4.4.3.2. Non-pharmacological rhythm control

Synchronized DC electrical cardioversion quickly converts AF to sinus rhythm, and it is the method of choice in patients with hemodynamic instability. Electrical cardioversion can also be performed to restore sinus rhythm in persistent and long-standing persistent AF to control AF-related symptoms (116). The other type of non-pharmacological rhythm control is catheter ablation, which is discussed separately in the next section.

2.4.4.4. Catheter ablation

Pulmonary vein isolation is the most effective method of the rhythm control treatment (116, 127). Recently, contact force-sensing ablation catheters (CFSAC) were introduced, and nowadays, they became part of the everyday practice worldwide (128-133).

2.4.4.4.1. The background of pulmonary vein isolation

The exact pathophysiology of AF in the case of individual patients is unknown; thus, it is one of the most exciting research topics nowadays. The cornerstone research was presented in 1998 by Haissaguerre and colleagues, where they demonstrated the essential role of the pulmonary veins (PVs) in the pathomechanism of AF (Figure 5) (134). After that, different electrophysiological properties of the PVs were proven by Jais et al. in patients with AF compared with healthy patients' PVs. They found that PVs have a much shorter effective refractory period in patients with AF, which might play an important role in arrhythmogenesis (133, 135).

The refractory period of the atrial musculature and the PVs might further be shortened by recurrent episodes of AF, which precipitates the development of longer and oftener AF episodes ("AF begets AF") (121, 136). The majority of the ectopic beats arising from PVs have a multifocal pattern and proximal origin, as shown by a high-density mapping study (137). In addition to the PVs, many other factors are involved in the pathophysiology of AF, such as vagal ganglia, the ligament of Marshall, micro-reentrant circuits, and rotational activities (133, 138-141).

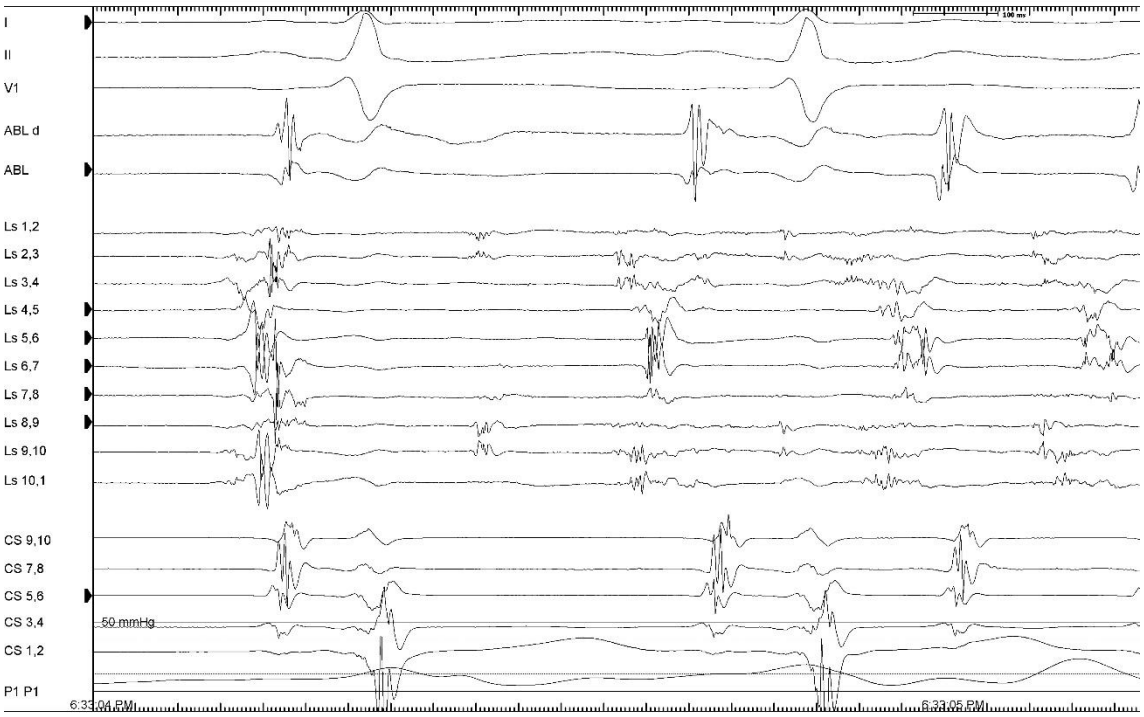

Figure 5. High-frequency electrical activity registered by the Lasso (Ls) catheter placed in the orifice of the right superior pulmonary vein. Electrophysiology Laboratory, Heart and Vascular Center, Semmelweis University.

Wide-area circumferential ablation around the PVs is likely to have more benefits besides the electrical isolation of PVs from the left atrium, by the modification of additional substrates located near the PVs, such as ganglionated plexi (142). Nowadays, the most frequently used PVI techniques are cryoballoon ablation and point-by-point radiofrequency ablation (133).

2.4.4.4.2. Point-by-point radiofrequency catheter ablation

Pulmonary vein isolation with radiofrequency energy is superior compared to the antiarrhythmic drug treatment (7-22% vs. 56-86%) (143-145). The amount of fluoroscopy can be reduced by using electroanatomical mapping systems. On the other hand, the need for a very accurate catheter manipulation necessitates extensive training for the operating physicians. It is effective in both paroxysmal and persistent AF (146, 147). Moreover, it might even have a mortality benefit in patients with impaired left ventricular ejection fraction (133, 148-150).

The clinical success rate of catheter ablation for AF fell short of expectations, likely caused by difficulties in achieving a durable PVI. Clinical efficacy may be reduced due to insufficient catheter tip-to-tissue contact force (CF) during ablation. Even though acute PVI is achieved in almost all cases, recurrences of AF are frequent, usually related to PV reconnection. The use of CFSAC-s during PVI results in a lower AF recurrence rate and shorter procedure duration compared to PVI performed with conventional ablation catheters. The results of the first studies verified the optimal minimum CF and force-time integral (FTI) value for the RF applications (128-132, 151, 152). The use of CF catheters during PVI improved AF-free survival; however, the recurrence rate remained significant. Recently developed lesion size predicting markers, such as ablation index and lesion size index, may further facilitate the procedure in terms of achieving durable PVI. When they are used with keeping the maximal inter-lesion distance below 6 mm (e.g., CLOSE protocol), PVI will be superior compared to previously used techniques (133, 153-159). An example of a PVI performed with the CARTO system and CLOSE protocol is shown in Figure 6.

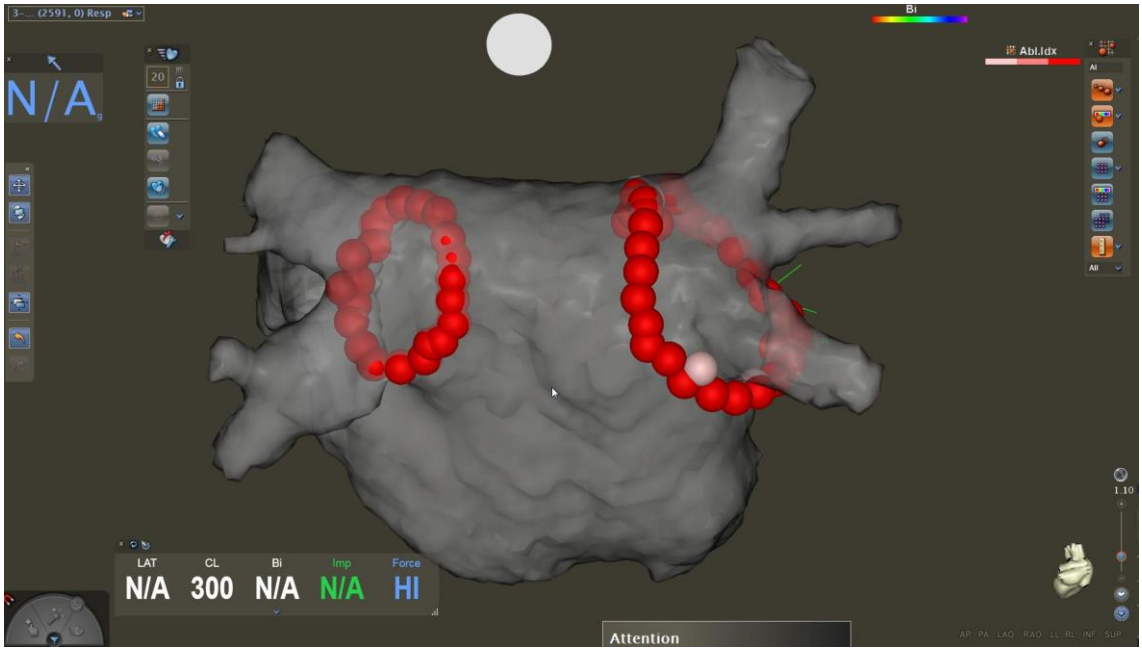

Figure 6. Pulmonary vein isolation performed with the CARTO system using the CLOSE protocol. Following the criteria of CLOSE protocol, red ablation tags indicate an ablation index value >400 on the posterior wall and >550 on the anterior wall. The overlap between the neighboring tags means that the distance between ablation points is <6 mm. Electrophysiology Laboratory, Heart and Vascular Center, Semmelweis University.

2.4.4.4.3. Cryoballoon ablation

Pulmonary vein isolation can be performed with a special balloon catheter. The orifice of the PVs is occluded by the cryoballoon, and PVI is completed with cryothermal energy. Proper occlusion of the PV by the balloon catheter is visualized with contrast injection under fluoroscopic imaging (shown in Figure 7). If the accurate occlusion of the PV orifice is verified, one might start the freezing. Fluoroscopic imaging is necessary for verification of the occlusion at each PV, which leads to a higher dose of radiation (133).

