CEREBRAL SAFETY AND LESION EFFICACY OF RADIOFREQUENCY ABLATION OF ATRIAL FIBRILLATION

PhD thesis book (short version)

Márton Boga, MD

Semmelweis University Doctoral School

Cardiovascular Medicine and Research Division

Supervisor:	Nándor Szegedi, MD, PhD
Official reviewers:	Attila Kardos, MD, PhD Péter Kupó, MD, PhD

Head of the Complex Examination Committee: István Édes, MD, PhD, med. habil.

Members of the Complex Examination Committee: Gábor Bencsik, MD, PhD
István Osztheimer, MD, PhD

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1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with increased morbidity, mortality, and reduced quality of life. Pulmonary vein isolation (PVI) is the most effective treatment for AF, with point-by-point radiofrequency (RF) ablation being one of the most widely used techniques.

Factors associated with the recurrence of AF after PVI are well known; however, there is a gap in the evidence regarding technical predictors for chronic PV reconnection (PVR). PVRs represent the primary failure of PVI procedures and are responsible for the majority of AF recurrences and repeated ablation procedures, thus worsening patient outcomes and wasting healthcare resources. The CLOSE protocol is an ablation strategy aiming to create continuous isolation circles based on ablation index (AI) and interlesion-distance (ILD) targets. Despite its growing use, data is scarce on how adherence to this approach impacts the long-term durability of PVI when evaluated through repeated electrophysiological studies. Previous research has shown that achieving first-pass isolation (FPI) is linked to better ablation success rates. Additionally, some studies suggest that the baseline generator impedance (BGI) at individual ablation points may influence the efficacy of RF ablation. However, their role in the durability of PVI has not yet been explored. Therefore, we investigated key predictors of long-term PVR following PVI procedures to support ongoing efforts to improve the efficacy of AF ablation.

The most recent technology for modern RF PVI is very high-power short-duration (vHPSD) ablation, which enables RF delivery with 90W of power for 4 seconds per ablation point. The vHPSD ablation is much quicker than conventional techniques, but its advantages need to be coupled with efficacy and at least non-inferior safety to be considered a better method than lower power settings. The efficacy and esophageal safety of 90W ablation have been previously demonstrated in several studies; however, concerns remained regarding its embolic risk. Stroke is a severe but rare complication of PVI; while its surrogate, silent cerebral embolism (SCE), which can be detected by brain magnetic resonance imaging (MRI), is much more frequent. Two initial studies of vHPSD ablation found an unexpectedly high SCE incidence of 24-26%, while the SCE rates described for low-power ablation are much lower (6-16%). Given that with vHPSD ablation, the left atrial dwell time is shorter, the lesion formed is smaller, and steam-pop is less frequent, we had not expected such a high SCE incidence compared to LPLD ablation. We hypothesized that vHPSD PVI with short left atrial time and adequate intraprocedural anticoagulation would be associated with a low incidence of symptomatic and MRI-detected asymptomatic cerebral events.

The ideal AI and interlesion distance ILD thresholds are well-established for low-power ablation. In contrast, AI is not available for vHPSD ablation, and there is limited evidence regarding the factors that influence both the immediate and long-term success of PVI performed with 90 W. Prior data indicate that vHPSD creates smaller lesions in terms of both width and depth when compared to traditional lower-power settings, suggesting a need to reassess ILD targets for the high-power approach. While BGI and RF current have been proposed to affect lesion size, as lower impedance may lead to higher current and therefore larger lesions, their potential influence on the continuity of ablation lines has not yet been explored.

2. Objectives

2.1. Predictors of PV reconnections

We aimed at identifying predictors of PV reconnections, including adherence to the CLOSE protocol, first-pass isolation, and baseline generator impedance.

2.2. Cerebral safety of vHPSD ablation

Our objective was to evaluate the incidence of procedural complications of vHPSD atrial fibrillation ablation, focusing on cerebral safety, and to evaluate predictors of silent cerebral embolisms.

2.3. Ablation parameters of vHPSD ablation

The objective of our secondary analysis was to evaluate the association of ablation parameters of vHPSD ablation with gaps in the ablation circles, and to determine optimal interlesion-distance targets.

3. Methods

3.1. Catheter ablation procedures

Ablation procedures were performed under conscious sedation with midazolam, propofol, and fentanyl. Femoral vein puncture was followed by fluoroscopy and pressure measurement-guided double transseptal puncture. After the first transseptal puncture, heparin was administered at a dose according to body weight. Further dosing was performed according to ACT measurements every 20 minutes; the target ACT was at least 300 seconds. An anatomical map of the left atrium was created using an electroanatomical mapping system (CARTO 3, Biosense Webster Inc., Diamond Bar, CA, USA) along with a multipolar mapping catheter (Lasso, PentaRay or OctaRay, Biosense Webster Inc., Diamond Bar, CA, USA). Point-by-point PVI was carried out using a steerable sheath and a CF sensing ablation catheter (either SmartTouch or QDOT Micro, Biosense Webster Inc., Diamond Bar, CA, USA). After completing the initial encirclement, the achievement of FPI was evaluated using the multipolar mapping catheter. If isolation was incomplete, additional "touch-up" ablations were performed until full PVI was established.

