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CATHETER ABLATION OF LONE ATRIAL FIBRILLATION

Running title: Lone AF Ablation

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ABSTRACT

Atrial fibrillation is the most common sustained arrhythmia in clinical practice, associated with increased mortality, risk of stroke and heart failure, as well as the reduction of the quality of life. Atrial fibrillation may be encountered in young otherwise healthy individuals, due to the isolated electrophysiological disorder limited mostly to the pulmonary veins and posterior left atrial wall, or associated with the presence of advanced underlying heart disease and numerous cardiac and non-cardiac comorbidities with significant structural remodeling of the atrial myocardium. Due to limited efficacy and serious side effects of antiarrhythmic drugs, catheter ablation of atrial fibrillation, based on the pulmonary vein isolation for paroxysmal atrial fibrillation and adjunctive substrate modification for persistent atrial fibrillation, has emerged as an attractive and promissing alternative therapeutic option for selected patients with atrial fibrillation. In this review article, we discuss the electrophysiological left atrial abnormalities underlying lone atrial fibrillation and the role of pulmonary veins in pathophysiology of arrhythmia, and we summarize results of the studies on the long term outcome of catheter ablation of atrial fibrillation, as well as the studies on comparison of antiarrhythmic drugs with catheter ablation for treatment of atrial fibrillation. In addition, we present available data that provide better understanding of mechanisms, diagnosis, prevention and treatment of specific procedure-related complications and discuss current periprocedural anticoagulation strategies and their impact on the thromboembolic risk reduction.

Key words: atrial fibrillation; lone atrial fibrillation; pulmonary vein isolation; catheter ablation.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia, with prevalence in general population of at least 1% [1]. The presence of AF increases mortality and risk of stroke and heart failure (HF), and the arrhythmia is often accompanied by limiting symptoms, such as palpitation and fatigue, thus reducing the quality of life (QoL) [1, 2]. From the clinical point of view, AF can be the manifestation of an isolated electrophysiological disorder, such as in patients with lone AF, or it can be associated with the presence of advanced structural heart disease and numerous cardiac and non-cardiac comorbidities. Triggers within the thoracic veins, usually the pulmonary veins (PVs), and fibrous-inflammatory substrate in left atrial (LA) myocardium are responsible for initiating and sustaining the arrhythmia. AF is a progressive disease, which often begins with paroxysms that gradually progress to persistent AF episodes and eventually to permanent AF. A life-long antiarrhythmic drug (AAD) therapy has limited efficiency and many hazardous effects [1-3]. Over the last decade, catheter ablation of AF, based mainly on the electrical disconnection of PVs, has been considerably refined with the exponential increase in the number of the procedures each year, and today it represents one of the most common invasive electrophysiological interventions. The procedure provides non-pharmacological cure for selected patients with AF and is more efficient in rhythm control than medicament therapy [1, 3]. In this review article, we present an overview of (1) electrophysiological concept of catheter ablation of AF, (2) efficiency of AF ablation, (3) complications of AF ablation and (4) periprocedural anticoagulation.

ELECTROPHYSIOLOGICAL AND STRUCTURAL ABNORMALITIES IN LONE AF

AF occurs as the consequence of complex interaction of triggers, substrate and autonomic nervous system. Triggers are responsible for initiation of AF, while presence of substrate is responsible for its maintenance [1, 4]. Changes in cardiac autonomic nervous system activity have significant influence on activity of the triggers and substrate for AF [1, 5]. AF is evolving disease and its pathophysiology and clinical presentation can vary. At one end of clinical spectrum there are younger patients with paroxysmal lone AF, which represents dominantly electrophysiological disorder, whereby the AF triggers are fundamental. At the opposite end are older patients with structural heart disease and persistent AF, whereby the development of atrial fibrous-inflammatory substrate could take the leading role in the AF mechanism [4, 6]. The most common AF triggers are the runs of atrial ectopic beats originating from the rapid firing foci. These foci are located mainly in the ending parts of PVs and rarely in other thoracic veins and atrial myocardium. PVs play the major role in the AF initiation and maintenance, especially among patients with lone AF. It has been shown that, in majority of patients (94%), foci that initiated AF were located in ≥1 PV [3, 7]. Non-PV triggers can be found in 6-10% of the patients, most often in superior caval vein, vein of Marshall, coronary sinus, LA posterior wall, crista terminalis and LA appendage [3, 8]. During the embryonic heart development, PVs and LA posterior wall develop together from the sinus venosus containing numerous pacemaker cells with spontaneous automaticity,

which originated from the remnants of primary specialized conduction tissue [9]. Myocardial fibers extend from the LA over the outer side of PVs, where they gradually rarefy and disappear after 1-3 cm. These fibers have segmental distribution along circumference of PVs, with a multilayer spiral orientation and complex local non-uniform anisotropy and architecture; by their contractile function, these fibers regulate local vein blood flow [10]. Aforementioned histological features of PV-atrial junctions provide a precondition for increased automaticity, triggered activity, changes of the action potential duration, shortening of refractoriness, slow and decremental conduction and micro-reentry [11, 12]. Besides that, dynamic neural activity of anatomically close ganglionated plexi, located at the PV-atrial junction level can significantly modify the local electrophysiological properties of PVs [13]. Appearance of AF episode is initially preceded by an increase in adrenergic tone with subsequent sudden change towards parasympathetic predomination [5]. Thus, a complex electrophysiological environment for induction and maintaining of lone AF episodes is formed.

The PVs and LA posterior wall are probably crucial for induction and maintaining of lone AF [4]. In one of the studies, the key role of PVs and LA posterior wall in pathophysiology of lone AF was clearly demonstrated. After surgical "en-block" isolation of PVs and LA posterior wall, electrophysiological study was carried out among the patients with lone AF (mean age 51, left atrial diameter 40 mm, 78% paroxysmal AF). In the isolated segment of LA, sustained AF was registered or short-lasting AF was induced, with signs of electrical dissociation from the remaining part of the LA, where sinus rhythm was maintained. On the other hand, AF could not be induced by aggressive stimulation of the remaining (non-isolated) part of the LA [14]. Another research showed that among patients with prolonged episodes of paroxysmal AF (43% of the patients did not have structural heart disease) AF substrate was often limited to the PV region. By PV isolation during an ongoing episode of AF, cycle length of AF was gradually prolonged in all patients, and AF was terminated in 75% of the patients. Furthermore, after PV isolation, AF remained non-inducible in 75% of the patients in whom it was induced prior to ablation [15]. Other authors also indicated that dominant rotors in lone AF were localized mostly in the region between LA posterior wall and PVs [9].

It was believed that progression of atrial disease with development of structural substrate in lone AF occurs solely as a consequence of tachycardia-induced (and potentially reversible) electrical LA remodelling due to frequent and prolonged episodes of the arrhythmia. However, in patients with paroxysmal lone AF (who did not suffer recent episode of AF) complex biatrial abnormalities were found in the form of structural changes with myocardial voltage reduction, slowing of conduction, prolongation of refractoriness and sinus node dysfunction, which could affect further progression of AF [16]. In addition, the histological examination revealed higher degree of patchy fibrosis of atrial myocardium among the patients with lone AF compared to healthy individuals [17]. Recent research with the use of cardiac MRI (Magnetic Resonance Imaging) showed that even in patients with lone AF extensive atrial structural remodelling can be found, primarily involving the LA posterior wall. Despite more frequent presence of paroxysmal type of arrhythmia among patients with lone AF, there was no significant difference in the degree of structural abnormalities in comparison with "non-lone" AF patients [18].

CATHETER ABLATION OF LONE AF

Ablation strategy for lone AF. The patients with lone AF are probably among the best candidates for catheter ablation treatment and they have the highest chance for successful outcome of the procedure. Strategy of catheter ablation for lone AF does not differ from non-lone AF, mostly because it is the clinical type of AF (paroxysmal vs. persistent) which defines the choice of adequate ablation approach [3, 9, 19-28]. Favourable prognosis and survival, as well as low thromboembolic risk and the risk of disease progression among younger patients with lone AF warn us to carefully consider application of any invasive intervention that may have some adverse effects, which is especially referred to the catheter ablation [4, 6].

Nowadays, electrical disconnection-isolation of PVs represents a cornerstone of each AF ablative strategy. Based on the scientific evidence accumulated over the last decade, it is considered that isolation of PVs is sufficient for majority of patients with paroxysmal AF, while additional modification of LA substrate could be very important in patients with persistent AF [3, 19-29].

The LA is the heart chamber that is most inaccessible to catheterization. Transseptal puncture ensures access to the LA and PVs [30-33]. Today, radiofrequency current (RF) is the most often used energy source for catheter ablation of AF. RF alternating current passes through the myocardium and, due to high electrical resistance of the tissue, generates heat and causes local coagulation necrosis. By subsequent tissue scarring, electrically non-conductive barrier at the level of PV-atrial junction is created (so called electrical isolation of PVs), while resolution of oedema and inflammation from the edges of RF lesions could establish conduction through surviving myocardial fibers [34, 35]. However, some operators prefer cryoablation, where local lesion in the atrial myocardium is created by the principle of tissue freezing [36, 37]. For application of certain energy modality different catheters can be used, designed for point-by-point ablation or shaped as single-shot devices in the form of circumferential multipolar catheter for RF ablation or balloons for cryoablation [36-39]. The ablation effects are continuously monitored by diagnostic circumferential multipolar catheter, positioned in proximal part of PV close to its ostium, which registers electrical activity inside the PV. The technique of catheter-based isolation of PVs has evolved considerably in the last decade. At the beginning, ablation was performed in segments at the level of PV ostium, whereby the local application of RF energy was guided by the earliest electrical potential of the PV at the circumferential multipolar catheter [7, 40]. However, the procedure is mostly abandoned due to its limited success and a significant risk of PV stenosis. The development of electro-anatomical mapping systems provided more precise 3-dimensional catheter navigation and continuous circumferential ablation at level of the PVs antra, as presented in Figure 1. Such isolation of a wider antral region (1-2 cm from the PVs ostia) minimizes the risk of the PV damage and eliminates not only the PV-triggers, but also potential non-PV foci and rotors in the PVs antra [41-43]. In addition, (collateral) destruction of neurovegetative ganglia and reduction of the LA electrical mass may contribute to the higher efficiency of this strategy [44-46]. Most often, electrical reconnection of one or more PVs is responsible for the paroxysmal AF recurrence after the PV isolation procedure. Therefore, it is considered that in patients with paroxysmal AF, permanent ablative lesion (and isolation of all PVs) is essential and more important than any other additional set of lesions [24, 47]. However, PV isolation is a template procedure and, therefore, it may not be sufficient for specific subpopulation of patients with paroxysmal AF initiated from non-PV foci, including patients with sleep

apnea syndrome, obese patients, women, patients with enlarged LA and older patients. In such cases, after PV isolation, non-PV triggers can be discovered by catecholamine challenge (for example, triggers in the superior caval vein), and elimination of these triggers significantly improves the clinical outcome of the procedure, as shown in Figure 2 [48, 49].

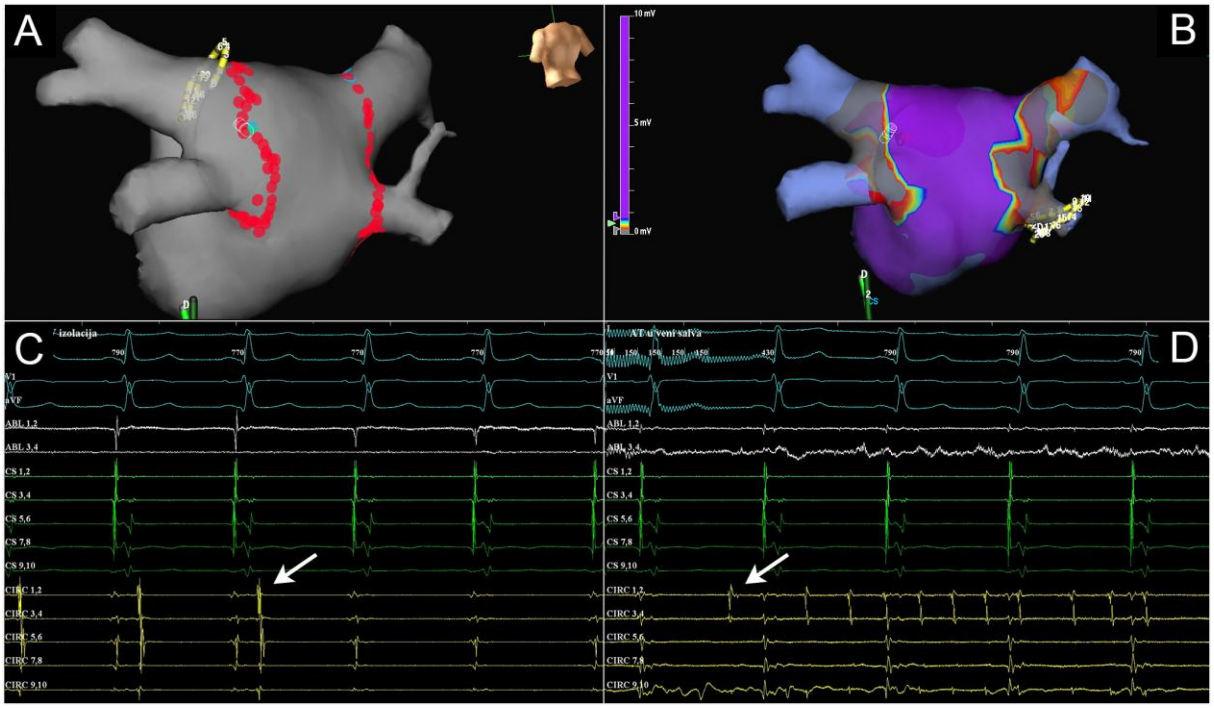

Figure 1. Catheter ablation of paroxysmal lone AF: PV isolation.