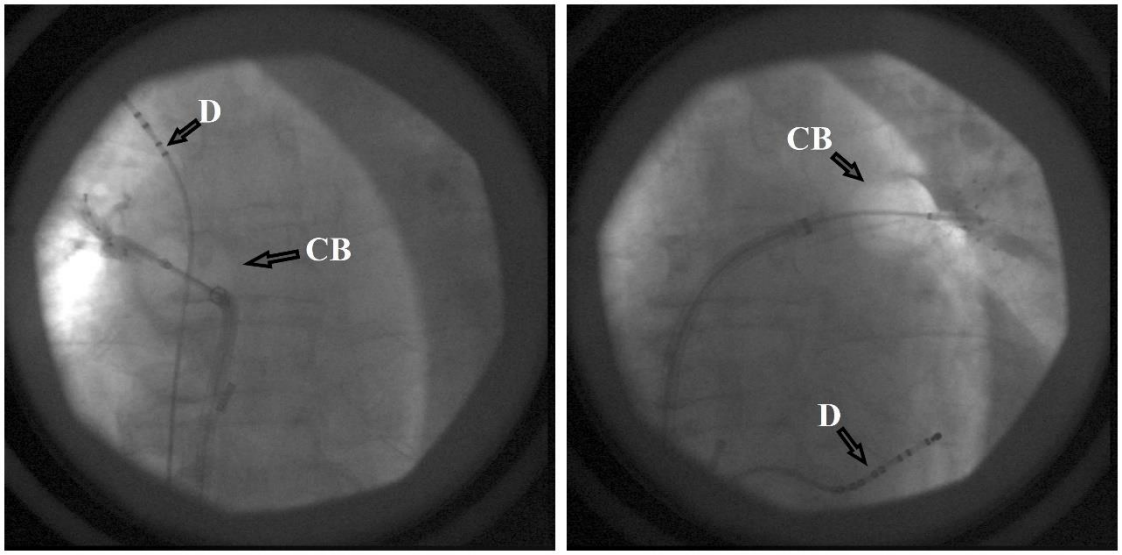

Figure 7. Left side: contrast is injected into the right inferior pulmonary vein, after cryoballoon occlusion (CB, arrow); decapolar catheter (D, arrow) is positioned in the superior vena cava to pace the phrenic nerve. Right side: contrast injection into the left superior pulmonary vein, after cryoballoon occlusion; decapolar catheter is placed in the coronary sinus. Electrophysiology Laboratory, Heart and Vascular Center, Semmelweis University.

First-generation cryoballoons delivered ablation only through the equator of the balloon. The Freeze AF randomized trial showed that first-generation cryoballoon was non-inferior compared to the radiofrequency point-by-point ablation in terms of efficacy. However, a higher rate of (mostly transient) phrenic nerve palsy was observed (0% vs. 5.8%) (160). The number of injection ports has been doubled, and those have been placed more distally on the second-generation cryoballoon (161). This development led to a higher rate of single-shot PVI and improved clinical efficacy (162). The Fire and Ice randomized trial showed that second-generation cryoballoon was non-inferior to radiofrequency ablation concerning effectiveness and safety (163). The most common adverse event was phrenic nerve injury in the case of cryoballoon procedures (2.7%); however, those are only transient in the vast majority of the cases (164, 165). Cryoballoon is also safe and effective in patients with persistent AF; moreover, additional isolation of the left atrial appendage may improve 12-month outcome compared with the PVI-only ablation strategy (166-168). The disadvantage of the cryoballoon is that it may be less

effective in some anatomical variations of the PVs, such as a long left common trunk or additional pulmonary veins (133, 169, 170).

2.4.4.4.4. Complex left atrial ablation for persistent atrial fibrillation

The pathophysiological background of persistent AF is more complicated compared to paroxysmal AF. Besides the triggers that induce arrhythmia, usually, a complex arrhythmogenic substrate is also present due to the atrial enlargement and fibrosis. Thus, PVI is generally not as useful as it is in paroxysmal AF. The efficacy of catheter ablation can be improved with substrate modification, such as ablation of complex fractionated atrial electrograms, additional linear ablation lines, or isolation of the left atrial appendage. The value of additional substrate modification beyond PVI is disputable. Of note, most of the studies that showed negative results regarding these additional ablation techniques were conducted before the contact force era and in low volume centers (133, 166, 168, 171-174).

2.4.4.4.5. Complications of atrial fibrillation ablation

The nature of AF ablation procedures exposes patients to a substantial number of complications, which can range between 1% and 8%. The most common adverse events are pericardial effusion and vascular access site complications. However, less frequent adverse events also need attention as they can be life-threatening or may cause severe long-term disability or death. These are stroke, transient ischemic attack (TIA), pulmonary vein stenosis, phrenic nerve palsy, or atrio-esophageal fistula. The relatively high number of complications drives a continuous need for more effective and safer ablation approaches. In the last few years, ablation has made impressive progress both for efficacy and safety, as new technologies have been developed and extensive research has also been conducted to understand the arrhythmia mechanisms. Recent studies analyzed many predictors of adverse events arising from AF ablation. However, most of these publications were restricted to initial AF ablation procedures, and limited data exist regarding the role of a repeated catheter ablation procedure (175-182).

3. AIMS

As an operating physician enhancing the outcome of catheter ablation is in the center of my interest. Thus, our aim was the examination of factors that may influence the outcome of catheter ablation of complex atrial arrhythmias. Our goal was to reveal those factors that were not known at the time when the examinations were performed.

First, we aimed to evaluate the additional value of the CARTO electroanatomical mapping system over conventional fluoroscopy based mapping method in terms of guiding catheter ablation of focal atrial tachycardias in a retrospective fashion. Data were collected from the computer database of two Hungarian Electrophysiology Centers. We sought to evaluate the following procedural parameters: procedure time, fluoroscopy time, acute and 6-month success rate, and complication rate.

The second part of our project dealt with an even more complex atrial arrhythmia: atrial fibrillation. As the success rate of the atrial fibrillation ablation was already well established at the time when our registry was started, we aimed to evaluate the potential predictors that may propose the patient to a higher probability of PVI-related adverse events. All patients who underwent catheter ablation for atrial fibrillation between 2013 and 2015 were prospectively included in our database, and all major and minor complications related to the ablation procedure were considered.

4. METHODS

Study protocols were reviewed and approved by the institutional review boards and were in accordance with the declarations of Helsinki (TUKEB 140/2017).

4.1. Patient population

4.1.1. Patients undergoing focal atrial tachycardia ablation

Our retrospective study evaluated all consecutive patients who underwent catheter ablation for incessant or paroxysmal focal atrial tachycardia in two Hungarian cardiology centers: Cardiology Institute of University of Debrecen, Hungary (2006 - 2011), and Cardiology Department of Military Hospital, State Health Center, Budapest, Hungary (2009 - 2011). The start of the data collection was set to the first availability when the CARTO electroanatomical mapping system in the given institutes (109).

4.1.2. Patients undergoing atrial fibrillation ablation

This prospective registry was started to determine the incidence and characteristics of adverse events related to atrial fibrillation ablation in the electrophysiology laboratory of the Heart and Vascular Center, Semmelweis University, Budapest, Hungary. Data of all complications linked to AF ablation procedures were prospectively collected between January 2013 to December 2015 (183).

4.2. Electrophysiological study

Written informed consent was obtained from all patients prior to the electrophysiological study and catheter ablation.

4.2.1. Electrophysiological study and ablation of focal AT

Antiarrhythmic drugs were stopped for a minimum of five half-lives before the procedure. The electrophysiological study was performed using quadripolar electrode catheters positioned in the high right atrium, right ventricular apex, at the bundle of His, and a decapolar catheter was placed in the coronary sinus. The arrhythmia was either induced by programmed atrial extrastimulation, or burst atrial pacing, and/or administration of isoprenaline. As soon as the FAT has been verified using conventional electrophysiological criteria, we proceeded to the catheter ablation. Mapping of the FAT was performed during ongoing arrhythmia. The mapping aimed to localize the earliest endocardial intracardiac signal that precedes the onset of the P-wave with at least 30 ms. All cases were considered as “conventional” procedures in our analysis, where the electroanatomical mapping system was not used. Additionally or alternatively to multipolar catheters, electroanatomical mapping system (CARTO XP V9.6 system and Navistar catheter family, Biosense Webster, Inc., Diamond Bar, CA, USA) might have been used based on the individual decision of the operating physician. A three-dimensional electroanatomical activation map was obtained in such cases during ongoing tachycardia to define the site of the earliest activation (see Figure 8).

