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- "AF HeartTeam" Guided Indication for Stand-alone Thoracoscopic Left Atrial Ablation and Left Atrial Appendage Closure.
- Clinical and Procedural Effects of Transitioning to Contact Force Guided Ablation for Atrial Fibrillation.
- Robotic Navigation Showssuperior Improvement Inefficiency for Atrial Fibrillation Ablation.
- Atrial Fibrillation in Heart Failure Patients with Preserved or Reduced Ejection Fraction Prognostic Significance of Rhythm Control Strategy With Catheter Ablation.
- Comparison of Cryoballoon and Hybrid Surgical Posterior Wall Isolation for Persistent Atrial Fibrillation to Conventional Ablation.

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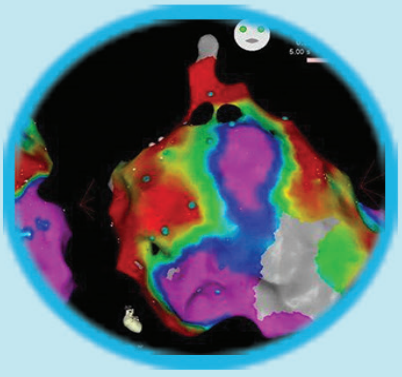

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Optimizing Access to Care and Outcomes in Atrial Fibrillation

Dhanunjaya (DJ)Lakkireddy
MD, FACC, FHRS
Editor-in-Chief

Dear Colleagues

Welcome to the May issue of the Journal of Atrial Fibrillation. Hope you had a relaxing Spring Break. At the Journal we are actively revamping the editorial board, organizational structure and the website. We have several energetic new editorial board members that will be coming on board. A new refreshed website will be launched in the next few weeks. We sincerely apologize for the inconvenience and the manuscript uploading issues we have faced in the last few months.

HRS 2019 is just a week away. Congratulations to the organization on reaching the 40-year milestone. Special thanks to Thomas Deering MD, outgoing President and Mr. James Youngblood, the outgoing CEO for their service. On behalf of the editorial board I would also like to congratulate the incoming HRS President Andrea Russo MD and the new CEO Ms. Patricia Blake. The late breaking clinical trials sound very exciting and ooking forward to the new science that is being explored.

In this issue of the Journal we have several interesting manuscripts one the impact of contact force on atrial fibrillation ablation outcomes; work flow optimization on improving access to AF care through emergency rooms and improving the lab efficiencies. The hybrid approach for ventricular tachycardia throws new insights into the pathophysiology and the potential role of collaboration between electrophysiologists and cardiac surgeons. Sharma etal presented a case series on incomplete left atrial occlude endothelialization in patients with mitral regurgitation Toro ketal showed the impact of remote magnetic navigation on the incremental improvement of AF ablation process and outcomes.

We wish you a great Summer.

Best wishes

DJ Lakkireddy

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Barriers to Emergency Department Utilization of AFIB Protocol in Uncomplicated Lone AFIB Patients-Results from an Online Survey Study

Britt T[1], Janson JP[1], Knisely T[1], LaBond VA[1]

[1] *Genesys Regional Medical Center One Genesys Parkway Grand Blanc, MI 48439 .*

Abstract

Background: Historically, atrial fibrillation (AFIB) management has focused on rate control and anticoagulation, necessitating hospital admission. Recently, some emergency departments (EDs) have implemented protocols to avoid hospital admission when managing lone AFIB. Despite this recent trend, there is still reluctance toward the implementation of these protocols by some emergency physicians (EPs).

Objective: This study investigates barriers to implementation of ED AFIB protocols by surveying which aspects may impede their use.

Methods: To analyze the perceived barriers from EPs, we formulated a survey assessing the various components of ED AFIB management to identify which aspects might impede EP utilization. It was distributed as an email to large national ED physician group. Data was analyzed using descriptive means and weighted averages.

Results: Of 185 respondents (response rate 6.1%), 17.4% already had AFIB protocols in place at their home institutions and 82.6% did not. Majority opinion of largest barriers toward the implementation of AFIB protocols were the extended ED length of stay and discharge with unclear follow-up. There was little concern with chemical and electrical cardioversion and very limited concern with rate control and initiating oral anticoagulation. EPs supported placement in Observation for implementation and involvement of discharge planning to establish prescriptions and follow-up.

Conclusions: EP input regarding the development of ED AFib protocols will be essential in order to develop cost effective, convenient and safe methods of treatment. This survey of EP suggests that ED length of stay and insuring close outpatient follow up are key issues to address as protocols are designed. reduce procedure and fluoroscopy times.

Introduction

Atrial Fibrillation (AFIB) is a common cardiovascular arrhythmia effecting 2.6-6.1 million Americans, and 9% of Americans greater than 65[1]. In addition to high disease prevalence, AFIB also carries a healthcare burden of 750,000 annual hospital visits and 130,000 annual deaths, costing the US healthcare system roughly six billion dollars per year[1].

AFIB is the most commonly diagnosed arrhythmia in US emergency departments[2,3]. The classical management of atrial fibrillation in the emergency setting consists of either heart rate control with anticoagulation or heart rhythm control with electrical or chemical cardioversion. Traditionally, emergency physicians (EPs) and Advanced Practice Providers (APPs) have opted for the former method, often starting patients on rate controlling and anticoagulant drips, requiring subsequent admission and transition to oral medications. This has resulted in high admission rates for AFIB as well as a significant cost burden to the US healthcare system[4,5].

Key Words

Utilization, Protocol, Cardioversion, Fibrillation, Pharmacology

Corresponding Author
Virginia Ann LaBond,
Genesys Regional Medical Center One Genesys Parkway Grand Blanc,
MI 48439

With the current US health care trends shifting away from hospitalization and toward outpatient management there has been an increased emphasis on ED management of AFIB with subsequent discharge home when possible[5]. This method has been shown to be both safe as well as offering significant cost reduction[6]. One retrospective analysis evaluated 35,255 combined inpatients and outpatients to compare annual costs of management in both settings, and found the average inpatient cost to be $11,307 versus an outpatient cost of $2,827 when AFIB was the primary diagnosis. This cost differential was also present when AFIB was a secondary diagnosis, costing $5181 for inpatient management and $1376 for outpatient management, respectively[7].

In response, hospital emergency departments have been taking steps to create protocols to safely identify candidates of ED treatment and discharge home with further management in the outpatient setting. One such protocol developed by Mansour et al. at Massachusetts General Hospital looked at 382 patients with AFIB over a one year period and was found to greatly reduce admissions (15% admission versus historical 79%)[5]. In the aggressive Ottawa protocol for AFIB, 385 patients with new onset (<48hr) AFIB were retrospectively evaluated after being electrically and chemically cardioverted with 42% and 91% discharge rates, respectively, with no deaths or cerebrovascular accidents[8].

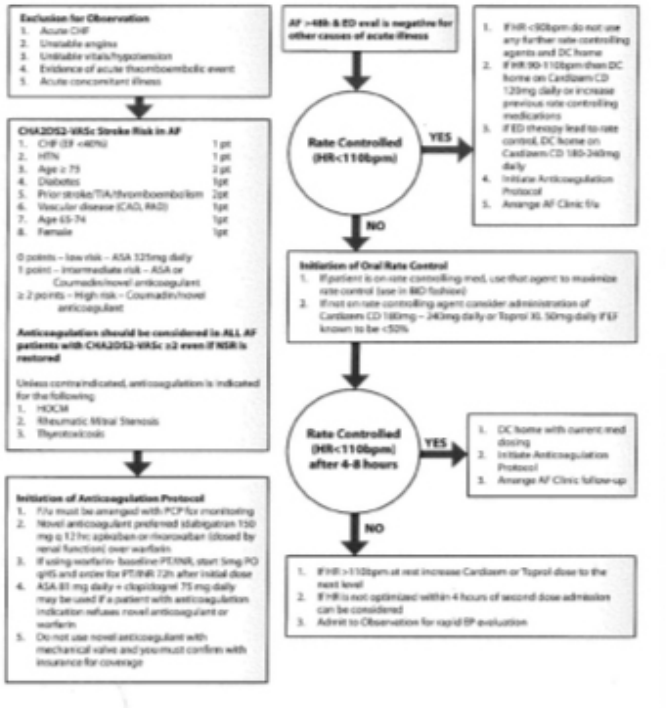

Figure 1: **AFIB Less Than 48 Hour Protocol**

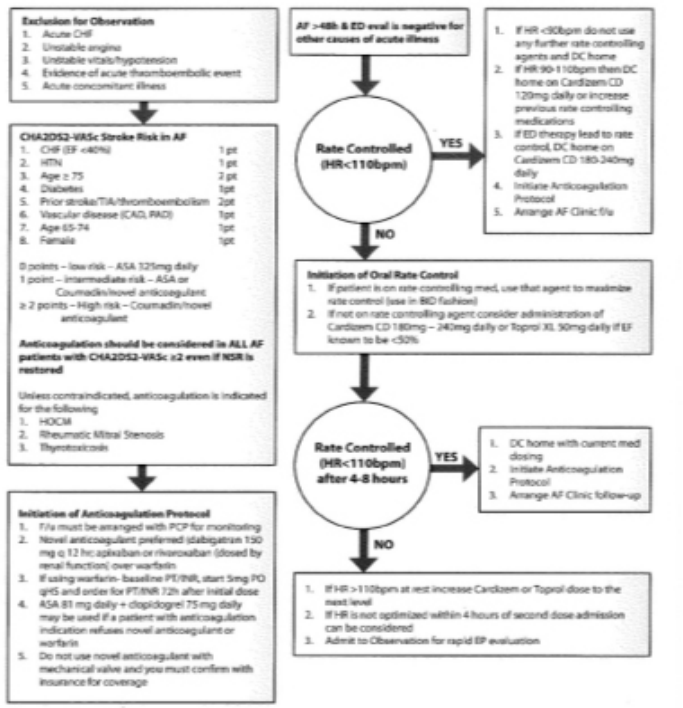

Figure 2: **AFIB Greater Than 48 Hour Protocol**

Despite success in discharging these patients, many EPs still opt for inpatient management, posing a significant barrier to changing traditional management practices. These barriers consist of increased length of stay while in the ED, inability to establish appropriate follow up, concern when initiating anticoagulation without clear follow-up, and concern surrounding electrical or chemical cardioversion. To evaluate these barriers, we designed an online survey distributed to various emergency departments throughout the country to evaluate barriers to the implementation of AFIB protocols.

Methods

Surveys (online supplement A) were created using an online survey software. Respondents were first asked to identify themselves as residents, attendings, or APPs. Next, they were asked if they had a protocol in place in their home institution. Sample protocols for ED AFIB management were provided for both less than and greater than 48 hours of AFIB onset for reference ([Figure 1] and [Figure 2]). If no protocol was in place in the respondent's home institution, they were asked to answer questions using the sample protocols.

Six domains of potential concern were identified for ED lone AFIB management: rate control, rhythm control, anticoagulation, feasibility, discharge, and patient satisfaction. The domains were measured by a 5-point Likert scale (Very and Relatively Concerned, Neutral, Very and Relatively Unconcerned). Scoring labels were 1 – 5 and responses were averaged for each domain. The percentage of respondents choosing each level of concern was also independently quantified. In each category, respondents were given the choice of choosing "not applicable". For those with established AFIB protocols at their home institution, free text boxes were provided where respondents were asked to elaborate and explain how key institutional differences which might invalidate or otherwise compromise the question.

In addition to the above questions relating to AFIB protocols, respondents were asked to rate their support for adjustments to the protocol to increase ED feasibility as it relates to discharge planning, observations management, and consultant evaluation prior to discharge.

Two free text boxes were provided at the end of the survey to offer suggested improvements as well as subjective experiences in using AFIB protocols at their home institutions to glean further qualitative evidence relating to EP AFIB utilization and barriers.

The study was reviewed and approved by the Institutional Review Board (IRB) on August 23, 2017 at the home institution (a community teaching hospital) to ensure informed consent and ethical standards were met in the surveys and study implementation.

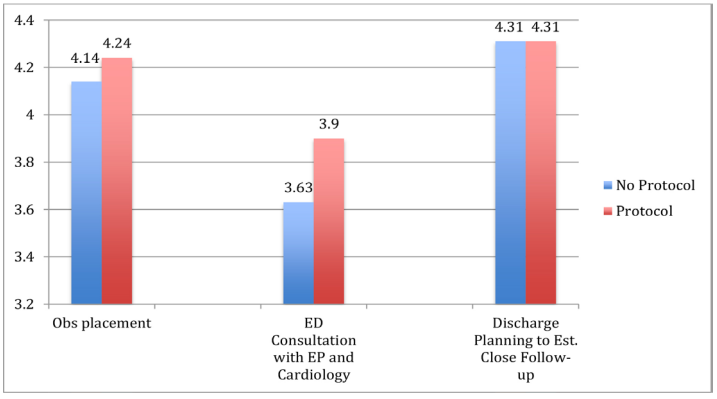

Figure 3: **Support of Suggested improvements to AFIB Protocol**

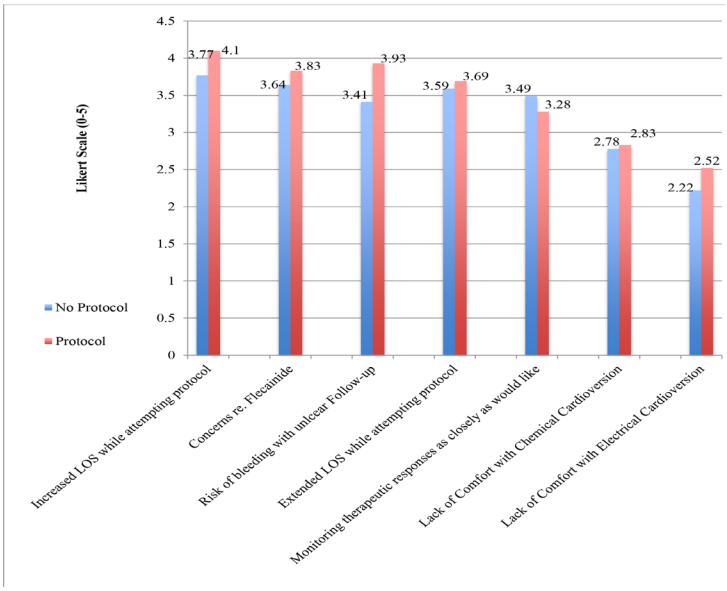

Figure 4: **Selected Barriers to Implementation of AFIB Protocol**

The survey was then embedded within a survey link contained within the body of an email describing the study and asking consent to fill out the survey. By completing the survey physicians consented to their participation within the study. The email and survey were distributed to members of a large national ED physician group. The emails were accessed after approval from the group's clinical governance board. The ED group mailing list encompassed one hundred eighty different emergency departments in twenty-one different states. No personal data was collected.

Results were collected Sept. 25th - Oct. 1st 2017 after the email was distributed and then closed for analysis. Descriptive analysis was used to describe survey results.different states. No personal data was collected.

Results

One-hundred-eighty-five EPs and APPs responded to the survey (6.1% response rate). Only one respondent (0.54%) was a resident, 154 were attendings (81.1%), and 34 APPs (18.2%) made up the group. Of those who responded, 17.4% had an AFIB protocol already in place ("P"- Protocol in place) while 82.6% did not ("NP"-No Protocol in place) and utilized the supplemental protocol to respond to the survey.

Using the weighted averages (from one to five) as an estimate of concern level regarding different aspects of AFIB protocols, the strongest levels of concern were regarding increased ED length of stay, extended ED length of stay while attempting protocol, lack of comfort discharging someone on flecainide or other oral anti-arrhythmic, and no clear way of establishing follow-up. Data is presented in [Figure 3] and [Figure 4].

Within the protocol group, there was a relative concern for initiating oral anticoagulation while there was less concern of this in the no protocol group. Both protocol and no protocol groups had relatively low concern for oral anticoagulants for stroke prevention and for time consumption for anticoagulant insurance availability.

With regards to rhythm control, both groups were both relatively unconcerned when it came to rhythm control methods in the

Table 1: **Free text comments offered by respondents. Organized by potential barriers.**

If you have used protocol in the ED: • Impossible to prescribed new oral anticoagulants due to insurance problems. • I found this worked well, when I worked at a hospital with this protocol in place. My only issue was that it was much faster to sedate and electrically cardiovert the patient than waiting for pharmacy to send the antidysrhythmic medication, then wait for a response.
Extended ED length of stay while attempting protocol: • The protocol takes way too long to read, it's too much in an ED situation. • We have not routinely utilized our similar protocol as it is burdensome for the ED with a long LOS.
Lack of comfort with electrical cardioversion: • DC cardioversion not permitted in ED by ED MD. Done by cardiology when admitted.
Lack of comfort on discharging patient on flecainide or other oral antiarrhythmic: • Not comfortable discharging with flecainide,etc .
Increased ED length of stay: • Time in ED if PO flecanide and then 4 hours wait/watch.
No clear way to ensure ok follow up: • We have specific A-Fib F/U with cardiology. • We can obtain this. • Our system can talk with cardiology 24/7 to arrange f/u and/or send electronic messaging to cardiology clinic, however sometimes uninsured cause an issue.
Any adjustments or improvements you would make to your protocol: • It's not feasible to have specialist come to the ED for every new onset afib patient. the wait time is too long. • I the above stated protocol should be implemented in an observation unit. However, pts that are virtually asymptomatic, relatively rate controlled (with minimal intervention; such as 1 or 2 IV dose of Cardizem) and have closed loop follow up can easily be discharged. All others should be admitted for obs as likely do not know EF or CAD status at time. • Discharge after discussion with EP or A fib clinic Physician.
If you have used the protocol in your ED: • I discharged someone with new onset Afib with RVR almost weekly with no known bad outcomes. • Similar to the above and works well. • EP follow up unreliable. • Is cardiology dependent- Patients that I feel comfortable to be DC they want in the hospital. • Time consuming. • Two patients with poor outcomes with protocol / Flecainide.

emergency department whether it be by chemical cardioversion or electrical cardioversion however there was more concern overall about discharging patients home on flecainide, as mentioned above.

