# COMPARISON OF THE CONTACT FORCE SENSING RADIOFREQUENCY AND THE CRYOBALLOON ABLATION EVALUATING CLINICAL OUTCOME AND PRESENCE OF IATROGENIC ATRIAL SEPTAL DEFECT

**Ph.D. thesis**

**Zsófia Nagy MD**

Clinical Medicine Doctoral School

Semmelweis University



Supervisor: Attila Kardos, MD, Ph.D.

Official reviewers: István Osztheimer, MD, Ph.D.
Péter Kupó, MD, Ph.D.

Head of the Complex Examination Committee:
Zoltán Járai, MD, Ph.D.

Members of the Complex Examination Committee:
Zsolt Piróth, MD, Ph.D.,
Endre Zima, MD, Ph.D., med. habil.

Budapest
2021

# 1 INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia with irregular atrial activation and ineffective atrial contraction. AF is recognized worldwide as a major cause of stroke, heart failure, sudden death, and cardiovascular morbidity, affecting between 2% and 4% of the general population. The integrated management of AF requires a complex approach, including optimized stroke prevention, symptom control with rate and/or rhythm control, and management of cardiovascular risk factors and comorbidities. Rhythm control therapy aims to restore and maintain sinus rhythm and is recommended to improve symptoms and quality of life in symptomatic AF patients.

Catheter ablation of AF has been a continuously evolving procedure since its introduction in the 1990s. However, there is still insufficient reliable information on the development of AF and the maintaining mechanisms, and there is extensive active research in this field of electrophysiology. Catheter ablation treatment has stimulated and responded to this growing body of knowledge. Over the last decade, many novel ablation strategies have developed, leading to technological advances, new catheter designs, innovations in electro-anatomical mapping (EAM) systems, and the advent of alternative energy sources. Nowadays, catheter ablation treatment of AF offers a safe therapeutic option for an increasingly wide range of patients and has an improving clinical success rate.

According to the current AF guidelines, electrical isolation of the pulmonary veins (PVs) is the cornerstone of AF catheter ablation and the only established endpoint for the first ablation procedure. The two most widely used ablation techniques for pulmonary vein isolation (PVI) are the contact force (CF) sensing radiofrequency (RF) ablation and the cryoballoon (CB) ablation.

Point-by-point ablation with an irrigated-tip RF catheter combined with a 3D EAM system can significantly reduce the fluoroscopy dosage and provide additional information by creating a left atrial (LA) activation and voltage map. In addition, with the recently developed CF sensing ablation catheters, the

operator can optimize tissue heating and thus achieve a more durable lesion set and improve procedural outcomes.

CB ablation is a single-shot ablation modality that has become the most commonly used alternative ablation method for PVI. Although the CB technique is a faster and simpler procedure than RF ablation, it may have the disadvantage of a significantly higher radiation dose due to the PV angiography required to demonstrate the PV occlusion by the balloon. The learning curve of the CB technology is steep, and the procedure is less operator-dependent; hence less experienced operators can achieve PVI in low-to-medium volume electrophysiology centers. However, the fixed size and shape of the balloon make it less adaptable to different PV anatomies. Furthermore, as the CB is a single-shot device suitable only for isolating the PVs, additional ablation targets require replacing the ablation set-up.

After left-sided cardiac procedures, such as catheter ablation of AF, iatrogenic atrial septal defect (IASD) is a relatively common phenomenon, but not much is known about IASD-related morbidity and complications. The spontaneous closure rate of IASDs after catheter ablation of AF is high, so IASD closure is only necessary in sporadic cases. The presence of IASD can lead to paradoxical embolism and stroke, especially in the setting of thrombi in the venous system. However, limited data are available on the risk of cerebrovascular accidents in patients with IASD.

## 2 OBJECTIVES

Our research project aimed to investigate the following:

1. Firstly, we aimed to compare the efficacy and safety of the CF sensing RF ablation and the second-generation CB ablation. We performed a single-center, retrospective study including patients with paroxysmal AF undergoing catheter ablation procedure for the first time. We evaluated the main procedural parameters and the clinical follow-up (FU) data obtained over two years after the ablation procedure.

2. Secondly, we investigated the presence of IASD after AF ablation. Our prospective study called "EVITA" (**EV**aulation of **I**atrogenic a**T**rial sept**A**l defect) aimed to describe the incidence and echocardiographic characteristics of IASD diagnosed by transoesophageal echocardiography (TOE) following CF sensing RF or CB ablation at 3 months and 12 months FU visits. In addition, we sought to examine the incidence of cerebrovascular accidents caused by paradoxical embolism associated with post-interventional IASD.