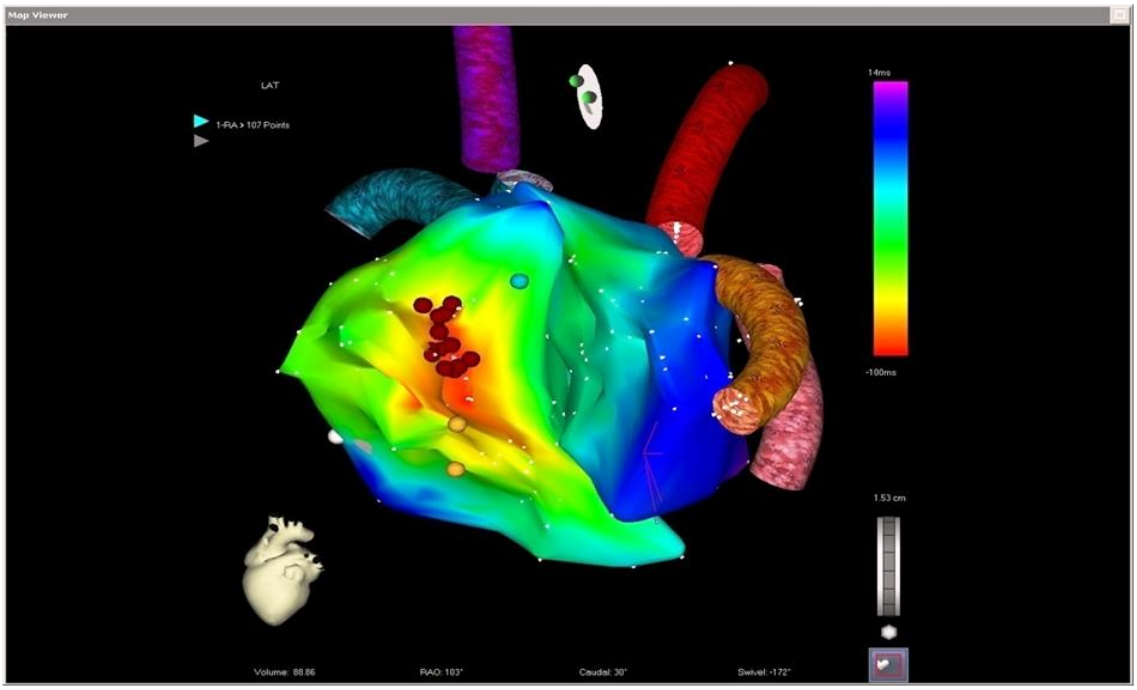

Figure 8. Activation electroanatomical map of a right anteroseptal focal atrial tachycardia acquired with the CARTO-XP mapping system (left-sided view). Electrophysiology Laboratory, Military Hospital, Budapest.

Radiofrequency ablations were applied at the site of the earliest endocardial activation with a 4-mm tip ablation catheter, during continuous impedance and temperature monitoring. The selection of a non-irrigated or irrigated catheter was left to the operating physician's preference. The predefined temperature limit was 60 ºC in cases where a non-irrigated catheter was used, and 41 °C in cases ablated with an irrigated catheter. Radiofrequency energy was started at a power of 20 Watts and increased up to 30 Watts; the maximal duration of an application was 60 seconds. After the ablation, the initially successful induction method was used to prove the effectiveness of the lesions. All the previously mentioned catheters and techniques were available in both centers throughout the studied period (109).

4.2.2. Catheter ablation of AF

Indications for AF ablation procedures and periprocedural anticoagulation were following the current guidelines (184). In the case of patients anticoagulated with vitamin K antagonists, the ablation procedure was performed if the INR value was between 1.8

and 3.5. Intravenous fentanyl, midazolam, and propofol were administered for conscious sedation. The blood pressure was measured every 10 minutes, and continuous pulse oximetry was used to monitor basic vital parameters. Pre-procedural left atrial computed tomography (CT) or magnetic resonance (MR) angiography was performed to reveal the left atrial and PV anatomy. On the day of the ablation procedure, transesophageal echocardiography (TEE) or intracardiac echocardiography (ICE) was performed to rule out the presence of a left atrial appendage thrombus. Catheters were inserted through the femoral vein in all cases. Transseptal puncture was performed under fluoroscopy guidance and pressure monitoring. In difficult cases, ICE was utilized for the direct visualization of the oval fossa. Unfractionated heparin was administered immediately after entering the left atrium (50-120 units per kilogram i.v. bolus depending on pre-procedural anticoagulation strategy), and it was titrated every 20-30 minutes throughout the whole procedure based on activated clotting time (ACT) measurements (target ACT level was > 300 sec). Protamine was not administered routinely at the end of the procedure to reverse the effect of heparin. All ablations were supported with the use of an electroanatomical mapping system (either CARTO, Biosense Webster, Inc., Diamond Bar, CA, USA; or EnSite, St. Jude Medical, Inc., MN, USA). Left atrial fast anatomical map was fused with the previously obtained CT/MR images to help the ablation. Radiofrequency ablations were applied in temperature-controlled mode, 43 °C, 25–35 Watts, with an irrigated 4-mm tip catheter, in the vast majority of cases. The most frequently used irrigated 4 mm tip catheters were the following: NaviStar ThermoCool (Biosense Webster), ThermoCool SmartTouch (Biosense Webster), TactiCath Quartz (Abbott), AlCath Flux Blue (Biotronik) and Blazer Open-Irrigated (Boston Scientific). In a smaller number of cases, nMARQ catheter (Biosense Webster, Irwindale, CA, USA) or cryoballoon (Arctic Front Advance, Medtronic, Minneapolis, MN, USA) was used. Complete electrical isolation of all PVs was the aim of each initial procedure. In cases of repeat ablation for persistent AF or ablation for long-standing persistent AF, additional lines might have been drawn on the discretion of the operating physician. After the procedure, a compression bandage was applied for 3–6 hours to prevent bleeding of the inguinal puncture site. Transthoracic echocardiography was performed to rule out pericardial effusion at the end of the procedure and on the next morning. A few hours after the procedure, patients were visited by medical staff, and vital parameters were

checked in the evening hours and the next morning. All patients with novel neurological symptoms underwent immediate brain CT or MR scan. In the case of suspicion of vascular access complication, an ultrasound was performed to rule out serious adverse events. All patients without complications were discharged the day after the procedure (183).

4.3. Follow-up of the patients

Outpatient clinical follow-up visits were scheduled at six months after FAT ablation and 3, 6, and 12 months and once yearly after that in case of AF ablation. The follow-up visits included clinical assessment of the symptoms, 24-hour Holter ECG recording, and exploration of adverse events. In the case of dyspnea, a chest X-ray was performed to rule out phrenic nerve paresis. If it was negative, a left atrial CT angiography was conducted to detect the potential stenosis of the PVs (109, 183).

4.4. Definitions

4.4.1. Definition of success of focal AT ablation

Acute success was defined as the absence and non-inducibility of clinical arrhythmia with the previously used effective induction method(s), 30 minutes after the last radiofrequency application. The ablation procedure was defined as unsuccessful (acute failure) if the tachycardia remained inducible.

Six-month success was defined as no recurrence of focal atrial tachycardia without antiarrhythmic drug therapy. Partial success was defined as asymptomatic tachycardia recurrences on 24-hour Holter monitoring or ECG recordings, or cases when symptoms improved but some shorter tachycardia episodes were still present (with or without antiarrhythmic drug therapy), or those cases when the absence of AT episodes was reached with the use of antiarrhythmic drugs (e.g., propafenone, sotalol, amiodarone). Failure was defined as the persistence of symptoms with or without antiarrhythmic drug therapy (109).

4.4.2. Definitions of major and minor complications of AF ablation procedures

All potential complications related to AF ablation were analyzed, including vascular access site complications, pericardial tamponade, and effusion, phrenic nerve palsy, stroke or TIA, pulmonary vein stenosis, atrioventricular block, atrio-esophageal fistula, and procedure-related death. A major complication was defined as an adverse event that required active, interventional, or surgical treatment. Therefore, pericardial effusion (> 5 mm was included in the analysis), and groin hematoma were considered as minor complications, if they did not necessitate interventional treatment (183).

4.5. Statistical analysis

Continuous variables showing parametric distribution according to the Shapiro-Wilk normality test are expressed as mean ± standard deviation (SD). In contrast, continuous variables showing non-parametric distribution are reported as median with interquartile ranges. Categorical variables are expressed as event numbers and percentages. Fisher's exact test and Mann–Whitney U test was performed for examining contingency between groups. Chi^2 for trend test was used for the 6-month success analysis of focal AT ablations. Multivariate analysis, logistic regression was conducted to determine predictors of complications. A two-tailed P-value <0.05 was considered significant. Statistical analysis was performed with GraphPad Prism, version 6.01 (GraphPad Software, Inc., La Jolla, CA, USA) and IBM SPSS Statistics, version 25 (IBM Corp., Armonk, NY, USA) software (109, 183).

5. RESULTS

5.1. Ablation of focal atrial tachycardias with and without CARTO electroanatomical mapping system

5.1.1. Patient population

Our study assessed 60 ablations (6 redo procedures) in 54 consecutive patients (age 54±17 years, 39 females). Baseline parameters were similar between the two patient groups (shown in Table 3). Antiarrhythmic drugs were used in 20 and 16 cases for the conventional and CARTO groups, respectively. Tachycardia-induced cardiomyopathy did not occur in any of the studied patient population. Hypertension was present in 21 cases, ten patients had ischemic heart disease, five patients had COPD, eight had other supraventricular tachycardia, as well, and 5 of them underwent prior cardiac surgery (109).

Table 3. Baseline parameters of the patient population who underwent focal atrial tachycardia ablation either with conventional fluoroscopy-based mapping (second column) or with CARTO electroanatomical mapping (third column). The reason for having only 24 patients in the CARTO mapping column is that six patients had repeated procedure with CARTO guidance (109).

Abbreviations: AVNRT= atrioventricular-nodal reentrant tachycardia, COPD= chronic obstructive pulmonary disease, EF= ejection fraction, FAT= focal atrial tachycardia, max= maximum, min= minimum, mm= millimeter, ns= non-significant, MI= mitral insufficiency, SD= standard deviation, TI= tricuspid insufficiency.

