Atrial Fibrillation: Electrophysiological Mechanisms and the Results of Interventional Therapy

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Summary

Atrial fibrillation (AF) is frequently initiated from the pulmonary veins (PVs), but little is known about the electrophysiological properties of PVs. In total, 77 patients (58 males; mean age 43.7 ± 11.5 years) with symptomatic AF were included in this study. In 14 patients, local ablation of arrhythmogenic foci or distal isolation (> 5 mm from the ostium) were achieved by targeting veins that trigger AF. In 63 patients, the PVs were isolated in the ostium at the opening to the left atrium. The PVs' effective and functional refractory periods were shorter than those of the left atrium and of non-arrhythmogenic PVs. AF was more frequently induced when pacing was performed in PVs than in the left atrium. Electrophysiological guided radiofrequency ablation (RFA) of AF was highly successful in patients with frequent ectopy. The use of electroanatomical mapping allowed for successful RFA in 80% of patients with persistent and chronic AF. This study demonstrates very distinctive electrophysiological properties of PVs in patients with AF. These PVs have a short or very short effective and functional refractory periods with decremental and slow conduction properties; they probably play a major role in arrhythmogenicity, particularly reentry in or around the PVs, which may perpetuate AF and thus act as a substrate for AF maintenance.

Key Words

Atrial fibrillation (AF), radiofrequency ablation (RFA), reentry mechanism, gold-tip RFA catheter

Introduction

Atrial fibrillation (AF) is the most common type of arrhythmia in clinical practice. Its negative clinical consequences are life-threatening thromboembolies, development of arrhythmogenic cardiomyopathies, and dramatically increased mortality rates among patients suffering from congestive heart failure [1,2]. New approaches to AF treatment are based on the application of modern class I and III antiarrhythmic drug therapy (AAT) that can maintain sinus rhythm after its restoration for 12 to 24 months only in 40% – 50% of patients with a stable form of AF [3].

Since 1982, one of most common surgical methods used in patients with tachysystolic AF was to create a total artificial heart block with the implantation of a dual-chamber and/or rate-adaptive pacemaker [4]. However, the latter method is only effective in patients without risk of thromboembolies, e.g., causing cerebral ischemia. In addition, several studies have demonstrated that an annual rate of 2% – 5% of patients undergoing radiofrequency ablation (RFA) of the His bundle and pacemaker implantation will experience sudden death [4].

A RFA therapy for AAT-refractory, symptomatic AF suggested by Cox in 1987 is the so-called MAZE operation that preserves sinus rhythm and excludes the risk of thromboemboly in more than 90% of patients (over 10 years) [5]. In Russia, such an operation was performed for the first time by L. Bockeria at the Bakoulev Center [6]. In 1998, Haissaguerre et al. suggested a concept to eliminate the AF triggers, i.e., ectopic foci in the pulmonary veins (PVs), by applying the RFA procedure [7]. Along with the new method of linear RFA in the left atrium (LA), it enables the efficient elimination of both the paroxysmal and stable forms of AF (Figure 1). The present study was conducted to explore the electrophysiological mechanisms