In line with a concern for lack of follow-up for those patients who are discharged home, respondents were likely to see Cardiology/electrophysiology consultation in the ED prior to discharge as reassuring. Both groups also endorsed the ideas of placement in observation and/or discharge planning to establish follow-up and medication prescription prior to discharge.

A sub-group analysis of the greatest area of concern, ED length of stay, was performed comparing attending physicians to APPs. Attendings demonstrated a weighted average of 3.76 and 4.04 (no protocol, protocol). The group demonstrating the greatest area of concern were APPs who had a protocol at their facility with a weighted average of 4.4. APPs with no protocol were about equal to their attending counterparts (3.81).

Select comments offered regarding respondent opinions and experience are included in [Table 1].

Discussion

AFIB is a common cardiac arrhythmia that poses a significant healthcare burden in the US. There are multiple barriers surrounding the implementation of protocols emphasizing patient discharge from the ED. Our results indicate that among emergency physicians with AFIB protocols in place there is a relative concern surrounding the lack of clear follow-up after discharge as well the time and attention necessary to implement these protocols in busy ED settings.

It is not surprising that EPs and APPs were found to be relatively unconcerned with chemical and electrical cardioversion as these are common practice in EDs for many cardiovascular diseases. Similarly, the use of AV nodal blocking agents and initiation of anticoagulation has been the mainstay of ED AFIB treatment in the past. While often administered in IV formulations and followed by admission to telemetry units, EPs and APPs are familiar with the mechanism of action and adverse reactions of AV nodal blockers and comfortable with their administration and prescription following discharge. Similarly, the initiation of the so called Noval Oral Anticoagulants (NOVACs) in both DVT management as well as AFIB is now common practice in the ED and there is a relative lack of concern surrounding their prescription and discharge.

With regards to initiation of rate control, the majority of concern centers around the time needed to achieve rate control rather than discomfort with placing the patient on a new AV nodal blocking agent prior to discharge. This is consistent with the overall lack of comfort with an increased ED length of stay also demonstrated in the survey. There were six comments re-emphasizing the time-consuming nature of this protocol feature. One respondent stated that their home institution abandoned their AFIB protocol altogether due to the time burden associated with the protocol.

Given these barriers, emergency physicians supported two major areas of adjustment to AFIB protocols: after initiation of the protocol in the ED, placement of patients in observation for the remaining steps to relieve the time burden of frequent re-evaluation and intervention. When observation is unavailable, ED consultation with cardiology/electrophysiology in combination with discharge planning to establish close follow-up was largely supported by respondents. This latter option fails to alleviate the concern surrounding the time burden in the ED but may have the benefit of facilitating discharge and avoiding unnecessary admission with IV drips and long hospital stays.

Notably, there was an overall lack of support for adjusting protocols to include EP and Cardiology evaluation of patients in person while in the ED prior to discharge. Three comments were made on this point, two suggesting telephone conversation or direct messaging to "close the loop" and one stating that routine AFIB cases should be discharged from the ED with concern for over utilizing these consultants in Routine AFIB cases. On the whole, respondents favored discussion with Cardiology/electrophysiology but it seems they did not feel the need for ED evaluation in person by these consultants.

Current US healthcare trends are going away from admission where possible and appropriate. In addition, there is increasing emphasis on emergency departments to meet metrics regarding ED length of stay, door to doc time, and boarding time, among others. There is significant pressure on EPs and APPs to both see patients quickly, facilitate turnover in emergency department beds, and discharge where appropriate and possible. The sample protocol provided at longest would take six hours (<48 hour onset) or eight hours (>48 hours). With many EDs having door to discharge goals of four hours (and often less), AFIB protocols can pose a significant hurdle to meeting these ED metrics. To this end, it is not surprising that EPs have concern surrounding the time needed to implement such protocols.

When taken together with our data, it seems that EPs and APPs are relatively comfortable managing the medical side of AFIB but remain concerned with their ability to do so in a time sensitive manner while optimizing emergency department patient flow. Although APPs with a protocol in place did show the highest level of concern regarding increased length of stay, our subgroup analysis demonstrated minimal difference in the comfort levels of EPs versus APPs.

Based upon our results, we suggest two possible solutions to ED AFIB protocols to alleviate concerns and improve utilization. If present, cardiac observation or clinical decision units can be utilized for stable lone AFIB patients. Treatment can be rapidly initiated in the ED with subsequent placement of patients in observation under the supervision of healthcare providers who are able to reassess, intervene, establish follow-up, and discharge patients without compromising ED metrics or necessitating frequent re-evaluation and intervention from emergency physicians.

In institutions where this is not feasible, consultation with cardiology/electrophysiology in conjunction with discharge planning to establish medication regimens and close follow-up may be useful

adjuvants in the discharge of AFIB patients.

This study did face limitations with regards to the sample pool. The respondent pool takes into account EPs and APPs across 22 states, most of which are clustered in the midwest, mountain west, northeast, and southeast and are not symmetrically distributed between these regions. For this reason, regional differences may not be reflected in the survey.

While 185 respondents participated in the survey, this number reflects a small proportion (roughly 0.5%) of the total estimated pool of potential respondents and for this reason may not be an accurate reflection of the total group of physicians and APPs. While there were over 180 sites the survey was sent out to, there was no way of knowing exactly which respondents came from which sites and significant geographical variations may have been missed. A study with a larger sample size from a multitude of different groups and regions would need to be performed to eliminate these areas of potential sampling bias.

Despite efforts of many hospitals toward the implementation of outpatient driven protocols, emergency physicians in this study reported reluctance toward implementation of these protocols due to increased emergency department length of stay, the need for close and frequent observation, and lack of follow-up with specialists. While these protocols may be effective in decreasing hospital admissions, hospital length of stay, and financial burden to the patient, EP utilization of such protocols are impeded by the ability to implement the frequent re-evaluations and interventions in crowded emergency departments. These results beg the question of implementing such protocols in cardiac observation units or similar which would obviate the need for frequent patient re-evaluation and serve to free-up emergency department beds. Alternatively, EPs are in favor of closed loop communication with cardiology and/or electrophysiology in conjunction with discharge planning for close follow-up as a suitable alternative in lieu of observation and clinical decision units.

Conclusions

EP input regarding the development of ED AFib protocols will be essential in order to develop cost effective, convenient and safe methods of treatment. This survey of EP and APP opinion on the topic suggests that ED length of stay and insuring close outpatient follow up are key issues to address as protocols are designed.

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9. The data for this survey was collected using SurveyMonkey Audience. Information on how respondents are recruited to SurveyMonkey is available here: www.surveymonkey.com/mp/audience.

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Comparison of Cryoballoon and Hybrid Surgical Posterior Wall Isolation for Persistent Atrial Fibrillation to Conventional Ablation

Eric Nordsieck[1], Zhang Xin J[1], Pankaj Malhotra[1], Dali Fan[1], Nayereh G. Pezeshkian[1], Uma N. Srivatsa[1]

[1] *Division of Cardiovascular Medicine, University of California Davis.*

Abstract

Background: Optimalablation strategy for persistent atrial fibrillation (AF) is unclear;PWI of the left atrium may improve outcome.Our aim was to compare outcomes of posterior wall isolation (PWI) ablation for persistent AF achieved by cryoballoon ablation (CRYO) or hybrid surgical ablation (HABL) to matched patients undergoing conventional radiofrequency ablation (CRA).

Methods: In our single center retrospective study,patients underwent HABL and CRYO withcircumferential pulmonary vein ablation (CPVA),roof and floor lines to complete PW box lesion. CRA consisted of CPVA, roof line and lateral mitral isthmus line (MVI).

Results: Of 61 patients (mean duration of AF 1.3 ± 0.4 yrs)who underwent ablation, after follow-up of 366 ± 62 days, AF recurrence was 10.5% and 48% (p=0.001) and the need for repeat ablation 5% vs 30% (p=0.007) in PWI and CRA groups respectively, without a significant difference in incidence of AT/FL 18 vs 26 % or cardioversion 5.2 vs 7.1 %. Total procedure time and fluoroscopic time were 242 ±70 min vs 279 ±53 min (p=0.08) and 20±9 min vs 12 ± 4 min (p=0.003) for PWI and CRA respectively. CRYO had less AF recurrence and complications than HABL. Mean length of stayfor CRYO patients was 41 hrs compared to 145 hrs in HABL group, who underwent two procedures.

Conclusions: PWI in persistent AF patients decreases recurrence of AF and need for repeat procedure compared to CRA; PWI by CRYO is superior to HABL due to less LOS and complications.

Introduction

Catheter ablationis indicated for treatment of drug refractory symptomatic atrial fibrillation (AF)[1]. Circumferential Pulmonary Vein Ablation (CPVA) for PV isolation (PVI) is the corner stone of all AF ablations regardless of stage of disease; recurrence is common particularly in persistent AF compared to paroxysmal (PAF) patients. There is no consensus on the optimal ablation strategy persistent AF patients.

Cryothermal energy delivered by cryoballoon catheter[2] ablates a wider area including triggers from the antral tissue, leaving a small area of the posterior left atrium (LA) wall unablated[3]. Techniques have been described to create linear lesions in the LA with cryoballoon to avoid gaps[4]. We expanded these techniques to create lesions in LA roof and floor for complete posterior wall isolation (PWI) in patients with persistent AF.

In this study, we compare the clinical outcomes in patients undergoing PWI by CRYO or hybrid surgical ablation (HABL) to historical controls from our institution with persistent AF who had been treated with our previous conventional endocardial radiofrequency ablation (CRA). Within the PWI group, we compare CRYO to HABL strategies for procedural and clinical outcomes.

Key Words

Persistent Atrial Fibrillation, Ablation, Posterior Wall

Corresponding Author
Uma Srivatsa,
Professor of Medicine, UC Davis, Sacramento, CA

Methods

After approval from Institutional review board, we evaluated the records of patients ablated for AF between 2014-2017. We included age and gender matched patients (> 18 yrs) with symptomatic persistent AF with left ventricular ejection fraction (LVEF) >30%, who had failed at least one an tiarrhythmic drug. Patients with PAF were excluded. Direct oral anticoagulants were held onthe day prior to the procedure, resumed the same evening; warfarin was continued during the procedure. Class I agents, sotalol and dofetilide were held for five days and amiodarone for 30 days prior to the procedure. All patients had CT scan prior to evaluate PV anatomy and was used to navigate during mapping.

Mapping

Electroanatomic mapping was performed in all cases with CARTO 3 system (Biosense Webster Inc) in sinus rhythm for voltage map, in the setting of 0.05 to 0.5 mV to assess PVI and PWI. Activation window for atrial flutters was set at 50% -50% of the cycle length. Roof was the line drawn between the upper ends and floor was the line drawn between the lower ends of the right and left superior PVs. The area contained within roof, floor and PV antra were designated as the PW. The attenuated area < 0.05 mV after ablation divided by the total area of the PW was considered the percent of PWI.

Ablation strategy

For patients in group CRYO, ablation involved two applications to create lesions using cryoballoon (ArcticFront Advance™, 28 mm

second generation, Medtronic, Inc., Minneapolis, MN) for 180 sec and 120 sec at all the PVs, after ensuring adequate occlusion by pressure monitoring and PV Doppler signals on the intra-cardiac echocardiogram. Then anchoring the Achieve mapping catheter (Abbott Inc.) in the PVs, sequential retraction and posterior rotation of the balloon was employed to create overlapping and contiguous stamp lesions spanning the LA roof and floor to complete PWI. [Figure 1] We incorporated the use of CartoSound™ (Biosense Webster Inc, Diamond Bar, CA) to integrate catheter position and orientation in real time into the electro-anatomical map during PW applications to draw "CartosOund Rings" (COR Imaging). [Figure 1D] Esophageal temperature monitoring [Figure 1A] and phrenic nerve pacing for right sided lesions were employed during ablation and applications were stopped for loss of phrenic capture or esophageal temperature drop < 29°C. Lesions on the roof and floor were created with single applications of 180sec and were stopped early if esophageal temperature dropped. Remapping with Pentarray multipolar catheter (Biosense Webster Inc) following ablation was used to confirm complete and well-demarcated PVI, roof, and floor lines to demonstrate dense PWI with no electrograms >0.05mV; if necessary additional ablation with thermo-cool radiofrequency catheter was applied to close gaps. If atrial flutter was inducible, additional RF ablation was applied to eliminate the atrial flutter circuit. Posterior wall was considered isolated if there was complete electrogram attenuation to < 0.05 mV.

Patients in group HABL underwent surgical ablation: bilateral video assisted thoracoscopic surgery (VATS) with bipolar PVI (Atricure Inc), LA roof/floor lines, RA bicaval line, ablation of ganglionic plexi/the ligament of Marshall, and LA appendage clipping. After recovery from surgery, the patients returned for electrophysiology study/ablation for confirmation of PVI, PWI and additional ablations if required to achieve this as well as ablation of clinical or inducible atrial flutter.

Group CRA consisted of patients who had received conventional endocardial ablation including CPVA for antral PVI with the addition of empiric linear lines in the LA roof and MVI with thermo-cool RF catheter. Confirmation of bidirectional block was documented for linear lesions. Inducible flutters were targeted for further ablation.

Follow up

Patients were seen post ablation at 1 week, 3 month, 6 month and 1 year and were monitored by ECG, Holter or event monitor or through existing implantable cardiac device. All patients discontinued antiarrhythmic therapy 8-12 weeks after the procedure; continuation of anticoagulation was based on their $CHADS_2VASC$ score.

Outcomes

Primary outcomes were first recurrent AF> 30 seconds, Atrial flutter (AFL)> 30 seconds or any atrial arrhythmia (AF or AFL) at one year, after the three month blinding period. We also analyzed antiarrhythmic drug utilization, referral for repeat ablation, peri-procedural complications, length of stay and control of AF at one year follow up. Procedural time was as recorded in the Apollo LX (version 6.2.0) records and includes time from femoral venous access to the patient exiting the electrophysiology laboratory. If patients remained in sinus rhythm after the initial recurrence assisted by cardioversion or antiarrhythmic drug, they were considered to have controlled AF.

Statistics

STATA 13.1 was used for all statistical analyses. Continuous variables are expressed as mean + SD or SE; categorical variables are presented as percentages, comparisons were performed with t-test and X^2 test respectively. Differences between three groups were assessed using ANOVA for continuous variables, and Kruskal -Wallis for nominal variables. Adjustment of comorbidities for the clinical outcomes were performed with models as: (1) demographics-age and sex; (2) consisted of cardiovascular risk factors- hypertension, diabetes, coronary artery disease/peripheral vascular disease , transient ischemic attack / stroke, heart failure; (3) included body mass index (BMI), chronic obstructive pulmonary diseaseand obstructive sleep apnea; (4) LA dimension and left ventricular ejection fraction. Kaplan Meier survival analysis was used to compare freedom from AF, or AFLamong the groups; p-value < 0.05 was considered significant.

Results

Baseline characteristics

There were 61 patients [Table 1]with persistent AF who fit the inclusion criteria; mean duration of AF was 1.3 ± 0.4 yrs. Majority was anticoagulated,without significant differences among the three groups, however more patients in group HABL had long standing persistent AF.