	Conventional mapping	**CARTO mapping**	**Significance**
Number of patients	30	24	ns
Female	21 (70%)	18 (75%)	ns
Age (years, mean±SD)	61±14	48±18	ns
Hypertension	8 (26%)	13 (54%)	ns
Diabetes mellitus	4 (13%)	5 (21%)	ns
COPD	3 (10%)	3 (12%)	ns
Heart surgery	3 (10%)	2 (8%)	ns
Ischemic heart disease	3 (10%)	7 (29%)	ns
Valvular disease	4 (13%)	3 (12%)	ns
MI grade II-III.	3 (10%)	1 (4%)	ns
TI grade II-III.	1 (3%)	2 (8%)	ns
EF (%, mean±SD)	53±12	57±12	ns
Left atrial diameter (mm, mean±SD)	41±7	40±9	ns
Right ventricular systolic pressure > 35 mmHg	4 (13%)	1 (4%)	ns
Other arrhythmia beside FAT	2 (6%)	6 (25%)	ns
Atrial flutter	1 (3%)	3 (12%)	ns
AVNRT	1 (3%)	3 (12%)	ns
Antiarrhythmic drugs	20 (66%)	16 (66%)	ns
Beta-blockers	15 (50%)	11 (46%)	ns
Amiodarone	1 (3%)	2 (8%)	ns
Propafenone	1 (3%)	2 (8%)	ns
Sotalol	1 (3%)	0	ns
Verapamil	2 (6%)	1 (4%)	ns
Antiarrhythmic drug combination	4 (13%)	5 (20%)	ns

5.1.2. Distribution of ectopic foci

Forty-six right-sided foci were present: 14 coronary sinus, 11 crista terminalis, seven superior vena cava, three tricuspid annulus, three para-Hisian, two septal, three anterosuperior, two lateral wall, and one inferior vena cava. Distribution of sixteen left-sided foci was the following: 4 coronary sinus, three pulmonary vein, three mitral annulus, three septal, two anterosuperior, and one appendage (lateral wall). The laterality of one septal focus was not determinable. Two distinct foci were ablated in the case of 3 procedures. No difference was found regarding the distribution of foci between the CARTO and conventional groups (Figure 9) (109).

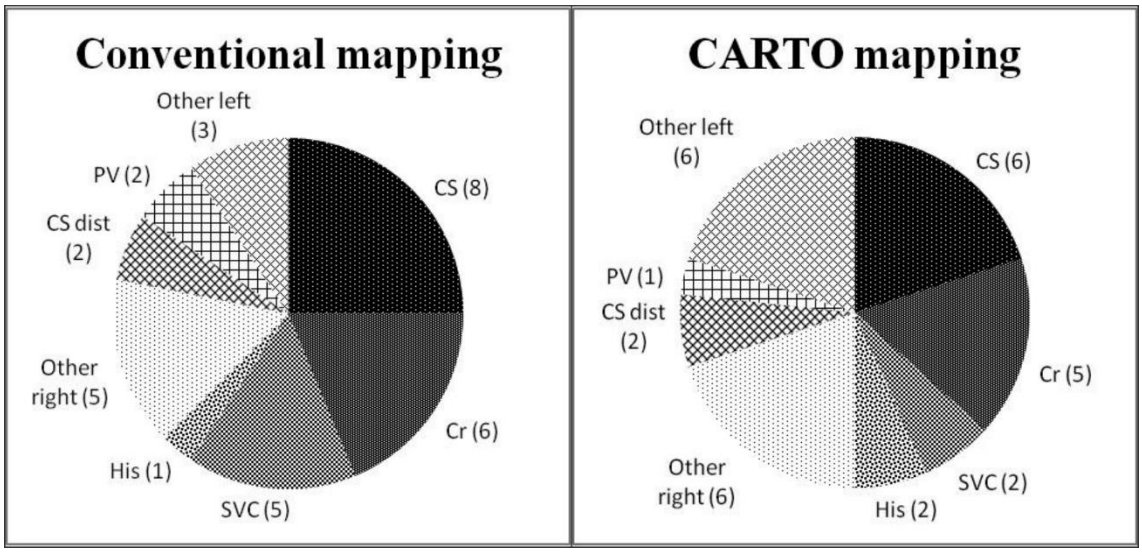

Figure 9. Distribution of ectopic foci in case of procedures with conventional mapping and CARTO mapping. Absolute numbers of ectopic foci are shown in parenthesis. Abbreviations: CS= coronary sinus, Cr= crista terminalis, SVC= superior vena cava, His= para-Hisian, CS dist= distal coronary sinus, PV= pulmonary vein. Other right and other left categories mean septal, tricuspid annulus, inferior vena cava, mitral annulus, anterosuperior and lateral wall (109).

5.1.3. Ablation procedure

Overall, 60 ablation procedures were analyzed, out of which 30 were mapped with conventional methods only, whereas the CARTO electroanatomical mapping system was also used in the remaining 30 cases. The vast majority of AT-s were paroxysmal; however, incessant AT also occurred in 11 cases. Six incessant AT-s were ablated with the support of the CARTO system, while conventional mapping was used alone in 5 cases. There was a better acute success rate (Figure 10) in cases guided by the CARTO electroanatomical mapping system (27/30, 90%), compared to procedures guided by fluoroscopy only (18/30, 60%; $p < 0.01$). A difference in outcome was neither observed between operating physicians, nor between irrigated and non-irrigated ablation catheters. Procedure time (139 ± 59 vs. 96±44 min, p: ns) and fluoroscopy time (18 ± 12 vs. 11 ± 6 min, p: ns) was also similar for CARTO-based procedures and conventionally mapped ablations; although there was a trend for the longer procedure- and fluoroscopy times in case of the CARTO group. No procedure-related adverse events occurred (109).

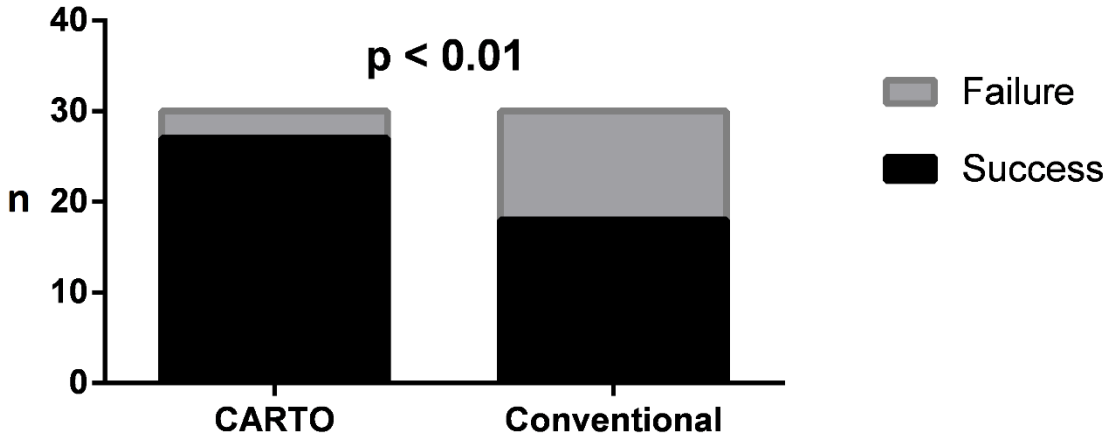

Figure 10. The acute success rate of focal atrial tachycardia ablation procedures in case of CARTO mapping and conventional fluoroscopy-based mapping. Success was defined as the non-inducibility of clinical arrhythmia at the end of the electrophysiological study. Failure was defined as the tachycardia episodes remained inducible at the end of the procedure. Statistical test: Fisher's exact test. Abbreviation: n= number of cases (109).

5.1.4. Follow-up

The 6-month follow-up data were available in 56 cases, as two patients were foreigners, and two patients died. One of them was 70 years old and had a malignant tumor, the other patient was 80 years old, but the cause of death is unknown in her case. The procedure was successful in 11 cases after CARTO-guided ablation, and 4 cases after conventional mapping ablation. Partial success (12 vs. 18) and failure (4 vs. 7) occurred less often in the CARTO group compared to the conventional group (Figure 11). A better outcome was obvious in cases where CARTO guidance was used (p = 0.045). Repeated ablation was necessary in six cases (after 2 CARTO and four conventionally mapped procedures); all were successfully performed with the CARTO system (109).

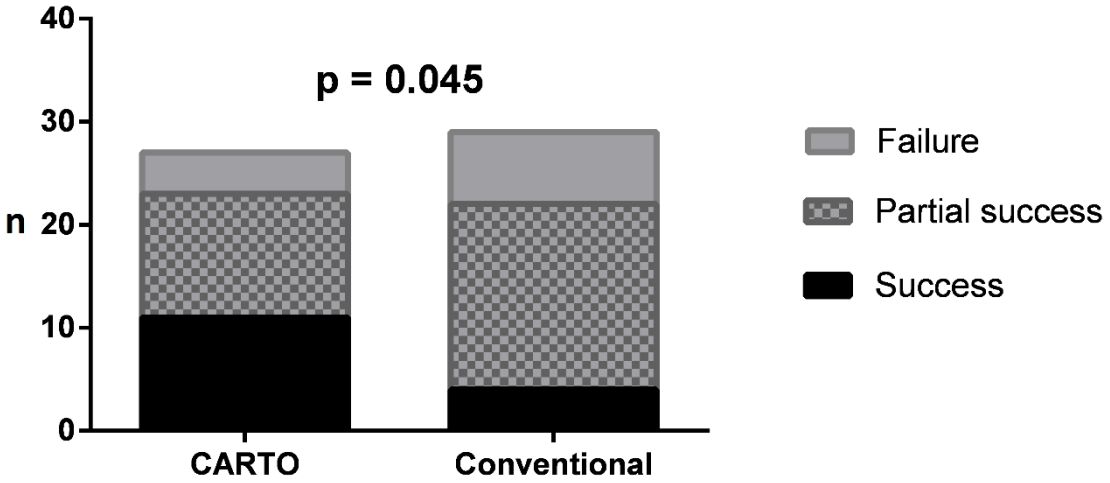

Figure 11. The six-month success rate of focal atrial tachycardia ablation procedures in case of CARTO mapping and conventional fluoroscopy-based mapping. Success was defined as no FAT recurrence without any antiarrhythmic drug (AAD). Partial success was defined as asymptomatic tachycardia recurrence without AAD; or if the arrhythmia-free survival was only achievable with AAD-s. Failure means the persistence of arrhythmia symptoms, either with or without antiarrhythmic drug therapy. Statistical test: chi-square for trend test. Abbreviation: n= number of cases (109).