A 47-year-old male underwent catheter ablation due to a 10-year history of daily attacks of symptomatic paroxysmal lone AF, refractory to drug therapy with beta-blockers, sotalol, propafenone, and, finally flecainide. Echocardiography showed normal LA dimension (38 mm) and left ventricular ejection fraction (65%). Using the electroanatomical mapping system (Ensite NavX, St Jude Medical) with CT-image integration, geometrical LA 3D-map was reconstructed and irrigation radiofrequency ablation (red dots) was performed with en-block isolation of ipsilateral PVs.

Panel A: postero-lateral LA view with circumferential antral ablation encircling left sided PVs, circumferential diagnostic (Lasso) catheter is positioned within the left superior PV.

Panel B: voltage map of LA and PVs in sinus rhythm after PV isolation. Grey and violet colors represent electrically silent regions within the PVs and electrically healthy myocardium in the remaining part of LA, respectively.

Panel C: electrical isolation of PV in sinus rhythm, with abrupt loss of PV potential recorded by circumferential diagnostic catheter (yellow signals, labeled with white arrow).

Panel D: after PV isolation, the occurrence of spontaneous repetitive short bursts of atrial tachycardia within the "arrhythmogenic" PV is recorded by the Lasso catheter (yellow signals, labeled with white arrow). However, stable sinus rhythm is maintained, due to exit PV-LA block after ablation.

During the one-year follow-up after the procedure, the patient was free of AF without drug therapy.

AF=atrial fibrillation; LA=left atrium; CT=computed tomography; PV=pulmonary vein.

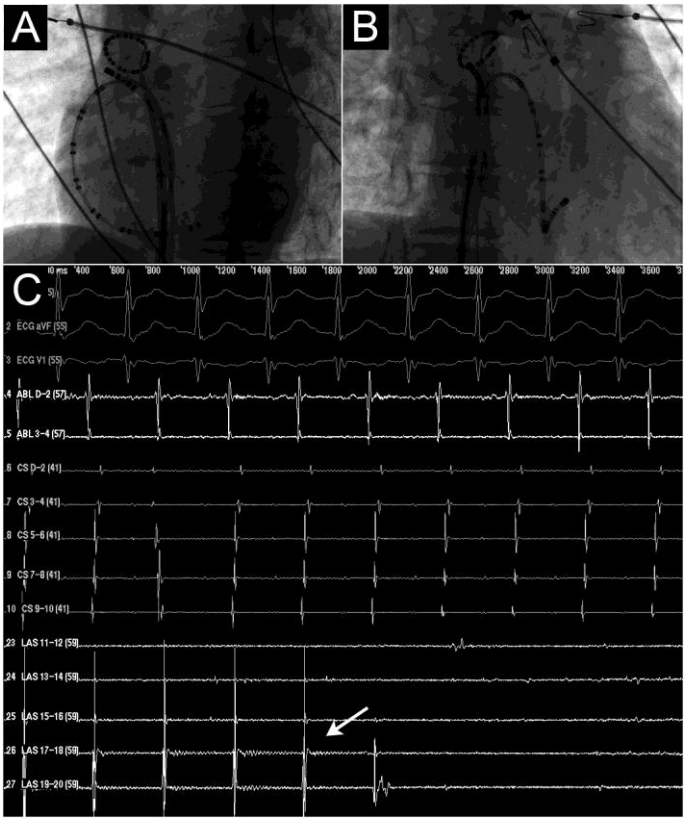

Figure 2. Catheter ablation of paroxysmal AF: elimination of non-PV triggers.

A 37-year old female patient has been referred for the second catheter ablation procedure due to highly symptomatic and frequent episodes of paroxysmal AF. In the index procedure fluoroscopically guided segmental ostial isolation of all PVs was successfully accomplished, however the patient experienced recurrence of AF in the following weeks. At the beginning of the redo procedure, all PVs were revisited and their stable electrical isolation was confirmed. Using the catecholamine challenge and pacing maneuvers, an ectopic focus in SCV was identified. Using irrigation radiofrequency catheter, electrical isolation of SCV was successfully achieved in association with AF noninducibility at the end of procedure. Over the follow up of 6 months the patient was free of symptomatic AF without antiarrhythmic drugs.

Panels A and B: fluoroscopic position of circumferential diagnostic catheter within the SCV and ablation catheter at the posterolateral aspect of SCV-atrial junction. Before RF application, high output pacing was performed to evaluate the proximity to right phrenic nerve.

Panel C: ablation at this site resulted in electrical isolation of SCV during sinus tachycardia, with elimination of SVC potentials at the Lasso catheter (white arrow).

AF=atrial fibrillation; PV=pulmonary vein; SCV=superior caval vein.

Among patients with persistent AF, PV isolation is most often combined with the LA substrate modification. There are three basic strategies for modification of AF substrate: LA defragmentation by ablation

of the complex fragmented atrial electrograms (CFAE), linear ablation of LA and ganglionated plexi ablation [3, 21-29]. CFAE are the electrograms during AF which have short cycle length (<120ms) or which are fractionated into two or more components, or show continuous atrial electrical activation [50]. From the electrophysiological aspect, CFAE may represent dominant rotors of AF and pivot points of microreentry, but also the sites of passive wavelet collision that are not critical for maintaining of AF. CFAE can be identified by visual inspection or automatically by dedicated software of electro-anatomical mapping system. The result of local ablation and elimination of CFAE is a prolongation of AF cycle length and, finally, termination of AF with conversion into "organized" atrial tachycardia/flutter or sinus rhythm [25, 51]. AF substrate also can be modified by the linear atrial ablation, which imitates the surgical MAZE procedure, in form of the roof line and, eventually, the inferior line on the LA posterior wall, connecting both superior and both inferior PVs. In this way, a complete electrical isolation of the whole LA posterior wall is achieved (so called "posterior box lesion"), as shown in Figure 3 [9, 52]. Linear ablation of mitral isthmus between the mitral annulus and the left inferior PV can significantly modify AF substrate [53]. Completeness and transmurality of linear lesions are very important for the successful treatment of AF as well as for the prevention of iatrogenic atrial tachycardia after ablation [54]. Linear ablation leads to compartmentalization of the LA and reduction of the area with CFAE, thus resulting in an additional AF cycle length increase, which can be critical for the AF termination during a stepwise approach to the ablation of longstanding persistent AF [55]. Ganglionated plexi are usually located 1-2 cm outside the LA-PV junctions at the left superolateral, right superoanterior, left inferoposterior and right inferoposterior area, and it has been shown that their anatomical RF ablation is accompanied by substantial AF substrate modification [56]. This adjunctive AF substrate modification strategy may significantly improve the midterm outcome of persistent AF catheter ablation.

AF catheter ablation outcome. Catheter ablation of AF is efficient in both short and long term rhythm control [7, 9, 24, 27, 28, 29, 40-44, 47, 52, 53, 56]. However, inconsistency in the ablation technique and technology, different definitions of success and arrhythmia recurrence and differences and limitations in the methods of clinical follow-up after the procedure complicate the realistic appreciation of the results and, therefore, it is not surprising that significant differences in outcome of AF ablation exist in the published series [3]. Besides that, the long term outcome data after ablation of AF are still scarce and limited to period of only 3-5 years. Early recurrences of atrial tachyarrhythmias in the first 3 months (so called "blanking period") are common (30%-60%) and may reflect transient inflammation of atrial tissue and immaturity of the ablative lesion. These arrhythmias can be prevented by antiarrhythmic and antiinflammatory drugs and gradually subside in 40-60% of the patients [57-59]. Therefore, final outcome of the procedure should be evaluated only after this early postoperative period.

The results of catheter ablation of lone AF are not easy to interpret, because in majority of reported series patients with lone AF are not separated from those with AF and minimal structural heart disease and/or comorbidities. Only few studies selected 'pure' lone AF population among young patients and athletes and showed excellent results after the first procedure with over 90% of patients being free from arrhythmia without medications, during the clinical follow-up period of more than 1-3 years [60, 61].

It has been shown that the efficacy of initial procedure was significantly higher for paroxysmal compared with persistent AF, but after multiple procedures, comparable results can be achieved in both types of AF. For acceptable long term success of ablation of AF, multiple procedures are frequently required, which

emphasizes the importance of creating irreversible ablative lesion in the first procedure [25, 28, 29, 47]. Indeed, the inability to create permanent and continuous ablative lesions in the first procedure represents one of the principal limits of the actual ablation technology. After achieving the PV isolation, pharmacological stimulation with adenosine and catecholamines enables wakening of dormant and partially damaged myocardial connections between the PV and LA. Subsequent ablation of these fibers can significantly increase the efficiency of the first intervention [62-64]. It seems that the loss of capture on the ablative line, ablation guided by atrial unipolar signal modification and development of contact-force technology could provide better transmurality, continuity and durability of ablative lesion [27, 65-68].

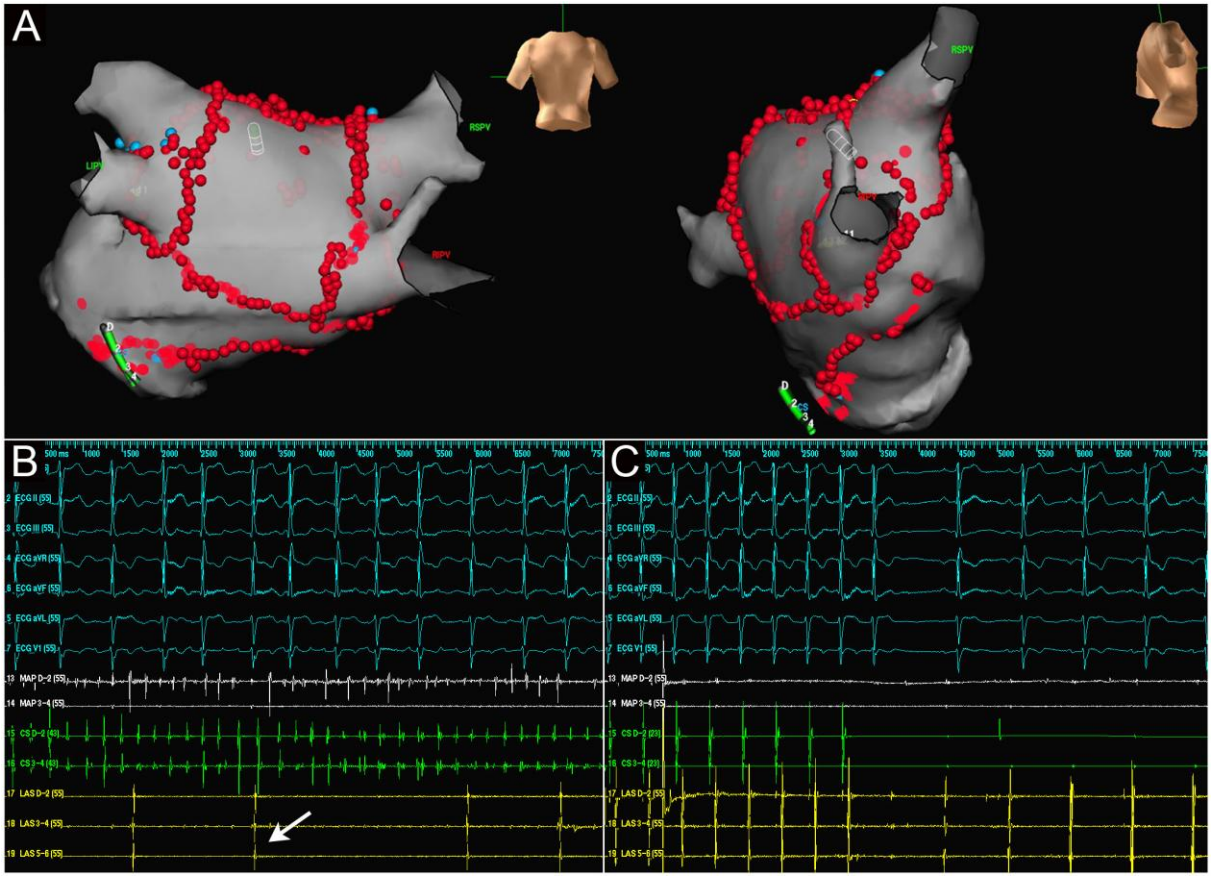

Figure 3. Catheter ablation of persistent AF: PV isolation and substrate modification.

A 57-year-old male presented with previously undiagnosed persistent AF with uncontrolled rate and symptoms and signs of congestive heart failure. Echocardiography revealed left ventricular systolic dysfunction with EF of 35% and moderate LA dilatation (44 mm), while coronary angiogram was normal. Treatment with amiodarone and a beta blocker as well as therapy for heart failure were instituted. Several months later he was subjected to catheter ablation of AF, due to the clinical suspicion of tachyarrhythmia-related cardiomyopathy.

Panel A: fusion of 3D anatomical LA map with CT image (Ensite NavX, St Jude Medical), posterior LA view (left side of image) and right lateral view (right side of image). Irrigation RF ablation (red dots) included circumferential antral PV isolation coupled with LA substrate modification by means of linear ablation. Linear set consisted of roof line + inferior line ("posterior box" lesion) and endocardial linear disconnection of coronary sinus.

Panel B: isolation of PVs during ongoing AF. Spontaneous slow automaticity within the PV was recorded (white arrow), while AF continued in the remaining part of the LA.