Procedural characteristics

[Table 2] All patients had CPVA to accomplish PVI, more than half the patients utilized magnetic robotic navigation in HABL

Table 1: Baseline characteristics

	Cryo (n=24)	Hybrid (n=14)	Minimaze (n=23)	P value
Age (years)	66 ±10	70 ± 6	63 ± 9	ns
Sex (male %)	70.8	71.4	61	ns
Hypertension (%)	71	57	61	ns
Diabetes (%)	37.5	7.1	17.4	ns
Coronary artery disease (%)	25	28.6	26.1	ns
Heart failure (%)	29.2	28.6	34.8	ns
Sleep apnea (%)	37.5	35.7	22	ns
Body mass Index	33 ± 6	29 ±5	29 ±5	ns
Cerebrovascular disease (%)	4.3	none	none	ns
Chronic obstructive pulmonary disease (%)	8.3	14.2	4.3	ns
CHADS2VAsc	2.4 ±1.3	2.5 ±1.5	2.3 ±1.5	ns
Newer anticoagulant /warfarin (%)	66.7/29.2	42.8/50	30.4/69.5	ns
Antiarrhythmic drugs (class III/I)	33.3/29.2	14.3/14.3	30.4/21.7	ns
Left atrium (cm)	4.5 ± 0.67	4.2 ± 0.64	4.3 ±0.6	ns
Left ventricular ejection fraction(%)‡	53 ± 10	59 ± 6	54 ± 10	ns
Long standing Persistent AF (%)	25	78.6	13	<0.0001
Prior endocardial ablation (%)	33.3	43	21.7	ns
Alcohol use	46	57	65	ns
Smoking	54	36	22	ns

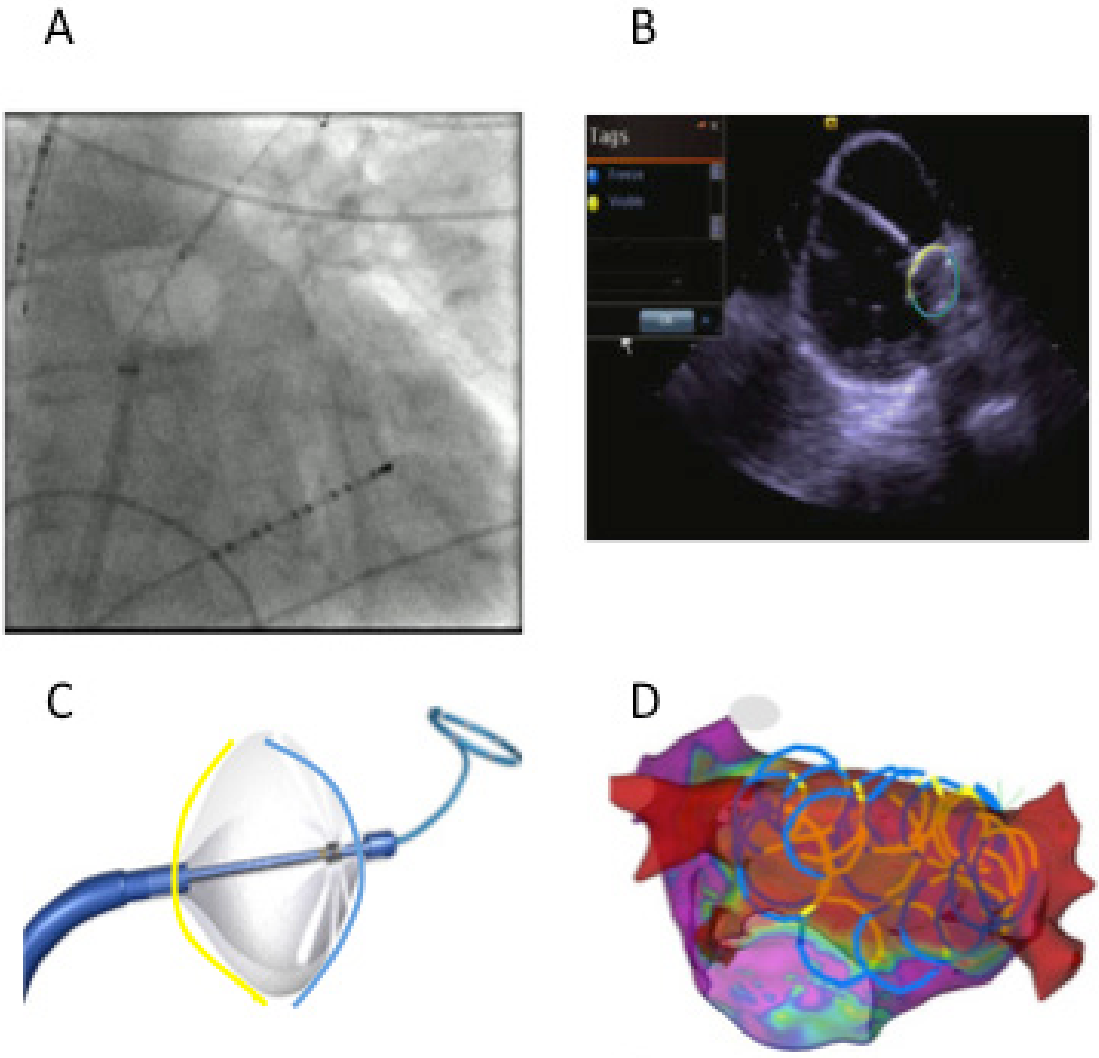

Figure 1: **A - Fluoroscopic view of Cryoballoon retracted from left upper pulmonary vein position at the roof; White arrowhead indicates esophageal temperature probe. B -Visualization of cryoballoon with intracardiac echo; C-CartosOund contours (COR imaging); D- Contours drawn on the cryo balloon yellow and blue lines represent non ablating and ablating segments respectively.**

and CRA. There was more MVI in HABL and CRA vs CRYO (p= 0.001); there was no difference in cavo-tricuspid isthmus (CTI ablation). More patientsin HABL converted to SR during ablation compared to other groups; there was no difference in conversion to AFL. Majority of the patients had inducible AFL, without differences among the groups. Electrophysiology procedure time was longest at 321± 98 min in CRA, (p=0.02) without a significant difference in fluoroscopy time or Dose Area Product among the groups.

In CRYO, the total number of cryo applications to achieve PVI and PWI was 23.5± 5 for total 3675±776 seconds. Esophageal temperature nadir was -31± -2.6°C. Additional RF ablation was necessary to close small gaps for PWI in 46% of patients with mean RF time 136 ±42 sec (SE). Common locations for PWI gaps were in the mid floor and mid roof. No additional RF ablation was necessary to complete PVI. Additional ablations in LA for inducible AFL were required in 70%. COR imaging had a reduction in the procedure time (257 ± 52 vs 270 ± 59 min, ns), and fluoroscopy time (20 ± 5 vs 26 ± 10, p=0.08), and a reduced need for PW touch up with radiofrequency ablation catheter (33% vs 67%, ns) compared to those without COR imaging.

In HABL, EP/ablation was performed 75 ± 26 (SE) days after VATS maze, when 59% of the PW area had low voltage at baseline representing the extent of PWI due to surgery. The gaps noted in roof and mid floor were closed (radiofrequency time 2754 ± 1572 sec) to accomplish > 90% area of low voltage in the PW [Figure 2b] and [Figure 2C]; due to gaps in PV, ablation for PVI was required in 43%. Four patients presented for the second stage in AF, three patients in AFL, which terminated on ablation. Although not statistically

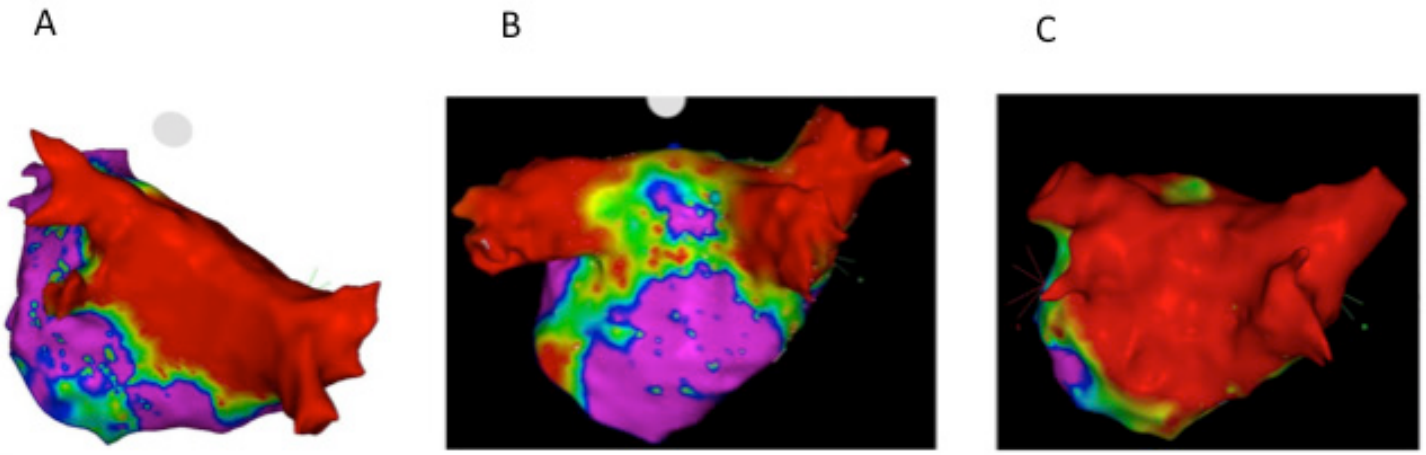

Figure 2: A shows left atrial posterior wall voltage mapping with dense homogeneous isolation of the pulmonary veins and posterior wall. B shows voltage mapping (0.05-0.5mV) following surgical ablation (pre-endocardial). The bilateral pulmonary veins are isolated and posterior wall is partially isolated with gaps in floor line. C is a different hybrid ablation patient also pre-endocardial ablation; as compared to middle panel posterior wall is densely isolated. All voltage maps 0.05-0.5mV.

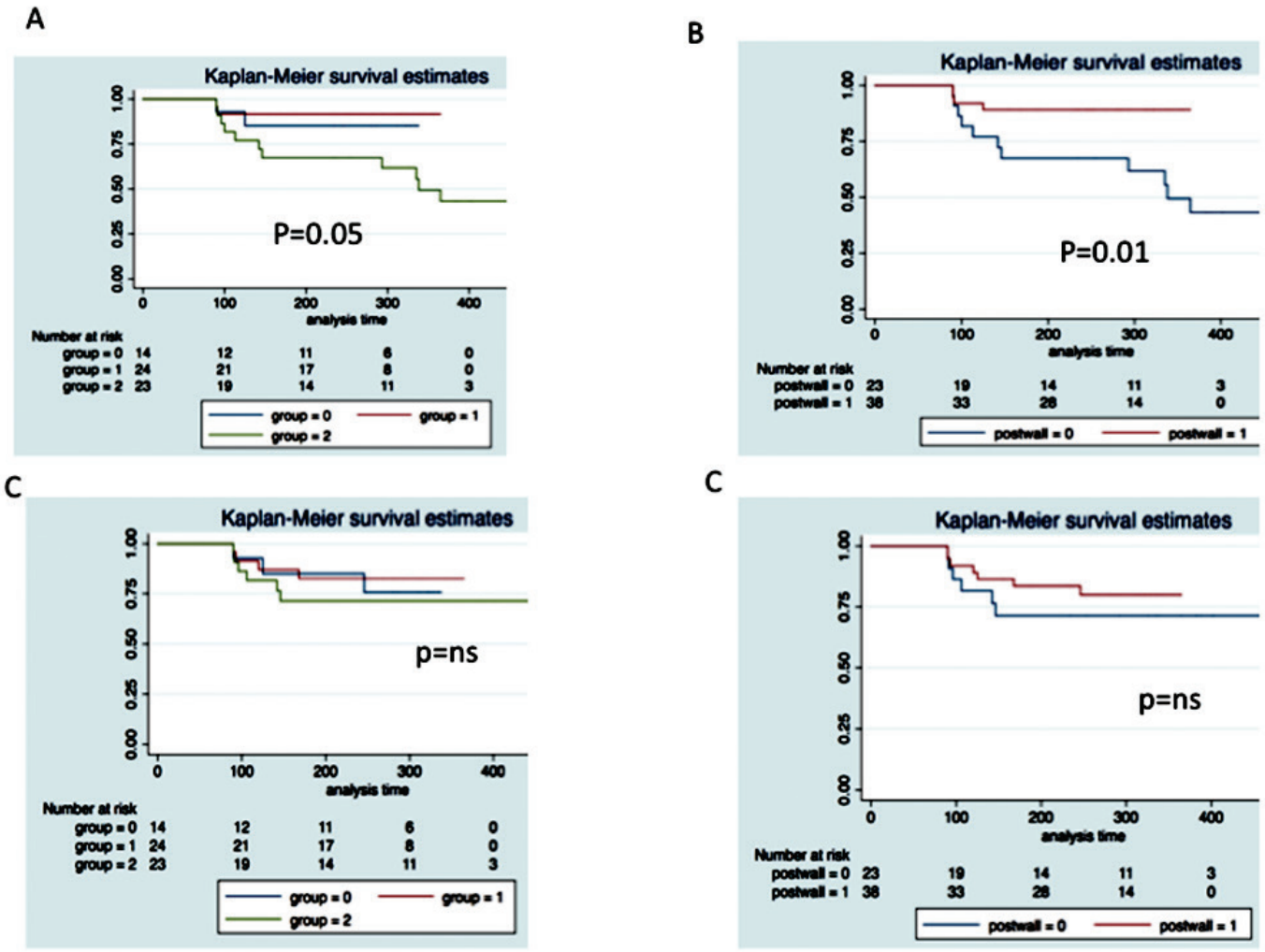

Figure 3: Kaplan Meier survival estimates of freedom from recurrent AF (A and B) and Atrial flutter (C and D). A&C: comparison of three groups- cryo ablation (red line), hybrid ablation (blue line), and conventional radiofrequency ablation (green line). B&D: Comparison of posterior wall isolation (red line) vs conventional radiofrequency ablation (blue line)

significant, there were more inducible AFL (mean 1.8 ± 0.8) in this group localized to CTI, MVI, and roof requiring additional LA ablation in all the patients.

All CRA patients had CPVA and roof line; 87% had MVI line with 95% achieving bidirectional block. Induced AFL was treated by activation mapping and ablation in 65% of the patients with a total of 5355 ± 1666 sec ablation time in this group.

Clinical outcomes

Recurrent AF occurred in 24.6%, recurrent AFL in 21.3%, any atrial arrhythmia in 31% and repeat ablation in 16.3% of the entire cohort. Age, sex, hypertension, diabetes, cardiovascular disease, prior stroke, heart failure, chronic pulmonary obstructive disease, sleep apnea, smoking and alcohol use did not predict recurrent arrhythmia. Patients with recurrent AF had lower BMI 27.8 ±3 (vs 31.4 ±6.3, p=0.05) and27% had coronary artery bypass surgery (vs 4%, p=0.01) compared to those without recurrence. Recurrent AFL was not predicted by any of these demographics or comorbidities.

Table 2: Comparison of procedural characteristics:

	Cryo ablation (n=24)	Hybrid ablation n=14)	Conventional ablation n=23)	P value (three group)	P value Group (Cryo vs Hybrid)	P value (Cryo vs conventional ablation)
Procedure time (min)	262 ± 54	208 ± 82	321 ±98	0.02	0.04	0.01
Fluoroscopy time (min)	22.5 ± 8	15.3 ± 9	20 ± 17	<0.0001	ns	ns
DAP*dose	3302 ±1912	3045 ±4306	2450 ±2719	0.003	ns	ns
Magnetic Robotic navigation (%)	4.2	57.1	74	0.0001	0.0002	<0.0001
Mitral valve isthmus ablation (%)	46	92	87	0.001	0.004	0.003
Mitral Valve isthmus block (%)	80	100	95	ns	ns	ns
CTI†ablation (%)	71	71	74	ns	ns	ns
Additional Posterior wall ablation (%)	45.8	7.1	-	-	0.01	-
Additional ablation for PVI ‡(%)	none	42.9	13	0.003	0.001	0.07
Conversion to sinus rhythm during ablation (%)	8.3	50	22	0.01	0.004	ns
Conversion to Atrial flutter during ablation (%)	16.7	14.3	35	ns	ns	ns
Inducible atrial flutter (%)	71	93	65	ns	ns	ns

*DAP- Dose area product, † CTI- cavotricuspid isthmus, ‡ PVI- pulmonary vein isolation

Comparison of group P to group CRA

[Table 3] Since CRYO and HABL had PWI, they were together (group P) and compared to CRA. Group P had less recurrent AF (10.5% vs 47.8%, p=0.008), any atrial arrhythmia (23.7 vs 52.2%, p=0.02), but no difference in AFL [Figure 3B],[Figure 3D]; there was less repeat ablation (5.3% vs 30.4%, p=0.007) and more control of AF (95% vs 73%, p=0.02), compared to CRA. There was no difference in time to recurrence in both these groups.

Adjustment for co-morbidities

AF recurrence remained less for group P (< two times less likely) compared to CRA, after adjusting for models one (p=0.01), two (p=0.03) and three (p=0.003), model four (p=0.01) and duration of AF (p=0.002). Please see methods section for details regarding the models. After adjustment of individual comorbidities of hypertension (p=0.005), diabetes (p=0.005), coronary artery disease/ peripheral vascular disease (p=0.005), heart failure (p=0.004) and TIA/ stroke (p=0.001), the recurrent AF remained lower by multivariate logistic regression analysis.

Comparison of three groups

[Table 3] For a follow-up of 366± 62 days AF recurrence was highest in CRA compared to CRYO and HABL (p=0.005), [Figure 3A] without a difference in recurrent AFL among the groups.[Figure 3C] Occurrence of any atrial arrhythmia was highest in CRA mainly due to recurrent AF; there was no difference in cardioversion among the groups. While repeat ablation was not required in HABL (who already had the second ablation as a planned procedure), there were more repeat ablations and antiarrhythmic drug use use in CRA compared to other groups.

Length of stay was longest in HABL(145 ± 53 hours) as it included both stages vs CRYO (42 ± 58 hours, p<0.0001) or CRA (38 ± 25 hours, p<0.0001). At the end of follow up control of AF was achieved in 95.8, 93% and 72.7% (p=0.001) of the patients in CRYO, HABL and CRA respectively.

Conversion to sinus rhythm or AFL, inducibility of AFL, achievement of MVI block, CTI ablation and prior ablation did not predict recurrence of AF or AFL. Robotic magnetic navigation used predominantly in HABL and CRA had higher risk for recurrent AF 40% vs 14.3% in manual ablation cases (p=0.02). Patients with PWI were 1.9 times less likely to have recurrent of AF (p=0.002) after adjustment for robotic magnetic navigation catheter utilization.

Complications

In CRYO, small hematoma and transient phrenic nerve palsy resolving by hospital discharge occurred each in one patient. In group HABL, there was drug reaction in onepatient, abdominal ileus in one patient, pleural effusion in two patients, and pneumonia in three patients one of whom died within one year post procedure due to non cardiac problems. In CRA, two patients had prolonged hospitalization (> 23 hours) for heart failure exacerbation one of who also had pneumonia. Other complications such as atrial-esophageal fistula, CVA, pericardial effusion/ tamponade, or peri-procedural

mortality did not occur in this cohort.

Discussion

The main finding in our study is the improved efficacy of PWI compared to conventional ablation in patients with persistent AF regardless of the method of ablation. Of the two methods used to isolate the posterior wall, CRYO had less complications, required less number of procedures and had less total length of stay to achieve the same result compared to HABL.