5.2. Evaluation of predictors of complications associated with atrial fibrillation ablation

5.2.1. Patient population

Overall, 1243 AF ablation procedures were analyzed. The median age was 62 years (55-69 years), and 32% were females. AF was persistent or long-standing persistent AF in 397 cases (32%). The most common secondary diagnoses were hypertension (70%), diabetes mellitus (16%), and coronary artery disease (11%). Previous AF ablation was present in the past medical history in 18% of the patients (183). Baseline characteristics for the studied population are shown in Table 4.

Table 4. Baseline characteristics of the patients who underwent AF ablation procedure in the study period. Abbreviations: AF= atrial fibrillation, DOAC= direct oral anticoagulant, ICE= intracardiac echocardiography, TIA= transient ischemic attack, VKA= vitamin-K antagonist (183).

	Total study population (n= 1243)
Female	394 (32%)
Age (years)	62 (55-69)
Hypertension	876 (70%)
Diabetes mellitus	197 (16%)
Coronary artery disease	140 (11%)
Kidney disease	30 (2%)
Dilated cardiomyopathy	49 (4%)
Hypertrophic cardiomyopathy	5 (0.4%)
Peripheral vascular disease	41 (3%)
Previous stroke/TIA	75 (6%)
Left ventricular ejection fraction (%)	57 (55-60)
CHA_2DS_2-VASc score	2 (1-3)
Previous AF ablation	221 (18%)
Persistent AF	397 (32%)
Drug therapy	
Anticoagulation with DOAC	378 (30%)
Anticoagulation with VKA	862 (69%)
Amiodarone	102 (8%)
Propafenon	26 (2%)
Sotalol	22 (2%)
Ablation method	
Point – by – point	1186 (95%)
Contact force catheter	462 (37%)
Non-contact force catheter	724 (58%)
Cryoballoon	32 (3%)
nMARQ	25 (2%)
ICE catheter	162 (13%)

5.2.2. Complications related to AF ablation procedures

The vast majority of adverse events occurred during the same hospitalization when the ablation was performed. Obviously, late complications such as PV stenoses were only diagnosed during the follow-up period. Moreover, there was one case of a late pericardial effusion, diagnosed on the 15th postprocedural day. No phrenic nerve paresis, atrio-esophageal fistula, or procedure-related death was recorded in this cohort (183). The incidence of overall and major complications in the case of de novo and repeat procedures are shown in Table 5 and Figure 12.

Table 5. Incidence of complications associated to initial (de novo) and repeated AF ablation procedures (183).

Type of complication	**Number of complications of de novo ablations (total n= 1022)**	**Number of complications of repeat procedures (total n=221)**	**Summary (total n= 1243)**
Major complications	18	17	35 (2.82%)
Pericardial tamponade	8	10	18 (1.45%)
Stroke / transient ischemic attack	5	1	6 (0.48%)
Pseudoaneurysm of femoral artery	4	1	5 (0.40%)
Pulmonary vein stenosis	0	3	3 (0.24%)
III. degree atrio-ventricular block	0	2	2 (0.16%)
Arteriovenous fistula	1	0	1 (0.08%)
Phrenic nerve palsy	0	0	0
Atrio-esophageal fistula	0	0	0
Procedure-related death	0	0	0
Minor complications	33	17	50 (4.02%)
Pericardial effusion	17	11	28 (2.25%)
Groin hematoma	16	6	22 (1.77%)
Overall complications	51	34	85 (6.84%)

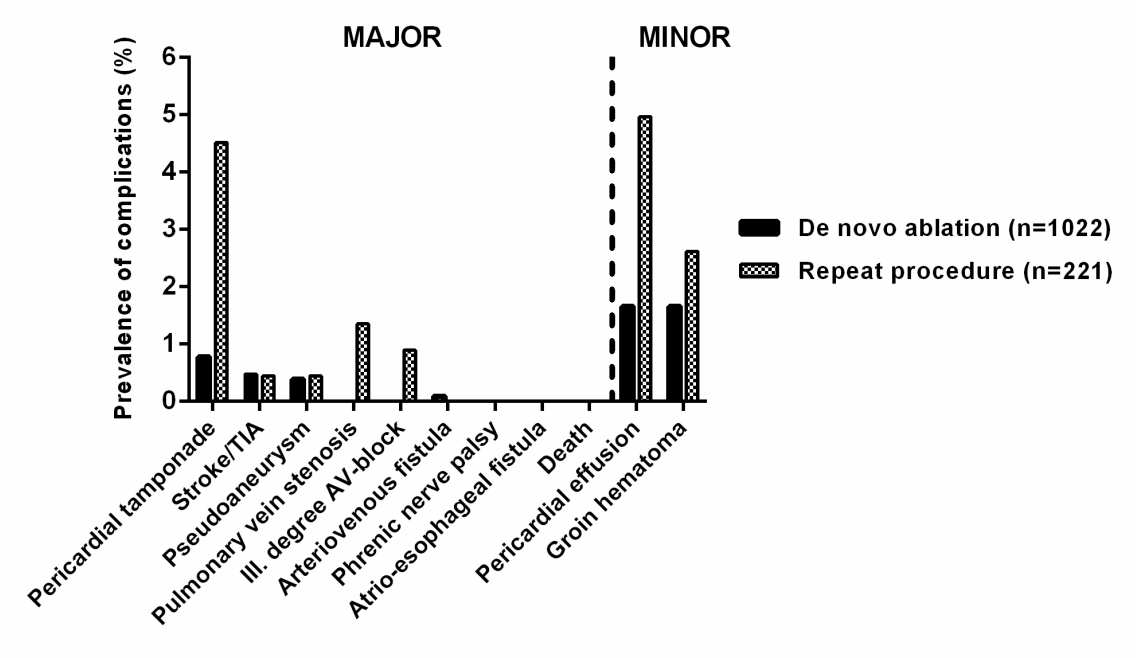

Figure 12. Distribution of complications of de novo ablations and repeat procedures (183).

Complications occurred in 85 cases (6.84%). Most of these were minor complications that did not require active treatment (28 pericardial effusions and 22 groin hematomas). The ratio of major complications - where interventional treatment was necessary - was 2.82% (35 cases) (183).

Pericardial tamponades occurred in 18 cases. Fifteen tamponades were managed with pericardiocentesis only. However, heart surgery with hematoma evacuation was necessary in the remaining 3 cases. The cause of the bleeding was not identifiable in these cases; the suspected mechanism was "per diapedesis" bleeding. The duration of hospitalization was prolonged to 8.5 (6.0-14.5) days in cases where pericardial tamponade occurred. Thirteen tamponades were diagnosed during or immediately after the procedure. Four other cases were recognized a few hours after the ablation, and one late tamponade occurred on the 15th postoperative day. Blood transfusion was required in four patients. The incidence of pericardial effusion, which did not require intervention, was 28/1243 (2.25%); these patients resolved spontaneously without sequelae (183).

The most common major vascular adverse event was pseudoaneurysm of the femoral artery, the incidence of which was 5/1243 (0.4%). Surgical operation or percutaneous closure with the injection of thrombin was successfully performed in all cases. One arteriovenous (A-V) fistula occurred, which was treated surgically (1/1243, 0.08%). Twenty-two groin hematomas were found; none of these require active treatment (22/1243, 1.77%). All adverse events related to the access site were diagnosed by ultrasound, and in case of need, the diagnosis was also confirmed by CT angiography. All of these complications resolved without sequelae (183).

Six thromboembolic events occurred: 4 strokes and 2 TIA-s (6/1243, 0.48%). Brain MR and neurological consultation were organized immediately after recognizing the symptoms. All patients were treated with parenteral anticoagulants only. Neurological symptoms resolved without sequelae in all cases (183).

Significant pulmonary vein stenoses occurred in 3 cases out of 1243 AF ablations. The number of previous ablation procedures for individual patients was 2, 2, and 3, respectively. One patient had stenoses of the left inferior, right inferior, and right superior PVs. The second patient was diagnosed with left superior pulmonary vein stenosis. The third patient had stenoses of the left superior, right superior, and right inferior pulmonary veins. Successful percutaneous transluminal angioplasty of the stenotic PVs was performed in all patients (183).

Third-degree atrioventricular block occurred in two cases. Both of these happened during repeated ablation for a long-standing persistent AF with additional left atrial lines, including the ablation of the septum. A Dual-chamber pacemaker was implanted in both patients (183).

The majority of the patients were anticoagulated with vitamin K antagonists (VKA, no= 865), while direct oral anticoagulants were administered in fewer patients (DOAC, no= 378). No difference was found in the rate of adverse events for different anticoagulation strategies (46/865 vs. 14/378; p=0.2517) (183).