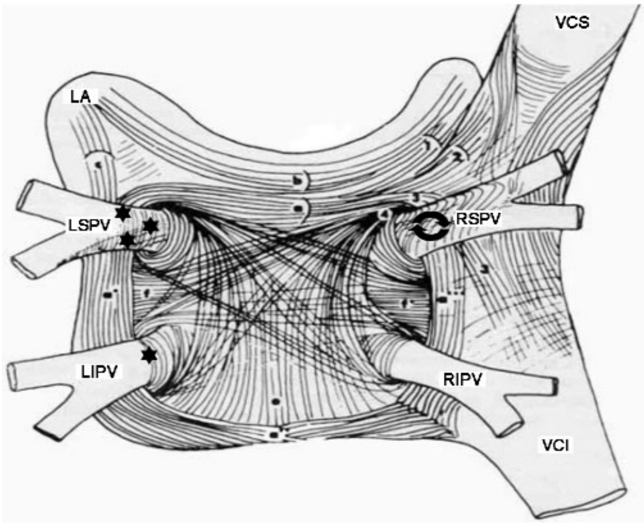

Figure 1. Anatomical structure of the pulmonary veins (PVs) opening into the left atrium (LA) and topical localization of atrial fibrillation triggers. VCS = vena cava superior; VCI = vena cava inferior; RSPV = right superior PV; LSPV = left superior PV; RIPV = right inferior PV; LIPV = left inferior PV; ✸ = ectopic foci in PV sleeves; ⟳ = re-entry mechanism in the RSPV.

Gender (m/f)	59/18
Age (mean ± standard deviation)	43.7 ± 11.5 years
AF age (mean ± standard deviation)	4 ± 3.5 years
Various antiarrhythmic drugs per patient	3 ± 1.5
Episodes of thromboemboly	4
Arterial hypertension	16
Post-myocarditis cardiosclerosis	27
Coronary artery disease	8
WPW syndrome	4
Type I atrial flutter	18
Paroxysmal AF	32
Persistent AF	36
Chronic AF	9

Table 1. Clinical characteristics of patients with documented atrial fibrillation (AF).

	AF patients		Control group		p-value
	No. of patients	Diameter (mm)	No. of patients	Diameter (mm)	
RSPV	58	19.1 ± 3.7	14	15.5 ± 2.7	< 0.02
LSPV	63	17.9 ± 1.4	11	15.4 ± 1.9	< 0.02

Table 2. Diameter of the right superior pulmonary vein (RSPV) and the left superior pulmonary vein (LSPV) in a subgroup of patients with atrial fibrillation (AF), i.e., arrhythmogenic pulmonary veins, and in the control group of patients without AF paroxysms measured with the contrast spiral computer tomography.

of AF in an electrophysiological laboratory and to develop new methods of radically eliminating all AF forms in a structurally normal heart.

Materials and Methods

From February 2000 to April 2003, 77 patients (59 male, mean age 43.5 ± 11.5 years) with the tachysystolic form of AF refractory to AAT (including Amiodarone) underwent an invasive electrophysiological investigation and the RFA procedure (Table 1). A fraction of 31% of the patients had syncopal and presyncopal episodes. In nine patients, Holter monitoring revealed episodes of distinctive bradycardia with the heart rate down to 31 – 33 beats/min on a background of frequent (bigemeny type) "blocked" atrial extrasystoles. In all patients, AAT was suspended 48 – 72 hours prior to the electrophysiological investigation. A transesophageal echocardiogram was performed on all patients to exclude thrombosis of the upper left atrium. Contrast spiral computer tomography (CT) was performed in 80% of the patients to study the topographic anatomy of PVs as well as to define the size of the left atrium and the degree of PV stenosis in the late follow-up period (Table 2). Indirect anticoagulants (phenylin, warfarine) under the international normalized ratio (INR = 2.0 – 3.0) control were administered for all patients 4 weeks before and 3 months after the procedure.

Electrophysiological Study

To study AF mechanisms, four different intracardiac multipolar leads were applied for electrical mapping in all patients. A decapolar lead (Biosense Webster, USA) was introduced into the coronary sinus via the left subclavian vein approach. A 20-polar lead was positioned along the crista terminalis of the right atrium, introduced by puncturing the left femoral vein. The LA and the PVs were mapped and paced after puncturing the atrial septum near the fossa ovalis by using a Brokenburg needle. The needle was inserted through the introducer by puncturing the right femoral vein. After a transseptal puncture with the aid of one or two