# 3 METHODS

Study protocols were approved by the Hungarian Ethics Committee and were following the declarations of Helsinki.

## 3.1 Study group

### 3.1.1 "Clinical outcome" patient group

This non-randomized, retrospective, single-center study included 98 symptomatic patients with drug-refractory, paroxysmal AF from September 2012 to December 2013, who underwent PVI using either RF energy with CF sensing ablation catheter ($n$=58) or the CB catheter ($n$=40) for the first time.

### 3.1.2 "EVITA" patient group

Our prospective, single-center cohort study enrolled 94 consecutive, symptomatic, drug-refractory patients with paroxysmal AF between July 2014 and September 2016. An index procedure of PVI using the CF sensing RF catheter (n=48) or the CB catheter (n=46) was performed in all cases. Exclusion criteria were regarded as previously performed transseptal puncture (TSP), previously documented atrial septal defect or patent foramen ovale, congenital heart disease, pregnancy, LA thrombus before the procedure, and any contraindications to TOE and/or ablation procedure.
The ablation technique of choice in both patient groups depended on the operator's preference, in agreement with the patient. All patients provided written informed consent before the procedure.

## 3.2 Transseptal puncture and ablation technique of cryoballoon ablation

All CB ablation procedures were performed using the second-generation 28 mm CB catheter (Arctic Front Advance™, Medtronic, Minneapolis, MN, USA). A single TSP was accomplished with a Brockenbrough needle (BRK-

1™, St. Jude Medical, St. Paul, MN, USA) placed in the SL0 standard transseptal (TS) sheath (SL0™, St. Jude Medical, St. Paul, MN, USA) under fluoroscopic and/or intracardiac echocardiography (ICE) guidance. The inserted SL0 sheath is then replaced with a steerable TS sheath (FlexCath Advance™; Medtronic, Minneapolis, MN, USA) with an inner diameter of 12 Fr and an outer diameter of 15 Fr over the wire. After that, the CB and the circular mapping catheter (Achieve Mapping Catheter™, Medtronic, Minneapolis, MN, USA) were inserted through the sheath into each PV ostium, and complete PV occlusion was achieved by PV angiography. Initial cryoablation of 240 seconds was applied to each vein at temperatures no colder than minus 55-60°C. If complete isolation of PVs was not achieved based on the intracardiac electrograms, further cryo applications were performed. In order to prevent phrenic nerve damage, the diaphragmatic motion was routinely monitored during cryoablation of the right superior pulmonary vein (RSPV).

### 3.3 Transseptal puncture and ablation technique of radiofrequency ablation

For the RF ablation procedures, CF sensing catheters (Navistar Thermocool SmartTouch®, Biosense Webster Inc., Diamond Bar, CA, USA) and the CARTO® system (BiosenseWebster Inc., Diamond Bar, CA, USA) for 3D EAM were employed. Two different TSP techniques were used during the procedure; a single and a double TSP method.

A single TSP technique with Brockenbrough needle and SL0 TS sheath was performed under fluoroscopic and/or ICE guidance. Subsequently, a multipolar, steerable, circular mapping catheter (Lasso®Nav, Biosense Webster Inc., Diamond Bar, CA, USA) was placed in the SL0 TS sheath, positioned in the left superior pulmonary vein (LSPV), and the sheath was retracted into the right atrium. Then, from a separate femoral venous puncture, an 8.5 Fr non-steerable or steerable (Agilis™ NxT, St. Jude Medical, St. Paul, MN, USA) long sheath was inserted over the wire in the superior vena cava, gently redrawn, and stabilized against the interatrial septum. After the guidewire of the sheath was inserted into the LA at the previous TSP site, the

second long sheath was also guided into the LA through the TS defect along the shaft of the Lasso catheter.
In the case of a double TSP, after inserting the Lasso catheter into the SL0 TS sheath, a second TSP with a Brockenbrough needle was applied to gain second access to the LA using a non-steerable or steerable long sheath. The CF sensing ablation catheter was guided into the LA in this long sheath in the next step. The RF ablation catheter was set to power-controlled mode, with a maximum power of 25 W on the posterior wall and 35 W in the other regions of the LA. A maximum temperature of 48°C was adjusted. CF parameters were measured in real-time during the procedure.
Conscious sedation was used during all ablation procedures. Before the first TS access, complete anticoagulation with intravenous heparin bolus was given and repeated as necessary to achieve an activated clotting time above 300 seconds.
Figure 1. shows the position of the TS sheaths and ablation catheters during RF and CB procedures.