The complication rates for the three different ablation techniques that were used in our institute were also analyzed. Groin hematoma occurred in one out of 25 cases ablated with nMARQ catheter (4.0%). One pericardial effusion and one groin hematoma occurred

out of 32 procedures performed with cryoballoon (6.25%). The overall complication rate for point-by-point ablation was 82/1186 (6.91%). There was no difference between the complication rates for the abovementioned ablation techniques (p=0.8419), which might result from the dominance of point-by-point ablation method and the low number of cases with single-shot devices (183).

Procedures were performed by five different operators. We did not find any difference between the complication rate of the individual operators: the number of procedures with and without complication was 38/539, 20/382, 27/225, 0/3, and 0/9, respectively; (p=0.0593) (183).

5.2.3. Predictors of complications

Patients' baseline characteristics and procedural characteristics were analyzed to evaluate the predictors of complications (Table 6 and Table 7). Univariate analysis for overall complications revealed that age≥65 years (p=0.0231), hypertension (p=0.0488), female gender (p=0.0438), CHA_2DS_2-VASc score≥2 (p=0.0156) and previous AF ablation procedure (p<0.0001) was associated with a higher risk for complications. Multivariate analysis for overall complications showed that the only independent predictor of overall complications was previous AF ablation procedure (OR 3.13; 95% CI 1.95-5.03; p<0.0001). A similar analysis was conducted to determine the predictors of the major complications. We found that the only independent predictor of the major complications was also the previous AF ablation procedure (OR 3.65; 95% CI 1.84-7.24; p<0.0001) (183).

Table 6. Univariate analysis for predictors of adverse events associated with AF ablation procedures (183). Abbreviations: AF= atrial fibrillation, DOAC= direct oral anticoagulant, LA-LD= left atrium longitudinal diameter, LA-TD= left atrium transversal diameter, LVEF= left ventricular ejection fraction, OR= odds ratio, TEE= trans-esophageal echocardiography, TIA= transient ischemic attack, VKA= vitamin K antagonist.

Examined parameter	**Parameter present (total n=1243)**	**Overall complications**		**Major complications**	
		P value	**OR (95% CI)**	**P value**	**OR (95% CI)**
Female	**394 (32%)**	**0.0438**	**1.60 (1.03-2.48)**	0.4671	1.28 (0.63-2.57)
Age ≥ 65 years	**525 (42%)**	**0.0231**	**1.67 (1.07-2.60)**	0.4892	1.30 (0.66-2.55)
Hypertension	**876 (70%)**	**0.0488**	**1.73 (1.00-2.99)**	0.2609	1.69 (0.73-3.92)
Diabetes mellitus	197 (16%)	0.8777	1.05 (0.57-1.90)	0.2426	1.59 (0.71-3.57)
Coronary artery disease	140 (11%)	0.7223	0.80 (0.38-1.71)	0.4184	0.46 (0.11-1.98)
Kidney disease	30 (2%)	0.7167	0.46 (0.06-3.44)	0.5799	1.19 (0.15-9.04)
Heart failure	48 (4%)	0.7677	0.58 (0.13-2.44)	1.0000	0.72 (0.09-5.42)
Dilated cardiomyopathy	49 (4%)	0.2493	0.27 (0.03-2.02)	1.0000	0.71 (0.09-5.30)
Hypertrophic cardiomyopathy	5 (0.4%)	0.2987	0.29 (0.37-31.09)	0.1333	8.85 (0.96-81.37)
Peripheral vascular disease	41 (3%)	0.5209	1.49 (0.52-4.30)	0.6265	0.39 (0.02-6.57)
Previous stroke/TIA	75 (6%)	0.0922	1.95 (0.94-4.08)	0.0548	2.71 (1.02-7.20)
LVEF	57 (55-60)	0.9640		0.3078	
LA-LD	39 (35-44)	0.7500		0.8971	
LA-TD	49 (41-55)	0.7570		0.4419	
CHA_2DS_2-VASc ≥ 2	**752 (60%)**	**0.0156**	**1.83 (1.12-2.99)**	0.1139	1.91 (0.89-4.13)
Previous AF ablation	**221 (18%)**	**< 0.0001**	**3.10 (1.94-4.93)**	**0.0004**	**3.65 (1.84-7.25)**
Ablation for persistent AF	397 (32%)	0.9041	0.93 (0.57-1.50)	0.0656	0.43 (0.17-1.05)
Spontaneous echocontrast on TEE	138 (11%)	1.0000	0.93 (0.48-1.80)	0.5764	1.36 (0.51-3.62)
Atypical pulmonary vein anatomy	236 (19%)	0.8858	0.92 (0.51-1.64)	0.8285	1.06 (0.46-2.47)
Use of a contact force sensing catheter	462 (37%)	0.1560	1.49 (0.86-2.57)	0.1018	1.55 (0.92-2.63)
Anticoagulation with VKA (vs. DOAC)	865 (70%)	0.2517	1.46 (0.79-2.69)	0.2754	1.39 (0.78-2.48)
Additional ablation over PVI	283 (23%)	0.1068	1.48 (0.95-2.32)	0.1133	1.61 (0.92-2.82)
Use of ICE	162 (13%)	1.0000	0.99 (0.51-1.91)	0.2052	1.69 (0.72-3.95)

Table 7. Multivariate analysis for predictors of adverse events associated with AF ablation procedures (183). Abbreviations: AF= atrial fibrillation, OR= odds ratio.

Examined parameter	**P-value**	**OR (95% CI)**
Overall complications		
Female	0.3550	1.25 (0.78-2.00)
Hypertension	0.1060	1.59 (0.91-2.81)
Age ≥ 65 years	0.0900	1.50 (0.94-2.40)
Previous AF ablation	**< 0.0001**	**3.13 (1.95-5.03)**
Major complications		
Previous AF ablation	**< 0.0001**	**3.65 (1.84-7.24)**

6. DISCUSSION

6.1. Ablation of focal atrial tachycardias with and without CARTO electroanatomical mapping system

To the best of our knowledge, our working group reported the first direct comparison between the CARTO electroanatomical mapping system and the conventional mapping method in guiding catheter ablation of FAT. The distribution of the ectopic foci is congruent with previously published data (73, 75, 78, 97, 110, 185). Better acute (90% vs. 60%) and 6-month (85% vs. 75%) success rates were found in CARTO-guided ablations compared to procedures without electroanatomical mapping (109). This success rate is congruent with the literature data (29, 41, 75, 96, 108, 114). However, a direct comparison between CARTO mapping and conventional mapping for FAT ablations was never conducted previously.

The aim of the antiarrhythmic drug administration in the case of FATs is to improve the quality of life by reducing symptoms. However, the efficacy of AAD treatment is limited in the case of FATs. Catheter ablation has been shown to be more effective, especially when it is combined with pharmacological therapy. Thus, radiofrequency catheter ablation is currently the first-line therapy in all symptomatic FAT cases, particularly when tachycardia-induced cardiomyopathy develops (29, 41, 73, 106).

Fifteen publications dealing with catheter ablation of FAT are summarized in Table 8. These data report the efficacy of FAT ablations either with electroanatomical mapping or conventional fluoroscopy based mapping; however, no direct comparison of acute and mid-term outcome of the two different mapping methods was conducted. The catheter ablation fluoroscopy based mapping was acutely successful in 93% of cases, while the mid- or long-term success rate was 90%. On the other hand, a summary of 156 FAT ablations supported by the CARTO system revealed a 93% acute success rate and an 89%

mid- or long-term efficacy. A solid meta-analysis of these data was not possible. Reasons are the different clinical endpoints, the various follow-up periods, and the lack of data. Some studies used a very strict endpoint, e.g., success was defined as the absence of FAT without AADs, confirmed with Holter-ECG monitoring. On the other hand, other authors used a lenient definition for "clinical success," meaning the improvement or lack of arrhythmia symptoms, with or without pharmacological therapy.

*Table 8. Publications dealing with FAT ablation guided by conventional mapping (panel A), CARTO mapping (panel B), and ablation with either conventional or CARTO mapping technique (panel C). Abbreviations: conv.= conventional mapping; EAM= electroanatomical mapping; EM= endocardial mapping; ICE= intracardiac echocardiography; n.d.= no data available; n.s.= nonsignificant; p= „p" value. *weighted average, calculated based on data published in the given article*

Panel A:

Author, year of publication (reference)	***Mapping method***	***Number of cases***	***Comparison: CARTO vs. conv.***	***Acute success***	***Follow-up (month)***	***Long-term success***
Walsh, 1992 (106)	Conv.	13	-	92%	13	92%
Tracy, 1993 (96)	Conv.	10	-	80%	6.5±3.8	70%
Lesh, 1994 (114)	Conv.	13	-	92%	10±1	92%
Kalman, 1998 (75)	ICE	31	-	94%	9.9±6.3	91%
Manolis, 2019 (103)	Conv.	63	-	96%	29±22.9	93.5%
Summary: Conv.		**130**	**-**	**93.5%**	**19**	**90.7%**

*Table 8 (cont.). Publications dealing with FAT ablation guided by conventional mapping (panel A), CARTO mapping (panel B), and ablation with either conventional or CARTO mapping technique (panel C). Abbreviations: conv.= conventional mapping; EAM= electroanatomical mapping; EM= endocardial mapping; ICE= intracardiac echocardiography; n.d.= no data available; n.s.= nonsignificant; p= „p" value. *weighted average, calculated based on data published in the given article*

Panel B:

Author, year of publication (reference)	***Mapping method***	***Number of cases***	***Comparison: CARTO – conv.***	***Acute success***	***Follow-up (month)***	***Long-term success***
Natale, 1998 (97)	CARTO	30	-	100%	n.d.	96%
Cavaco, 2002 (41)	CARTO	10	-	90%	6	90%
Hoffmann, 2002 (44)	CARTO	42	-	84%	18±12	82%*
Gurevitz, 2005 (101)	EAM	16	-	82%	20±9	67%*
Zhou, 2010 (82)	CARTO	5	-	100%	3	100%
Toyohara, 2011 (90)	CARTO	39	-	100%	36±5	89%
Yang, 2012 (78)	CARTO	14	-	93%	60±24	93%
Summary: EAM		**156**	**-**	**93%**	**26**	**89%**

Panel C:

Author, year of publication (reference)	***Mapping method***	***Number of cases***	***Comparison: CARTO – conv.***	***Acute success***	***Follow-up (month)***	***Long-term success***
Kammeraad, 2003 (186)	EAM, Conv.	42	only in case of acute success: +	79% (80% vs. 72%, p= n.s.)	29.3	75%*
Biviano, 2012 (185)	CARTO, EM, conv.	22	-	86%	29±13	75% *
Busch, 2018 (108)	Conv., EAM	413	-	84%	12	81%
Summary: both (EAM and conv.)		**477**	**+/-**	**83%**	**14.3**	**80%**

In summary, conventional fluoroscopy based mapping is still a beneficial choice to guide FAT ablation because of its good efficacy and low cost. Published data do not seem to show a relevant difference between the outcome of conventional mapping and CARTO-guided procedures (Table 8). However, statistical analysis of these data was not possible due to the various study settings. On the other hand, our direct comparison revealed that the CARTO electroanatomical mapping system has an additional value in the case of FAT ablations (109).

6.1.1. Limitations

Our retrospective analysis revealed that CARTO-guided ablations have a better clinical outcome than conventionally mapped procedures. However, the success rate of procedures with conventional mapping was lower than reported elsewhere (75, 96, 103, 106, 114). Moreover, the ablation strategy was selected by the operating physician on an individual basis, it was not randomized, which makes the theoretical possibility to quit conventional ablation and plan a second CARTO based procedure in difficult cases. However, only two patients had a reablation with CARTO mapping after an acutely failed conventional procedure, so these treatment decisions are not likely to influence our main findings significantly (109).

6.2. Evaluation of predictors of complications associated with atrial fibrillation ablation

6.2.1. Main findings

Our main finding is that the only independent predictor of complications is the previous AF ablation procedure. Similarly to literature data, the female gender, advanced age, and higher CHA_2DS_2-VASc score were predictors at the univariate level; however, they were not independent predictors according to the multivariate analysis in our cohort (183). Recent studies reported different predictors of adverse events related to AF ablation. However, the vast majority of these studies included initial AF ablation procedures only

(147, 178-182, 187-198). Thus, scarce data exist about the role and predictive value of a repeat procedure on the outcome of AF ablation (188, 191, 194).

6.2.2. Incidence and outcome of complications

Our prospective observational study describes the incidence and predictors of adverse events related to AF ablation procedures at a high-volume center in consecutive patients. The uniqueness of our study is given by the high number of repeat procedures. Our analysis revealed that AF ablation is associated with acceptably low risk, and even if adverse events occur, those can be managed adequately, as neither procedure-related death occurred, nor major complication resulted in significant permanent sequelae in our study cohort (183).

A worldwide survey conducted between 1995 and 2002 showed that the incidence of major complications related to AF ablation is 6.0%. The update of the survey between 2003 and 2006 reported an adverse event rate of 4.5% (178, 179). The overall complication rate of AF ablation was 6.9% in the United States based on the results of Deshmukh et al., whereas 4.5% was found in a Japanese registry (180, 181). Recently published data from the ESC-EHRA atrial fibrillation long-term registry revealed an overall in-hospital complication rate of 7.8% (188). The overall rate of adverse events related to AF ablation was 6.84% in our cohort, while the rate of major complications was 2.82%. The incidence of complications is within the previously reported range in our electrophysiology laboratory (183).

The rate of pericardial tamponade was 1.2% in the first worldwide AF survey, while the updated survey reported a 1.3% incidence. Another dataset from the United States found a 1.5% tamponade rate (178-180). The incidence of pericardial tamponade was 1.45% in our patient population. The incidence of ischemic cerebrovascular accidents was reported to range between 0.94% and 1.4% (178-180). Transient ischemic attacks and ischemic strokes occurred in 0.48% in our patient group. Noteworthy, all events resolved without sequelae. Adverse events related to the vascular access site are common, but usually do not lead to long-term disability. Vascular access site complications associated with AF ablation procedures range between 1 - 3.3% (147, 178, 179, 181, 187-189). The incidence

of major vascular access site complications was 0.48% in our study, which might be explained partly with the routine use of a compression bandage. The mortality rate of AF ablation procedures was reported to vary between 0-0.46% (147, 178, 179, 181, 187-189). No procedure-related death happened in our patient population. Neither phrenic nerve palsy nor atrio-esophageal fistula occurred in our series (183).

6.2.3. Predictors of complications

Independent predictors of complications related to AF ablation were reported by recent studies (195). A meta-analysis revealed that the female gender is an independent predictor of cardiac tamponade (193). De Greef et al. reported that higher CHA_2DS_2-VASc score and female gender predict a higher risk of complications (190). An "early institutional experience" might also increase the incidence of adverse events (198). The abovementioned studies included only de novo AF ablation procedures; however, repeated ablations were not considered. Alike these findings, univariate analysis of our study cohort also revealed that female gender, advanced age, a higher CHA_2DS_2-VASc score, and hypertension is associated with a higher risk of adverse events. On the other hand, none of these risk factors were found to be independent predictors according to the multivariate analysis in our study. Still, awareness of the potentially higher risk of complications has to be considered when scheduling AF ablation in these patients (183).

Limited data exist about the predictive value of a repeat procedure on the incidence of complications. Guhl et al. analyzed 450 patients who underwent PVI with cryoballoon, but they did not find any independent predictor of complications. Repeat procedures were also included in this study, but one has to consider the relatively small study population, and thus, the low absolute number of complications when interpreting their results (191). The EORP registry also included repeated AF ablation procedures, but this paper only aimed to describe the characteristics of AF ablation procedures across Europe. Therefore, statistical analysis was not performed, and no predictors were demonstrated (188). The incidence and predictors of pericardial effusion were published by Murakawa et al., in a large multicenter registry involving 8319 AF ablation procedures. They found that the use of an electroanatomical mapping system and direct oral anticoagulants are associated with a lower probability of pericardial effusion. Repeat AF ablations were also included,

but they did not find any difference regarding the incidence of pericardial effusion between initial and repeated AF ablation procedures (194). It should be noted that they only evaluated pericardial effusions, and no other adverse events were considered, which might be an explanation of why these findings do not converge with our results (183).

Previous AF ablation was the only independent predictor of adverse events in our cohort (183). Many potential explanations exist for our findings. Patients with the history of previous AF ablation may present adhesions at the vascular access site, causing difficulties during the introduction of the sheaths. Moreover, the oval fossa may also get thicker due to scarring, which can result in a more difficult transseptal puncture (192, 196). A more extensive ablation might be necessary during repeat procedures, which can expose patients to a higher risk of complications, e.g., injury of the atrial wall, or PV stenosis (197). However, we would like to highlight that ablation of additional lines by itself (including patients having their first procedure) was not associated with higher procedural risk in our cohort (183).

Based on our findings, the type of atrial fibrillation, anatomical variations of the PVs, heart failure, diabetes mellitus, previous stroke, kidney disease, and peripheral vascular disease did not influence the incidence of complications (183). Thus, initial AF ablation was shown to be safe even in patients with significant comorbidities, when the procedure is performed in a high-volume electrophysiology laboratory. However, repeated ablation for AF must be performed with more caution. Routine monitoring of vital signs during the procedure and in the early postoperative period, and control echocardiography are of high importance to recognize adverse events in an early phase (199). Certainly, the main goal is to prevent complications. Novel technological developments such as contact force sensing catheters improve both the safety and efficacy of AF ablation procedures (200, 201).

6.2.4. The consequence of the results

Most of our adverse events were pericardial complications: pericardial effusions and tamponades. This might arise from the ablation itself, even though the ablation time of repeat procedures is usually low. The routine use of contact force sensing catheters

became a part of our everyday practice in order to prevent cardiac perforation due to high catheter-tissue contact. However, there was no difference in complications with and without CF sensing catheter in our analysis (183). Thus, the most probable cause of the high number of pericardial adverse events was the transseptal puncture technique itself. It happens many times, especially in redo cases – as the fossa is usually thicker in these patients – that high forces are needed to break through the septum. In such cases, there is a possibility that we hit the posterior or lateral wall as the transseptal assembly jumps into the left atrium. Moreover, the thickness of the fossa causes another problem: the transseptal assembly is less likely to cause pronounced tenting at the fossa; thus, it slips up to a higher position, resulting in a suboptimal puncture site with all type of its negative consequences. After consulting many electrophysiologists across Europe regarding their transseptal puncture approach, we decided to change our practice. The most important change in our clinical routine was the implementation of Brockenbrough – 1 eXtra Sharp (BRK-1 XS) needle in our transseptal puncture toolbar and routine use of RAO projection for the punctures. The RAO view helps us to determine the anteroposterior direction of the transseptal assembly more precisely; thus, the possibility of a too anterior or too posterior puncture is very low. The BRK-1 XS needle made our transseptal puncture very easy and straightforward, even in case of thick fossas (e.g., redo procedures). As the tip of the needle is sharper than the conventional BRK needle (Figure 13), it enables a better engagement at the targeted part of the fossa and the puncture is less traumatic as we do not have to use high forces to break through the septum thus the accidental puncture of the left atrial wall is less likely.