Table 3: Clinical outcomes

	Cryo ablation (n=24)	Hybrid ablation n=14)	Conventional ablation n=23)	P value	PWI*-yes	PWI*-no	P value
Atrial arrhythmias < 3 months after ablation (%)	25	28.6	39.1	ns	26.3	39.1	ns
AF†>3 months (%)	8.3	14.3	47.8	0.005	10.5	47.8	0.008
Atrial flutter > 3 months(%)	16.7	21.4	26.1	ns	18.4	26	ns
Any atrial arrhythmia	28.6	20.8	52.2	0.03	23.7	52.2	0.02
Control of AF (%)	95.8	93	72.7	0.001	94.7	72.7	0.02
Cardioversion <3 months after ablation (%)	8.3	7.1	13	ns	7.9	13	ns
Cardioversion > 3 months	12.5	None	8.7	ns	7.9	8.7	ns
Repeat ablation within one year	8.3	None	30.4	0.01	5.3	30.4	0.007
Antiarrhythmic Drug class I	4.2	None	8.7	ns	2.6	8.7	ns
Antiarrhythmic Drug class III	21	None	30	ns	13	30.4	ns
Follow up (days)	347 ± 70	373 ± 48	381 ± 59	ns	357 ± 63	381 ± 59	ns
Time to recurrence (days)	245 ± 87	254 ± 90	269 ± 129	ns	248 ± 87	269 ± 128	ns

* PWI- Posterior wall isolation; †AF- Atrial fibrillation.

With wide area of antral CPVA, gaps in the LA at roof or MVI can be a source of recurrent atrial arrhythmias, which have been targeted for ablation[5,6].Triggers in the PV antrum, PW and non PV locations have been shown to be significant source for target inpersistent AF[7].However, additional ablations beyond CPVA for persistent AF has been questioned after the results of the STAR-AF II trial[8]. A meta analysis of PVI plus substrate ablation vs PVIand a recent randomized trial of PVI vs PWI + PVIhas revealed superiority of PVI plussubstrate strategy compared to CPVA[9,10].

LA PW is known to have a shared embryology and histology with the pulmonary veins and as such may represent similar substrate to that of the PVs.The demonstration of complete PWI by mapping is important to confirm absence of gap[11]. Our findings are consistent with this concept in that regardless of CRYO or HABL, PWI had higher success rate to prevent recurrence and for control of AF. Though any recurrence > 30 sec is considered a failure of ablation, we have also included "control of AF" as an alternative outcome for those who have persistently been in AF.

A hybrid approach to ablation in the atria can replicate the original cox maze IV surgery[12]. Mid term follow up after such an approach has shown that about two thirds of the patients maintain sinus rhythm without the need for antiarrhythmic drugs leading an increasing interest in this procedure[13].

Due to limitations ofthe conventional ablation for persistent AF[8], and the potential replication of Cox maze IV with hybrid approach, we started performing the latter for long standing persistent AF in our institution.When these patients were brought to electrophysiology laboratory for the second stage, mapping revealed gaps in roof and floor lines, which required ablation to achieve PWI; gaps in PV also required re-ablation consistent with prior investigation[14]. Sinus rhythm was maintained in 86% off antiarrhythmic drugs, without repeat ablation. While this experience was encouraging, our patients reported significant intercostal pain, had longer length of stay with other morbidities.Persuaded by the early reports of ability to close roof gaps with cryoballoon[4], we started using this approach to isolate PW in patients with persistent AF. We found that the total area of the antra and posterior wall was more extensively and homogeneously ablated with the cryoballoon.Potential reentry circuits due to non homogenous scaras noted in MRI studies[15], perhaps were eliminated contributing to the success in maintaining sinus rhythm.

Our results in group P are similar to a recent investigation comparing PVI to PWI + PVI;[10] our patients have similar antiarrhythmic drug utilization during follow up. We had more cryo-ablation time as we performed two freezes for every PV; we also found from early experience that a cold temperature of <-30°c and a duration of >180 seconds was needed to avoid gaps in the LA roof and floor if nadir <-300 C occurred later than 30 sec after onset of freeze. We stopped ablation if esophageal temperature dropped to <29o C. This was arbitrarily chosen as we noted up to 3-4°c reduction after cessation of freeze. Although esophageal temperatures up to 15° C have been recommended vs lower nadir, they do have incidence of esophageal ulcer[16]. Since we only have the conventional esophageal probe [Figure 1A] at our institution, and could miss a wider area of collateral damage, we chose a higher nadir for safety reasons. Locations of drop in esophageal temperature were posterior wall or pulmonary veins in proximity to the esophageal temperature probe.

Despite additional ablation targets in HABL, the clinical outcomes at one year was similar to CRYO group, reinforcing the significance of posterior wall for thepathogenesis of persistent AF. Surgical group also had LAA clipping which would electrically isolate the LAA. While the significance of this step is unclear from our study, other investigators have shown it to be relevant to prevent recurrence

in persistent AF[7,17]. The benefit of LAA isolation beyond complete homogenization of posterior wall remains to be investigated. Less ablation of MVI in CRYO group but similar results to HABL and better results than CRA reiterates the need for MVI only if there is inducible mitral flutter.

We used CARTO mapping system for voltage and activation map of the left atrium and the atrial flutters. Even though pentarray catheter added to the cost, the dense multipolar map created by this catheter helped reduce the time needed to diagnose and ablate atrial flutters; the latter also justified utilization of radiofrequency ablation catheter in addition to cryo balloon. Overall, the shorter procedure time and reduced EP lab utilization time can be cost effective and warrants further study.

To our knowledge, ours is the first study to compare surgical or endocardial PWI vs conventional ablation for persistent AF and first to report the benefit of PWI regardless of the method of ablation.

Limitations

Our study is small, from a single center and has limitations attributable to retrospective analysis. Besides this, historical control is limited by selection and lead time bias. Future large multi-center randomized controlled trials regarding the efficacy of PWI using CB forpersistent AF compared to surgical or RF ablation would be a valuable area of future research.

Conclusions

Complete PWI is safe and feasible with cryoballoon ablation; the efficacy of cryothermal PVI/PWI is comparable in our experience to that of hybrid surgical technique, which replicates Cox maze IV, with additional advantage ofshorter length of stay and less morbidity. PWI is superior to conventional ablation as defined in this study in patients with persistent AF for recurrence and control of AF.

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Atrial Fibrillation in Heart Failure Patients with Preserved or Reduced Ejection Fraction - Prognostic Significance of Rhythm Control Strategy with Catheter Ablation

Nicolás Vecchio[1], Leonardo Ripa[2], Agustín Orosco[1], Leandro Tomas[1], Ignacio Mondragón[1], Adriana Acosta[1], Lujan Talavera[1], Santiago Rivera[1], Gastón Albina[1], Mirta Diez[1], Fernando Scazzuso[1]

[1] *Electrophysiology Fellowship. Instituto Cardiovascular de Buenos Aires.*
[2] *General Cardiology Fellowship. Hospital Central. Mendoza, Argentina.*

Abstract

Introduction: Atrial fibrillation (AF) and heart failure (HF) often coexist with an increase in morbidity and mortality. AF catheter ablation (CA) has proved to be a safe and efficient option for HF patients, but long-term evolution and prognosis remain uncertain. The aim is to assess the efficacy and safety of CA in HF patients with AF, and analyze HF long-term evolution.

Methods: We prospectively analyzed consecutive patients with AF and congestive HF or left ventricular ejection fraction (EF) less than 45%, who underwent CA of AF between 2011 and 2016. We excluded patients who did not complete one year of follow-up.

Results: Seventy-nine patients were included. Mean age was 62.1 years, 72.4% were men, 67.2% had hypertension and 8.6% were diabetics. Mean EF was 49%, left atrial area was 26.5 cm2 and mean CHA_2DS_2-VASc score was 2. 70.6% were on NYHA FC II-III.

The recurrence rate of AF was 60%, and after a second CA the rate decreased to 27.8%. Only persistent AF prior to the procedure was identified as independent predictor of recurrence. There was a significant NYHA FC improvement in the sinus rhythm (SR) group vs those with recurrence (63.6% vs 36.4%; p=0.047). None of the patients in SR were hospitalized, whereas six with recurrence were hospitalized due to HF (0% vs. 18.2%; p = 0.07). The rate of complications was 9.1%.

Conclusions: Catheter ablation of atrial fibrillation in heart failure presents an adequate success rate, improving symptoms and reducing rehospitalizations due to heart failure.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in patients with and without heart failure (HF), affecting 1-2% of the population and up to 50% of the patients with heart failure[1,2]. AF is associated with increased mortality, with a 5-fold increased risk of stroke and a 3-fold increase in the risk of HF and hospitalizations[3,4].

The association between both conditions is well-known. There is a direct correlation between left ventricular ejection fraction (LVEF), New York Heart Association functional class (NYHA) and the prevalence as well as the duration of AF,[1,3] generating a loop that perpetuates both conditions, increasing morbidity and mortality[5].

Several studies comparing rhythm control versus rate control failed to demonstrate significant differences favoring either strategy in terms of NYHA or mortality[6-8]. This could be due to the fact that sinus rhythm (SR) was difficult to maintain in the rhythm control group.Atrial fibrillation catheter ablation (CA) has proved to be a safe and efficient option for patients with HF[9-11]. Although the efficacy of this procedure is lower in HF patients compared with those without structural heart disease, recent studies have indicated that the rate of SR at the long-term is higher than that achieved with medical therapy[12,13]. Several studies have analyzed CA in HF patients with reduced LVEF (with different cut-off points), but few have included those with preserved LVEF (HFpEF). We believe that improving the SR rate with CA will improve NYHA, quality of life, morbidity and mortality by reducing hospitalizations in HF patients.

The aim of the study is to evaluate the success rate, freedom from AF and complications associated with AF CA in HF patients with preserved or reduced LVEF. The predictors of AF recurrence, the rate of HF hospitalizations and the NYHA functional class after one year of follow-up according to the presence or absence of SR will also be analyzed.

Key Words

Atrial Fibrillation, Heart Failure, Preserved Ejection Fraction, Catheter Ablation, Hospitalization, Prognostic

Corresponding Author
Nicolás Vecchio.
Cuba 2628 12 C. Capital Federal. Argentina.1428.

Methods

Study design and population

We conducted a prospective, observational and single-center study. Consecutive patients with a history of AF and signs and symptoms of HF or LVEF less than 45%, who underwent CA between July 2011 and March 2016, were included. The patients were refractory to or

did not tolerate therapy, presenting inadequate ventricular response, recurrent AF or adverse events associated with the treatment.

The exclusion criteria were previous CA of AF, cardiogenic shock, contraindication to anticoagulation, left atrial appendage thrombus, pregnancy or severe comorbidities. Patients who did not complete one year follow-up were also excluded.

HFpEF was defined as LVEF equal to or greater than 50% and at least one of the following: -Signs and symptoms of HF (dyspnea, fatigue or fluid retention) -Echocardiographic evidence of diastolic dysfunction (left atrial enlargement, engorged inferior vena cava, pulmonary hypertension or elevated E/e´ filling velocity). -and elevated brain natriuretic peptide (BNP).

Strategy of anticoagulation

All the patients presented a CHA_2DS_2-VASc score ≥ 1 and received oral anticoagulation with new oral anticoagulants or vitamin K antagonists (VKAs) for at least 3 weeks. In patients receiving VKAs, therapeutic international normalized ratio (INR) was monitored and the anticoagulant was replaced by subcutaneous enoxaparin (1 mg/kg bid) before the procedure. In those cases receiving new oral anticoagulants, only the last dose was stopped.

During the procedure and before transseptal puncture, an intravenous bolus of unfractionated heparin was administered (200 UI/kg) and activated clotting time (ACT) was monitored every 30 minutes until it reached 350 seconds or greater. Intravenous protamine was administered after the procedure to revert anticoagulation before removing the intravascular introducers and sheaths. Two hours after the procedure ended, unfractionated intravenous heparin was administered by infusion pump. The following morning, subcutaneous low-molecular-weight-heparin (LMWH) and a VKA were administered. LMWH was not administered in patients taking new oral anticoagulants.

Catheter ablation procedure

All the procedures were performed under general anesthesia. All the patients underwent a 64-detector row computed tomography scan or cardiac magnetic resonance imaging if the patient had contraindications. Transesophageal echocardiography was performed during the procedure only if the levels of anticoagulation were inconsistent to exclude left atrial thrombi or to guide difficult transseptal punctures. 12-lead electrocardiogram (ECG) and intracardiac bipolar electrograms were recorded using electronic calibrators (EP-WorkMate 4.2 System, St. Jude Medical, Inc.) at a screen speed of 50 to 200 mm/s and were filtered at band-pass settings of 50 to 500 Hz.

A non-fluoroscopic mapping navigation system was used in all the cases (Ensite® Velocity® cardiac mapping system, St.Jude Medical Inc.). After both femoral veins were punctured, a decapolar catheter was placed in the coronary sinus. Under radioscopic guidance in the 40° left anterior oblique projection, two transseptal punctures were performed with Brockenbrough needles; then, two long preshaped introducers SL1 and SL2 (St. Jude Medical Inc.) were positioned. A circular duodecapolar Optima Plus® catheter and an irrigated-tip ablation catheter Therapy-Cool® (St. Jude Medical Inc.) were advanced through the introducers. The anatomical reconstruction was performed using the circular Optima Plus® mapping catheter which is capable of simultaneous recording from multiple points. The ablation catheter was used to identify the ostia and the antrum of the pulmonary vein (PV).

The electric activity of each PV was obtained using the circular catheter. Isolation started in the left superior PV and continued in the left inferior PV. The same sequence was used for the right PVs. Radiofrequency energy was delivered at the anterior and posterior aspect of each pulmonary vein with a power output of 40W and of 35 W, respectively. The lesions were applied to the antrum but not the ostia of the veins. The electrograms recorded by the ablation catheter before and after applying the ablation lesion were analyzed in each patient. The target was a reduction of the potential amplitude by 75% and the elimination or dissociation between atrial and PV activity. Once the isolation was completed, the presence of persistent block in each PV was evaluated.If necessary, ablation was repeated to consolidate the line of bidirectional block.

We used all the methods available to discriminate local or remote electrical activity: After pulmonary veins isolation, all the patients with persistent AF underwent electrical cardioversion. In sinus rhythm , other AF ablation techniques were used at the discretion of the treating physician: ablation lines at the cavotricuspid isthmus in the case of atrial flutter history; superior venae cavae or coronary sinus were mapped using the circular duodecapolar catheter and ablated in case of electric activity; complex fractionated atrial electrograms (CFAEs) were mapped with the circular duodecapolar catheter; finally a voltage map was made and those areas with intermediate voltage values (between 0.1 and 0.5 mV) in the left atrium were homogenized.

Patients underwent neurological examination after recovery from anesthesia at the electrophysiology laboratory and before discharge. Upon discharge, the patient continued with the same antiarrhythmic and anticoagulant agent prior to the procedure.

Follow-up

Follow-up visits were scheduled with the electrophysiology service at 1, 3, 6, 9 and 12 months with ECG and 24-hour Holter. In all the cases, the patients underwent physical examination and were interrogated about symptoms suggestive of arrhythmia and HF. If necessary, medical treatment was adjusted and laboratory tests or cardiac imaging tests were ordered. All the visits to the emergency department and hospitalizations due to HF or arrhythmia were also recorded.

Blanking Period

Due to the inflammatory process after catheter ablation, episodes of AF, atrial flutter (AFL) or atrial tachycardia (AT) within the first three months are not considered arrhythmia recurrence.

Success

Success at follow up was defined as the absence of episodes of AF, AFL or AT lasting for more than 30 seconds and documented by Holter monitoring, ECG or centralized monitoring station after the 3-month blanking period. In case of AF recurrence, a second ablation procedure was suggested to the patient.

Clinical improvement

Clinical improvement was defined as improvement by at least one NYHA and a reduction of signs of venous congestion without need of drug adjustment.

Complications

The following events related to the procedure were included:

1.Vascular complications: groin hematoma with a 5-point fall in hematocrit, pseudoaneurysm or femoral arteriovenous fistula.

2.Cardiac tamponade.

3.Stroke or transient ischemic attack (TIA).

4.Worsening of heart failure during the procedure-related hospitalization.

5.Prolonged hospitalization not due to social issues.

Statistical analysis

Discrete variables are expressed as percentages and continuous variables as mean with its corresponding standard deviation. The chi square test was used to compare discrete variables and continuous variables were analyzed using the Student's t test or the Mann-Withney test depending on the distribution of the sample. A multivariate analysis was performed using the Cox proportional hazard regression model. The Kaplan-Meier method was used to compare the groups with and without success. A p value < 0.05 was considered statistically significant. All the statistical procedures were performed using the software package SPSS 21.0.

Ethical considerations

The study protocol was evaluated and approved by the Committee on Ethics of the Instituto Cardiovascular de Buenos Aires. The Argentine personal data protection law 25,326 ensures the confidentiality of all the information. The study was conducted following the recommendations of the Declaration of Helsinki. The principles of the Declaration of Helsinki are fulfilled as the study was approved by the Committee on Ethics, underwent risk benefit assessment and each individual involved in this study was qualified by training to perform the task.

Results

A total of 796 consecutive drug-refractory patients who underwent an AF CA were enrolled. Of these, 99 patients presented signs and symptoms of HF or LVEF less than 45%. We excluded 4 patients with cardiogenic shock, 7 with contraindication to anticoagulation, and 6 with left atrial appendage thrombus, leaving 82 patients in the final analysis.

Baseline characteristics of the population

The cohort was made up of 82 patients undergoing AF CA with signs and symptoms of HF or a LVEF < 45%. Three patients did not complete the 1-year follow-up period and were excluded from the recurrence analysis. Mean age was 62.1 ± 10.5 years and 72.4% were men; 67.2% had hypertension and 8.6% were diabetics. Left ventricular ejection fraction was 49 ± 13.1% and 48.3% had a LVEF < 45%. 25 patients had HFpEF (45%). Left atrial area was 26.5 ± 7 cm2, mean CHA_2DS_2-VASc score was 2, 44.8% presented paroxysmal AF, 38% persistent and 17.2% long-standing persistent AF (total persistent 55.2%). NYHA II-III was present in 70.6%. The antiarrhythmic treatment included amiodarone (63.8%), propafenone (15.5%) and sotalol (6.9%), and 13.8% were not receiving any antiarrhythmic drug due to intolerance[Table 1].