3.2. Predictors of PV reconnections

This retrospective, observational study enrolled patients who underwent their first PVI using the CARTO system and also had a repeat procedure due to AF recurrence. The primary outcome of the study was the presence of pulmonary vein reconnection observed during the repeat ablation procedure. At initial procedures, the power settings and adherence to the CLOSE protocol were determined at the operator's discretion. Energy delivery followed either a low-power long-duration (LPLD) approach with 30–35 W settings or a HPSD strategy at 40–50 W, with consistent power settings maintained throughout each procedure. All operators performed both CLOSE-guided and non-CLOSE PVI procedures. For CLOSE-guided ablations, the objective was to create wide, contiguous circumferential lesions around the ipsilateral pulmonary veins, with ILDs ≤5 mm and an AI target of ≥400 on the posterior wall and ≥500 on the anterior wall. Adherence to the CLOSE protocol was assessed by reviewing CARTO maps, and CLOSE compliance was confirmed when a continuous lesion set with the specified ILD and AI thresholds was achieved. After the initial procedure, patients were followed according to standard clinical practice, with 12-lead electrocardiograms and 24-hour Holter monitoring conducted at 3, 6, and 12 months, as well as in response to any arrhythmia-related symptoms. All participants included in this analysis experienced symptomatic AF recurrence

and subsequently underwent a repeat ablation procedure. Repeat procedures were performed using either a decapolar Lasso or a PentaRay catheter (Biosense Webster Inc., Diamond Bar, CA, USA) alongside a contact force-sensing ablation catheter. PVR was identified when near-field electrical signals were detected within the pulmonary veins using the multipolar mapping catheter.

3.2. Cerebral safety of vHPSD ablation

In this prospective, observational, single-center study, we included 328 patients undergoing their first PVI procedure with the QDOT Micro catheter (Biosense Webster, Inc., Irvine, CA, USA) using the QMODE+ setup (90 W for 4 seconds). A subgroup of participants underwent brain MRI within 24 hours after the procedure to screen for potential SCE. The primary outcomes of this study were procedure-related cerebral complications: stroke, TIA, and SCE. A subgroup of consecutive patients, without contraindications to MRI and who underwent their procedures between July 2022 and April 2023, received MRI within 24 hours after PVI. Imaging was conducted on a 1.5 T MR scanner (Magnetom Aera, Siemens). SCEs were identified by detecting new ischemic lesions demonstrating restricted diffusion on diffusion-weighted images (DWI) and apparent diffusion coefficient (ADC) maps.

3.3. Ablation parameters of vHPSD ablation

Patients in this study underwent 90 W PVI, and three months after the initial procedure, left atrial high-density mapping was performed in all participants to evaluate the long-term durability of PVI, as part of the "HPSD Remap" study.

During index procedures, all ablation sites corresponding to first-pass conduction gaps and acute PVR (following a 20-minute waiting period after ablation) were documented. A protocol-mandated electrophysiological study was performed in all patients three months after the initial ablation, regardless of the presence or absence of symptoms. Chronic PVR was assessed based on high-density voltage maps. Reconnection sites were precisely annotated and compared to the original ablation maps to localize the initial lesion sites associated with reconnection. Data from the CARTO system were used to extract ablation parameters from the initial procedures for further analysis. The collected parameters included: application duration (seconds), average power delivered (W), peak temperature reached (°C), baseline generator impedance (Ω), impedance drop (Ω), minimum contact force (g), mean contact force (g), maximum contact force (g), and the inter-lesion distance (mm) between adjacent ablation points. From these values, additional parameters were calculated: total radiofrequency energy delivered (J), average RF current applied (A), and total electrical charge delivered (C).

4. Results

4.1. Predictors of PV reconnections

One hundred patients meeting inclusion and exclusion criteria were included in this study. The mean age was 60 ± 12 years, with women representing 36% of the cohort, and 44% of patients with persistent AF. Of these patients, 38 underwent an initial PVI strictly following the CLOSE protocol, while 62 received non-CLOSE PVI. Thirty procedures were carried out with high-power settings (40–50W), and 70 with low-power settings (30–35W). Baseline characteristics did not differ significantly between the CLOSE and non-CLOSE groups.