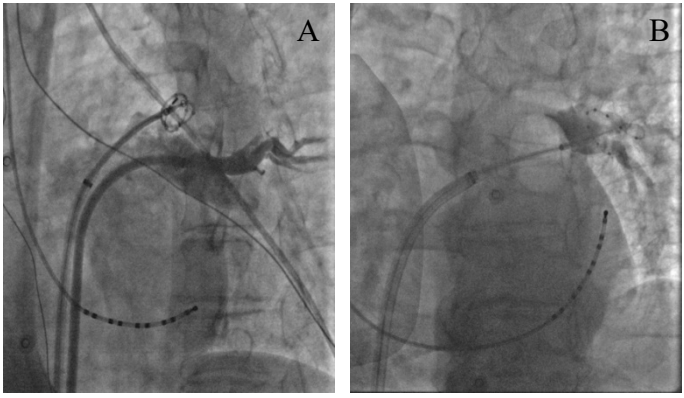


*Figure 1. Fluoroscopic LAO 30° views of the position of the transseptal sheaths during radiofrequency (SLO and Agilis) (A) and cryoballoon (FlexCath) (B) procedure. Electrophysiology Laboratory, Gottsegen National Cardiovascular Center*

### 3.4 Follow-up

At 3, 6, and 12 months after the ablation procedure, and every six months after that, all patients were recalled for outpatient clinical visits, including physical examination, 12-lead electrocardiogram (ECG), 24-hour Holter, and/or 1-week transtelefonic ECG monitoring. A 3-month blanking period was used in the studies. AF recurrence was defined as atrial tachycardia/AF/atrial flutter lasting >30 seconds, and any symptoms similar to previous AF episodes were considered as AF recurrence. The success rate was defined as the percentage of patients with no documented AF episodes during the FU period or no evidence of AF recurrence after the blanking period.

### 3.5 Transoesophageal echocardiography

In all patients in the “EVITA” group, the day before ablation, TOE was performed to exclude LA thrombus, confirm an intact atrial septum and assess LA and PV anatomy. TOE was obtained at the 3-month FU also to confirm persistent IASD. In patients who were proven to have IASD at the 3-month FU, TOE was repeated at the 12-month FU. We used a color Doppler technique and an echo contrast solution to detect persistent IASD. The incidence, diameter, and shunt flow of IASD were assessed at 3 and 12 months after CB (single TSP) or RF (single or double TSP) ablation. The main clinical and echocardiographic parameters were compared in patients with and without IASD at the 3 and 12-month FU, hereafter known as patients in the "IASD" or "NoIASD" group.

### 3.6 Statistical analysis

Continuous variables were expressed as mean ± standard deviation, and comparisons between groups were made using the two-sided $t$-test after testing for normal distribution with the method of Kolmogorov and Smirnov. The probability of freedom from AF was calculated using Kaplan-Meier survival analysis, and differences between groups were determined with the log-rank statistic test. Binary endpoints were multivariate modeled using logistic regression, and time-to-event endpoints were determined using a Cox proportional hazard model. Continuous covariates were first augmented with restricted cubic splines and checked for deviations from linearity. A value of $p<0.05$ was considered significant. All analyses were performed in the R statistical software package version 3.6.0 (R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

# 4 RESULTS

## 4.1 Baseline demographic and clinical characteristics

Both study groups included symptomatic patients with paroxysmal AF refractory to at least one antiarrhythmic drug (AAD) undergoing catheter ablation for the first time. The "clinical outcome" study group involved 98 patients [33 (33.7%) women, mean age=60±10 years] who underwent AF ablation (CB: 40, RF: 58) from September 2012 to December 2013. The „EVITA" study group enrolled 94 consecutive patients [30 (31.9%) women, mean age=60±9.7 years]. The procedure of PVI with CF sensing RF (n=48) or CB catheter (n=46) was achieved between July 2014 and September 2016. The investigated clinical and echocardiographic parameters did not differ between the different ablation groups (RF or CB) in any of the study groups.