Panel C: during the LA linear ablation, AF has "organized" to an atrial tachycardia with fast ventricular response and further LA substrate ablation resulted in tachycardia termination with restoration of sinus rhythm. At the end of the procedure revision of all PVs and lines was performed to confirm the conduction block.

Three months following the procedure, echocardiography demonstrated complete recovery of the left ventricular systolic function (EF 60%) and all drugs, except beta blocker, were discontinued. Over the next 12 months, the patient was free of AF.

AF=atrial fibrillation; LA=left atrium; PV=pulmonary vein; EF=ejection fraction; CT=computed tomography; RF=radiofrequency.

Recently, a meta-analysis of the large number of trials depicted the long term efficiency of single and multiple procedures of AF ablation based on the clinical follow-up period of >3 years [29]. The technology and strategy of AF ablation and post procedure follow-up in the included trials mostly correspond to the contemporary clinical practice. After the first procedure, long term efficiency of ablation of paroxysmal AF and persistent AF was 54.1% [95% CI: 44.4% to 63.4%] and 41.8% [95% CI: 25.2% to 60.5%]. However, multiple procedures achieved significantly better results: for paroxysmal AF 79.0% [95% CI: 67.6% to 87.1%] and for persistent AF 77.8% [95% CI: 68.7% to 84.9%]. The average number of procedures per patient was higher for persistent than for paroxysmal AF (1.7 [95% CI: 1.3 to 2.1] vs. 1.4 [95% CI: 1.3 to 1.6]. Long term outcome of AF ablation in the studies published in the last 5 years, each of which comprised more than 100 patients, mean age of ≤60 years with no or minimal organic heart disease, are presented in Table 1 [28, 47, 69-75].

There are concerns about the durability of the AF ablation effect. AF recurrences occur most often in the first year after the procedure, but longer follow-up is mandatory because there is still possibility of a later arrhythmia recurrence. Among the patients with AF recurrence, the arrhythmia occurred in 66% of them in the first 6 months, in 76% in the first year and even in 88% in the first 2 years after the procedure [76]. Although some studies confirmed low rates of late AF recurrences (only 8.9% to 16% at >1 year after the procedure) and showed that AF ablation has a quite long effect (in 5-year-follow-up even 71% of patients remained in stable sinus rhythm), other studies pointed towards the disturbing fact that among patients who did not have the arrhythmia in the first year after AF ablation, a progressive increase in the rate of late AF recurrences could be expected [74, 77-79]. Such studies reported cumulative rates of late AF recurrences after the first year post ablation: after 2 years the rate was 13%, after 3 years 22%, after 4 years it was 35 %, after 5 years 47% and after 6 years 55% [79]. While the most common finding at repeated electrophysiological study among the patients with AF recurrence within the first year after ablation was the PV reconnection, the appearance of late AF recurrences can be related not only to reconnection of the PVs but also to the development of non-PV triggers of AF and evolution of the AF substrate, especially among the older patients with structural heart disease and comorbidities [76, 78, 80]. Numerous pre-procedural clinical predictors of AF recurrence are identified, such as: the LA dilatation, early recurrence of atrial tachyarrhythmia (during the "blanking" period), previous history of persistent AF, the presence of structural heart disease, hypertension, hyperlipidemia, sleep apnoea, older age,

obesity, biochemical markers of inflammation, atrial fibrosis on MRI and increased $CHADS_2$ and CHA_2DS_2-VAS_C score [18, 74, 80-84]. Therefore, among younger patients with lone AF and normal or minimally remodelled LA, not only higher efficiency but also more stable long term effects of catheter ablation can be expected. Thus, after RF catheter ablation procedures with PV isolation performed in middle-aged athletes with idiopathic AF (mean age 44 years), 90% of the patients were free of AF at 3-year follow-up [61]. Similarly, after the PV isolation using cryoballoon technique, symptomatic AF was eliminated in 89% of younger patients (mean age 44 years, 83% males) with lone AF and normal size of the LA during the period of 14 months after the procedure [60].

Some of the patients with AF recurrence respond well to the AAD, which was not efficient before the procedure, and in such cases new procedure is not obligatory. Among these patients, repeated electrophysiological study performed 3 months after the index ablation revealed reconnection with substantial atrio-PV delay of conduction. Moreover, AADs may additionally slow conduction, causing an exit block from the PV(s) and successfully controlling AF initiation [85].

Ablation versus drugs for lone AF. The presence of AF doubles the mortality and morbidity and it increases risk of ischemic stroke by fivefold [1, 2]. On the other hand, long term prognosis of lone AF is favourable and significantly better in comparison with patients with non-lone AF. During the long term follow-up period of 12 years, 27% of the patients with newly diagnosed paroxysmal lone AF progressed towards permanent AF with low rate of mortality (1.4%), thromboembolism (0.4%) and HF (0.4%). However, progression to permanent AF, aging and subsequent development of underlying heart disease among patients with initially paroxysmal lone AF were independent predictors of adverse cardiovascular events, including systemic thromboembolism and HF [86].

Randomized controlled trials failed to demonstrate benefits of the maintenance of sinus rhythm with AADs in comparison to the pharmacological control of ventricular rate in patients with AF [87-89]. Indeed, both pharmacological strategies (i.e., rhythm control and rate control) showed comparable rates of mortality and stroke among patients with AF. However, subsequent sub-analysis showed that sinus rhythm was associated with a survival increase of 47% compared with AF, whilst the use of AADs was associated with a 49% increase in mortality. Thus, the advantages of sinus rhythm over AF were annulled by the adverse effects of AADs used for prevention of the arrhythmia [87-89]. Catheter ablation of AF provides a possibility to maintain sinus rhythm without the use of AADs in the large proportion of selected patients with AF, and it represents a promising alternative to available pharmacological therapy for rhythm control.

Table 2 presents several randomized studies which compared efficiency and safety of AADs versus catheter ablation for the treatment of patients with AF [90-99]. Clinical follow-up in these studies most often was 1 year, whilst only one study reported long term results. Most of the studies included population of younger AF patients with low prevalence of structural heart disease. Seven trials analyzed efficacy of ablation and antiarrhythmic therapy in the treatment of AF refractory to at least one “true” class I (i.e. propafenone, flecainide and disopyramide) or class III AAD (i.e. sotalol, amiodarone and dofetilide) [91-97, 99]. In addition, two studies compared the results of transcatheter and pharmacological therapy as the first therapeutic option in patients with previously untreated AF [90, 98]. Freedom from atrial tachyarrhythmias was registered significantly more often after catheter ablation than with drug therapy (74% vs. 25%). In the studies, which included mostly patients with paroxysmal AF, the efficacy of ablation was 63-85% with single, and 85-89% with multiple ablation procedures.

Table 1. Studies on long term outcome following catheter ablation of atrial fibrillation in patients with no or minimal structural disease.

Year of the study	№ pts	Age (years)	Males	PAF	Lone AF	SHD	Co-MBD	LA (mm)	Ablation strategy	Redo ablation	Follow-up (months)	Freedom of AF (multiple ablations + AAD)	AADs
2008 [69]	139	55	78%	100%	42%	7%	NA	41	RF 8 mm, PVI ostial	22%	33	58%	23%
2008 [70]	110	52	80%	100%	NA	-	52% (HTA)	39	RF 4 mm, EAM PVI ostial vs.PVAI	34%	48	89% vs. 91%	10%
2008 [28]	204	55	79%	61%	NA	14%	NA	42-49	RF irrigation, EAM, PVAI vs. PVAI+lines	40% (PAF) 54% (PeAF)	41	62% vs. 85% (PAF) 39% vs 75% (PeAF)	-
2010 [47]	161	60	75%	100%	NA	20%	67% (HTA) 5% (DM)	43	RF irrigation, EAM-PVAI	41%	55	79%	15%
2011 [71]	100	54	79%	100%	NA	6%	27% (HTA) 2% (DM)	42	RF irrigation, EAM-PVAI	22%	39	82%	30%
2011 [72]	260	54	90%	61%	NA	9%	28% (HTA)	39	RF 8 mm, EAM-PVAI (+CFAE)	27%	30	95%	-
2011 [73]	100	56	86%	63%	NA	36%	43% (HTA) 3% (DM)	NA	RF irrigation, PVI ostial (+lines)	51%	54	63%	NA
2011 [74]	831	59	77%	69%	NA	14%	35% (HTA) 8% (DM)	NA	RF irrigation, ICE-PVAI (+SVC)	23%	55	90%	12%
2013 [75]	605	59	77%	96%	46%	12%	42% (HTA)	42	Cryo-balloon (+RF irrigation)	18%	33	77%	NA

Abbreviations:

PAF=paroxysmal AF; AF=atrial fibrillation; SHD=structural heart disease; Co-MBD=comorbidities; LA=left atrium; AAD=antiarrhythmic drugs; NA=not available; RF=radiofrequency; PVI=pulmonary vein isolation; HTA=hypertension; EAM=electro-anatomical mapping system; PVAI=pulmonary vein antral isolation; PeAF=persistent AF; DM=diabetes mellitus; CFAE=complex fragmented atrial electrograms; ICE=intracardiac echocardiography; SVC=superior vena cava.

On the other hand, among patients with paroxysmal AF refractory to previous pharmacological therapy, successful maintenance of sinus rhythm by changing the AAD was achieved in only 9-23% of patients [91, 93, 95, 96]. However, among patients with previously untreated paroxysmal AF, AADs successfully prevented the occurrence of arrhythmia in as many as 71% of patients [98]. Indeed, it was shown that the failure of prior AAD therapy predicts the failure of subsequent attempts to pharmacologically control the rhythm and that the administration of alternative drug can effectively prevent AF only in a small portion of the patients [91, 93, 95, 96]. Overall, the superiority of catheter ablation over pharmacological treatment is the most evident in patients with paroxysmal AF who failed AAD therapy. Recently, a randomized study showed that even among patients with persistent AF, catheter ablation is more efficient for rhythm control in comparison to medical therapy. At one-year follow-up, 60% of patients were free of AF after the procedure (36% of them were also taking an AAD) in comparison to 29% of patients treated with AADs only [99]. In addition, it has been demonstrated that after a failure of the initial PV isolation in patients with paroxysmal AF, a repeated AF ablation was significantly more effective than AAD therapy in control of AF (58% vs. 12%, $p<0.01$) [100]. Besides that, during the one-year follow up, AAD therapy was more often associated with side effects compared to invasive treatment (17% vs. 8%) [101]. A meta-analysis of 8 randomized trials with total of 844 patients confirmed safety of catheter ablation. Fewer adverse effects were registered among patients treated with AF ablation than in those treated with AADs (RR 0.72 [95% CI: 0.40 to 1.30]; $p=0.28$) [102].

Potential benefits of AF ablation

Survival and thromboembolism. AF is associated with significant increase in mortality and risk of stroke [1, 2]. Therefore, it is expected that proven superiority of a non-pharmacological method (which offers the possibility of curing AF) over potentially dangerous medical therapy could be transferred to the reduction of rates of "hard endpoints" such as mortality and systemic thromboembolism.

However, the meta-analysis of 8 randomized studies did not find significant differences in mortality rate and rate of cerebrovascular events between patients treated by catheter ablation (486 patients) and by AADs (444 patients) [103]. The mean age of patients was 51 to 64 years, with low prevalence of structural heart disease of 4% to 24% (only in one study the prevalence of underlying heart disease was higher, reaching about 50% of participants). During the one-year follow up of patients treated with catheter ablation and AADs, 3 and 4 deaths ($p=0.74$), and 3 and 1 cerebrovascular events ($p=0.54$), respectively, were reported [103]. In these studies, low mortality and cerebrovascular event rates in both subgroups of patients could be the result of the selection of low-risk AF population with high prevalence of lone AF and short follow-up after the intervention.

On the other hand, several nonrandomized trials, which mainly analyzed "sicker and older" AF population, demonstrated a beneficial effect of ablation to the survival of patients with AF. In the study where prevalence of cardiovascular and lung disease was 58% and the mean age was 65 years, mortality was significantly reduced (6% vs. 14%) as well as the rate of cerebrovascular events (2% vs. 8%) among the patients treated by catheter ablation compared to AAD therapy, respectively, during the follow-up of 2.5 years [104].

Another study also included high-risk AF patients with mean age of about 67 years (median 69 years) and ≥1 risk factor for stroke, who were followed up for 2.3 years. The mortality rate after catheter ablation was significantly lower compared to antiarrhythmic drug treatment (3% vs. 12%) and sinus rhythm was the strongest factor associated with the reduction of mortality rate (HR 0.14 [95% CI: 0.06 to 0.36], p<0.0001) [105]. In addition, an international multicenter registry encompassed 1273 patients (mean age of 58 years, an average $CHADS_2$ score of 0.7), who underwent catheter ablation of AF [106]. Their outcomes were compared with a cohort of AF patients treated medically and a hypothetical cohort without AF, age and gender matched to the study group (total of 5333 patients). Stroke rate (2.8% vs. 0.5% per patient year) and mortality rate (5.3% vs. 0.5% per patient year) were significantly lower among the patients treated by catheter ablation of AF. Freedom from AF after the procedure was a significant predictor of stroke-free survival (HR 0.33 [95% CI: 0.17 to 0.67]; p=0.002) [106]. A recent study reported that during a 4-year follow-up of 953 patients (mean age 57 years) with AF and an increased CHA_2DS_2-VASc score of ≥1, total mortality (11.5% vs. 2.9%) as well as central and/or peripheral vascular thromboembolism (8.6% vs. 2.3%) were considerably lower among patients treated with catheter ablation in comparison to patients treated pharmacologically, respectively [107]. Moreover, among the patients treated with catheter ablation, the recurrence of AF was an independent predictor of severe cardiovascular (HR 2.63 [95% CI: 1.15 to 5.9]; p=0.02) and thromboembolic vascular events (HR 2.52 [95% CI: 1.05 to 6.06]; p=0.04) [107]. Therefore, the more beneficial effect of catheter ablation on survival and systemic thromboembolism (in relation to medical therapy) could be expected in high risk population of older AF patients with structural heart disease and increased thromboembolic risk, as compared to the low risk younger patients with lone AF and generally favourable prognosis.