Procedure and complications

The acute procedural success rate was 90%. In one year of follow-up, 47 presented AF after the blanking period (success rate of 40% after one procedure).

The AF freedom rate in HFpEF was lower than in the general population and there was no significant difference compared with reduced LVEF (48% vs 32% respectively; p= 0.28). Median time to recurrence was 4 ± 3.2 months in patients with reduced ejection fraction and 6 ± 2.8 months in HFpEF (p= 0.67). Twenty eight patients underwent a second ablation procedure. The recurrence rate after the second procedure was 44.4% at one year. Therefore, the success rate of SR maintenance after two procedures increased to 72.2%. In addition to pulmonary veins isolation, ablation of extrapulmonary foci was performed in 25 patients (43%). There were no significant differences between patients with recurrence or AF freedom (48% vs. 40%; p= 0.12).

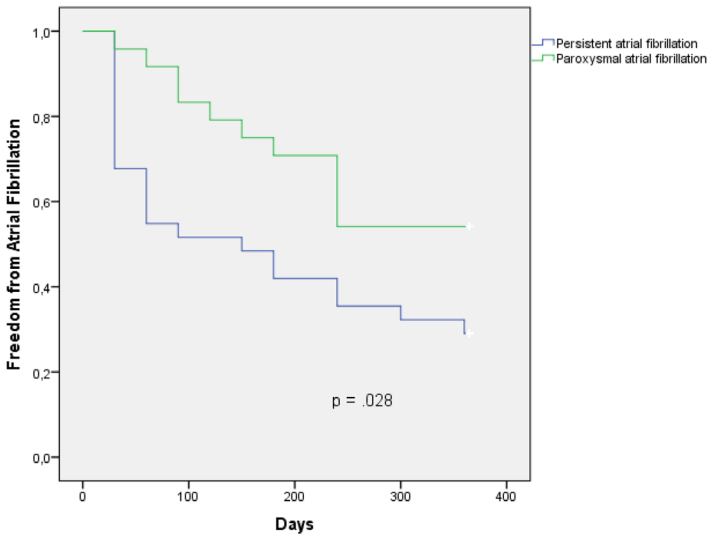


Figure 1: **Freedom from atrial fibrillation compared by the Kaplan-Meier curves with the log-rank test for overall survival. Persistent atrial fibrillation showed a higher recurrence rate compared to paroxysmal atrial fibrillation.**

Of the 110 ablations (82 in the first and 28 in a second procedure), 10 complications occurred (five in reduced and five in HFpEF; total 9.1%): 8 after the first procedure and 2 after the second ablation, and included: 4 HF worsening, 3 vascular complications, 2 cardiac tamponade requiring pericardiocentesis and 1 extreme bradycardia. None of the patients presented stroke, atrioesophageal fistula, symptomatic pulmonary vein stenosis or procedure-related mortality [Table 2].

The rate of complications was 9.1%. There were no significant differences between cardiac tamponade (1.81% vs. 1.9%; p= 0.36) or vascular complications (2.72% vs. 2.3%; p = 0.62%) compared with the trials published for the general population in our country[14].

Predictors of recurrence and follow-up

Patients with recurrence of AF were compared with those who remained free from AF to identify predictors of recurrence and to evaluate the clinical outcome during follow-up. Baseline characteristics such as NYHA functional class, persistent AF, left atrial area or LVEF were analyzed by multivariate analysis using Cox regression. Only persistent AF prior to the procedure was identified as an independent predictor of AF recurrence at 1-year follow-up. [Table 3] A Kapplan-Meier survival curve was performed with the Log-Rank test to compare the free survival from AF according to paroxysmal or persistent AF. [Figure 1] Finally, 79 patients who completed 12 months of follow-up after the first procedure were analyzed. Fourteen patients who remained free from AF presented significant improvement of their functional class, while only twelve patients with recurrent AF had improvement (63.6% vs. 36.4%; p = 0.047). Also, none of the patients in SR were hospitalized, whereas 6 patients with recurrent AF were hospitalized due to HF (0% vs. 18.2%; p = 0.07) [Figure 2]. Thus, 95.5% of the patients in SR and

Table 1: Baseline characteristics before ablation

	Total(82)	Recurrence(47)	Freedom from AF (32)	p
Age	62.1 +/- 10.2	61.0 +/- 11.5	63.8 +/- 9.1	0.41
Male sex	72.4%	72.7%	81.8%	0.43
Hypertension	67.2%	63.6%	77.3%	0.28
Diabetes	8.6%	6.1%	13.6%	0.33
Smoking habit	58.6%	63.6%	54.5%	0.50
Coronary artery disease	20.7%	24.2%	13.6%	0.33
Idiopathic cardiomyopathy	43.3%	41.2%	36.4%	0.79
Myocarditis.	13.3%	11.8%	18.2%	0.77
Tachycardiomyopathy	13.3%	17.6%	9.1%	0.52
Stroke	5.2%	6.1%	4.5%	0.80
CHA_2DS_2-VASc score	2	2	2	0.48
Preserved ejection fraction	43%	40%	54%	0.59
Previous HF hospitalization	41.4%	33.3%	54.5%	0.11
Type of atrial fibrillation				
Paroxysmal	44.8%	33.3%	59.1%	0.59
Persistent	55.2%	66.7%	40.9%	0.6
NYHA				
I	25.9%	24.2%	31.8%	0.53
II	67.2%	69.7%	68.2%	0.63
III	3.4%	6.1%	0.0%	0.23
Medication				
Amiodarone	63.8%	78.8%	40.9%	0.004
Beta blockers	55.2%	57.6%	54.5%	0.82
Propafenone	15.5%	9.1%	22.7%	0.15
Oral anticoagulant	91.4%	93.9%	90.9%	0.67
Echocardiography				
LVEF (%)	49 +/- 13	48 +/- 14	50 +/- 11	0.61
LA (cm2)	26.5 +/- 6	29 +/- 6	26 +/- 6	0.11
LVEF <= 45%	48.3%	48.5%	45.5%	0.82

AF: Atrial fibrillation. HF: Heart failure. NYHA: New York Heart Association. LVEF: Left ventricular ejection fraction. LA: Left atrium.

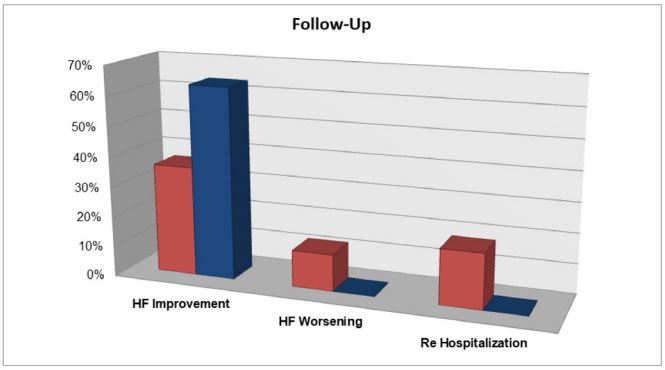
Table 2: Major complications.A higher rate of complications is observed due to the inclusion of worsening of heart failure. The same is not a reported complication in the general population.

Complications: 10 in 110 procedures (9.1%)	
Worsening of Heart Failure	4 (3.63%)
Cardiac tamponade	2 (1.81%)
Groin hematoma	3 (2.72%)
Extreme bradicardia	1 (0.91%)

Table 3: Multivariate Cox regression analysis of predictive factors in recurrence for overall survival. Persistent atrial fibrillation was the only independent predictor (p = 0.042).

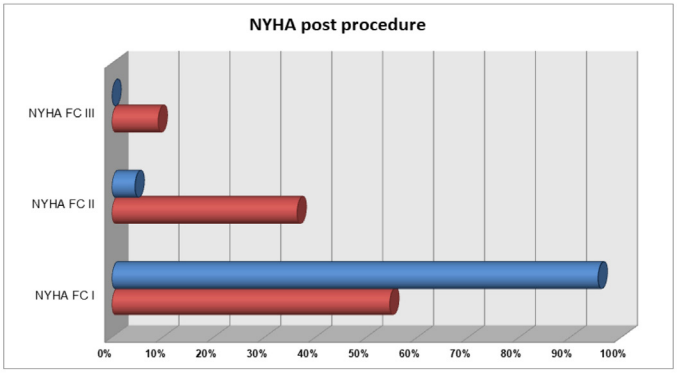
	log HR	(95% IC)	p
Age	0.98	(0.95 – 1.01)	.33
Persistent AF	2.41	(1.38 – 5.47)	.042
LVEF	0.99	(0.96 – 1.02)	.5
LA size	0.99	(0.94 – 1.06)	.97
NYHA	1.24	(0.66 – 2.55)	.54

AF: Atrial fibrillation. NYHA: New York Heart Association. LVEF: Left ventricular ejection fraction. LA: Left atrium.



	Recurrence (47)	Freedom from AF (32)	p
HF Improvement	36.4%	63.6%	0.047
HF Worsening	12.1%	0.0%	0.09
Re Hospitalization	18.2%	0%	0.07

Figure 2: Differences at one year follow-up between patients with recurrence or freedom from atrial fibrillation. Heart failure functional class improvement was statistically significant using Chi-Square Test



	Recurrence (47)	Freedom from AF (32)	p
NYHA post			0.004
NYHA FC I	54.5%	95.5%	0.001
NYHA FC II	36.4%	4.5%	0.008
NYHA FC III	9.1%	0.0%	0.14

Figure 3: **NYHA Functional Class at one year follow-up. Patients free from atrial fibrillation have better functional class than those with recurrence using Chi-Square Test.**

54.5% of those with recurrence of AF were free from HF or in functional class I (p = 0.001)[Figure 3].

Discussion

Main findings

The results reported in this study indicate that AF ablation in HF patients with reduced or preserved LVEF is a safe and acceptable therapeutic option. The acute success rate was high, 90% after the procedure, and although 47 patients had arrhythmia recurrence, a second procedure was successful in maintaining SR at one year in 72.2% of the cases, without increasing the incidence of complications. The improvement of symptoms and the hospitalization rate showed that SR maintenance had significant benefits in these patients. Of the variables analyzed, persistent AF before the procedure had a significant association with AF recurrence at one year. Probably, early intervention of AF in HF patients will improve SR rate during follow-up.

Our study also analyzed the population with preserved LVEF. The recurrence rate of AF at one year of follow-up was higher than in the general population, however, they also benefited clinically with catheter ablation[14].

The rate of complications was higher in our study due to HF worsening, a complication that was not included in publications evaluating the general population (9.1% vs. 4.6%; p = 0.03)[14]. We did not register major events such as death or stroke. Also, no patient required inotropic agents, vasopressors or mechanical ventilation.

Pathophysiology and previous studies

Atrial fibrillation and HF are two conditions that impair quality of life and reduce longevity. The prevalence of AF in patients with HF enrolled in clinical trials ranges between 15 and 45%[15-19]. Atrial fibrillation increases the risk of embolic stroke and tachycardiomyopathy, and is associated with reduced survival. The association between HF and AF worsens the prognosis, with a survival rate between 25 and 40% at 5 years according to the previous NYHA. Each condition increases the severity and worsens the outcome of the other.

There are several pathophysiological mechanisms that perpetuate both pathologies. Heart failure produces diastolic insufficiency, electromechanical remodeling of the left atrium, increased sympathetic tone and hydrosaline retention. This increases the rate of episodes of AF. Atrial fibrillation begins as an isolated ectopic activity mainly from the pulmonary veins. Subsequently, with the chronicity of both pathologies, the electrical and mechanical remodeling of the left atrium worsens, causing the perpetuity of the arrhythmia from multiple wave fronts. The electrical and anatomical changes associated with AF worsen heart failure, a situation that also worsens the evolution of atrial fibrillation, generating a vicious loop[20].

Several studies have compared the efficacy of rate control versus rhythm control in HF patients, but did not show better outcomes with one strategy over the other. However, these studies only used medical treatment for rhythm control with suboptimal efficacy to maintain patients in SR[6]. In addition, 21% of the patients in the rhythm control group crossed over to the rate control group due to impossibility to maintain SR, and 10% of those in the rate control group crossed over to the rhythm control group, mostly due to HF worsening[21]. The adverse events of the medications and the presence of contraindications in patients with structural heart disease were other factors that failed to maintain SR.

The superiority of CA over antiarrhythmic treatment in patients with symptomatic AF has been already demonstrated[22-25]. several studies analyzed the role of CA in HF patient using functional endpoints with different results.

The study by McDonald et al., included patients with persistent AF and advanced HF and failed to demonstrate significant improvement in LVEF and in other secondary endpoints as six-minute walk distance, quality of life and NTproBNP, compared with a rate control strategy. After 14 months, only 50% of the patients in the CA group remained in SR The inclusion of patients with persistent AF and advanced HF could explain the high rate of recurrence without achieving the final endpoints.

In patients with AF refractory to antiarrhythmic treatment, left ventricular dysfunction and HF in NYHA class II-III, pulmonary veins isolation showed significantly better quality of life, longer six-minute walk distance and higher LVEF compared with ablation of the AV node and biventricular pacing after 6 months[11].

The CAMTAF trial analyzed CA in patients with persistent AF, HF and LVEF < 50% and showed significant improvement of LVEF, oxygen consumption and quality of life at 6 months compared with rate control. Freedom from AF was achieved in 81% of patients at 6 months of follow-up without antiarrhythmic drugs[12]. Despite the short follow-up period, the high rate of freedom from AF is associated with clinical improvement.

More recently, a study compared CA versus rate control in patients with persistent AF, HF and LVEF < 35%. The primary endpoint

-improvement in oxygen consumption at 12 months was significantly higher in patients undergoing CA. The Minnesota score and BNP also showed significant improvement[26]. None of the studies mentioned above analyzed rehospitalization due to HF, a significant prognostic indicator.

Finally, the CASTLE-AF study,[27] a randomized trial recently presented in the 2017 ESC congress, enrolled 363 patients with symptomatic paroxysmal or persistent AF, intolerance to take at least one antiarrhythmic drug, LVEF less than 35% and NYHA FC ≥2 with implantable cardioverter-defibrillator or cardiac resynchronization therapy-defibrillator with home monitoring capabilities. This study showed that catheter ablation was superior at preventing death or heart failure admissions (28.5% vs. 44.6%; p = 0.007). However, unlike our work, HF patients with preserved LVEF were not included. It is known that atrial fibrillation is a frequent cause of diastolic failure and that diastolic failure predisposes to AF recurrence after medical treatment or radiofrequency ablation[28,29]. Therefore, HFpEF patients would also benefit from catheter ablation.

Clinical Implications

The clinical impact found in our work is due to keeping patients with HF in SR. The success achieved with catheter ablation improves the functional class and reduces re-admissions for heart failure in HF patients with reduced or preserved LVEF.

This is achieved without increasing the rate of complications, as has occurred in pharmacological treatment trials to maintain SR. As we have previously seen, most of the studies evaluating CA in HF patients showed benefits in terms of quality of life, six-minute walk distance and LVEF. Our initial experience shows that the success rate at one year in patients with HF and AF treated with CA was acceptable, and that the patients who remained in SR had better NYHA functional class and fewer re-hospitalizations. Symptoms relief and reduction of hospitalizations are endpoints with a positive impact on the evolution of the disease and on the healthcare system. Likewise, patients with preserved LVEF, a poorly studied population, benefited as much as those with reduced ejection fraction.

Study Limitations

This study has several potential limitations. Firstly, it is a single-center and observational study. The rate of success and of complications could be different in each center. In addition, the ablation technique varies according to each case and to the discretion of the attending physician. Secondly, although we recorded the complications in our database, those occurring after discharge could have been lost. Thirdly, the information about patients living in other cities or neighboring countries followed-up by telephone calls could be underestimated.

Conclusions

Catheter ablation of atrial fibrillation in heart failure patients presents an adequate success rate in patients refractory or intolerant to antiarrhythmic treatment, improving symptoms and reducing re-hospitalizations due to heart failure. The benefit was observed both in preserved and reduced ejection fraction. Persistent atrial fibrillation is an independent predictor of recurrence.

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Immediate and Long Term Effects Of Percutaneous Mitral Balloon Valvuloplasty On Atrial Conduction Velocities In Patients With Mitral Stenosis

Hicaz Zencirkiran Agus[1], Serkan Kahraman[1], Begum Uygur[1], Arda Guler[1], Gokhan Demirci[1], Ali Kemal Kalkan[1], Mehmet Erturk[1], Mustafa Yildiz[1]

[1] *Istanbul Sağlık Bilimleri Univercity Mehmet Akif Ersoy Cardiology and Cardiovascular Surgery Institute, İstanbul.*

Abstract

Background: P-wave dispersion (PWD) is an electrocardiographic (ECG) marker of nonuniform and heterogeneous atrial conduction with ECG leads of different orientation. The aim of our study was to investigate the immediate and long term effects of successful percutaneous mitral balloon valvuloplasty (PMBV) on PWD in severe rheumatic MS patients and to analyse the restenosis, atrial fibrillation (AF) and redo balloon valvuloplasty rate.

Methods: We enrolled 41 consecutive MS patients with sinus rhythm who underwent PMBV. A 12-lead ECG and transthoracic echocardiography were performed for each patient one day before, within 72 hours after the procedure and followed up by clinical visit at a mean of 5,57±1,46 (3-8) year.The mean patient age was 44.1±10.86 years.