## 4.2 Procedural Data

In both study groups, the procedure time, which is defined as the time from venous puncture to removal of sheaths, was significantly shorter with CB ablation than with RF ablation (in the „clinical outcome" study group: CB: 74.3±17.0 min vs. RF: 120.1±49.2 min, $p<0.05$; in the „EVITA" study group: CB: 66.0±18.3 min vs. RF: 99.0±25.5 min, $p<0.001$). In the „clinical outcome" study group, fluoroscopy times were similar using both ablation techniques (CB: 14.4±7.1 min vs. RF: 16.0±5.5 min, $p=0.45$). In contrast, in the „EVITA" study group, fluoroscopy time was significantly shorter in the RF group (CB: 11.6±4.4 min vs. RF: 8.6±5.7 min, $p=0.004$). There was no significant difference in radiation exposure between the ablation groups in the „clinical outcome" study group (CB: 666.7±379.7 vs. RF: 557.7±353.1 $cGycm^2$, $p=0.11$). However, in the „EVITA" study group, CB ablation resulted in a higher radiation exposure to control PV occlusion after contrast administration (CB: 988.1±770.4 vs. RF: 620.1±554.6 $cGycm^2$, $p=0.016$).

In the "clinical outcome" study group, 98% (39 out of 40) of patients in the CB group and 96% (56 out of 58) of patients in the RF group had a complete PVI during the procedure.

The 28 mm CB was used during all CB procedures. Left common pulmonary vein (LCPV) was confirmed in 3/40 patients in the CB group. The mean number of CB applications per PV was 1.5±0.8 for LSPV, 1.3±0.6 for left inferior pulmonary vein (LIPV), 1.5±0.8 for RSPV, 1.7±0.9 for right inferior pulmonary vein (RIPV) and 2.0±1.3 for LCPV. The minimum balloon temperature indicative of balloon-tissue contact was significantly "warmer" in the inferior PVs: LSPV: -49.5±6°C vs. LIPV: -44.6±7°C ($p<0.05$) and RSPV: -50±7°C vs. RIPV: -41±10°C ($p<0.001$).

The CF and force-time integral (FTI) values indicating real-time catheter-tissue contact were continuously monitored during the RF procedures. With non-steerable sheaths, lower FTI values were observed in the anterior and inferior region of the left PVs and the posteroinferior part of the right PVs than in the other PV regions (illustrated in Figure 2.).

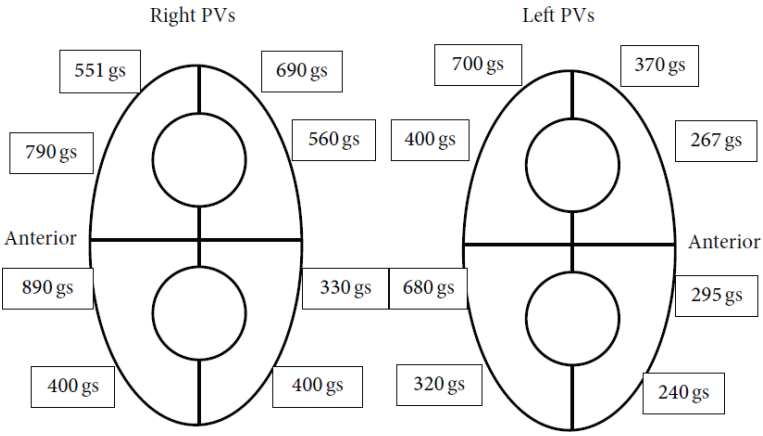


*Figure 2. Distribution of mean force-time integral (FTI) values (gs) per PV quadrant in the RF group. Electrophysiology Laboratory, Gottsegen National Cardiovascular Center*

The periprocedural complication rate was low in both studies. In the "clinical outcome" study group, there was one case of pericardial tamponade requiring pericardiocentesis during RF ablation and 3 cases of transient phrenic nerve palsy during CB ablation. In the "EVITA" study group, 2 patients in the CB ablation group developed transient phrenic nerve palsy, and no major complications occurred during RF ablation. No death, stroke, or transient ischaemic attack occurred during any of the procedures.