Progression of AF. The rate of progression of paroxysmal to persistent AF increases with multiplication of well-known risk factors such as hypertension, aging, history of previous transitory ischemic attack (TIA) or stroke, chronic obstructive lung disease and HF (so called HATCH score). Depending on presence and number of risk factors, the rate of AF progression among unselected population of patients with paroxysmal AF ranges from 6% to 50% during the first year of follow-up [108]. In contrast with these findings, among younger patients with paroxysmal and "truly" lone AF, 10-year-cummulative rate of progression towards permanent AF was only 19.1% (95% CI: 12.8 to 25.4%) [86]. In another long term study, paroxysmal and persistent lone AF have progressed to permanent form of the arrhythmia with 30-year cumulative probability of 29% (95% CI: 16 to 42%) [109]. While aging of the patients and subsequent development of structural heart disease and other comorbidities were associated with the risk of progression of lone AF, the progression of lone AF itself was an independent predictor of adverse events such as thromboembolism [86]. Catheter ablation of paroxysmal AF might delay further progression of the disease. After ablation of paroxysmal AF, the progression of AF was evident among 1.5% of the patients during the follow-up of 27 months, with annual incidence of 0.6% [110]. However, among patients treated medically, the progression rate of paroxysmal AF was markedly higher, reaching 8.6% in the first year and 24.7% after 5 years [111]. Since the result of catheter ablation is significantly better for paroxysmal AF than for persistent AF, with lower recurrence rates and simpler procedure (most often limited only to PV isolation) in the former, the question arises about preventive ablation of paroxysmal AF in selected patients in order to slow down the progression of AF and reduce the potential risks of such disease progression.

Table 2. Randomized studies that compared the antiarrhythmic drugs and catheter ablation for the treatment of atrial fibrillation.

Year	№ pts	Age (years)	Study design	AF type	SHD	LA (mm)	Ablation strategy	AAD strategy	Follow-up (months)	Ablation results			AAD results		
										Freedom of AF	Cross-over to AADs	Adverse events	Freedom of AF	Cross-over to ablation	Adverse events
2005 [90]	70	≈54	First line therapy for AF: ablation vs. AADs	96% PAF	26%	≈42	RF, 8 mm, ICE-PVI	77% flecainide 23% sotalol 5% amiodarone	12	85%	3%	3% (PV stenosis)	21%	51%	9% (bradycardia)
2006 [91]	137	62	AF refractory to ≥1 AAD: ablation+AAD vs. „new“ AAD	67% PAF	63%	≈45	RF, 8 mm or irrigated-tip, EAM-CPVA (± lines)	62% amiodarone 26% flecainide 10% propafenone 6% sotalol 1% disopyramide	12	56%	-	4% (1 CVI, 1 tamponade, 1 phrenic nerve palsy)	9%	57%	3% (1 SCD, 1 TIA)
2006 [92]	146	57	PeAF>6 m: amiodarone vs. ablation	100% PeAF	8%	45	RF, 8 mm, EAM-CPVA (± lines)	100% amiodarone (first 3 months)	12	74%	1%	-	4%	77%	-
2008 [93]	112	51	PAF refractory to ≥1 AAD: ablation vs. „new“ AAD	100% PAF	26%	40	RF, irrigated-tip, PVI (± non PV triggers)	83% Class I 76% Class III (59% amiodarone)	12	89% (1.8 procedures/ pt.)	9%	3% (155 procedures: 2 tamponades, 2 hematomas, 1 PV stenosis)	23%	63%	2% (1 hypothyreosis) + 2 unrelated deaths
2009 [94]	70	≈64	AF refractory to ≥AAD: ablation vs. „new“ AAD	41% PAF	50%	45	RF, irrigated-tip, EAM-PVAI (± lines)	77% Class IC 63% amiodarone 9% sotalol	12	80%	-	3% (1 hematoma)	43%	-	17% (5 bradycardias, 1 AFL)
2010 [95]	167	56	PAF refractory to ≥1 AAD: ablation+AAD vs. „new“ AAD	100% PAF	11%	40	RF, irrigated-tip EAM-PVAI (± lines or CFAE)	41% propafenone 36% flecainide 20% sotalol 4% dofetilide	9	63%	7%	5% (2 CHF, 1 pericardial effusion, 1 vascular complications, 1 pneumonia)	17%	76%	9% (2 proarrhythmia, 3 intolerance)
2006 [96] & 2011 [97]	198	56	PAF refractory to ≥1 AAD: ablation vs. „new“ AAD	100% PAF	≈6%	≈39	RF, 8 mm or irrigated-tip, EAM-CPVA (± lines)	33% flecainide 33% sotalol 33% amiodarone	48	72%	-	5% (3 AT, 1 pericardial effusion, 1 TIA)	12%	88%	68% (19 hyperthyreosis, 15 bradycardia, 11 sexual dysfunction, 10 wide QRS, 2 visual and

														dermatological events, 1 hepatitis)
2012 [98]	294	55	First line therapy for PAF: ablation vs. AADs	100% PAF	10%	40	RF, 8 mm or irrigated-tip, EAM-PVAI (± lines)	88% Class IC 10% Class III	24	85% (1.6 procedures/ pt.)	9%	14% (1 CVI-death, 1 SCD, 3 tamponades, 1 CVI, 1 TIA, 1 PV stenosis, 3 AFL)	71%	36%	11% (1 SCD, 5 AFL)
2013 [99]	146	55	PeAF (<1 year) refractory to ≥1 AAD: ablation vs. AAD	100% PeAF	≈3%	≈42	RF, irrigated-tip, EAM-PVAI (± lines or CFAE)	44% Class IC (flecainide) 56% Class III (amiodarone)	12	60% (8% redo)	36%	6% (2 pericarditis, 1 pericardial effusion, 3 vascular complications)	29%	0% (48%)	2% (1 intoxication with flecainide)

Abbreviations:

CPVA=circumferential pulmonary vein ablation; SCD=sudden cardiac death; TIA=transitory ischemic attack; CHF=congestive heart failure; AT=atrial tachycardia; AFL=atrial flutter.

Other abbreviations as in table 1.

Heart failure. AF and HF often coexist, because they share common risk factors such as aging, hypertension, diabetes, obesity, valvular, ischemic and non-ischemic structural heart disease. The prevalence of AF increases with the severity of HF and it ranges from 5% in patients with mild up to 50% in patients with severe HF [112]. Sometimes it is not easy to define the cause and the consequence among patients clinically presenting with AF and HF. AF associated with fast and uncontrolled ventricular response is the most common cause of tachycardia-induced cardiomyopathy and low-output HF [1]. Pathophysiology of tachycardia-induced cardiomyopathy is not elucidated completely, but myocardial ischemia, depletion of myocardial energy and abnormalities of intracellular transport of calcium probably play important role [113]. The true prevalence of this secondary myocardial dysfunction among the patients with AF and HF is not known, but it is estimated that about 10% of the patients have "pure" tachy-cardiomyopathy, while among 25% up to 50% of the patients there is some component of tachycardia-related HF [113]. It is very important to maintain a high level of suspicion for tachycardia-induced cardiomyopathy in patients with AF and HF, because if tachyarrhythmia is the primary cause of HF, the restoration of sinus rhythm may lead to complete or significant improvement of systolic left ventricular function. In fact, tachycardia-induced cardiomyopathy is presently the most common unrecognized but potentially reversible cause of HF [1, 3, 112, 113]. During the evaluation of patients with AF and non-ischemic cardiomyopathy one should bear in mind the possible clinical scenario in which the progression of paroxysmal to persistent lone AF, associated with rapid ventricular rate, could be responsible for secondary left ventricular myocardial dysfunction. Since the medical therapy of AF in patients with HF is limited due to potentially negative inotropic and proarrhythmic effects of the drugs, catheter ablation of AF emerges as an attractive therapeutic option.

In the research that included 299 patients with normal and 67 patients with reduced left ventricular ejection fraction (EF) ≤50% and AF, longitudinal echocardiographic study was conducted [114]. At 6 months after the catheter ablation of AF, among the patients with myocardial dysfunction significant recovery of EF from 42% before to 56% after the procedure was reported. The success of the catheter ablation treatment was similar among the patients with reduced and normal EF (86% vs. 87%) but at the cost of higher number of repeated procedures in patients with left ventricular systolic dysfunction (1.6 vs. 1.3 procedures per patient). These findings were in line with the results of another study that demonstrated favourable effect of ablation on myocardial function among 58 patients (mean age 56 years) with congestive HF, average baseline EF of 35% and predominantly persistent and permanent AF [115]. At the end of the first year following the procedure, a similar proportion of patients undergoing catheter ablation and control patients (with normal baseline EF) remained free of AF (78% vs. 84%), with the rate of redo procedures of 50%. An increase of EF for >20% or complete normalization of EF (≥55%) was registered in 72% of the patients. Importantly, EF significantly increased not only among patients with poor rate control (average increase of EF by 23%), but also among those with seemingly adequate control of ventricular response prior to the procedure (EF increased by 17%) [115]. Moreover, among the patients with paroxysmal AF and systolic left ventricular dysfunction, the PV isolation procedure was followed by a significant rise of EF from 41% to 51% [116]. These findings confirm that not only prolonged episodes of persistent AF, but also frequent attacks of paroxysmal AF can lead to development of reversible tachy-cardiomyopathy. Recently, in the long term follow up study of 196 patients with EF<50% (77.6% of patients had persistent AF) who were subjected to catheter ablation of AF, the maintenance of sinus rhythm was independently associated with clinical improvement in terms of the reduction in New York Heart

Association (NYHA) class of symptoms for ≥1 and relative increase in left ventricular EF ≥10% (OR 4.26 [95% CI: 1.69 to 10.74], p=0.002) [117].

Quality of life. Patients with AF, similar to other cardiovascular patients, have considerably reduced QoL in comparison with general population [3]. Using a standard questionnaire before and after procedure (such as The Short Form (SF-36) Health Survey and Symptom Checklist), it was found that the QoL already improved at 3 months after ablation, and the improvement was sustained in the following 2 years, until the end of the research [118]. Several clinical parameters were identified to be the independent predictors of limited improvement of QoL score after catheter ablation of AF, including obesity, continuation of oral anticoagulant therapy after the procedure and good QoL score prior to the procedure. It could mean that in the presence of significant comorbidities, which limit functional capacity (such as obesity), or when chronic oral anticoagulation therapy is recommended (such as in patients at high risk of thromboembolic events), favourable effects of ablation with respect to symptoms can be mitigated. Thus, more pronounced symptomatic benefit of the procedure could be expected among highly symptomatic patients with "true" lone AF.

Among patients with paroxysmal AF refractory to ≥1 AAD, the QoL and symptomatic status were much more improved in those treated by catheter ablation of AF, compared to the patients who continued with AAD therapy [118-120]. In addition, the improvement of QoL scores among patients with persistent AF was greater after catheter ablation than after cardioversion only [92]. The improvement of QoL after ablation comprised all segments valuated by SF-36 questionnaire, including physical functioning, social functioning and mental health, and it reached the general population norms [3, 119]. Furthermore, change of QoL was directly related to the recurrence of arrhythmia after AF ablation. However, although there was a trend toward greater improvement of QoL after the procedure among patients whose AF was completely eliminated by ablation, significant improvement of life quality was also noted among patients with good pharmacological control of AF after ablation and even among those with arrhythmia recurrences [118, 119]. This can be explained by the reduction of AF burden following the procedure, i.e. a transition towards less frequent and more asymptomatic episodes of arrhythmia due to destruction of local autonomic nerve fibers and increased efficiency of AADs after ablation as a result of partially damaged myocardial PV-atrial connections [45, 85]. Thus, catheter ablation provides an opportunity for very efficient symptomatic treatment of patients with AF, which is one of the primary aims of AF therapy [1].

COMPLICATIONS OF AF ABLATION

Nowadays, catheter ablation of AF represents the most commonly performed interventional procedure in modern electrophysiological laboratories. In the last few years, number of AF ablation procedures increased, and procedure is carried out worldwide [3]. Leading experts described the distinctive strategic approaches, the technology they used and the experience gained so far [120]. Catheter ablation of AF is one of the most complex interventional procedures and its certain segments are associated with higher incidence of complications as compared to the conventional procedures of catheter ablation [120-123]. Complications of AF ablation depend

on specificity of the energy source used for the procedure, the procedure itself, characteristics of used device and the need for increasing the procedure efficiency [121]. Since there is no firm evidence that AF ablation affects the life expectancy, the primary goal of treatment is the improvement of symptomatic status and QoL. Therefore, it is necessary to discuss with each patient all the risks and benefits of this kind of treatment before the procedure.

Updated worldwide survey on catheter ablation of AF included 16.309 patients with a total of 20.825 procedures performed [123]. Compared to previous report, procedure efficiency and proportion of patients who were free of symptomatic AF without AAD therapy increased significantly in the last 5 years (52% vs. 70%, $p<0.0001$), even though the major complication rate was not notably reduced (6% vs. 4.5%, $p=0.691$) [122, 123]. However, the analysis, which encompassed 192 studies with 83.236 patients, showed a significant decrease of the AF ablation periprocedural complication rate during the period from 2007-2012, compared to the period from 2000 to 2006 (2.6% vs. 4.0%, $p=0.003$) [124]. On the other hand, in the series of 500 consecutive PV-antral isolation procedures, performed in relatively younger patients (average age 54) with low prevalence of structural heart disease and a low $CHADS_2$ score (the score ranged 0-1 in 92% of patients), an extremely low major complication rate of only 0.8% was reported [125]. It is very important to keep in mind that the complications of AF ablation do not have to be acute (i.e., do not have to occur during or immediately after the procedure), but also can be delayed, emerging in the upcoming weeks or months following the intervention [3, 120, 122, 123].