Results: Pmax 1(pre PMBV) and PWD 1(pre PMBV) decreased 1-3 days after PMBV. MVA improved immediately after the procedure; but lately the mean MVA decreased significantly indicating the initiation of restenosis. Composite endpoints were associated with LA 1 ($p = 0.02$), MVA 2 (1-3 days after PMBV) ($p= 0.019$), mean gradient 2 ($p= 0.028$), PWD 3 (3 years after PMBV) ($p < 0.001$) and Pmax 3 (3 years after PMBV) (<0,001). AF incidence was associated with PWD 2 (p=0,019) and PWD 3 (p=0,010). There was 14 composite endpoint on follow up and at multivariate analysis PWD 3 was identified as an independent predictor of the composite endpoint (p=0.048, hazard ratio=1.36, 95% confidence interval (CI): 1,002−1.867).

Conclusions: This study has demonstrated that Pmax and PWD significantly decreased within 3 days after PMBV. Furthermore, long term PWD was associated with AF and identified as an independent predictor of the composite endpoint.

Introduction

Rheumatic mitral stenosis (MS) is frequently seen in developing countries and causes significant morbidity and mortality[1]. Percutaneous mitral balloon valvuloplasty (PMBV) has become an effective and safe procedure for symptomatic or hemodynamically significant MS with favorable valve anatomy[2]. This procedure is highly successful with a low complication rate and significant short and long term improvement in hemodynamics and symptoms[3,4]. P wave dispersion (PWD) is an electrocardiographic (ECG) marker of nonuniform and heterogeneous atrial conduction with ECG leads of different orientation[5]. It can be defined as the difference between maximum and minimum P wave duration. Previous investigations have shown that Pmax and PWD are increased in patients with rheumatic MS and decreased with PMBV[5,6]. In addition the prolongation of intraatrial and interatrial conduction time and the inhomogeneous propagation of sinus impulses are well known electrophysiologic characteristics of the atrium prone to fibrillate. Prolonged P-wave duration and increased PWD have been reported to carry an increased risk for atrial fibrillation (AF)[5]. Therefore, we aimed to investigate the immediate and long term effects of successful PMBV on PWD in severe rheumatic MS patients with sinus rhythm (SR) and to analyse the restenosis, AF and redoballoon valvuloplasty rate.

Key Words

Percutaneous Mitral Balloon Valvuloplasty, Mitral Stenosis, P Wave Dispersion.

Corresponding Author
Hicaz Zencirkiran Agus,
İstasyon Mah.Turgut Özal Bulvarı No:11 Küçükçekmece- İSTANBUL İstanbul Mehmet Akif Ersoy Eğt. Araşt. Hast., Kardiyoloji Kliniği, İstanbul

Methods

Study Population

Seventy one patients who were in sinus rhythm were initially recruited in this study. Patients who had intraventricular conduction defect (n=2), developed AF within three years of the study (n=11) and patients lost to follow-up (n= 17) were excluded from the study. Therefore, we enrolled 41 consecutive patients with MS in sinus rhythm who underwent PMBV in our institution between 2009 and 2012. Of these patients, we analyzed those who had regular follow up visits. The mean follow up period was 5,57±1,46 (3-8) years. Because having AF at 3rd year for four patients, we examined ECG at 3rd year for all patients and continued to follow up clinically and echocardiographicly. We wanted to demonstrate our long term observation; so who developed AF within 3 years excluded.

Furthermore we showed the effect of differentiation in PWD to AF and composite endpoint in long term (mean duration of 5,57 years), for patients who were in normal sinus rhythm during first 3 years.

A 12-lead ECG at 25 mm/s (paper speed) and transthoracic echocardiography using Vivid S5 with the GE 3S-RS Probe were performed for each patient one day before and within 72 hours after the procedure. They also underwent transesophageal echocardiography (TEE) 1 day before the procedure in order to rule out left atrium or appendage thrombosis. Evaluations included mitral valve area (using planimetry or the Doppler pressure half-time method), mitral gradient, echocardiographic score, mitral regurgitation (MR), tricuspid regurgitation (TR), pulmonary artery pressure. Mitral valve anatomy was scored according to the Wilkins echo scoring system[7]. The indications for PMBV were; symptomatic patients with moderate or severe MS with favorable valve morphology; symptomatic patients with unfavorable valve morphology but at high risk for surgery and asymptomatic patients with high thromboembolic risk and haemodynamic decompensation. Procedural success was defined as MVA >1.5 cm2 without severe mitral regurgitation. Exclusion criteria were having a significant valve disease other than secondary tricuspid regurgitation, left ventricular hypertrophy , left ventricular disfunction, coronary heart disease, atrial fibrillation, bundle branch block or evidence of any other intraventricular conduction defect, previous pacemaker implantation, electrolyte abnormalities, hyperthyroidism, hypertension, diabetes mellitus, taking any chronotropic medication such as digoxin.

Echocardiography

Comprehensive 2-dimensional transthoracic echocardiograhy (TTE) was performed using Vivid S5 in all patients before PMBV, within 72 hours and at follow up visits. All patients were examined in the left lateral and supine position by precordial M-mode, 2-dimensional, Doppler, and Doppler tissue echocardiography. Left ventricle (LV) enddiastolic and endsystolic diameters, and endsystolic left atrial (LA) diameter were measured from M-mode in the parasternal long-axis views according to the standards of the American Society of Echocardiography. The mitral valve area (MVA) was measured by direct planimetry of the mitral orifice in a 2-dimensional short axis view early in diastole and also by the pressure half-time method. Continous wave Doppler was used to calculate the mitral gradient and the peak pressure gradient of TR by using the Bernoulli equation. Color flow Doppler was used to detect the presence of mitral regurgitation.

Electrocardiography

A 12-lead electrocardiogram was recorded for each patient 1 day before PMBV, on the first day after successful PMBV and at third year at a rate of 25 mm/s in a supine position. P- wave durations were measured manually by two investigators blinded to the clinical details of the patient, using digital calipers and magnifying lens (fivefold magnification) to define the electrocardiographic deflections. Intra- and interobserver coefficients of variation were found to be 3% and 4% for PWD. P-wave duration was measured from the onset to the offset of the P wave. The longest P-wave duration measured on any of the 12 ECG leads was defined as the P maximum (Pmax) and the shortest P-wave duration on any lead was defined as the P minimum (Pmin). The difference between Pmax and Pmin was calculated and defined as P-wave dispersion (PWD).

Percutaneous Mitral Balloon Valvuloplasty

The procedure was performed by experienced interventional cardiologists. PMBV was performed via the transvenous (antegrade) approach through the femoral vein using a transseptal Brockenbrough needle, following the technique described by Inoue et al.[8]. Initial balloon size was selected according to body surface area. Maximum balloon size was determined by the following formula: (Patient's height (cm)/10) + 10. Procedural success was defined as MVA >1.5 cm2 without severe mitral regurgitation (MR) (≤ 2/4 MR) in the absence of in-hospital major adverse cardiac and cerebrovascular events, including any death, stroke, mitral surgery and cardiac tamponade.

Follow Up

Demographic, clinical, and procedural variables were collected. All patients were followed up for 5,57±1,46 (3-8) years after the index PMBV. Restenosis was defined as MVA <1.5 cm2 from follow up TTE. Composite endpoints included AF, restenosis, redoballoon, mitral valve surgery.

Statistical Analysis

Statistical analysis was made using the computer software Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 21.0. released 2012, IBM Corp., Armonk, New York, USA) and data were expressed as "mean (standard deviation; SD)" for variables with normal distribution, "n (%)" for categorical variables and "median (minimum- maximum)" for variables with abnormal distribution. Fisher's exact test and Pearson chi- square analysis performed for categorical variables. Fitness to normal distribution was analyzed with the shapiro wilk test. Mann-Whitney U test was used for comparing quantitative variables with abnormal distribution while Student t-test was used for comparing the means between two groups with normal distribution. Spearman and Pearson correlation tests were performed for correlations between ordinal variables or continuous variables with normal or abnormal distribution. Friedman's 2-way ANOVA test was used to analyze related samples with abnormal distribution while Greenhouse Geisser test was used to analyze related samples with normal distribution. A p-value < 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curve was used to compare the prognostic ability of the PWD to predict the rates of major advers cardiac events.

Results

In this study, we enrolled 41 patients. The mean patient age was 44.1±10,86 years and 95% (n:39) of the patients were female. The median Wilkins echo score in all patients was 8 (range: 6-12). All patients' mitral regurgitation grade was <2/4. Baseline characteristics were shown in [Table 1]. All patients underwent successful PMBV. We grouped patients as 1 (prePMBV), 2 (1-3 days after PMBV), 3 (long term after PMBV) according to the time of PMBV. All patients had normal LV systolic function. There were no significant differences

with respect to left ventricle enddiastolic (LVEDD) and endsystolic diameter (LVESD), left ventricle ejection fraction (LVEF) and Pmin between three groups. Statistically significant improvement in LA diameter, MVA, PAPs, max mitral gradient, mean mitral gradient, Pmax and PWD were achieved in all patients (p<0.001), [Table 1]. A comparison of changes in electrocardiographic and echocardiographic parameters between three groups are displayed in [Table 1]. Mean pre-PMBV MVA (MVA 1) was 1.07±0.19 cm2 and significantly improved to 1,91 ± 0,35 cm2 after PMBV (MVA 2) (p<0.001). At long term the mean MVA (MVA 3) was significantly decreased to 1,63±0,40 (p<0,001). Mean pre-PMBV mean gradient was 14,51±6, 22mmHg, which significantly decreased to 5,76±3,04 mmHg (p<0,001) within 72 hours after PMBV. At long term the mean gradient significantly increased to 7,29±3,92 mmHg (p=0,004). Median PAPs 1 was 45 (30-120) mmHg and significantly decreased to 35 (25-120) mmHg (p:<0,001) ; at long term the mean PAPs was 35 (20-115) mmHg indicating nonsignificantly difference (p=1,0). The median LA 1, LA 2, LA 3 diameter was 44 (34-69), 42(33-54), 42 (33-54) cm (p<0,001, p<0,001, p=0,673). Pmax 1 and PWD 1 decreased 1-3 days after PMBV (Pmax 2;PWD 2); (p<0,001) but the difference at 3 year was insignificant (Pmax 3; PWD 3) (p=1,0 for Pmax; p=0,961 for PWD) ([Figure 1], [Table 1]). Pmin didn't differ between groups (p=0,092). Median PWD 1 was 45 (30-68 ms, PWD 2 was 35 (20-59) ms indicating significantly difference (p<0,001).

Table 1: Baseline and after PMBV clinical, electrocardiographic and echocardiographic characteristics of patients

	pre-PMBV	1-3 days after PMBV	long term after PMBV	p
Age (years)	44,1±10,86	-	-	-
Echo score	8 (6-12)	-	-	-
Gender (F/M)	39/2	-	-	-
MVA	1,07±0,19	1,91±0,35	1,63±0,40	<0,001
Max grad	23±8,6	12±5,54	15,1±6,02	<0,001
Mean grad	14,51±6,22	5,76±3,04	7,29±3,92	<0,001
PAPs	45 (30-120)	35 (25-120)	35 (20-115)	<0,001
LA diameter (cm)	44 (34-69)	42 (33-54)	42 (33-50)	<0,001
LVESD (cm)	28 (19-37)	29 (21-39)	30 (15-39)	0,142
LVEDD (cm)	46 (38-52)	47 (33-55)	48 (32-53)	0,058
LVEF (%)	65 (55-65)	65 (50-65)	60 (50-65)	0,131
P-max (ms)	143 (120-165)	130 (110-157)	130 (110-155)	<0,001
P-min (ms)	100 (75-115)	95 (75-115)	95 (80-111)	0,092
PWD (ms)	45 (30-68)	35 (20-59)	35 (22-59)	<0,001

In correlation analysis, negative correlation was detected between MVA 1 and PWD 1 (r=-0.097, p=0.047). PWD 2 was positively correlated with echo score , PAPs 1, LA 1 and LA 2. Furthermore, PWD 3 was also correlated with LA 1, LA 3, PAPs 3, MVA 3 positively. In long term follow up; 4 AF, 12 restenosis occurred and 2 patients underwent mitral valve replacement with mechanical prosthesis, 3 patients underwent redoballoon. We therefore analyzed patients, who had composite endpoints (atrial fibrillation, restenosis, redoballoon, mitral valve surgery). Fourteen composite endpoints were seen. Restenosis occured at an average of 3,92±2,15 year. Composite endpoint was associated with LA 1 (p = 0.02), MVA 2 (p= 0.019), mean gradient 2 (p= 0.028), PWD 3 (p < 0.001) and Pmax 3(<0,001) ([Table 2], [Figure 2]). Additionally the incidence of the AF endpoint was associated with PWD 2 (p=0,019) and PWD 3 (p=0,010). By receiver operating characteristic (ROC) curve analysis, increased PWD was significantly associated with adverse cardiac events (area under ROC curve [AUC]:0,905, %95 confidence interval [CI]:0,813-0,996). The best cut-off value was defined as 39 ms for MACE (Accuracy = 90.5%, sensitivity = 85,7%, specificity = 81,5%) [Figure 3].

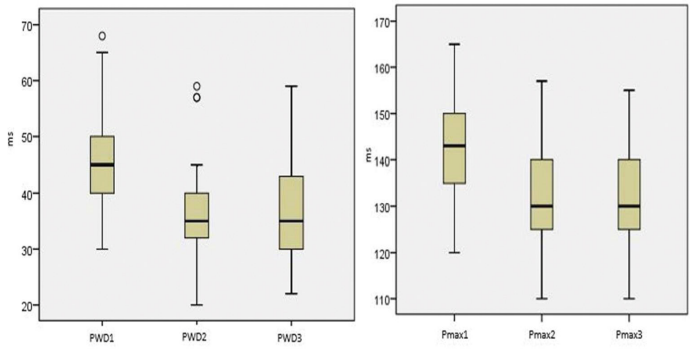

Figure 1: Box-plot representations for PWD and Pmax between three groups. PWD 1/Pmax 1:pre PMBV, PWD 2/Pmax 2:1-3 days after PMBV, PWD 3/Pmax 3:3 years after PMBV.

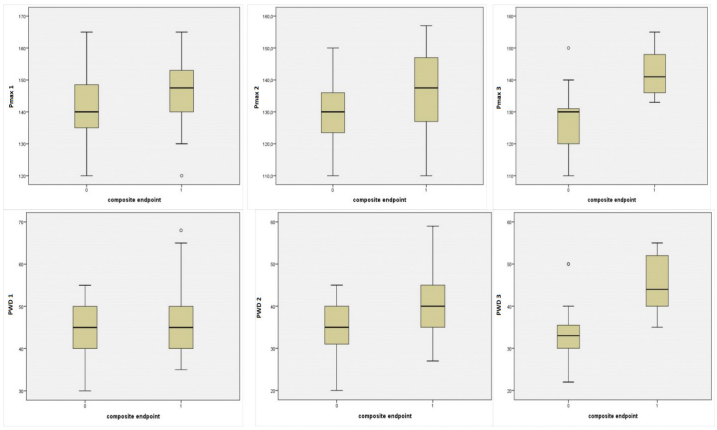

Figure 2: Box plot of ECG parameters comparing MACE – and MACE +.

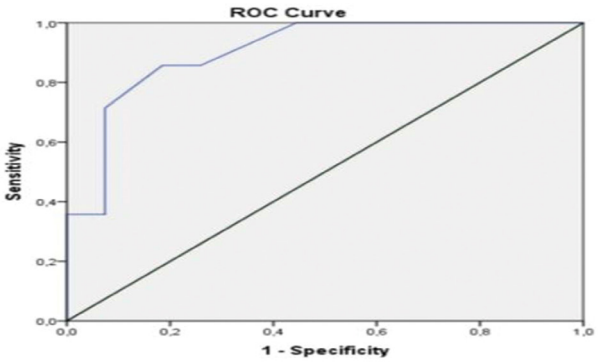

Figure 3: ROC curve analysis for PWD. To determine the best cut-off value that discriminated between MACE+ and MACE-. The cut-off was defined as 39 ms [Accuracy = 90.5%, sensitivity = 85,7%, specificity = 81,5%]

Discussion

This study has demonstrated that PWD 2 and PWD 3 were associated with AF and PWD 3 was an independent predictor of long term event. We also found that Pmax and PWD significantly decreased 1-3 days after PMBV as previously described by other studies[6,9,11]. Three years later median Pmax and PWD didn't change. MVA improved immediately after the procedure but later the mean MVA decreased significantly indicating the initiation of restenosis. The constancy of PWD lately, can be explained by the onset of restenosis. Greater ECG changes are achieved acutely and persist in the long term. However, patients with detoriated ECG parameters were interpreted as composite endpoint precursors in long term.

We found that PWD 1 was negatively correlated with MVA 1 and also PWD 3 was correlated with age, MVA 3, LA 1 and LA 3. These findings suggest that increasing mitral stenosis and larger LA volume are associated with more severe structural changes in the left atrium, leading to greater electrical inhomogeneity, non-uniform conduction velocities within the atrial myocardium, which manifests on the ECG as increased P-wave dispersion. So if PWD is longer than before, we can think about small MVA, larger left atrium requiring therapy.