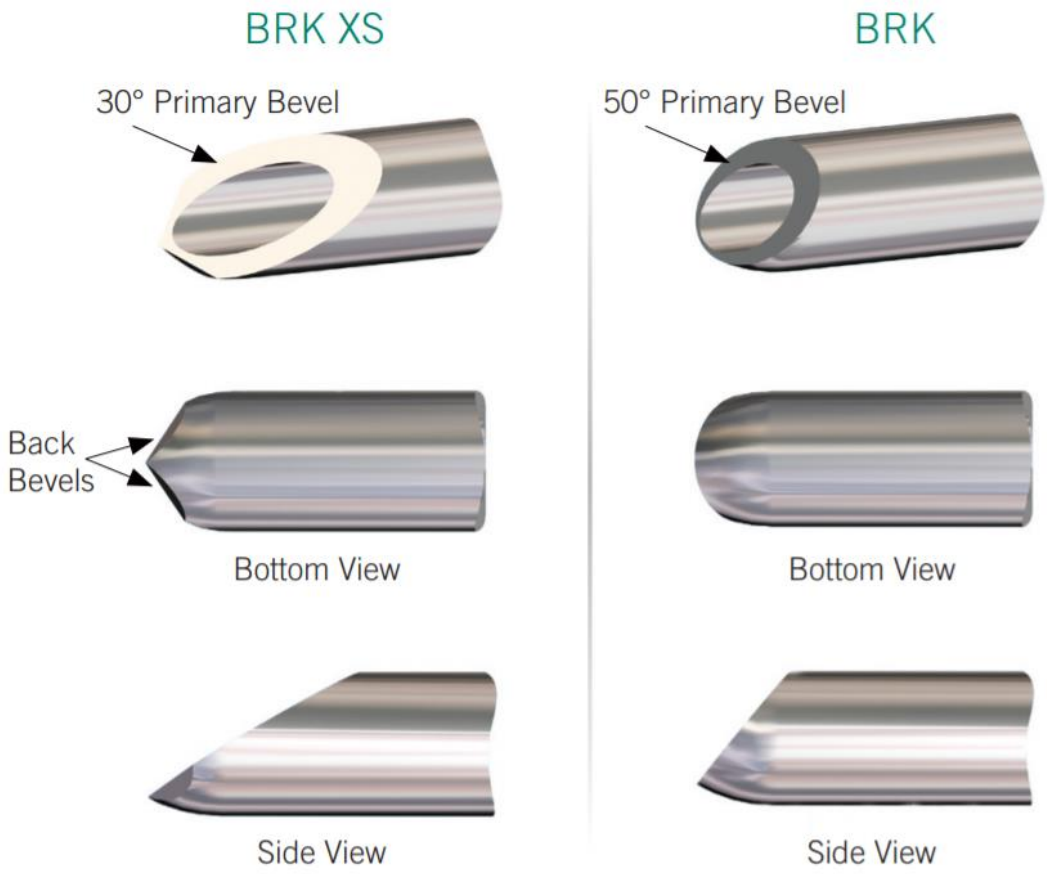

Figure 13. The difference between the tip of BRK-1 XS (left side) and BRK-1 (right side) needle is shown in the picture. The BRK-1 XS has a sharp ending, thus enabling better engagement at the targeted part of the oval fossa and making an easier breakthrough possible (Abbott Medical, EP catalog).

In 2019, we performed 596 catheter ablation procedures for atrial fibrillation (including 131 redo procedures). Three pericardial tamponades occurred; all were treated successfully with percutaneous pericardiocentesis. The number of pericardial effusions (larger than 5 mm) that did not require any active treatment was 7 (3 out of these happened in redo cases). The drop in our pericardial complications is statistically significant (2013-2015: 46 procedures with complication, 1197 procedures without complication; 2019: 10 procedures with complication, 586 procedures without complication; p=0.0196). The routine use of BRK-1 XS needle and RAO view dramatically reduced the rate of pericardial effusions and tamponades in our Electrophysiology Laboratory.

6.2.5. Limitations

The major limitation of our study is that it was conducted in a single center. Our electrophysiology laboratory has a large referral territory. Consequently, there is a probability of missed complications, especially when patients were referred from longer distances. However, the vast majority of the adverse events occurred shortly after the ablation, thus it is unlikely that a significant number of adverse events were missed (183).

7. CONCLUSION

Focal atrial tachycardias represent a relatively rare form of supraventricular tachycardias. The efficacy of pharmacological treatment is limited; thus, catheter ablation should be considered in symptomatic cases. Based on our retrospective analysis, CARTO electroanatomical mapping system is safe and effective to guide catheter ablation of focal atrial tachycardias, as success rates were higher in the case of CARTO-enhanced procedures compared to conventional fluoroscopy-based mapping. Therefore, electroanatomical mapping guided ablation seems to be more appropriate as an initial ablation strategy in the case of a focal atrial tachycardia because of the precise localization of the arrhythmia substrate. These results have led to the routine use of electroanatomical system backup for all electrophysiological procedures where the arrhythmia potentially might be focal AT in our Electrophysiology Laboratory.

Atrial fibrillation is the most common sustained cardiac arrhythmia. Catheter ablation is the cornerstone of rhythm control treatment of AF. The nature of these procedures exposes patients to a considerable number of potential complications. Our analysis revealed that the rate of complications for atrial fibrillation ablation in our Electrophysiology Laboratory is within the previously reported range. In our series, the only independent predictor of complications was previous atrial fibrillation ablation procedure in medical history. This supports that initial atrial fibrillation ablation procedure can be performed relatively safely in a high-volume center even in patients with more comorbidities. However, repeated ablation for AF should be carried out with more caution. As the majority of the complications were pericardial effusions and tamponades, we changed our transseptal puncture approach: the routine use of BRK-1 XS needle and RAO view dramatically reduced the rate of pericardial complications in our Electrophysiology Laboratory.

8. SUMMARY

We examined 30-30 patients (2006 – 2011, in two Hungarian centers) undergoing catheter ablation for focal atrial tachycardia and evaluated the success rate of different approaches. CARTO electroanatomical mapping system is a safe and effective method to guide catheter ablation of focal atrial tachycardia. Acute and mid-term clinical results were better in case of procedures guided by CARTO electroanatomical mapping compared to conventional mapping in our dataset. Therefore, CARTO guided ablation seems to be more appropriate as an initial ablation strategy in the case of a focal atrial tachycardia because of the precise localization of the arrhythmia substrate.

In the second part, we prospectively evaluated the procedure-related complications of 1243 patients undergoing either initial or repeated ablation for atrial fibrillation between 2013 January and 2015 December in the Electrophysiology Laboratory of the Heart and Vascular Center, Semmelweis University. The rate of minor and major complications for atrial fibrillation ablation is within the previously reported range in our electrophysiology laboratory. No procedure-related death occurred in our cohort due to the appropriate management of these patients. This was the first study that evaluated the complication rates for initial and repeated atrial fibrillation ablation procedures, as well. The only independent predictor of complications was previous atrial fibrillation ablation procedure in our series.

9. ÖSSZEFOGLALÓ

Vizsgálatunk során 30-30 betegen, fokális pitvari tachycardia miatt végzett katéter ablációs kezelést végeztünk. A kezelésekre 2 centrumban, 2006 és 2011 között került sor, CARTO rendszerrel, illetve konvencionális térképezéssel. Vizsgálataink kapcsán e két módszer hatékonyságát hasonlítottuk össze. Kimutattuk, hogy a CARTO elektroanatómiai térképező rendszer alkalmazása hatékony és biztonságos a fokális pitvari tachycardia abláció során. Eredményeink alapján a CARTO használata mellett jobb akut és középtávú kimenetelre számíthatunk, mint a konvencionális térképezés esetén. Mindezek alapján a fokális pitvari tachycardiák ablációjához már az első beavatkozás során optimálisabb a CARTO térképező rendszer használata, mivel általa az aritmia szubsztrát precízebb lokalizációja lehetővé válik.

Második, prospektív vizsgálatunk során pitvarfibrilláció miatt iniciális vagy ismételt ablációt végeztünk 1243 betegen, 2013 és 2015 között, a Városmajori Szív- és Érgyógyászati Klinika Elektrofiziológiai Laboratóriumában. A minor és major szövődmények előfordulási gyakorisága Laboratóriumunkban a korábban közölt irodalmi adatoknak megfelelő tartományban volt. A beavatkozáshoz köthetően nem fordult elő halálozás, a megfelelő betegellátásnak köszönhetően. Regiszterünk a világon elsőként mind az iniciális, mint pedig a redo beavatkozások szövődményeit egyidejűleg vizsgálta. A szövődmények egyetlen független rizikófaktorának a korábbi pitvarfibrilláció ablációs beavatkozás bizonyult.

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11. LIST OF PUBLICATIONS

1. Publications related to the Ph.D. thesis

1. **Szegedi N**, Széplaki G, Herczeg S, Tahin T, Salló Z, Nagy VK, Osztheimer I, Özcan EE, Merkely B, Gellér L: Repeat procedure is a new independent predictor of complications of atrial fibrillation ablation. Europace. 2019 May 1;21(5):732-737. doi: 10.1093/europace/euy326. **IF: 5.047**

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2. Publications not related to the Ph.D. thesis

1. **Szegedi N**, Széplaki G, Kovács A, Nagy KV, Németh T, Kutyifa V, Molnár L, Osztheimer I, Zima E, Szilágyi Sz, Emin EÖ, Gellér L, Merkely B.: Reszinkronizációs terápia – Primer implantáció és upgrade. Cardiologia Hungarica 2015; 45 : 5–11.

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