## 4.3 Iatrogenic atrial septal defect

In the "EVITA" study group, we examined the followings:

### 4.3.1 Incidence of IASD at the 3 and 12-month follow-up

At the 3-month TOE, IASD was observed in 17/94 (18.1%) patients [RF: 9/48 (18.8%), CB: 8/46 (17.4%), p=0.866]. In the RF group, IASD was detected in 6/30 (20%) patients after single TSP compared to 3/18 (16.7%) patients after double TSP (p=0.780). The mean IASD diameter was 2.2±1.1 mm in the RF group and 2.5±1.4 mm in the CB group (p=0.624). All IASDs showed spontaneous left-to-right shunt flow. Based on the 12-month repeat TOE, the IASDs had a spontaneous closure rate of 82.4% (14/17 patients). Two of 46 patients in the CB group (4.3%) and 1/48 (2.1%) patients in the RF single TSP group had persistent IASD (p=0.529). Table 1. summarises the incidence of IASD 3 and 12 months after the procedure.

*Table 1. Incidence of iatrogenic atrial septal defect at the 3-and 12-month follow-up. Abbreviations: CB: cryoballoon, IASD: iatrogenic atrial septal defect, RF: radiofrequency, TSP: transseptal puncture*

| **IASD incidence at 3- and 12-month follow-up** | | |
|---|---|---|
| | 3 month, *n* (%) | 12 month, *n* (%) |
| Study population (*n*=94) | 17 (18.1) | 3 (3.2) |
| RF (*n*=48) | 9 (18.8) | 1 (2.1) |
| RF, single TSP („sliding technique") (*n*=30) | 6 (20.0) | 1 (3.3) |
| RF, double TSP (*n*=18) | 3 (16.7) | 0 (0.0) |
| CB (*n*=46) | 8 (17.4) | 2 (4.3) |

### 4.3.2 Clinical characteristics of patients with and without IASD

Patients with IASD at the 3-month FU had a significantly higher body mass index than patients without IASD (32.4±6.1 vs. 28.9±4.2, p=0.01). The "IASD" and "NoIASD" groups did not show differences in the other clinical and the main echocardiographic parameters during the 3- and 12-month FU periods (Table 2.).

*Table 2. Risk factors of iatrogenic atrial septal defect at the 3-month and 12-month follow-up. Abbreviations: IASD: iatrogenic atrial septal defect*

| **Study population at 3-month follow-up (*n*=94)** | | | |
|---|---|---|---|
| | NoIASD (n=77) | IASD (n=17) | *p* value |
| Women, *n* (%) | 25 (32.5) | 5 (29.4) | n.s. |
| Age (years) | 59.5 ± 9.4 | 64.7 ±10.0 | n.s. |
| Hypertension, *n* (%) | 53 (70.1) | 11 (70.6) | n.s. |
| Body mass index | 28.9 ± 4.2 | 32.4 ± 6.1 | *p*=0.01 |
| Left ventricular ejection fraction (%) | 51.8 ± 5.2 | 59.4 ± 8.7 | n.s. |
| Left atrial diameter (mm) | 41.3 ± 6.2 | 42.9 ± 5.3 | n.s. |

| Study population at 12-month follow-up with patients who presented with IASD at 3-month follow-up (n=17) | | | |
|---|---|---|---|
| | NoIASD (*n*=14) | IASD (*n*=3) | *p* value |
| Women, *n* (%) | 5 (35.7) | 0 | - |
| Age (years) | 63.2 ± 10.1 | 71.4 ± 6.6 | n.s. |
| Hypertension, *n* (%) | 9 (64.3) | 2 (66.7) | n.s. |
| Body mass index | 32.5 ± 6.4 | 31.6 ± 5.0 | n.s. |
| Left ventricular ejection fraction (%) | 58.8 ± 9.2 | 63.0 ± 4.2 | n.s. |
| Left atrial diameter (mm) | 43.7 ± 7.7 | 40.5 ± 5.4 | n.s. |
| Stroke/paradoxical embolism | 0 | 0 | - |

### 4.3.3 Predictors of IASD at the 3-month FU

In the multivariate model of IASD at the 3-month FU, ablation method, sex, and LA size were not significantly predictive of the occurrence of IASD (p=0.895, p=0.438, and p=0.854, respectively). However, age was predictive (p=0.049, 7.1% higher odds of having IASD at 3 months for each year increase in age, 95% confidence interval: 1.00–1.15).

### 4.3.4 Relationship between IASD and AF recurrence

In the multivariate model for AF with IASD as a – time-varying – covariate, the effect of IASD was not significant on the hazard of the onset of AF (p=0.321) after controlling for age, sex, LA size, and ablation method.