Predictors of procedural complication

The identification of potential predictors of AF ablation procedure complications has important implications and could affect the choice of ablation strategy and technology for a given patient, as well as the selection of patients for the ablation. Several potential predictors of periprocedural complication have been identified.

Age. Although the smaller studies have shown comparable efficacy of AF ablation in both younger and older patients, a conservative approach is generally preferred for older patients, mostly because of the fear from thromboembolic and vascular complications [3]. Controversial data about influence of older age on the periprocedural complications were published. For example, one study showed no significant difference between major complication rates of the AF ablation in three different age groups of patients, namely <65 years, 65-74 years and ≥75 years (1.6% vs. 1.7% vs. 2.9%, p=ns) [126]. On the contrary, the other two studies demonstrated strong association between the occurrence of complication and older age of >70 and ≥75 years [127, 128]. These findings were recently confirmed by another group of authors who identified age as one of the independent predictors of severe non-fatal procedural complications and death (OR 1.04 [95% CI: 1.01 to 1.07]; p=0.0155) [129].

Female gender. There is consistency of the data from several studies on the increased procedural risk in women [127, 130-132]. An analysis of 517 AF ablation procedures showed that female gender was an independent predictor of major complications (OR 3.0 [95% CI: 1.3 to 7.2]; p=0.014), while in another study female gender was independently associated with the occurrence of vascular complications (OR 4.4 [95% CI: 1.72 to 7.75]; p=0.01) [127, 130]. Common femoral artery is much shorter in women compared to men (38 mm

vs. 46 mm), which could complicate adequate access to the femoral vein during vascular puncture and increases the risk of forming the pseudoaneurysm and/or arteriovenous fistula [130].

Body weight. During the AF ablation-related risk evaluation, the anthropometric indices of patients must be taken into consideration. An analysis of the 512 AF ablation procedures identified remarkably higher major complication rate among morbid obese patients (body mass index [BMI] >40 kg/m2) compared to patients with lower BMI (14.3% vs. 6.2%, p=0.046) [132]. For every unit of BMI increment, the probability of complications (mostly vascular) increased by 5% in the entire group, and more than twice (OR 2.23 [95% CI: 1.09 to 4.56]; p=0.03) among women. However, the other group of authors identified lower body weight as the only independent predictor of complications, with a 0.8% increased risk for every 10 kg of body weight reduction, most likely due to a tendency of the underweight patients to be overdosed with anticoagulant drugs during the procedure. The distribution of complication rate among patients ≤80 kg, 81-90 kg, 91-100 kg and >100 kg was 4.8%, 3.5%, 2.5% and 2.0%, respectively [133].

Structural heart disease. The presence of structural heart disease represents a risk factor for periprocedural complications of AF ablation. In one study, the history of coronary disease before procedure was identified as an independent predictor of hemorrhagic complications (OR 5.6 [95% CI: 1.6 to 20.1]; p<0.008) [134]. In another series of 1000 consecutive RF catheter AF ablation procedures, a significant association between congestive HF and periprocedural complications was found (HR 5.2 (95% CI: 2.0 to 13.4); p=0.001) [128]. According to data from the German multicenter registry which included 6211 patients, the rate of all complications was significantly higher among patients with hypertensive heart disease than among those without structural heart disease (7.28% vs. 6.01%, p<0.01), with special regard to the periprocedural stroke rate, which was 6.8 times higher among patients with hypertensive heart disease (0.95% vs. 0.14%, p<0.001). Furthermore, the presence of hypertensive heart disease was an independent predictor of death and severe non-fatal procedural complications (OR 1.97 [95% CI: 1.02 to 3.83]; p=0.0442) [129].

The type of ablation procedure. It is well known that the recurrence of AF after initial AF ablation is common. Among patients treated with catheter ablation of AF, 10-25% were subjected to the repeated procedure [120]. In one study, history of previous RF ablation of AF was associated with increased probability of cardiac tamponade at the redo procedure (OR 3.32 [95% CI: 0.95 to 11.61]; p<0.05), which could be related to scarring and thinning of the LA wall after the first RF ablation [130].

Some studies indicated that the additional ablation of complex AF substrate either with linear ablation or CFAE ablation increases procedure risk [50, 53, 133]. The long procedure time, prolonged catheter manipulation in the LA, a higher energy output and ablation within the coronary sinus in order to achieve transmural lesion, may all increase the risk of perforation and embolism [135]. Interestingly, a systematic literature review (192 studies with 83.236 patients) did not find any significant relation of procedure duration, ablation time and ablation strategy with the occurrence of acute complications [124].

The selection of ablation technology may also affect the occurrence and nature of specific complications. Data from the German registry included 3.775 patients with paroxysmal AF who underwent the PV isolation procedure [136]. A direct comparison of cryoballoon ablation and RF ablation indicated the identical overall complication rate (4.6% vs. 4.6%). The phrenic nerve palsy was significantly more frequent with cryoballoon as compared to RF ablation (2.1% vs. 0.0%, p<0.001), but the prevalence of other complications was considerably higher with RF current (4.6% vs. 2.7%, p<0.05).

Experience of the operator and centre. AF ablation is very demanding and complex procedure and operator's experience in many ways influences the occurrence, recognition and treatment of complications. Learning curve of the catheter ablation procedure was emphasized by many authors. For example, in a series of the first 100 consecutive AF procedures complication rate was 9.0% and in the following 541 procedures it was twice lower (4.3%) [127]. Decennial results from the United States registry were recently presented, showing that the intrahospital complication probability regarding AF ablation was notably lower among the operators who perform 25-50 procedures per year (OR 0.51 [0.33 to 0.80]; p<0.004) and >50 procedures per year (OR 0.38 [0.21 to 0.69]; p<0.002) compared to less experienced operators (<25 procedures per year) [137].

Specific complications of catheter-ablation of AF

(Specific procedural complications are presented in details in table 3)

Fatal outcome. Fatal outcome is a rare complication of catheter ablation of AF with incidence of 1:1000, which is similar to the fatality incidence with catheter ablation of supraventricular tachycardias [120, 123]. A multicenter analysis, which included 32.569 patients who underwent AF ablation, showed that the most common causes of death were cardiac tamponade (25%), stroke (16%) and atrioesophageal fistula (16%) [138]. However, although cardiac tamponade was a rather frequent periprocedural complication (1%), it had fatal outcome in merely 2.2% of cases. On the other hand, atrioesophageal fistula was a rare complication (0.02%), but most commonly with fatal outcome (71.4%). The incidence of intraprocedural stroke was 0.2%, with a moderate rate of fatal outcome (5.1%). It is controversial whether to run the AF ablation procedure without appropriate back up from the cardiac surgery. Namely, an urgent surgical approach was necessary in 13.3% of patients with cardiac tamponade after an unsuccessful percutaneous pericardiocentesis [139]. It is particularly important to recognize that 25 of 32 fatal outcomes occurred within 30 days of the procedure, of which 12 were intraprocedural (five of them due to cardiac tamponade, two due to stroke) and 13 occurred in the first hours or days after the procedure (five of them due to atrioesophageal fistula, two due to anoxic encephalopathy and two due to massive pneumonia). Majority of patients (71%) with late fatal outcome at >30 days after the procedure experienced some of the intraprocedural acute complications [138]. These data underline the necessity of a careful follow-up of patients during the first weeks after the procedure, especially of those who suffered any of the acute periprocedural complications.

Cardiac tamponade. Cardiac tamponade is the most common life-threatening complication of catheter ablation of AF, with incidence of 1% to 6% [120, 123, 124, 125, 133, 125]. Cardiac tamponade may occur due to an inaccurate transseptal puncture, mechanical perforation with catheter or excessive local RF ablation with tissue overheating and steam-popping in the presence of anticoagulation [3, 123]. Rapid accumulation of blood in pericardial sac leads to myocardium compression, sudden hypotension, lack of movement of cardiac silhouette at the fluoroscopy and circulatory shock, demanding an urgent echocardiographic confirmation of the diagnosis and intervention. By direct visualization of the fossa ovalis, using transesophageal or intracardiac echocardiography, the risk of inadvertent perforation of adjacent cardiac structures during the transseptal puncture could be minimized, especially in case of a redo procedure, resistant septum and/or altered anatomical relationships of the relevant structures [30]. Gentle catheter manipulation in the LA and careful energy titration

using irrigated-tip catheters could reduce the complication rate. In one study, 80% of myocardial perforations resulting in cardiac tamponade occurred during endocardial linear RF ablation of mitral isthmus and in 80% of cases popping phenomenon with impedance increase preceded the tamponade, while mechanical perforation of the LA was responsible for the remaining 20% of cardiac tamponade cases [135]. Energy reduction to ≤42W significantly reduced the cardiac tamponade rate from 2.9% to 1.0% (p=0.047). The use of intracardiac echocardiography (ICE) during ablation provides an opportunity to titrate local application of RF and prevent popping phenomenon [140]. Besides that, ICE enables early detection of fluid accumulation in pericardial sac (behind posterior and lateral wall of the LA), before hemodynamic deterioration [139]. Due to local thinning, several anatomical regions such as the LA appendage, vestibular component surrounding mitral valve, the LA posterior wall and roof, and the coronary sinus are considered as the predilection sites for mechanical perforation, necessitating a careful catheter manipulation [141]. The new technology development enables better control of contact-force between the catheter tip and the endocardium, which could prevent complications [65, 66]. The emergency percutaneous pericardiocentesis followed by anticoagulation reversal is a life-saving procedure and could be performed with subxyphoid, apical or parasternal approach, but in 13% of patients it could lead to new complications in the form of pneumothorax, hemothorax and liver injury, while 53% of patients require treatment because of acute inflammatory pericarditis after the hemopericardium evacuation, which could be followed by recurrent AF [139]. Some authors proposed an alternative transcardiac approach to pericardial space with ongoing autotransfusion of evacuated blood in order to stabilize the patient before surgery [142]. However, the long-term prognosis after successful acute treatment of cardiac tamponade is very good and after complete rehabilitation, ablation procedure could be repeated [120, 135, 142]. Delayed cardiac tamponade, which occurs after an hour or more from the AF ablation (up to 50 days after the procedure) draws special attention. Its incidence is 0.2% and mechanism is not fully explained. However, it is speculated that this type of pericarditis is mediated by inflammation due to transmural ablation. Majority of such patients present with gradually progressive symptoms (such as agitation, tachycardia, oliguria and others), whilst 13% of patients experience sudden hypotension and shock [120].

Thromboembolic complications. *Preprocedural thrombosis.* Transesophageal echocardiography (TEE) performed prior to catheter ablation of AF (mean age of patients was 57 years, 69% with paroxysmal AF) demonstrated the prevalence of LA appendage thrombus in 1% of patients, despite adequate anticoagulation with warfarin during ≥1 month before the procedure [143]. The prevalence of thrombus in LA was significantly higher among patients with persistent AF in comparison to those with paroxysmal AF (3% vs. 0.2%). In addition, high thromboembolic risk (as measured by a $CHADS_2$ score of >2 or a CHA_2DS_2-VASc score of >2) was more frequently identified among patients with LA thrombus, than in those without LA (86% vs. 18% for $CHADS_2$ >2 and 100% vs. 33% for CHA_2DS_2-VASc >2, respectively) [143]. The finding of both scores <2 had almost maximal negative predictive value for the presence of thrombus in the LA appendage (99.8% for the $CHADS_2$ and 100% for the CHA_2DS_2-VASc score). In concordance with these results, in another study, TEE prior to ablation revealed LA thrombus in 1.9% of patients despite the 4-week preparation by oral anticoagulants [144]. Moreover, patients with the finding of thrombus had significantly larger LA dimension (51±6 mm vs. 44±8 mm, p=0.006). The strongest predictors of the LA thrombus before the procedure were hypertension (OR

Table 3. Specific complications of catheter ablation of atrial fibrillation [3, 120, 123-202].