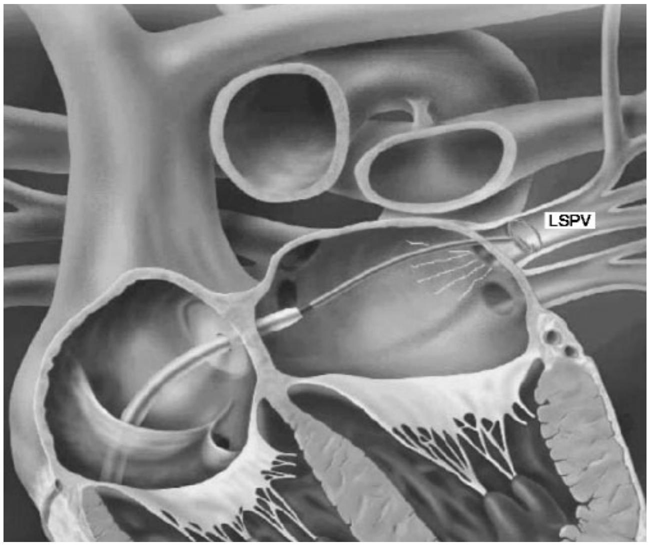

Figure 2. Invasive electrophysiological study of the pulmonary veins with the aid of a steering circular multipolar lead (Lasso catheter) positioned in the left superior pulmonary vein (LSPV).

Figure 3. Formation of atrial fibrillation via ectopic activity in the left superior pulmonary vein. Channels I, II, III = ECG leads; channel MAP = mapping lead in the right superior pulmonary vein; channels Lasso 1 – 10 = bipolar IEGM0 registered at the electrodes of the 20-polar Lasso catheter positioned in the left superior pulmonary vein; channel CS 9, 10 = bipolar IEGM registered from the coronary sinus. The arrow in channel Lasso 8 indicates the moment of atrial fibrillation triggered by the earliest spike of ectopic activity.

Preface 8F introducers (Biosense Webster), either a 7F quadropolar Marinr MC catheter (Medtronic, USA), an AlCath gold tip catheter (Biotronik, Germany), or a 7F irrigation cooled catheter Thermo cool (Biosense, Webster) were introduced for pacing and RFA isolation of the PVs. To register potentials around the PV ostium, circular 10- or 20-polar steering catheters (Lasso and Lasso 2515 with modified steerable diameter, Biosense Webster, USA) were applied (Figure 2). The ostium diameter and the anatomy of the PVs were measured by selective angiography in all patients and then compared with the data of 3-dimensional CT of the PVs. Immediately after transseptal puncturing, 0.5 mg/kg heparin was injected intravenously followed by titration to maintain an activation clotting time (ACT) > 300 s. The PV was considered to be arrhythmogenic with solitary or firing ectopic activity including also those with a subsequent episode of AF or atrial flutter (AFl) (Figure 3).

While registering potentials around the PV perimeter, double or multi-component spikes in sinus rhythm were documented in 75 patients. The first (low-frequency) spike reflects the activity of the LA wall, while the second is an intrinsic spike of electrical activity involving the muscular sleeve of the PV. To discriminate the LA and PV potentials (spikes) in complicated cases, the RA, the distal coronary sinus, or the LA appendage were paced. During the PV ectopic activity, a retrograde activation sequence was registered: the PV high-frequency spike was followed by the low-amplitude, low-frequency spike of the LA adjacent to the PV ostium (Figure 4).

RFA System

RFA was performed with the aid of the Atakr II (Medtronic, USA) and the EP Shuttle (Stockert, Germany) with a maximum temperature of 52°C at 25 – 40 W RF power. By using irrigated catheters, the temperature did not exceed 40 – 42°C at 25 – 40 W power and 17 ml/min physiologic bolus flow through the distal electrode. The duration of the RFA application in the affected region was 45 – 60 s. Electrophysiological characteristics of PVs were compared prior to and after the procedure:

- effective refractory period
- functional refractory periods
- fragmented activity
- pulse conduction time in the PV
- possibility of inducing AF or AFl