Table 2: Comparison of clinical and echocardiographic paremeters of patients with and without composite endpoint

		composite endpoint - n:27	composite endpoint + n:14	p
Age		44±12	44±10	0,202
Echo score		8 (6-12)	9 (6-10)	0,376
Pmax				
	Pmax 1	141±11	146±13	0,202
	Pmax 2	129,3±10	135,6±14,3	0,104
	Pmax 3	126,4±9,8	142,4±7,7	<0,001
PWD				
	PWD 1	45±7	46±10	0,578
	PWD 2	35(20-45)	40 (27-59)	0,081
	PWD 3	33±7,2	46,1±7,8	<0,001
MVA				
	MVA 1	1±0	1±0	0,968
	MVA 2	2 (2-3)	2 (2-2)	0,019
Max grad				
	max grad 1	24 (12-46)	22 (8-34)	0,379
	max grad 2	11 (5-24)	13 (7-32)	0,194
Mean grad				
	mean grad 1	15±7	14±5	0,788
	mean grad 2	5 (2-13)	5 (4-18)	0,028
PAPs				
	PAPs 1	45 (30-110)	53 (35-120)	0,406
	PAPs 2	35 (25-62)	35 (30-120)	0,577
LA				
	LA 1	44 (34-69)	47 (37-62)	0,020
	LA 2	42±5	42±2	0,568

Rheumatic MS still remains a major health problem in developing countries. A common arrhythmic complication encountered in patients with MS is AF. Indicators of electromechanical heterogeneity along the atria reflect the pathological changes within the atrium and also indicate an increased risk for AF development [10]. For patients with MS, disorganization of the atrial muscle bundles may be present. Structural changes in LA due to MS cause inhomogeneous electrical properties, abnormal conduction velocities and local dispersion of refractoriness within the atrial myocardium. This electrophysiological characteristic results in increased PWD and Pmax on electrocardiographic measurements. It has been reported that patients with rheumatic MS have increased PWD compared with control subjects[11-13]. Demirkan et al.[6] have shown in a study including 30 patients who were eligible for PMBV, that there was statistically significant decrease in atrial electromechanical delay (AEMD) with P-max and PWD in the early period after PMBV (in 72 h). In another study, it was shown that only successful PMBV was associated with a decrease in Pmax and PWD[14]. Similar to our results; successful PMBV procedure results in a decrease in PWD. The decline of PWD immediately after PMBV was not supported by Beig et al[15]; they found statistically significant decrease in inter and intraatrial electromechanical delays. Prolongation of P-wave duration and increased PWD were correlated with increased AF risk according to previous studies[5,16]. The correlation between the presence of intraatrial conduction abnormalities and the induction of paroxysmal AF have been well documented[17]. All these findings suggest that mechanical dilation of the mitral valve with a balloon also reduces susceptibility to AF even in the early period[18]. In our study finding an association between AF and PWD 2 / PWD3 support these results.

Our study is the first study that has long term follow-up for PWD in patients with MS. Consistent with previous studies, we documented a significant decrease in P-max and PWD after successful PMBV. The supplementary finding of this study is that after PMBV, late term PWD was associated with AF and identified as an independent predictor of the composite endpoint. By ROC curve analysis, increased PWD was significantly associated with major advers cardiac events. The 39 ms PWD cut-off level was of significant diagnostic value for MACE by the ROC curve analyses ([Figure 3]). In the light of these information, following MS patients with atrial conduction properties can be useful for restenosis and AF prediction. Further prospective randomized studies are required to confirm our results.

Limitations

The main limitation of our study was relatively a small sample size. We were obliged to get ECG at 3rd year because of having patients with AF at that year.Therefore long-term follow up was not possible electrocardiographicly. Additionally, we measured the conduction

times only with ECG and did not use electrophysiological study which is the gold standard method, to validate our results. Further prospective studies should be carried out to clarify the relationship between atrial conduction properties and the incidence of AF and restenosis.

Conclusions

This study has demonstrated that Pmax and PWD significantly decreased within three days after PMBV, furthermore, late term PWD was associated with AF and identified as an independent predictor of the composite endpoint. Patients without any decrease in Pmax and PWD long term after PMBV may potentially be at greater risk for atrial fibrillation and restenosis. By electrocardiographicly P wave indices, immediate and long term effects of PMBV on relieving mitral valve obstruction can be reflected and also AF and restenosis can be predicted.

Conflict of Interest

None.

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Hybrid Ablation of Ventricular Tachycardia: A Single-Centre Experience

Mindy Vroomen[1], Bart Maesen[2], Mark La Meir[3], Justin G.L Luermans[1], Kevin Vernooy[1], Jos G. Maessen[2], Harry J. Crijns[1], Laurent Pison[1]

[1] Department of Cardiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht, Maastricht, the Netherlands.
[2] Department of Cardiothoracic Surgery, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht, Maastricht, the Netherlands .
[3] Department of Cardiac Surgery, UZ Brussel, Brussels, Belgium.

Abstract

Background: The long-term results of endocardial and percutaneous epicardial catheter ablation of ventricular tachycardia (VT) in patients with structural heart disease are disappointing. Arrhythmia recurrence after ablation, and VTs with an epicardial substrate remain a clinical challenge. The purpose of this manuscript is to elaborate on feasibility and potential advantages of a surgical hybrid ablation (i.e., combined endocardial and surgical epicardial ablation) based on our initial experience consisting of five cases.

Methods: Endocardial electro-anatomical voltage and activation maps were created (Carto, Biosense Webster, California, USA), and endocardial radiofrequency applications were applied at exit sites, low voltage areas and isthmi. Next, after surgical access, epicardial voltage and activation maps were produced in combination with visual assessment of the epicardial substrate. Epicardial low voltage areas, isthmi and exit sites were identified and ablated using radiofrequency energy.

Results: After the procedure, VT was non-inducible in 80% of the cases (4/5, in one case no induction was performed). No peri-procedural complications occurred. After a mean follow-up of 18 months, one patient remained in sinus rhythm without, and 2 with use of antiarrhythmic drugs. One patient needed a redo procedure after 21 months, and in one patient the amiodarone dose was raised because of 2 sustained VTs. After this additional treatment, both kept sinus rhythm.

Conclusions: Hybrid VT ablation is a safe and effective patient tailored procedure that comprises the major advantage of combining direct anatomical visualization and enhanced catheter stability with high-density 3D mapping. As a consequence, this procedure should be considered as a valid treatment option in complex VT management.

Introduction

Ventricular tachycardia (VT) is an important cause of cardiac morbidity and mortality. In structurally diseased hearts, like coronary artery disease, the mechanism of VT is predominantly based on macro reentry due to scars in the myocardial tissue[1,2]. Achieving transmural ablation lesions in these scars remains challenging because they often consist of fibrotic strands branching out into the myocardial wall. Examples of non-ischemic VT causing diseases are, among others, arrhythmogenic right ventricular cardiomyopathy (ARVC) and Chagas disease[3].

Implantable cardioverter-defibrillators (ICDs) are critical to prevent sudden cardiac death, whereas preventing recurrence of the arrhythmia is of utmost importance for patient well-being and long-term survival[4,5]. Endocardial catheter ablation has emerged as an important option in preventive VT treatment[6]. Epicardial ablation usually is performed only in cases where endocardial mapping fails to identify the site of the arrhythmia, or if the source of the VT is suspected to be located in the epicardium, as suggested by electrocardiographic characteristics of the VT, the underlying disease or imaging. In case of suspicion of epicardial involvement, first-line simultaneous endo-epicardial ablation might be considered[7,8]. Epicardial access and ablation can be performed percutaneously using a subxiphoid puncture[9], however, dry pericardial puncture has its known complications (e.g. cardiac perforation, vessel and nerve injury and pneumothorax)[10].

Combining an endocardial approach with epicardial surgical access during the same procedure, i.e. hybrid VT ablation, could overcome the mutual technical challenges and result in enhanced visualization and characterisation of the substrate and superior outcome. This manuscript aims to describe the feasibility and potential advantages of this hybrid procedure. Based on our single-centre experience, a

Key Words
Ventricular Tachycardia, Hybrid Ablation, Endocardial-Epicardial Ablation, Endo-Epicardial Ablation, Surgical Ablation

Corresponding Author
B. Maesen,
Department of Cardiothoracic Surgery PO Box 5800, 6202 AZ, Maastricht, The Netherlands

series of five complex cases with frequently recurring monomorphic sustained VTs of different aetiologies is discussed.

Methods

The five procedures were carried out between November 2013 and February 2016 in the hybrid operating room (OR) of the Maastricht University Medical Center, Maastricht, The Netherlands. The interventions were performed under general anaesthesia with double-lumen endotracheal tube placement for selective single lung ventilation. In case 3 a single-lumen tube was placed. All patients were placed in supine position on the operating table, with arms next to the body. A His bundle catheter (St. Jude Medical, Minnesota, USA) was positioned through a 6 Fr sheath in the right femoral vein, and a ThermoCool irrigated tip contact force mapping and ablation catheter (Biosense Webster, California, USA) was advanced through an 8 Fr sheath in the right femoral vein or artery. All patients except one (case 3), then underwent heparinization to maintain an activated clotting time above 300 seconds. In case of sinus rhythm (SR), an endocardial electro-anatomical voltage map (cut-offs 0.5 – 1.5 millivolt (mV)) was created and subsequently VT was induced through programmed ventricular stimulation via the His catheter, with or without administration of isoprenaline. If VT was induced and hemodynamically tolerated, an activation map was constructed (Carto, Biosense Webster). Radiofrequency (RF) applications (maximum output 40Watt (W)) were then applied at the exit sites (i.e. sites of presystolic potentials during VT, or pacing sites with identical QRS morphology to the clinical VT), isthmi (i.e. conductive myocardial tissue delineated by nonconductive tissue, 0.5-1.5mV) and low voltage areas (i.e. nonconductive tissue, <0.5 mV). If no VT was inducible, or if the patient became hemodynamically unstable after VT induction, only substrate modification was performed: ablation of local abnormal ventricular activities (LAVA), i.e. low voltage and fractionated potentials annotated after the QRS complex[11].

Next, in the first two cases, the left lung was deflated, followed by left anterolateral mini-thoracotomy without rib spreading using a soft tissue retractor [Figure 1]. The serratus anterior muscle and the intercostal muscles were cleaved, the pectoralis muscle was spared. The pericardium was opened ventrally of the phrenic nerve. In the third case, a re-sternotomy was performed. In the last two cases the access to the heart was provided by one-sided thoracoscopy using three access ports. An epicardial activation and voltage map (Carto, Biosense Webster; cut-offs 0.5 – 1.5mV) of the area of interest, as identified by endocardial mapping, were created using the endocardial catheter (Thermocool irrigated tip, Biosense Webster). Epicardial low voltage areas, isthmi and exit sites were identified. Using the same catheter (30-40W), epicardial applications were performed.

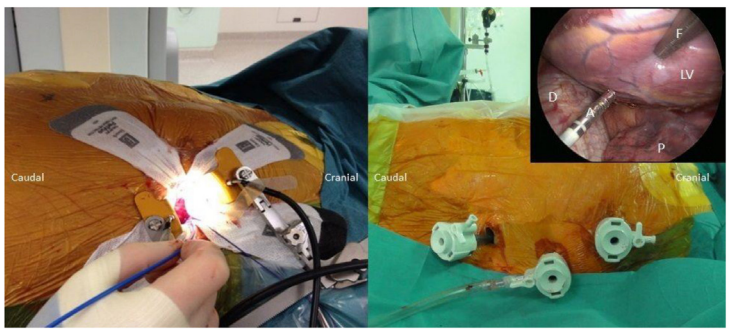

Figure 1: **Intra-operative Images**

Left: Left-sided view of the chest with anterolateral thoracotomy. The endocardial radiofrequency catheter is placed on the epicardial surface. Right: Left-sided view of the chest with thoracoscopy using three access ports. Right upper: Left-sided thoracoscopic view of the heart. D = diaphragm, A = ablation catheter, P = left lung, F = forceps, LV = left ventricle.

After endo- and epicardial ablation repeated VT induction (ventricular stimulation with or without administration of isoprenaline) was performed. If necessary, mapping or ablation was repeated.

Results

Baseline demographic and clinical characteristics

In the following section each case will be discussed separately. A summary of the five cases is depicted in [Table 1].

Case 1 : A 70-year-old man suffering from ischemic VTs with recurrent ICD shocks despite use of amiodarone, underwent 3 endocardial VT ablations. Using an activation map, an isthmus was located and targeted in the middle of the inferoposterior to septal area of the left ventricle (LV) (areas 3/4/5/6 according to Josephson[12,13], [Figure 2]). Substrate modification of the inferior LV was performed during the second ablation. Since this neither provided long-term freedom of VT, and because of suspicion for an epicardial origin on ECG (wide QRS, pseudo delta wave, [Figure 3A]), a percutaneous epicardial ablation was proposed. Access to the pericardium with a subxiphoideal puncture failed (dry tap), and per hospital protocol surgical access is not performed in the electrophysiology (EP) lab. Therefore, only an endocardial ablation was conducted. The exits of 2 induced VTs were mapped at areas 7 to 10 (apical low lateral/inferoposterolateral/anterolateral/lateral basal), where several RF applications were performed. Another VT led to supplemental RF applications at areas 5/6/7 (inferior/inferoposterior/apical low lateral).

In the next days the patient again suffered from sustained VTs and therefore underwent a hybrid VT ablation in the OR, during which an endo- and epicardial ventricular substrate modification (LAVA) was performed (Fig.3B-C-D). A total of 55 applications were performed endocardially in area 5/6/7 (inferior/inferoposterior/apical low lateral), and 19 epicardially. The duration of each application was 30 seconds, the average power 36W and the maximum power 41W. No VT could be induced at the end. The patient was discharged after 3 days in the intensive care unit and 4 days on the regular ward.

After the hybrid procedure the incidence of VT while on beta-blockade was significantly reduced to sporadic sustained VT less than once per year. Twenty-one months after the ablation a sustained VT recurred (RBBB, undefined axis, R/S transition V4, CL440ms), leading to repeat endocardial ablation inferior/lateral (areas 5 to 10). In the following 18 months the patient did not suffer recurrences.

Case 2 : An 80-year-old male with a history of MI and bilateral pulmonary vein isolation for paroxysmal AF, presented with a sustained VT two years after cardiac surgery. Despite amiodarone,

Table 1: Patient demographic and clinical data

			Pre-operative								Operative		Post-operative
Case	Gender	Age	VT Etiology	Location	EF (%)	First VT	Other VT	AAD	ICD	CA	Access	Scar	FU
1	M	70	Ischemic	RCA, LCX, LMA	37	LBBB, superior axis, R/S V2, CL 320ms	2/3. RBBB, inferior axis, CL 310-360ms, 4. LBBB superior axis, R/S V6, CL 390ms, 5. LBBB, superior axis, R/S V2, CL 530ms	Amiodarone	+	3	Left Lateral	AL/I	1 CA, AAD-
2	M	80	Ischemic	LAD, LMA, RDP	41	RBBB, inferior axis, R/S V4, CL 400ms	2. superior axis, CL 395ms, rest unknown	Amiodarone	+	2	Left Lateral	IL	SR, AAD+
3	M	56	ARVC	N.A.	35	LBBB, superior axis, R/S V5, CL 560ms	2. LBBB, superior axis R/S V4, CL 440ms 3.LBBB, inferior axis, R-S V4, CL 420ms	None	-	3	Sternotomy	N.A.	SR, AAD-
4	M	68	Unknown	N.A.	57	RBBB, inferior axis, R/S V5, CL 230ms	-	None	+	0	Left thoracoscopy	N.A.	VT, AAD+
5	M	35	ARVC	N.A.	57	LBBB, inferior axis, R/S V3, CL 380ms	2. PVC: LBBB, superior axis, R/S V5-6 3. PVC: LBBB, inferior axis, R/S V5-6	Sotalol	+	1	Right thoracoscopy	N.A.	SR, AAD+

EF = ejection fraction, VT = ventricular tachycardia, AAD = antiarrhythmic drug, ICD= implantable cardioverter-defibrillator, CA = catheter ablation, FU = follow-up, M = male, ARVC = arrhythmogenic right ventricular cardiomyopathy, RCA = right coronary artery, LCX = left circumflex artery, LMA = left marginal artery, LAD = left anterior descending artery, RPD = right posterior descending artery, N.A. = not applicable, LBBB = left bundle branch block, RBBB = right bundle branch block, R/S = r-wave/s-wave transition, CL = cycle length, AL = anterolateral, I = inferior, IL = inferolateral, SR = sinus rhythm

recurrences with a ventricular rate below the detection zone of the ICD recurred. The LV voltage map during the first endocardial VT ablation showed a low voltage area from area 5/6 (inferior/inferoposterior) to 7/8 (apical low lateral/inferoposterolateral), and an early activation at area 7 (apical low lateral). RF applications in that area terminated the VT. Substrate modification in the exit zone of the VT was also performed (ablation line around the border zone and additional applications at areas 7/8, apical low lateral/inferoposterolateral). Ten days later the same VT recurred, followed by endocardial substrate modification in area 9 (anterolateral).

One month later a hybrid VT ablation was performed for recurrences despite the use of amiodarone and metoprolol ([Figure 4A]). Endocardially, the exit site of the clinical VT was mapped at area 8 (inferoposterolateral). A second VT with a more septal exit could be induced as well. The exit zones and late potentials [Figure 4B] were ablated (14 applications, mean 70 seconds, average output 39W). Adhesions and grafts of the previous cardiac operation, hindered the procedure, but safe mapping and ablation could be performed. The epicardial voltage map correlated with the endocardial map [Figure 4C-Figure 4D]. The exit was also mapped at area 8

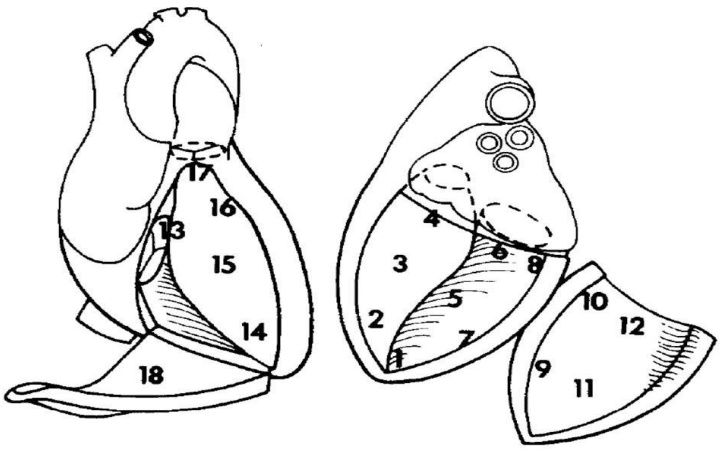

Figure 2: Endocardial Areas of Josephson[13]

Left ventricle: 1 = apex, 2 = apical septum, 3 = mid septum, 4 = basal septum, 5 = inferior, 6 = inferoposterior, 7 = apical low lateral, 8 = inferoposterolateral, 9 = anterolateral, 10 = lateral basal, 11 = midanterior, 12 = superior basal. Right ventricle: 13 = tricuspid annulus/basal septum, 14 = apex, 15 = mid septum, 16 = anterior septum, 17 = outflow tract, 18 = lateral/free wall.