Complication	Incidence	Time to complication	Risk factors	Diagnosis	Treatment
Cardiac tamponade	acute: 1-6% delayed: 0.2%	acute: at the procedure delayed: up to 50 days	• mechanical perforation • excessive ablation • linear ablation (mitral isthmus)	• fluoroscopy – cardiac silhouette • pressure monitoring • echo (TTE; TEE; ICE)	• pericardiocentesis • surgical repair
Systemic thromboembolism (CVI/TIA)	manifest: 0.94% silent: 11-38%	acute: at the procedure delayed: up to 2 weeks	• low anticoagulation • persistent AF, cardioversion • PVAC • enlarged LA, echo contrast	• neurologic examination • CT/MRI	• conservative • thrombolysis • intervention
Air embolism	NA	at the procedure	• transseptal puncture • long sheaths in LA • rapid removal of a catheter • long apnea episodes	• neurologic examination • CT/MRI	• supportive therapy • vasopressor drugs • oxygen treatment • aspiration
Pulmonary vein stenosis	symptomatic: 0.3% asymptomatic: 0.5-2%	mostly <3 months rare >3 months	• ostial, distal PV ablation • small PV diameter • small size cryoballoon, small PVAC	• CT/MRI • lung perfusion scan • Doppler echo	• angioplasty • stenting • surgery, lobectomy
Phrenic nerve injury	0-14%	at the procedure	• SVC isolation • cryoballoon RSPV isolation • small size cryoballoon, small size PVAC	• high output pacing • diaphragm movement at fluoroscopy	• supportive therapy • spontaneous recovery
Atrioesophageal fistula	0.04	2-6 weeks	• high output RF ablation • LA posterior wall ablation • enlarged LA, esophag. reflux	• CT/MRI • capsule endoscopy	• surgical • esophageal stenting
Esophageal & vagal nerves injury	esophageal ulcer: 17% vagal nerve: 0.3%	after 24-72h	the same as for atrioesophageal fistula	• endoscopy • fluoroscopy of upper GIT	• PPI • spontan.recovery • surgical
Vascular complications at access site	0.5-13%	at the procedure	• older patients, female patients • obesity, diabetes mellitus • repeated procedures	• vascular ultrasonography	• compression • intervention • surgery
Coronary artery injury	nonsignificant: 0-28% significant: case rep.	at the procedure	• previous lesions • inferior mitral isthmus ablation • ablation inside CS	• coronary angiography	• PCI with stenting
Circular catheter entrapment	0.01%	at the procedure	• vigorous manipulation of catheter in LA and LIPV	• fluoroscopy • echocardiography	• gentle catheter manipulation, advancing the sheath • surgery
Atrial tachycardia / flutter after ablation	5-44%	early: <3 months delayed: >3 months	• LA inflammation • ablation of persistent AF • incompl. lines, CFAE ablation	• ECG • Holter monitoring • loop recorder	• AAD • anti-inflammatory drugs • new RF ablation

Radiation injury	skin injury: 2 cases malignances: 0.1%	3-8 months late complication	• long radiation exposition • obesity	• dermatological examination • skin biopsy	• topical and oral steroids • antihistamines • antibiotics
Infective endocarditis	0.2%	few days – 4 weeks	• artificial valves • congenital heart disease	• blood tests, blood culture • echocardiography	• antibiotics • surgery
LA stiff syndrome	symptomatic : 1.4%	first 3 months	• LA size ≤45 mm, elevated LA pressure • diabetes mellitus, sleep apnea • extensive ablation in LA	• echocardiography • CT/MRI • right heart catheterization	• therapy for pulmonary hypertension

Abbreviations:

TTE=transthoracic echocardiography; TEE=transesophageal echocardiography; CVI=cerebrovascular insult; TIA=transitory ischemic attack; PVAC=pulmonary vein ablation catheter; CT=computed tomography; MRI=magnetic resonance imaging; SVC=superior vena cava; RSPV=right superiori pulmonary vein; AE=atrioesophageal; GI=gastrointestinal; PPI=proton pump inhibitors; CS=coronary sinus; PCI=percutaneous coronary intervention; LIPV=left inferior pulmonary vein;

Other abbreviations as in tables 1 and 2.

14.2 [95% CI: 2.6 to 77.5]; p=0.002), older age >75 years (OR 8.1 [95% CI: 1.5 to 44.9]; p=0.017) and cardiomyopathy (OR 10.5 [95% CI: 2.6 to 77.5]; p=0.002).

Among the patients free from clinical risk factors (such as age >75 years, diabetes, hypertension, valvular heart disease, stroke or TIA) thrombus was not found [144].

Intraprocedural (thrombo)embolism. Embolism related to catheter ablation of AF can be mediated by several factors, including tissue detritus during the transseptal puncture, thrombosis of long introducers and catheters in the LA, introduction of air in systemic circulation by exchanging the catheters through the long introducers, mechanical dislodgement of preexisting LA thrombus during the catheter manipulation, cardioversion of persistent AF during the procedure, catheter tip charing due to a high RF energy output without adequate local cooling, thermally-induced denaturation of plasma proteins during ablation, administering of protamine at the end of procedure, etc. [3, 120-123].

The incidence of (thrombo)embolism due to catheter ablation of AF ranges from 1% to 2% [26, 123]. Systemic thromboembolism can cause ischemic stroke or acute occlusion of coronary or peripheral artery, which determines specific clinical presentation [145-147]. A massive stroke during AF ablation can be fatal (5.1%) or can lead to significant neurological dysfunction [138]. According to one study, stroke was most often (60%) reported during the procedure or within 24h after the procedure, about 30% of cases were registered between 24h and 48h after the procedure, and additional 10% of strokes occurred by the end of the first week after the ablation [146]. Among the patients who have suffered the procedural stroke, the level of neurological impairment was severe in 11.5%, moderate in 38.5% and mild in 34.6% of patients. During a 38-month follow-up after the procedure, 7.7% of these patients died, while the remaining patients have achieved complete neurological recovery [147]. Symptomatic procedural thromboembolic cerebrovascular complications can be treated by emergency percutaneous intervention with mechanical recanalization of culprit artery or by administration of thrombolytic therapy [3, 120]. However, it seems that symptomatic stroke represents only "the top of the ice berg", because cerebral MRI scanning, performed just before and after catheter ablation of AF, detected a disturbing rate of asymptomatic brain embolism of 1.7-38% [148, 149]. Fortunately, follow-up MRI obtained several weeks later demonstrated complete regression of these brain lesions. In fact, only 1-3% of these lesions persisted on repeated MRI examination, and those were mainly the lesions with larger diameter at baseline (>1 cm) [149]. At this moment, true potential of such asymptomatic lesions for late deterioration of cognitive function and development of dementia is not clear. However, electrophysiologists are alarmed to identify and conduct adequate prevention measures in order to reduce occurrence of this complication.

Occurrence of procedural thromboembolic complications depends on the clinical characteristics of patients, the use of ablative technology, chosen ablative strategy (i.e. set of lesions) and anticoagulation regimen during the procedure [149]. Several authors emphasized the predictive significance of older age, presence of hypertensive heart disease, a high $CHADS_2$ score of ≥2 (OR 7.1 [95% CI: 1.3 to 38.0]; p=0.02) and history of cerebrovascular insult (OR 9.5 [95% CI: 2.2 to 40.9]; p<0.01) for high risk of occurrence of procedural thromboembolic cerebrovascular complications [3, 129, 146, 150]. In another study, the presence of a $CHADS_2$ score of ≥2 carried 9 times higher risk of procedural thromboembolism, in comparison with $CHADS_2$ score ≤1 (4.7% vs. 0.5%) [146]. Important role in the occurrence of procedural thromboembolism belongs to certain technical aspects of the procedure. Thus, for example, the long sheath perfusion rate (low flow vs. high flow) was one of the risk factors for the occurrence of cerebrovascular thromboembolism (OR 17.3 [95% CI: 1.1 to

260.8]; p=0.04) during the LA catheter ablation procedures [120, 151]. Indeed, with increasing the introducer perfusion rate (from 3 mL/h to 180 mL/h) the incidence of cerebral thromboembolism was reduced from 11.9% to 0% [151]. Furthermore, several recent studies demonstrated differences in embolic risk, depending on the ablative technology and strategy. The risk for the occurrence of new subclinical cerebrovascular embolization was similar with the use of irrigated-tip RF catheters (6.8% - 8.3%) and cryoballoons (4.3% - 8.9%), but it was significantly higher with ablation by phased multielectrode RF catheter (PV ablation catheter, so called PVAC) [152-154]. In addition, ablation strategy has a direct impact on the prevalence of new asymptomatic cerebral (thrombo)embolizations after the procedure: 5.4% with isolation of PVs only, 16.0% with additional linear ablation (PV isolation + lines) and 31.5% with further CFAE ablation (PV isolation + lines + CFAE). Moreover, CFAE ablation was independently related to the occurrence of asymptomatic cerebral lesions on early postprocedural MRI (OR 6.7 [95% CI: 1.7 to 25.6]; p=0.006) [155].

Thromboembolism after procedure. Thromboembolic events may arise within the weeks and months after the procedure, due to a number of various factors, such as endothelial disruption induced by local ablation, loss of the LA transport after extensive ablation, artificial isolation of the LA appendage, LA stunning following cardioversion, recurrence of AF after the procedure and intrinsic thromboembolic risk of the patient [1, 3, 120].

The previous studies have shown potential value of the CHA_2DS_2-VASc scoring system in evaluation of thromboembolic risk after AF ablation. Over the long term follow-up period of 38 months after AF ablation, 4.8% of a total of 565 study patients have suffered some adverse event, including thromboembolism [156]. Adverse events were more common among patients with AF recurrence than among those who were free of AF (9.6% vs. 2.8%, p=0.001). The only independent predictors of stroke or TIA were the $CHADS_2$ score (HR 1.9 [95% CI: 1.4 to 2.6] for each unit increment; p<0.001) and the CHA_2DS_2-VASc score (HR 1.7 [95% CI: 1.3 to 2.2] for each unit increment; p<0.001). It is critically important that even 2.4% of "low risk" patients with $CHADS_2$ score 0 to 1 were affected by some of adverse events. Furthermore, among patients with low $CHADS_2$ score ≤1, the risk of adverse events gradually increased, in parallel with the value of CHA_2DS_2-VASc score (0.6% for score 0, 1.6% for score 1, 6.2% for score 2 and 11.8% for score 3) [156]. Therefore, it seems that the CHA_2DS_2-VASc scoring system is more sensitive (than $CHADS_2$) for assessment of thromboembolic risk after catheter ablation of AF. Recently, another study confirmed these results [157]. During the 18-month follow-up after the procedure the prevalence of thromboembolic events was 0.72%. Among patients with low $CHADS_2$ score (0-1), the use of CHA_2DS_2-VASc score provided additional differentiation of thromboembolic risk. The risk was only 0.13% with a CHA_2DS_2-VASc score of 0-1 and 0.71% with a CHA_2DS_2-VASc score of >2. In addition, it seems that the CHA_2DS_2-VASc score has the best predictive value in patients with AF recurrence after catheter ablation [157].

Periprocedural anticoagulation strategies. The presence of thrombus in the LA appendage is a contraindication for catheter ablation of AF [3, 120]. Thus, it is necessary to take appropriate measures for prevention of thrombus formation and for its early detection. The patients should be anticoagulated systemically with a vitamin K antagonist at the therapeutic level (International Normalized Ratio [INR] between 2 and 3) or with a new oral anticoagulant drug (direct thrombin or Factor Xa inhibitor) for at least 3-4 weeks prior to the procedure [1, 3, 120]. TEE before ablation procedure probably is not necessary in all patients, but it could be very important for selected high risk patients, such as those with persistent AF, patients having AF on the day of the procedure, especially if episode of AF lasted >48h, as well as patients with high a $CHADS_2$ score of ≥2, a

subtherapeutic INR of <2 during the previous weeks and patients with considerably dilated LA [158]. Only with younger patients with low $CHADS_2$ score ≤1, normal LA dimension and paroxysmal lone AF, presenting in sinus rhythm at ablation procedure, simplified alternative therapy only with aspirin, can be considered [159].

Generally, there are two periprocedural anticoagulation strategies [3, 120]. According to the classical strategy, warfarin is interrupted 3-4 days before the procedure and during those days it should be overlapped with low-molecular-weight heparin (LMWH: enoxaparin or dalteparin). After procedure, warfarin is reinitiated (with LMWH bridging until the therapeutic INR of >2 is reached) [120, 158]. Another strategy is increasingly applied and it consists of continuous warfarin therapy throughout the whole periprocedural period, without interruption. During the procedure, INR is maintained in lower therapeutic range of 2 to 2.5, and application of subcutaneous LMWH in periprocedural period is not necessary [158, 160]. The main concern with uninterrupted warfarin strategy is related to possible procedural bleeding.

A reversion of anticoagulant effects of unfractionated heparin usually is achieved quickly with intravenous administration of protamine [120]. However, in case of bleeding under therapeutic INR, availability of fresh frozen plasma, vitamin K or recombinant Factor VIIa during the procedure is mandatory and complete neutralization of anticoagulant effect is much slower [3, 158, 160]. In recent years several studies analyzed effects of anticoagulant strategy in relation to thromboembolic and bleeding complications. A meta-analysis, which included 9 studies and total of 27402 patients who underwent AF ablation, showed that continuous warfarin strategy, in comparison with "overlapping" strategy, significantly reduces the risk of thromboembolic complications (OR 0.10 [95% CI: 0.05 to 0.23]; p<0.001) and minor bleeding (OR 0.38 [95% CI: 0.21 to 0.71]; p=0.002) during the periprocedural period [160]. On the other hand, the risk of major bleeding, including cardiac tamponade, was not significantly increased. It was pointed out that safe adoption of this strategy obligates to ICE monitoring during the procedure, due to tendency towards increase of the risk of major bleeding if ICE was not used (OR 2.69 [95% CI: 0.87 to 8.33]; p=0.086) [160]. A recent retrospective research confirmed these findings [161]. Comparing these two anticoagulation strategies in a total of 3280 patients, there was a significant reduction in the rate of ischemic stroke/TIA among patients on continuous warfarin therapy (0.67% vs. 0.15%, p=0.02), while the incidence of severe hemorrhagic complications (mostly cardiac tamponade) was similar (1.3% vs. 1.1%, p=0.80).