## 4.4 Cerebrovascular events

In the “EVITA” study group, no patients with IASD had a cerebrovascular event after the index PVI procedure in any ablation group.

### 4.5 Atrial fibrillation recurrence

Freedom from AF without AAD treatment in the "clinical outcome" study group 12 months after ablation was 77.5% (45/58) in the RF group and 80% (32/40) in the CB group, and then changed to 65.5% (38/58) in the RF group and 67.5% (27/40) in the CB group at the 24-month FU. In the EVITA study group, at 12 months FU, 34/48 (70.8%) patients in the RF group and 31/46 (67.4%) patients in the CB group were free of AF recurrence without AAD therapy (p=0.72). No significant difference in clinical success rate was observed between the two ablation groups in either study group.

### 4.6 Redo ablation procedures

In the "clinical outcome" study group, a total of 22 patients underwent a redo ablation (RF: 15, CB: 7) 13.3±7.8 months after the initial procedure. In the "EVITA" study group, a total of 9 patients required redo ablation, 6/48 (12.5%) patients after RF and 3/46 (6.5%) patients after CB ablation, a mean of 10.4±4.6 months after the index procedure (p=0.33). All redo procedures were performed using RF energy in either study group.

### 4.7 Pulmonary vein reconnections

In the „clinical outcome" study group, in the RF group, 37 of the 60 PVs (61%) in 15 patients (2.5 per patient), while in the CB group, 10 of the 28 PVs (35%) in 6 patients (1.4 per patient) showed PV reconnection gaps (p=0.01). The reconnection rates per vein in the RF group were: LSPV: 53% (8/15), LIPV: 66% (10/15), RSPV: 40% (6/15) and RIPV: 87% (13/15). In one patient after CB ablation, all PVs were isolated, and therefore non-PV foci were ablated. In the CB group, inferior PVs (LIPV and RIPV) were frequently reconnected (12/14 veins in total, 86%). In contrast, conduction gaps were documented in the superior PVs (RSPV and LSPV) in only one patient.

# 5 CONCLUSIONS

Based on our retrospective analysis, the second-generation cryoballoon and the contact force sensing radiofrequency catheter ablation techniques have similar safety profiles and a comparable single procedure success rate over the two-year follow-up period. As a single-shot device, cryoballoon ablation provides significantly shorter procedure time than the radiofrequency ablation technique. After cryoballoon ablation, late reconnection of the inferior pulmonary veins was predominantly confirmed, which correlated with the minimum balloon temperature indicating balloon-tissue contact. Following radiofrequency ablation, pulmonary vein reconnection was mostly detected in the anterior-inferior segments of the left pulmonary veins and in the inferior and inferoposterior parts of the right inferior pulmonary vein, with the lowest force-time integral values in the anterior part of the left pulmonary veins.

Iatrogenic atrial septal defect is a moderately common phenomenon in the early postprocedural period following atrial fibrillation ablation. In our prospective study, the ablation technique did not influence the incidence of iatrogenic atrial septal defect at three-month follow-up with transoesophageal echocardiography. During radiofrequency ablation, the single or double transseptal puncture technique did not significantly affect the presence of iatrogenic atrial septal defect. Iatrogenic atrial septal defects demonstrated a high spontaneous closure rate in the first year after the procedure. No cerebrovascular events were recorded in our patient cohort during the 12-month follow-up period.

# 6 BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

**Nagy Z**, Kis Z, Geczy T, Temesvari A, Som Z, Borbas S, Breuer T, Molnar D, Foldesi C, Kardos A. (2019) Prospective evaluation of iatrogenic atrial septal defect after cryoballoon or radiofrequency catheter ablation of atrial fibrillation-"EVITA" study. J Interv Card Electrophysiol, 56: 19-27. **IF: 1.277**

**Nagy Z**, Kis Z, Som Z, Foldesi C, Kardos A. (2016) Catheter ablation for paroxysmal atrial fibrillation: new generation cryoballoon or contact force sensing radiofrequency ablation?. Orv Hetil, 157: 849-854. **IF: 0.349**

Kardos A, Kis Z, Som Z, **Nagy Z**, Foldesi C. (2016) Two-Year Follow-Up after Contact Force Sensing Radiofrequency Catheter and Second-Generation Cryoballoon Ablation for Paroxysmal Atrial Fibrillation: A Comparative Single Centre Study. Biomed Res Int, 2016: 6495753. **IF: 2.476**