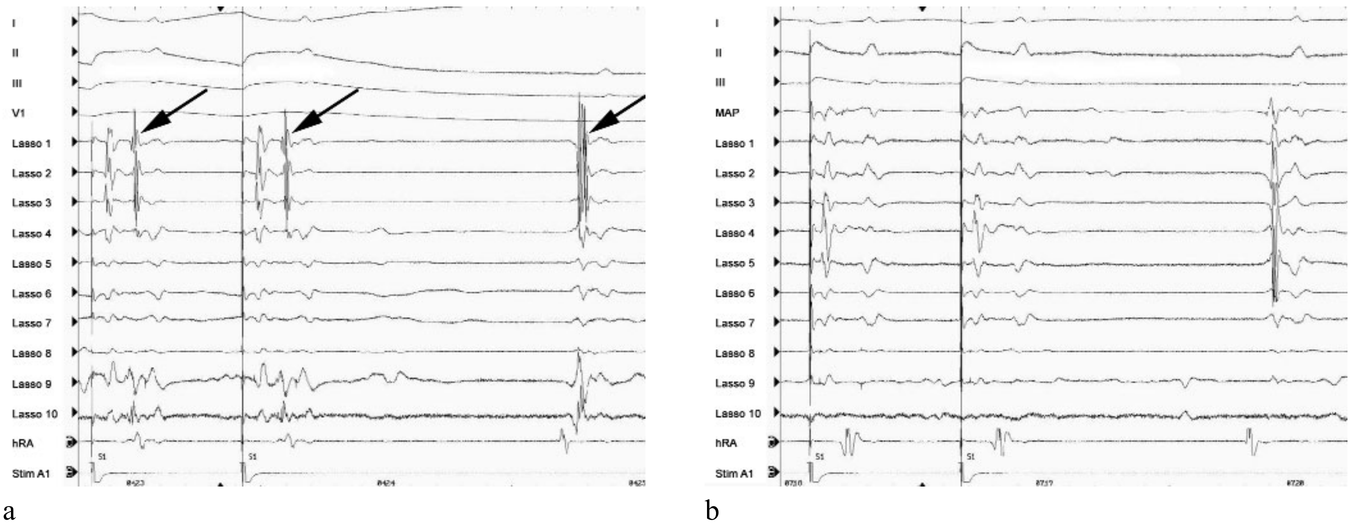

Figure 4. Patient's ECG and IEGM during coronary sinus pacing. Channels I, II, III, V1 = ECG leads; channels Lasso 1 – 10 = bipolar IEGM registered at the electrodes of the 20-polar Lasso catheter positioned in the left superior pulmonary vein; channel hRA = bipolar IEGM registered from the high right atrium; channel Stim A1 = coronary sinus pacing. The arrows indicate the high- frequency spikes of pulmonary vein activity prior to the radiofrequency ablation procedure (panel a) that was eliminated by the procedure (panel b).

Mapping System

In nine patients, AF mapping and RFA were performed with the aid of a nonfluoroscopic magnetic mapping system Carto (Biosense Webster) using 7F Navi-Star and Navi-Star Thermo-Cool (Cordis-Webster, USA) steering and irrigation catheters. The Carto system allowed online registration of electric potentials, measurement of the atrial activation time and of the signal amplitude, along with the three-dimensional localization of the mapping lead (Figure 5). Bi- and unipolar signals were registered at the steering lead with the reference catheter lead in the coronary sinus. Three-dimensional reconstruction of the LA and of the PVs was executed without any fluoroscopy within 10 – 15 min. The Carto system was operated along with a conventional 64-channel electrical registration system (Prucka Engineering, USA; or Elcart, Electropulse, Russia). A 4 – 12 channel ECG and up to 32 channel IEGM were registered simultaneously.

Follow-up Procedure after RFA

After the RFA of the PVs, 12-channel ECG Holter monitoring (several times) as well as transthoracal and transesophageal echocardiographs were performed. Contrast CT was repeated after 3 – 12 months of follow-up to reveal possible PV stenosis. Reduction of the PV ostium ≥ 50% was considered to be significant. Indirect anticoagulant warfarine under INR control was administered for all patients over the 3-month follow-up whereas AAT was administered upon indications. The follow-up period was 1 to 39 months (mean 15 ± 11.4 months).