In the last few years, novel oral anticoagulation drugs are being increasingly used in periprocedural anticoagulation [162-164]. Several recent studies investigated the efficacy and safety of periprocedural anticoagulation with dabigatran for catheter ablation of AF [162]. In a meta-analysis that included 11 studies, continuous warfarin therapy (therapeutic INR 2-3) was compared with dabigatran (at a daily dose of 2x150mg) for periprocedural anticoagulation in AF ablation procedure [163]. In most of the studies, dabigatran was discontinued at the morning of the procedure or 1 to 2 days prior to procedure, while the strategy with uninterrupted dabigatran throughout the entire periprocedural period was accepted in only two studies. A total of 3841 patients were enrolled (mostly with a low $CHADS_2$ score of 1.0-1.1), who were treated by irrigation RF ablation of AF, and dabigatran was as efficient and safe as warfarin [163]. There was no significant difference in the prevalence of thromboembolic complications (0.6% vs. 0.1%, p=0.12), major bleeding (1.9% vs. 1.6%, p=0.92), cardiac tamponade (1.4% vs. 1.1%, p=0.82) and minor bleeding (3.8% vs. 4.5%, p=0.40) between dabigatran and warfarin group, respectively. In addition, a multicenter observational study demonstrated that interrupted anticoagulation periprocedural strategy with rivoraxaban was safe and efficacious compared to

warfarin for the prevention of bleeding and thromboembolic events in patients who underwent AF ablation [164]. In this study, the rate of major bleeding complications (1.6% vs. 1.9%), minor bleeding complications (5.0% vs. 5.9%) and thromboembolic events (0.3% vs. 0.3%) were similar between patients treated with rivaroxaban and warfarin, respectively.

Throughout the procedure, regardless of the anticoagulation strategy used, intravenous unfractionated heparin is administered, with a loading dose of 100 IU/kg and then the application of the drug continues as an infusion or as repeated boluses in a dose of approximately 10 IU/kg per hour, keeping the activated clotting time (ACT) in therapeutic range [3, 120]. Catheter ablation of AF under therapeutic INR is simple and requires smaller dose of intravenous heparin during the procedure [165].

The study, which compared three different levels of procedural anticoagulation (250-300 sec, 300-350 sec and 350-400 sec), reported that more aggressive anticoagulation with target ACT >300 sec is associated with significantly lower prevalence of thromboembolic cerebral events, such as ischemic stroke and TIA [166]. It seems that more intensive anticoagulation during the procedure could be justified in the patients with high thromboembolic risk. For example, maintaining the procedural ACT >300 sec efficiently prevented thrombus formation in the LA, especially in patients with spontaneous LA echo contrast at the beginning of the procedure [167].

Anticoagulation therapy following procedure. Optimal duration of anticoagulant therapy after the procedure is not completely clarified. In the weeks after the ablation procedure, damaged endothelium represents possible nidus for thrombus formation [120, 158]. Although most of AF recurrences are registered in the first 1-2 years, the attention is drawn to appearance of later arrhythmia relapse [79]. Moreover, AF recurrences after the procedure can be completely asymptomatic [3]. Even after successful elimination of AF by ablation, some patients are still prone to thromboembolism due to the presence of many comorbidities and risk factors, remaining after the procedure [168]. Therefore, systemic anticoagulation is indicated in all patients in the first 2-6 months post procedure, depending on the ablation extensiveness (PV isolation vs. PV isolation + substrate modification) [3, 120]. Following this period, it is possible to discontinue oral anticoagulant therapy in some, but not all patients. Although some authors have successfully stopped the anticoagulation therapy in over 80% of the patients during long term follow-up, it is recommended to continue treatment indefinitely in selected patients with high $CHADS_2$ score ≥2 [168]. As already mentioned, several recent studies suggested potential value of CHA_2DS_2-VASc score in further stratification of so called "low risk" patients (based on a low $CHADS_2$ score of 0-1) after catheter ablation of AF. Thus, despite low $CHADS_2$ score, in patients with a CHA_2DS_2-VASc score of ≥2 and/or recurrence of AF, long term anticoagulation after the procedure should be considered [156, 157].

Pulmonary vein stenosis. PV stenosis is one of the most serious complications of catheter ablation of AF and could lead to a lifelong reduction of patient's functional capacity [3, 120, 123, 124]. By changing ablation technique, i.e. by relocating ablation site away from PV ostium (to more antral region), incidence of PV stenosis was significantly reduced in the last ten years, from 28% (in initial series) to current 1.3%, whilst incidence of PV stenosis that needed intervention is 0.3% [123, 169]. Arbitrarily, severity of PV stenosis was labelled as mild (<50% of diameter), moderate (50% to 70%) and severe or significant (>70%) [3]. Based on porcine models it is suggested that PV stenosis appears due to thermal injury of the PV wall, intensive periadventitial inflammation and progressive collagen deposition, which causes lumen narrowing [170].

Rather well balanced distribution in stenosis of left superior (32%), left inferior (26%) and right superior PV (35%) was noticed while involvement of right inferior PV occurred less frequently (6%) [171]. A repeated ablation procedure was responsible for 26% of all cases of PV stenosis. The onset of symptoms is often delayed (approximately 103±100 days after the procedure) and insidious in the form of exertional dyspnoea, cough, haemoptysis, chest pain or bronchitis/pneumonia [170-172]. Clinical presentation depends on number of PVs affected and degree of stenosis. Namely, symptoms occur as consequence of pulmonary congestion and usually begin when stenosis is >60-70%, especially among patients with involvement of >1 PV [170]. Thus, 82% of patients with substantial stenosis of one PV and 100% of patients with stenosis of 2, 3 or 4 PVs reported the symptoms [172]. Therefore, it is recommended to perform routine screening of patient three months after AF ablation, which enables timely detection and following of initial PV stenosis [120]. Anatomic lesion evaluation is performed with computed tomography (CT) and MRI scanning, whereas determination of the degree of physiological disorder is performed by lung perfusion scan [170]. Prevention of this complication could be accomplished with as accurate as possible identification of PV ostium before ablation by using selective venography, impedance map, local electrograms features, 3D electro-anatomical mapping systems with image integration from CT/MRI scan and ICE [3, 120, 170].

Until recently it was believed that development of PV stenosis was primarily associated with the usage of RF energy. However it is reported that this complication occurs also during cryoablation of AF, especially when smaller balloons are used [173]. Interventional angioplasty with stent implantation probably presents currently the most effective therapy of significant PV stenosis [174, 175]. Long-term rate of restenosis after stenting is lower than after the angioplasty (33% vs. 78%) and substantially higher in smaller PV with diameter less than 1 cm [3, 120, 174, 175]. There is no clear standpoint about therapy of asymptomatic PV stenosis because if PV occlusion happens prior to symptoms emerge, therapeutic possibilities may be lost and treatment outcome is unsatisfactory. Thus the procedure should be considered in younger asymptomatic patients without comorbidity, particularly if diameter of involved vein is larger [175]. Surgery is reserved for clinically significant occlusion or stenosis and after the failed percutaneous intervention [3].

Esophageal injury and atrioesophageal fistula. Atrioesophageal fistula is a rare but catastrophic complication of catheter ablation of AF and its incidence is estimated at 0.04% [123]. Esophagus is located behind the LA and it is in close anatomic relationship with its posterior wall, and contact area could be even larger in patients with LA dilatation, esophageal diverticulosis and thinner adipose-fibrous layer between the LA and esophagus [176]. Thermal injury of esophageal wall and impairment of small blood vessels cause ischemic necrosis of its mucosa and lead to local inflammation and ulceration formation, which are prerequisites for occurrence of atrioesophageal fistula [176]. One study shows that incidence of esophageal mucosal injury after the catheter ablation of AF was 17% [177].

It is considered that esophageal hypomotility, gastroesophageal reflux and hyperacidity could play important role in further local lesion evolution [120]. Clinical presentation of atrioesophageal fistula usually begins 2-6 weeks after the procedure with unspecific symptoms in the form of dysphagia, odynophagia, nausea, hemathemesis, melena, febricity, pericardial effusion, sepsis, seizures and stroke, due to cerebral embolization with air or food particles [178, 179]. Therefore, for prompt diagnosis it is necessary to maintain a high suspicion of this delayed complication in patients that had been subjected to catheter ablation of AF during previous weeks

[3]. In these circumstances, conventional endoscopy is contraindicated because insufflation of the esophagus during the procedure could lead to massive air embolism with consequent stroke or myocardial infarction [179]. Capsule endoscopy procedure is feasible and safe and the method of choice is contrast enhanced thoracic CT [176, 177]. Many different procedures aiming to prevent esophageal injury were presented during the last few years. During the procedure, direct and real-time visualization of esophagus enables operator to modify ablation trajectory in the LA and to move away from esophagus. It could be accomplished with simple esophageal opacification by ingestion of barium paste, using of ICE and creating 3D geometrical map of esophagus and LA with integration of CT/MRI scan by means of electroanatomical mapping system [3, 120, 176, 177].

In the first weeks after AF procedure, proton pump inhibitors are often prescribed prophylactically, hoping to accelerate healing of occult esophageal injury as possible precursor for atrioesophageal fistula [180]. Direct monitoring of intraluminal temperature with thermocouple esophageal probe during procedure provides an opportunity to adjust RF energy at ablation on posterior wall of the LA and reduces incidence of esophageal mucosal lesion from 36% to 6% [181]. Limiting the RF energy on the LA posterior wall at 25-30 W also significantly reduced occurrence of esophageal mucosal lesions [176]. In selected cases, esophagus protection during ablation was achieved with different techniques. Thus in smaller series it is attempted to temporarily relocate esophagus during RF ablation by deflection of the endoscope. In other report, with the percutaneous pericardial approach and by placing a balloon filled with liquid behind posterior wall of the LA it was possible to complete redo PV isolation procedure without esophageal injuries which limited index procedure [176].

Experiments on the porcine model revealed a tendency of RF energy to cause greater structural damage and tearing of elastic fibers of esophageal tissue in comparison with cryoenergy, suggesting that cryoenergy could eliminate the risk of collateral esophageal injury during left atrial ablation [182]. However, few clinical cases of atrioesophageal fistula even after cryoballoon isolation of PVs were recently described [183]. It is necessary to obtain proper diagnosis before appearance of dangerous systemic embolization. Surgical treatment requires cooperation between cardiac surgeon and abdominal surgeon, with correction of atrial and esophageal defect with pericardial patch and pericardial or muscular flap, respectively [3, 120, 176]. Case series of successful nonsurgical treatment with esophageal stenting and subsequent stent removal after fistula resolution was reported [178].

Periesophageal vagal plexus injury is rare complication of AF ablation and could lead to functional esophageal disorder. Vagal nerve fibers, which control peristalsis, pyloric sphincter and gastric antrum mobility, are located along the anterior esophageal wall and make anterior esophageal plexus which is placed adjacent to posterior wall of the LA [120, 176, 184]. The usage of RF energy at the posterior wall of the LA could be complicated by injuring this nerve plexus and causing an acute pyloric spasm, esophageal and gastric hypomotility as well as a slow/delayed gastric emptying [184]. In a series of 3.695 consecutive patients subjected to ablation of AF, vagal nerve injury was diagnosed among 11 patients (0.3%) [185]. Symptoms typically started within 72 hours from the procedure, usually after taking the first meal after procedure. Those were nausea, vomiting, flatulence, abdominal pain and constipation. Initially, stimulation of peristalsis with erythromycin and metoclopramide was applied. In the next 2-6 weeks, symptom resolution was registered in 72% of patients, while 28% of patients suffered from prolonged symptoms (3-12 months). Due to persistent pyloric stenosis in one patient, after two attempts of endoscopic dilatation, laparoscopic surgical correction with gastrojejunal anastomosis along with partial gastric resection was performed [185].

Acute occlusion of coronary arteries. Injury of epicardial coronary artery is not expected during the PV isolation, it could be a sporadic but very serious complication of ablation of AF substrate in the left or right atrium [120]. Circumflex coronary artery and distal coronary sinus are in close anatomical relationship. In one series of patients who underwent inferior mitral isthmus ablation, coronary sinus ablation using irrigated-tip catheters was performed in 71% of patients in order to obtain transmurality of the lesion [186]. Selective coronary angiography, performed before and after the ablation, demonstrated clinically silent but angiographically significant stenosis of distal segment of circumflex coronary artery in 28% of patients, which completely disappeared after intracoronary nitroglycerine administration. Distal coronary sinus, prolonged RF application inside the coronary sinus, smaller circumflex artery diameter, and shorter distance between circumflex artery and coronary sinus were identified as the risk factors for coronary artery lesion within this cohort [186]. Furthermore, other authors described cases of circumflex artery acute occlusion with the development of acute myocardial infarction after epicardial ablation of mitral isthmus via coronary sinus in redo procedure [187]. It is considered that artery occlusion was mediated by direct thermal injury of its wall with edema or spasm and/or cumulative injury from previous procedure. In complex AF procedures, ablation of substrate is not limited to the LA [25]. It has been shown that RF ablation of cavo-tricuspid isthmus could be accompanied by temporary but significant reduction of fractional flow reserve (FFR) in 21.2% of patients, or rarely by acute occlusion of distal segment of right coronary artery with inferior myocardial infarction [188, 189]. A coronary artery injury induced with RF ablation usually is treated by emergency percutaneous coronary procedure with artery recanalization and stenting [3, 187].

Phrenic nerve injury. Phrenic nerve injury occurs due to direct thermal injury of nerve fibers during ablation [190-192]. Importantly, potentially reversible functional disorder occurs prior to irreversible damage of nerve fibers, thus opening the window for early recognition and prevention of this complication [120]. The right phrenic nerve is in close anatomical relationship with anterolateral wall of superior caval vein, then goes down and posteriorly, and passes near the junction between the LA and anterior wall of the right superior PV at a distance of <2 mm in 32% of patients, while the left phrenic nerve passes over the roof of the LA appendage [190].