Repeat procedures occurred on average 23 ± 16 months after the initial PVI, during which 200 PV pairs (373 PVs in total) were assessed. PVR was detected in 192 of 373 PVs (51.5%). The distribution of PVRs was: left superior PV – 21.9%, left inferior PV – 19.3%, left common trunk – 3.6%, right superior PV – 29.2%, right inferior PV – 27.6%, and right middle PV – 2.6%. In 17 of 100 patients, all PVs remained isolated at the repeat procedure.

Patients and procedures with complete PV isolation were compared to those with at least one PVR. Factors associated with durable PV isolation included adherence to the CLOSE protocol (88% vs. 28%, $p < 0.001$), presence of FPI (88.2% vs. 40.4%, $p = 0.001$), use of higher power (37.5W vs. 30W, $p = 0.028$), and lower BGI (127.6 Ω vs. 136.6 Ω, $p = 0.003$). In the case of CLOSE-guided PVI the PVR rate per PV was significantly lower (26.1% vs. 68.3%, OR = 0.16, 95% CI: 0.10–0.26, $p < 0.001$) and the proportion of patients with all PVs isolated was significantly higher (39.5% vs. 3.5%, OR = 18.26, 95% CI: 2.00–4.47, $p < 0.001$).

Comparisons between CLOSE and non-CLOSE procedures revealed differences in fluoroscopy time (4.7 vs. 5.8 minutes, $p = 0.047$), radiation dose (152.6 vs. 232 uGym², $p = 0.033$), number of RF applications (72 vs. 82, $p = 0.020$), and FPI rate (73.7% vs. 25%, $p < 0.001$). Procedure time, left atrial dwell time, and BGI were not significantly different.

Analysis of 6562 ablation points showed significantly higher mean BGI in procedures with PVR (136.6 Ω vs. 127.6 Ω, $p = 0.003$). ROC analysis identified a BGI of 130 Ω as the optimal threshold for predicting PVR (AUC = 0.74, 95% CI: 0.61–0.87, $p = 0.003$), with 77.1% sensitivity, 68.8% specificity, 68.75% positive predictive value, and 75.44% negative predictive value. The odds of PVR were significantly increased when mean BGI was ≥130 Ω (OR = 6.76, 95% CI = 1.98–20.63, $p < 0.001$).

Bilateral FPI, documented in 70 procedures, was associated with lower PVR rates and higher likelihood of complete PV isolation (OR = 0.32, 95% CI = 0.19–0.53, $p < 0.001$; and OR = 7.26, 95% CI = 1.92–25.1, $p = 0.006$, respectively). Bilateral FPI also correlated with adherence

to the CLOSE protocol, higher power settings, smaller PV-pair perimeters, fewer RF applications, and lower BGI. Side-specific analysis showed that FPI of either left or right PVs reduced the chance of PVR (OR = 0.15 and 0.14, respectively) and increased the likelihood of complete isolation on the respective side (OR = 19.2 and 15.7, respectively).

Variables with $p < 0.1$ in univariate analysis predicting ≥1 PVR included CLOSE adherence, high-power settings, bilateral FPI, BGI ≥130 Ω, and catheter type. Multivariable logistic regression demonstrated that independent predictors of at least one PVR were CLOSE protocol adherence (OR = 0.055, $p = 0.019$) and BGI ≥130 Ω (OR = 16.09, $p = 0.016$), with the model showing strong discriminative ability (AUC = 0.900, positive predictive value = 83.33%, negative predictive value = 87.23%).

4.2. Cerebral safety of vHPSD ablation

A total of 328 consecutive patients were included in the study. The mean age of the participants was 62 ± 14 years, with females comprising 36% of the group. Paroxysmal atrial fibrillation was present in 70% of patients. Prior to the procedure, 16 individuals (5%) had a documented history of stroke or TIA. The average CHA_2DS_2-VASc score across the cohort was 3 ± 2.

Across the entire study cohort, the average procedure duration was 69.6 ± 24.1 minutes, while the mean left atrial dwell time was 46.5 ± 21.5 minutes. Intra-procedural cardioversion was required in 68 cases (20%). Within the bMRI subgroup, patients received an average of 79 ± 21 radiofrequency applications, totaling 309 ± 85 seconds of ablation time. The mean irrigation fluid volume was 146 ± 42 mL, and the average ACT was 324 ± 38 seconds. In the total population, acute PVI was achieved in 100% of cases, while FPI was successful in 82%. At six months, the arrhythmia-free survival rate based on standard monitoring was 84.5%.

No cases of clinically manifest stroke or TIA were observed among the 328 procedures. Vascular access complications occurred in seven instances, including one arteriovenous fistula, one pseudoaneurysm, and five groin hematomas. Two cases of pericardial tamponade were reported, both successfully managed with percutaneous pericardiocentesis. There were no incidents of phrenic nerve injury or clinically significant esophageal complications, and no audible steam pops were recorded during any procedure.