Results

AF was more frequently induced when pacing was performed in PVs than in the LA. Thus, the main ablation goal was total electrical isolation of the PV to eliminate propagation of electrical (normal and ectopic) activity from the PV into the LA. In total, 104 RFA procedures were performed to eliminate AF in the study patients. In all of 198 PVs studied (Figure 6), veins were circularly mapped by introducing a Lasso catheter from the ostium distally into the vein until electrical activity disappeared. Thus, the dimensions of the PVs' muscular sleeves were determined. In the first 14 patients, RFA of the PVs was performed 5 – 7 mm from the ostium: in two of them, only the ectopic focus was ablated, while the PVs were totally isolated around the entire perimeter in the remainder. In 63 patients, the PVs were isolated in the ostium, exactly at the opening to the LA. RFA was applied at sinus rhythm or coronary sinus pacing in the region of

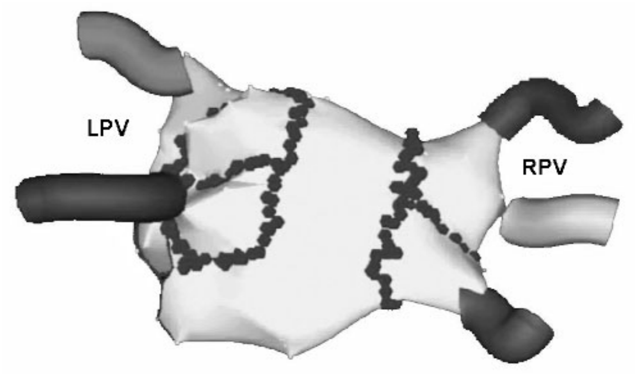

Figure 5. Method of linear radiofrequency ablation executed with the aid of the nonfluoroscopic Carto mapping system (Biosense Webster, USA). A scheme of the modified "MAZE" procedure performed to isolate the pulmonary veins in a patient with chronic atrial fibrillation. The dots indicate the ablation zones. LPVs = left pulmonary veins, RPVs = right pulmonary veins.

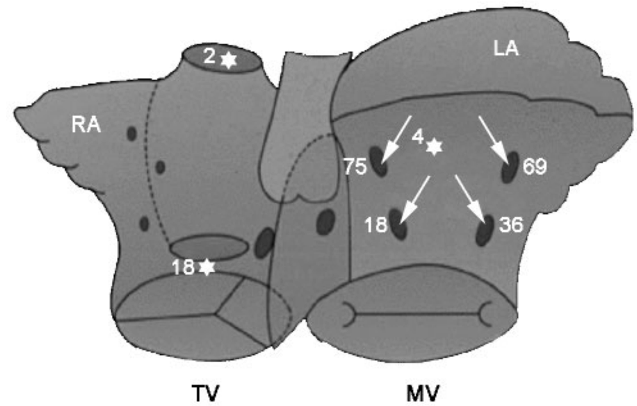

Figure 6. Localization of a total of 198 arrhythmogenic foci in isolated pulmonary veins (PVs) in the study patients with atrial fibrillation. In two patient, the ostium of the vena cava superior was isolated to eliminate the ectopic foci (✱) in its muscular sleeve. In 18 patients with type I atrial flutter, a bidirectional block was created in the right inferior isthmus of the heart. LA = left atrium, RA = right atrium, MV = mitral valve, TV = tricuspid valve.

the earliest activation of the PV sleeve that was theoretically divided clockwise into 12 sectors. In each case, total electrical isolation of the PV from the rest of the LA was successful. Application of the Lasso circular catheter enabled us to study clinical electrophysiology of PVs and paroxysmal AF:

- In 72% of cases, ectopic activity is registered in the upper PVs to certain extent due to their large diameter and length of muscular sleeves (from 1.5 to 3.0 cm).
- Besides ectopic activity as well as triggering and maintaining AF and AFl paroxysms, reentry is also an important electrophysiological mechanism for forming and sustaining AF (Figure 7).
- In RFA isolation of the upper PVs, 72% – 88% of patients need ablation of 60% – 100% of the PV ostium perimeter.