In clinical practice, the damage of right phrenic nerve is most frequently seen during the right superior PV isolation by cryoballoon and during the isolation of superior caval vein by RF ablation [3, 8, 136]. However, there are few reports on paresis of left phrenic nerve during cryoballoon isolation of the left inferior PV [191]. It is well known that cryoballoon isolation of the PVs is associated with the occurrence of this complication, and that the usage of balloon with a diameter smaller than 23 mm particularly increases complication risk (7.5%) due to more ostial energy application and distension of terminal part of the vein [190]. Recently, it has been reported that using balloons with a larger diameter (28 mm) the incidence of phrenic nerve palsy was reduced to 2.2%, but it was still significantly higher than while using RF current [136, 173, 192].

Nearly one-third of patients with phrenic nerve lesion are completely asymptomatic [190]. However, in symptomatic patients clinical presentation may be nonspecific and includes dyspnea, cough, hiccup, pneumonia, atelectasis and pleural effusion with hemidiaphragm elevation at conventional chest radiogram [3]. Unfortunately, at this moment specific treatment does not exist and, therefore, prevention is of primary importance. A high output pacing from the tip of the ablation catheter should be performed before applying RF

ablations at posterolateral segment of superior caval vein-right atrial junction, to avoid the damage of the right phrenic nerve [8]. During cryoballoon ablation, especially at the right PVs, continuous monitoring of diaphragm movement is essential and in case of decreased hemidiaphragm excursions at fluoroscopy and occurrence of hiccup and cough, further energy application should be immediately stopped [120, 190]. Clinical outcome of this complication is mainly auspicious. Spontaneous and complete recovery was registered in 81% of patients approximately seven months after the procedure [136, 190].

Vascular complications. Vascular complications of AF ablation occur at the vascular access site and present the most common complications of catheter ablation of AF with an incidence of 1.5% [123]. They include hematoma, arterial dissection, arteriovenous fistula, pseudoaneurysm and venous thrombosis at the vascular puncture site, mostly in the groins or in the subclavian region. These complications may lead to prolonged hospital stay, need for blood transfusion, or percutaneous vascular or surgical correction [193]. Women, older and obese patients, diabetics and patients subjected to repeated procedures could be particularly prone to occurrence of vascular complications [130].

Aggressive anticoagulation during the catheter ablation of AF, multiple large sheaths and prolonged procedure time make vascular complication rate higher than at the other electrophysiological procedures [3, 123]. Higher vascular complication rate also occurs with inexperienced operators at the start of the electrophysiological training [130]. Occurrence of vascular complications could be minimized with careful vascular access, manual hemostasis and observation of puncture site after the intervention. By changing the regimen of anticoagulation in the early post-procedural period and by the reduction of enoxaparin dose from 1 mg/kg twice a day to 0.5 mg/kg twice a day, the rate of vascular complications was significantly reduced from 5.7% to 1.6% [193]. Vascular complications often could be treated conservatively, by reversal of anticoagulation and echo-guided manual compression. However, treatment with artery stenting or vascular surgical reparation of blood vessel defect is sometimes required [3, 120].

Atrial tachycardia and flutter following AF ablation procedure. The incidence and mechanism of atrial tachycardia after catheter ablation of AF primarily depend on the ablation technique used in the first procedure and the type of AF before the ablation (paroxysmal vs. persistent) [194]. Atrial tachycardia could develop as a consequence of proarrhythmic effect of ablation due to incomplete circumferential or linear ablation, but also as a transitional atrial tachyarrhythmia from AF to sinus rhythm, resulting from the modification of substrate of AF and “organization” of AF to a regular tachycardia [25, 42]. Besides that, atrial tachycardia after ablation of AF could arise due to proarrhythmic effect of the class I and class III AADs [1]. Ablation limited to the ostial PV isolation is very rarely associated with a post-procedural atrial tachycardia, with an incidence of 2%-7.7% [7, 69, 194]. However, circumferential antral PV isolation, particularly if it is combined with additional modification of AF substrate, whether by the linear LA ablation and/or CFAE ablation, may lead to the occurrence of atrial tachycardia in 7.6%-44% of patients [24, 42, 54, 194-196]. After usage of similar ablative strategy (CFAE + PVI), post-procedural incidence of atrial tachycardia was remarkably higher after the ablation of persistent AF than after the ablation of paroxysmal AF (20.0% vs. 2.4%) [197].

Mechanism of atrial tachycardia generally is macro-reentry (42%-88%), and the arrhythmia is maintained by a large atrial circuit and conditioned by certain anatomical barriers (the atrioventricular annulus,

PV ostium) or by scar. Focal atrial tachycardias occur less frequently (12% to 37%) and originate from smaller and limited anatomical regions with centrifugal passive activation of remaining parts of the atrium [198, 199]. This type of tachycardia may be driven by different mechanisms, including an abnormal automaticity, trigger activity and micro-reentry (usually confined to an area of <2-3 cm). It is very important to keep in mind that even 70%-81% of patients suffer from multiple atrial tachycardias (1.8-3.4 per patient) and, not infrequently, those atrial tachycardias are very complex and in the form of double-loop reentry [200]. Macro-reentrant atrial tachycardia may occur in form of peri-mitral flutter (39%-61%), roof-dependent flutter (21%), macro-reentrant tachycardia around ipsilateral the PVs (9%-61%), typical peritricuspid atrial flutter (10%-15%) and scar-related atrial tachycardia [194, 199]. Typically, source of focal atrial tachycardia is located in the PV antrum (mostly near the previous ablation site), in inter-atrial septum, postero-inferior wall of the LA, the LA appendage and mitral isthmus [194]. Clinically, atrial tachycardia occurs early after the ablation procedure. One study showed that the average time for occurrence of atrial tachycardia was 3.2±3.1 months, while other authors noted an early occurrence, between 1-42 days from the procedure, in all patients [195, 200]. The early occurrence of atrial tachycardia (during the first 3 months) could be mediated by atrial inflammation, while subsequent maturation of ablative lesions in the first weeks after the procedure could lead to spontaneous disappearance of tachycardia in 39%-50% of patients [3, 120, 201]. The early occurrence of atrial arrhythmias after AF ablation could be reduced with antiarrhythmic or anti-inflammatory drugs, and in case of persistent forms, elective cardioversion should be performed [57-59]. Due to longer atrial cycle length, atrial tachycardia is usually followed by faster ventricular response and more severe symptoms than pre-procedural AF [194]. In extreme cases atrial tachycardia could cause progressive tachycardia-induced myocardial dysfunction and congestive HF. Generally, post-procedural atrial tachycardia poorly responds to AAD therapy, thus if atrial tachycardia does not subside spontaneously, it is necessary to perform repeated ablation [200].

Twelve-lead-electrocardiogram is not always reliable in predicting of anatomical origin of tachycardia because P-wave morphology after extended LA ablation could be considerably altered due to modified pathway of atrial activation [194]. The diagnosis is definitely made by an electrophysiological study, through conventional activation mapping and entrainment mapping [196]. The use of 3D-mapping systems may facilitate atrial tachycardia mapping and ablation [195]. Firstly, revision of all PVs as well as ablation lines has to be carried out, because up to 96% of patients actually suffer from tachycardia mediated by conduction gap at the incomplete ablation line from the first procedure [201].

Completing of the linear lesion and electrophysiological confirmation of bidirectional conduction block at the ablation line are very important for reducing the recurrence rate of atrial tachycardia. Namely, post-procedural rate of atrial tachycardia was 2-2.5 times higher among patients with incomplete linear lesions [202]. Acute success rate of ablation is 86%-100%, although during the one-year follow up recurrent atrial tachycardia could be expected in a considerable portion of patients (5% to 47%). However, in most of those patients (79%) a new type of atrial tachycardia was registered [194, 196, 200, 201].

CONCLUSION

Triggers and rotors within the PVs and on the posterior wall of the LA have dominant electrophysiological role in initiation and sustaining of episodes of lone AF. The concept of catheter ablation of AF consists of electrical isolation of the PVs in paroxysmal AF and an additional LA substrate modification in persistent AF. Creating a durable ablation lesion can be a challenge, and electrical reconnection of the PVs is the most common cause of AF reoccurrence. Long term rhythm control free of AADs is achieved in approximately 80% of patients, but often, for final result multiple procedures are necessary, especially in patients with persistent AF. Superiority of catheter ablation in comparison to pharmacological treatment comes to the fore in patients with paroxysmal type of the arrhythmia and after a failure of prior drug therapy. At this moment there is no strong evidence that catheter ablation can reduce mortality and risk of stroke. However, successful rhythm control after AF ablation can lead to significant recovery of systolic left ventricular function, especially in patients with true tachycardiomyopathy. In addition, AF ablation improves QoL and symptomatic status of the patients. Due to limited success, frequent need for re-intervention and a 1%-4% risk of life-threatening complications, such as cardiac tamponade, PV stenosis, atrioesophageal fistula or stroke, the procedure is presently reserved for selected AF patients. Younger patients with highly symptomatic paroxysmal lone AF represent the best candidates for the procedure. Although the new regimens of anticoagulation significantly reduce the risk of periprocedural thromboembolism without increasing the risk of bleeding, the optimal long term anticoagulation after the procedure is not clearly defined yet and the individual approach is necessary. The aim of the new technology development is to make ablation simpler, safer and more efficient, and thus feasible in majority of patients with AF.

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FIGURE LEGENDS

Figure 1. Catheter ablation of paroxysmal lone AF: PV isolation.

A 47-year-old male underwent catheter ablation due to a 10-year history of daily attacks of symptomatic paroxysmal lone AF, refractory to drug therapy with beta-blockers, sotalol, propafenone, and, finally flecainide. Echocardiography showed normal LA dimension (38 mm) and left ventricular ejection fraction (65%). Using the electroanatomical mapping system (Ensite NavX, St Jude Medical) with CT-image integration, geometrical LA 3D-map was reconstructed and irrigation radiofrequency ablation (red dots) was performed with en-block isolation of ipsilateral PVs.

Panel A: postero-lateral LA view with circumferential antral ablation encircling left sided PVs, circumferential diagnostic (Lasso) catheter is positioned within the left superior PV.

Panel B: voltage map of LA and PVs in sinus rhythm after PV isolation. Grey and violet colors represent electrically silent regions within the PVs and electrically healthy myocardium in the remaining part of LA, respectively.

Panel C: electrical isolation of PV in sinus rhythm, with abrupt loss of PV potential recorded by circumferential diagnostic catheter (yellow signals, labeled with white arrow).

Panel D: after PV isolation, the occurrence of spontaneous repetitive short bursts of atrial tachycardia within the "arrhythmogenic" PV is recorded by the Lasso catheter (yellow signals, labeled with white arrow). However, stable sinus rhythm is maintained, due to exit PV-LA block after ablation.

During the one-year follow-up after the procedure, the patient was free of AF without drug therapy.

AF=atrial fibrillation; LA=left atrium; CT=computed tomography; PV=pulmonary vein.

Figure 2. Catheter ablation of paroxysmal AF: elimination of non-PV triggers.

A 37-year old female patient has been referred for the second catheter ablation procedure due to highly symptomatic and frequent episodes of paroxysmal AF. In the index procedure fluoroscopically guided segmental ostial isolation of all PVs was successfully accomplished, however the patient experienced recurrence of AF in the following weeks. At the beginning of the redo procedure, all PVs were revisited and their stable electrical isolation was confirmed. Using the catecholamine challenge and pacing maneuvers, an ectopic focus in SVC was identified. Using irrigation radiofrequency catheter, electrical isolation of SCV was successfully achieved in association with AF noninducibility at the end of procedure. Over the follow up of 6 months the patient was free of symptomatic AF without antiarrhythmic drugs.

Panels A and B: fluoroscopic position of circumferential diagnostic catheter within the SCV and ablation catheter at the posterolateral aspect of SCV-atrial junction. Before RF application, high output pacing was performed to evaluate the proximity to right phrenic nerve.

Panel C: ablation at this site resulted in electrical isolation of SCV during sinus tachycardia, with elimination of SVC potentials at the Lasso catheter (white arrow).

AF=atrial fibrillation; PV=pulmonary vein; SCV=superior caval vein.

Figure 3. Catheter ablation of persistent AF: PV isolation and substrate modification.

A 57-year-old male presented with previously undiagnosed persistent AF with uncontrolled rate and symptoms and signs of congestive heart failure. Echocardiography revealed left ventricular systolic dysfunction with EF of 35% and moderate LA dilatation (44 mm), while coronary angiogram was normal. Treatment with amiodarone and a beta blocker as well as therapy for heart failure were instituted. Several months later he was subjected to catheter ablation of AF, due to the clinical suspicion of tachyarrhythmia-related cardiomyopathy.

Panel A: fusion of 3D anatomical LA map with CT image (Ensite NavX, St Jude Medical), posterior LA view (left side of image) and right lateral view (right side of image). Irrigation RF ablation (red dots) included circumferential antral PV isolation coupled with LA substrate modification by means of linear ablation. Linear set consisted of roof line + inferior line ("posterior box" lesion) and endocardial linear disconnection of coronary sinus.

Panel B: isolation of PVs during ongoing AF. Spontaneous slow automaticity within the PV was recorded (white arrow), while AF continued in the remaining part of the LA.

Panel C: during the LA linear ablation, AF has "organized" to an atrial tachycardia with fast ventricular response and further LA substrate ablation resulted in tachycardia termination with restoration of sinus rhythm. At the end of the procedure revision of all PVs and lines was performed to confirm the conduction block.

Three months following the procedure, echocardiography demonstrated complete recovery of the left ventricular systolic function (EF 60%) and all drugs, except beta blocker, were discontinued. Over the next 12 months, the patient was free of AF.

AF=atrial fibrillation; LA=left atrium; RF=radiofrequency; PV=pulmonary vein; EF=ejection fraction; CT=computed tomography.