In the subgroup undergoing screening for SCE, brain MRI was performed at a median of 18 hours post-procedure (IQR: 16–22 hours). SCE was identified in 5 out of 61 patients (8.2%). Four patients presented with a single DWI-positive lesion measuring between 2 and 9 mm, while one patient had multiple small lesions (2–4 mm) in the frontal lobe.

No significant procedural differences were observed between cases with and without SCE. In total, 4,773 ablation points were assessed. Procedures in which SCE occurred were characterized by significantly lower baseline generator impedance (105.8 vs 112.6 Ω, $p < 0.001$) and lower minimum contact force (5.9 vs. 7.1 g, $p < 0.001$). Additionally, the frequency of catheter–tissue contact loss was notably higher (14.1% vs. 6.1%, $p < 0.001$). Both maximum temperature (49.2 vs. 48.4°C, $p < 0.001$) and temperature rise during ablation (15.2 vs. 14.3°C, $p < 0.001$) were significantly elevated in SCE-positive procedures.

ROC analysis of baseline generator impedance yielded an AUC of 0.753 (95% CI: 0.726–0.781, $p < 0.001$). A baseline impedance value of 110 Ω was found to be the optimal cut-off point, offering a sensitivity of 73.9%, specificity of 64.9%, a positive predictive value of 16.5%, and a negative predictive value of 96.4%. The likelihood of SCE was significantly increased in cases of loss of catheter–tissue contact (OR = 2.53, 95% CI = 1.87–3.43, $p < 0.001$) and when the baseline impedance was below 110 Ω (OR = 5.23, 95% CI = 4.16–6.56, $p < 0.001$).

4.3. Ablation parameters of vHPSD ablation

Twenty patients were included in the study, all undergoing 90W PVI followed by a protocol-mandated repeat electrophysiological assessment three months after the index procedure. The average age was 65 ± 8 years, 45% were female, and 43% had persistent AF. The mean procedure time was 75.6 ± 12.9 minutes, with bilateral FPI achieved in 82.5% of cases. No major complications were reported. A total of 1357 ablation points were assessed.

FPI gaps were observed in 4 patients, affecting 7 sites and 19 ablation points. Acute PVR occurred in 1 patient, involving 1 site and 6 points, while chronic PVR was seen in 4 patients, affecting 11 sites and 20 points. Gaps were more frequently located at anterior segments (OR = 2.53, p = 0.008), and a right-sided location showed a non-significant trend towards more gaps (OR = 1.78, p = 0.072). Parameters with significant differences were ILD (3.3 vs 4.0 mm, p < 0.001), baseline generator impedance (112 vs 114 Ω, p = 0.018), mean current (858.4 vs 854.7 mA, p = 0.006), total charge (3.43 vs 3.4 C, p = 0.004), and LOC: 2.7% vs 13.3% (p = 0.002).

ROC analysis was used to identify the optimal ILD cut-off for predicting gaps, yielding a value of 3.5 mm (AUC = 0.61, 95% CI = 0.52–0.69, p = 0.016). ILDs >3.5 mm were associated with a significantly higher likelihood of gaps or reconnections (OR = 6.24; 95% CI = 2.94–13.24, p < 0.001). For anterior and posterior regions separately, optimal cut-offs were 3.5 mm (OR = 6.61, p < 0.001) and 4 mm (OR = 8.71, p < 0.001), respectively.

Variables with p < 0.05 were included in multivariable logistic regression models. Due to strong multicollinearity ($R^2 > 0.99$, VIF > 200) between application time, mean power, generator

impedance and the derived variables (total energy, mean current, total charge), six separate models were developed using only one of the correlated variables in each, along with ILD >3.5 mm, LOC, and anterior location. All variables remained independent predictors in all of the models. Out of the separate models, the one with total charge showed the highest predictive value (AUC = 0.745, $p < 0.001$). Among all predictors, LOC had the strongest association with the presence of gaps.

5. Conclusions

We identified that both non-adherence to the CLOSE protocol and a baseline generator impedance of ≥130Ω are independent predictors of PV reconnections. Our findings confirm that vHPSD radiofrequency ablation offers a favorable cerebral safety profile, characterized by a low incidence of SCEs and high acute procedural success. Baseline generator impedance <110Ω and intermittent loss of catheter-tissue contact during ablation may increase the likelihood of SCEs. In addition, key factors influencing lesion contiguity during vHPSD ablation include ILD, consistent catheter contact, energy delivery, as well as current and charge – all of which are affected by generator impedance. Achieving durable PVI with vHPSD requires smaller ILDs than those typically recommended for lower-power ablation strategies. Finally, given the fixed application time in vHPSD ablation, using smaller ILDs for anterior wall lesions appears necessary in comparison to posterior applications.

6. Bibliography of the candidate's publications

6.1. Publications related to the PhD thesis

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