The latter result underlines once more the diversity in anatomic structure of PV muscular sleeves and the benefit of a circular, multipolar catheter in reducing RFA time from 15 min down to 7 – 8 min. With the RFA parameters used in our study, formation of PV stenosis ≥ 30% was excluded. Note that application of other ablation methods in PVs, including application of high energy in the median and distal parts of the PVs, in 7% – 42% of cases (mean 11%) is accompanied by stenosis and a consequent necessity of balloon angioplasty and stenting [8,9]. Electrically isolated PVs were characterized by three different forms of electrical activity:

- In 30% of cases, episodes of electrical activity of low rhythm, AF or AFl were preserved (Figure 7a).
- In 70% of patients, electrical activity was eliminated, as a rule, by the RFA procedure in inferior PVs.
- Arrhythmogenic PVs, including also those isolated from the LA by RFA, had significantly lower functional refractory periods and effective refractory period in comparison to nonarrythmogenic PVs (Figure 8).

In nine patients with chronic AF, we were able to eliminate effectively the arrhythmia and preserve sinus rhythm during the period of 2 to 4 years with the aid of the Carto system. Presently, comparable results of effective RFA therapy in patients with AAT refractory paroxysmal and persistent forms of AF have been achieved in several clinics worldwide. Positive results, i.e., stable sinus rhythm after the operation, is registered in 50% – 70% of patients without AAT, and in 80% – 86% of patients with AAT which has been ineffective before RFA [11-15].

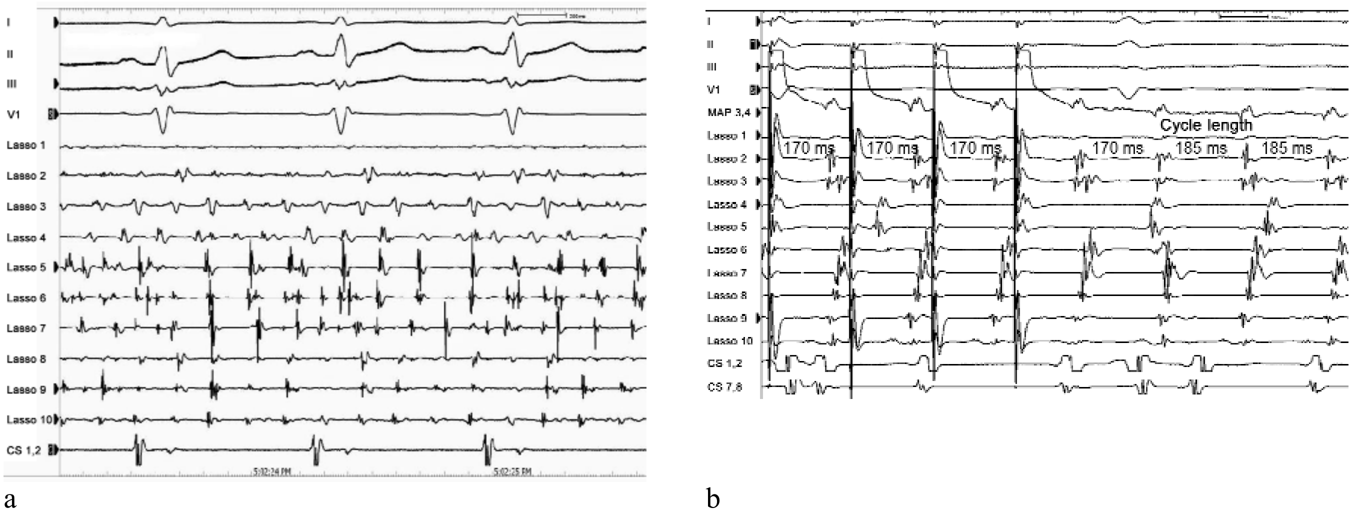

Figure 7. Results of the radiofrequency ablation of the arrhythmogenic right superior pulmonary vein. Panel a) A restoration of sinus rhythm was documented (channels I, II, III, V1 = ECG leads; CS 1,2 = bipolar IEGM registered from the coronary sinus) while the pulmonary vein remains arrhythmogenic (channels Lasso 1 – 10 = bipolar IEGM registered at the electrodes of the 20-polar Lasso catheter positioned in the left superior pulmonary vein). Panel b) Entrainment effect in the right superior pulmonary vein after its electrical isolation due to radiofrequency ablation, which confirms the role of the pulmonary vein muscular sleeve reentry mechanism in sustaining atrial fibrillation and atrial flutter.

Discussion

With the application of new catheter leads and RFA system positive therapeutic results were achieved in 82% patients over the follow-up period, which extended up to 3.3 years. This approach to treating AF by eliminating trigger mechanisms, i.e., ectopic foci in the PVs, is effective for so-called paroxysmal ectopic supraventricular tachycardia as well as AF if the volume of the LA does not exceed the normal value. In patients with sustained AF and, in particular, those with chronic forms of AF, we used the linear RFA procedure in the region of the left inferior isthmus or the modified endocardial MAZE procedure in addition to the isolation of PVs. This was necessary due to the dominating role of the LA in AF maintenance for the latter patient group.

To date, the rate of repetitive interventions in our patient group has been 38%, which is similar to the data of other studies [10]. This is due to the limited RFA regimen used, which resulted in 0% PV stenosis in the late follow-up period. The preferable ablation method seems to be the irrigation and cooled RFA with the aid of special irrigation catheters. Our first clinical experience with the gold-tip ablation catheter on PV isolation produced results comparable to those with the cooled RFA. We did not register any differences in the course and efficiency of RFA while in sinus rhythm or during the AF episode. In the later case, it is mandatory to isolate electrically the most arrhythmogenic vein (superior PVs, as a rule) in the first stage of the operation.

Conclusion

Application of new technologies in AF electrophysiological diagnostics makes it possible to reveal the mechanisms that help form and sustain arrhythmia to determine the so-called arrhythmogenic PVs. Muscular PV sleeves have specific electrophysiological characteristics that pre-condition the formation of paroxysmal AF. It is necessary to repeat the RFA procedure in 40% of patients to ensure total and stable electrical PV isolation that will also exclude their stenosis (due to special RFA regimens). Application of the linear RFA procedure as well as the modified MAZE procedure with the aid of the Carto nonfluoroscopic mapping system offers a tool for the successful elimination of sustained and chronic AF forms when the LA volume does not exceed 180 ml (measured by contrast spiral CT). Randomized studies will be necessary in the near future to confirm the effectiveness of

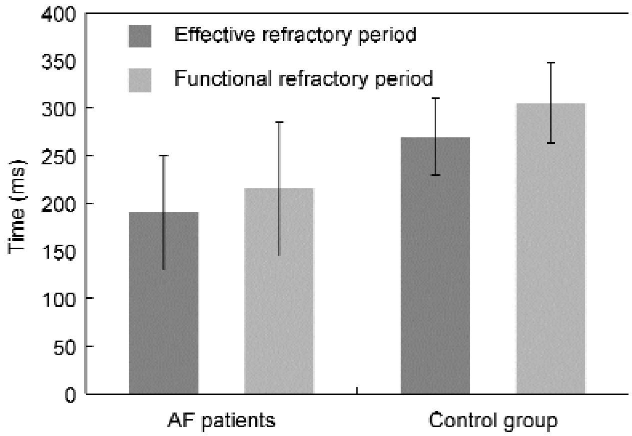

Figure 8. Electrophysiological parameters of the pulmonary veins in patients with atrial fibrillation (AF, N = 63) and in the control group without atrial fibrillation paroxysms (N = 14).

interventional methods in AF therapy, to choose the optimal method of ablating the arrhythmogenic substrate, and to implement this method in conventional clinical practice.

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