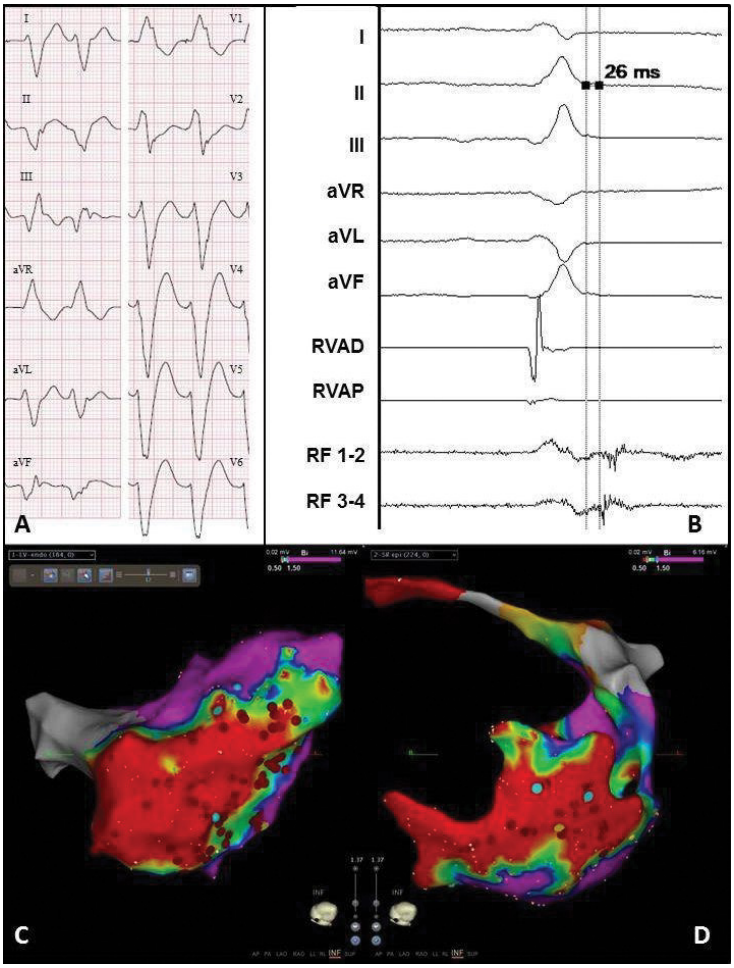

Figure 3: Electrocardiogram and electro-anatomical maps of case 1

A. Twelve-lead electrocardiogram showing a ventricular tachycardia (115bpm) with right bundle branch block morphology, right axis and early R-wave transition, suggesting a lateral mid-apical origin in the left ventricle. Pseudo delta wave and wide QRS suggest epicardial origin.
B. Recording obtained in sinus rhythm during the procedure showing local abnormal ventricular activation at the RF catheter. RVAD/P = right ventricular apex distal/proximal, RF = radiofrequency.
C. Inferior view of the bipolar endocardial voltage map showing a low voltage area from inferoposterior to low apical in the lateral wall (area 5/6/7). Red dots = RF applications.
D. Inferior view of the bipolar epicardial voltage map showing a low voltage area consistent with the endocardial map. Red dots = RF applications.

(inferoposterolateral), and this zone and late potentials were ablated epicardially (11 applications, mean 45 seconds, average output 34W). Because of transient ST-segment elevations inferior, no more VT induction or ablation was performed. After 2 days in the intensive care unit, and 2 days on the regular ward, the patient was discharged.

During 12 months follow-up the patient did not suffer from any recurrences, while using metoprolol 50mg and amiodarone 100mg once per day.

Case 3 : A 56-year-old man was admitted with a therapy refractory incessant VT. On echocardiogram LV function was decreased to 30%, and the right ventricle (RV) was minimally dilated with also decreased function. ARVC was not seen on magnetic resonance imaging (MRI), but 2 of the major ARVC criteria were present: biopsy showed minimal fibrosis and myocytes with vacuolisation, and ECG showed sustained VTs of LBBB morphology with superior axis and inverted T waves in the right precordial leads in SR. Due to hemodynamic instability the patient was connected to extracorporeal life support. An endocardial electro-anatomical map of the RV (Ensite NaVX, St. Jude Medical) showed focal activation (i.e. earliest activation time -20mS during VT) at areas 15 (mid-septum) and 18 (lateral), and RF applications at and between those areas terminated the VT.

When trying to reduce the flow of the external support in the next days, VTs of morphology 1 and 2 recurred. These could not be induced during the second and third endocardial ablation, and a RV bipolar voltage map (Carto, Biosense Webster) showed no zones of low voltages. However, using unipolar signals an extensive low voltage zone (<5.5mV [14]) at areas 17 (outflow tract) and 18 (lateral) was seen. Epicardial access failed because the injected contrast could

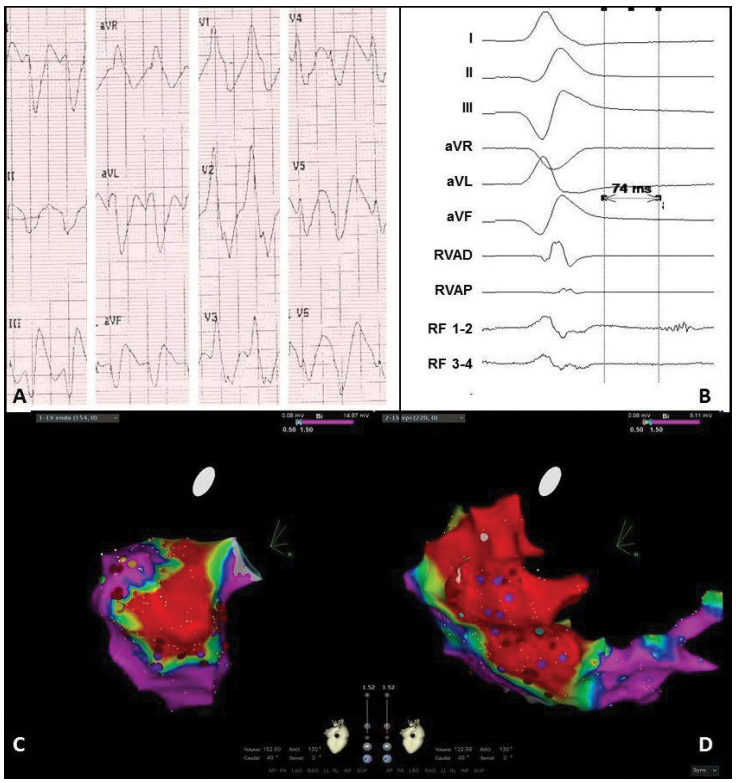

Figure 4: Electrocardiogram and electro-anatomical maps of case 2.

A. Twelve-lead electrocardiogram showing a ventricular tachycardia (150bpm) with right bundle branch block morphology, right axis and normal R-wave transition suggesting a lateral-basal origin in the left ventricle. Pseudo delta wave and wide QRS suggest epicardial origin.
B. Recording obtained in sinus rhythm during the procedure showing local abnormal ventricular activation. RVAD/P = right ventricular apex distal/proximal, RF = radiofrequency.
C. Inferior view of the bipolar endocardial voltage map showing low voltages inferior/inferoposterior (area 5/6). Red dots = RF applications, purple dots = late potentials.
D. RAO view of the bipolar epicardial voltage map showing low voltage area practically consistent with the endocardial map, though more extensive at the lateral wall (area 7/8). Red dots = RF applications, purple dots = late potentials.

not be seen in the epicardium. Therefore only endocardial ablation was performed at the lateral area 18 (48C, 40W). The last application resulted in a steam pop, substantial loss of blood via the inserted pigtail in the pericardium, and hemodynamic instability. A hole in the RV free wall was sutured via a sternotomy performed in the EP lab. One day after discontinuation of external support, a therapy refractory

sustained VT recurred (morphology no. 3). Since the VT terminated on arrival in the EP lab and could not be induced, it was decided to perform a hybrid VT ablation via resternotomy in the OR. After administration of isoprenaline a sustained VT was induced [Figure 5A-Figure 5B]. The endocardial activation map showed prepotentials at areas 13, 14 and 18 (basal, apical and RV free wall, [Figure 5C]), but hereafter the VT stopped. The bipolar epicardial voltage map showed low voltages in basically all areas of the RV ([Figure 5D]). Since the RF catheter could not be stabilized well on the beating hart, it was changed for a cryo-pen (AtriCure, Ohio, USA). A lesion of 4x4cm was made (8 applications of 120ms) at area 18 (lateral). No additional endocardial ablation was performed because of the recent perforation. No VT could be induced at the end of the procedure. After 6 days in the intensive care unit, the patient was transferred to his own hospital. Before discharge an ICD was implanted.

During one-year follow-up the patient maintained SR using metoprolol 100mg once per day.

Case 4 : A 67-year-old man, recently diagnosed with paroxysmal AF, was admitted to the hospital suffering a symptomatic monomorphic VT causing hemodynamic instability. Magnetic resonance imaging showed hypokinesia and subepicardial fibrosis of the basal inferolateral and inferior walls, and a normal RV [Figure 6]. DNA analysis showed a mutation in the PRKAG2 gene (c432dup mutation). Most probably this relates to a pathogenic mutation, however this mutation has not been described before nor is it known in genetic databases. A few months after ICD implantation, recurrent VTs (same morphology) occurred. Since there was clear evidence for an epicardial origin (imaging and ECG), it was decided to perform a left-sided thoracoscopic hybrid ablation. Macroscopically only minimal epicardial fibrosis was visible at area 8 and 10 (inferoposterolateral and lateral basal). The endocardial unipolar voltage map showed low voltages (<8.3mV, [15]) at those areas ([Figure 7C]), and the epicardial unipolar map also at the anterolateral area 9 ([Figure 7D]). No VT could be induced. Eight epicardial RF applications were performed at areas 9/10 (anterolateral/lateral basal) with a mean of 35seconds per application (average output 30W). Due to the proximity of a coronary artery, area 8/9 (inferoposterolateral/anterolateral) could not be ablated epicardially and was only ablated endocardially (6 applications with a mean of 60seconds and an average output of 25W). Because of AF during the procedure, isolation of the right and left pulmonary veins in pairs (bipolar clamp, AtriCure) was performed via the left-sided thoracoscopy. No VT could be induced at the end of the procedure. After 1 day in the intensive care unit, and 6 days on the regular ward, the patient was discharged.

In the first three months after ablation two sustained VTs recurred (RBBB, inferior axis, absent R/S transition, CL 340 ms). Blood analysis showed that the amiodarone level was subtherapeutic, and for one week the dose was raised to 600mg daily. The following year he maintained SR.

Case 5 : An 18-year-old male with working diagnosis ARVC (pre-syncopes, minimal dilated RV and frequent premature ventricular complexes (PVCs)), had recurrent ICD shocks and showed many non-sustained VTs. Despite the patient was suspected for being noncompliant to antiarrhythmic therapy and for excessive use of

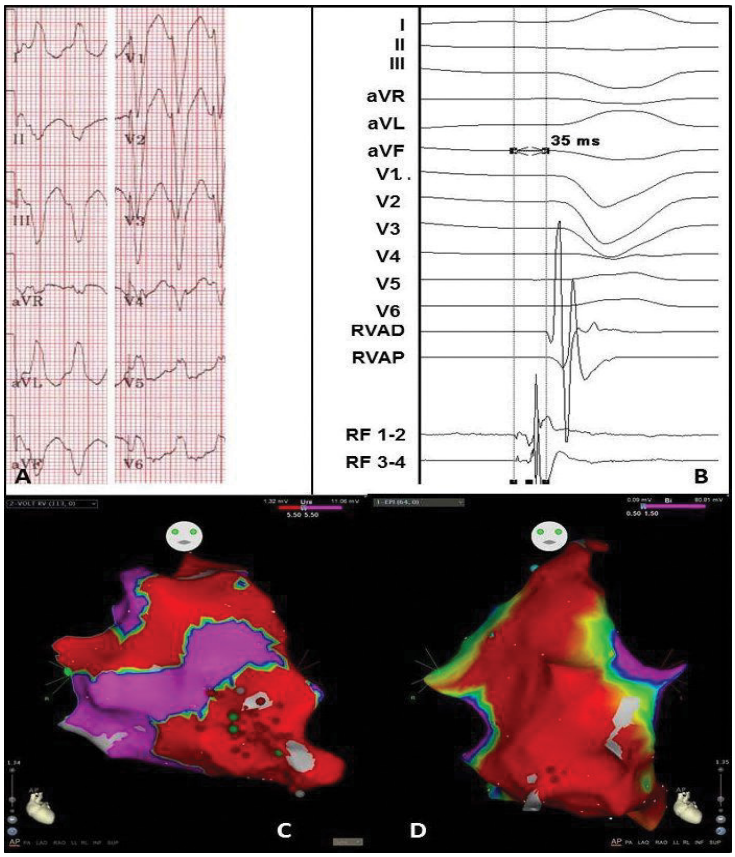

Figure 5: Electrocardiogram and electro-anatomical maps of case 3

A. Twelve-lead electrocardiogram showing a ventricular tachycardia (180bpm) with left bundle branch block morphology and superior axis, suggesting origin in the right ventricle (RV) free wall.
B. Recording obtained in sinus rhythm during the procedure showing prepotentials. RVAD/P = right ventricular apex distal/proximal, RF = radiofrequency.
C. Anterior-posterior (AP) view of the unipolar endocardial voltage map showing a low voltage area at the apex and RV free wall (area 14 and 18). Red dots = RF applications
D. Anterior-posterior (AP) view of the bipolar epicardial voltage map showing a low voltage area at basically the total apex and RV free wall (area 14 and 18). Red dots = RF applications

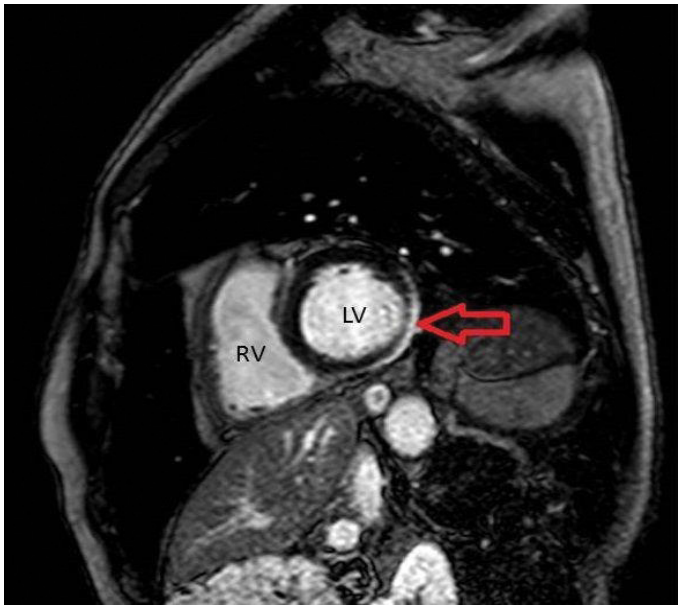

Figure 6: Cardiac magnetic resonance image of case 4, short axis

RV = Right Ventricle. LV = Left Ventricle. Red arrow: area of fibrosis (white).

cannabis and alcohol, an endocardial VT ablation was performed. The bipolar voltage map showed low voltages at the basal septum, outflow tract and basal inferior RV (areas 13/17/18), wherefore ventricular substrate modification. No VT could be induced afterwards. In the following period the amount of runs of PVCs, non-sustained VTs and VTs increased ([Figure 8A-Figure 8B]), and a hybrid VT ablation via right-sided thoracoscopy was performed. No VT could be induced, but the bipolar endocardial voltage map showed low voltages at areas 13/15-18 (basal septum/mid septum/anterior septum/outflow tract/basal inferior, [Figure 8C]). The bipolar epicardial voltage map showed low voltage zones and LAVA at area 13 (basal septum), and low voltages at area 17 (outflow tract, Fig 8D). The unipolar endocardial map showed low voltages (<8.0mV) involving almost all areas. A first PVC was endocardially mapped and epicardialy and endocardially ablated at area 18 using RF (7 applications with a mean of 51 seconds per application, an average power of 34W and maximum power of 38W). A second PVC could be mapped epicardially at area 17, and was ablated epicardially using RF (5 applications with a mean of 53 seconds, average power of 71W and maximum power of 75W). No VT could be induced at the end of the procedure. After 3 days on the regular ward the patient was discharged.

During 12 months follow-up SR was maintained using sotalol 40mg twice per day.

Discussion

In this report we describe five cases of patients with recurrent sustained VTs of variable etiology, treated with a hybrid VT ablation. Hybrid VT ablation is a novel technique as it combines endocardial and surgical epicardial ablation. In all patients, antiarrhythmic medication failed or was not tolerated, and four patients experienced arrhythmia recurrence after previous endocardial ablation. In two cases no percutaneous epicardial access could be obtained.

No perioperative complications occurred. one patient underwent a redo endocardial ablation for recurrent sustained VT after 21 months. In another patient two sustained VTs recurred under a subtherapeutic amiodarone dose which was treated with a dose

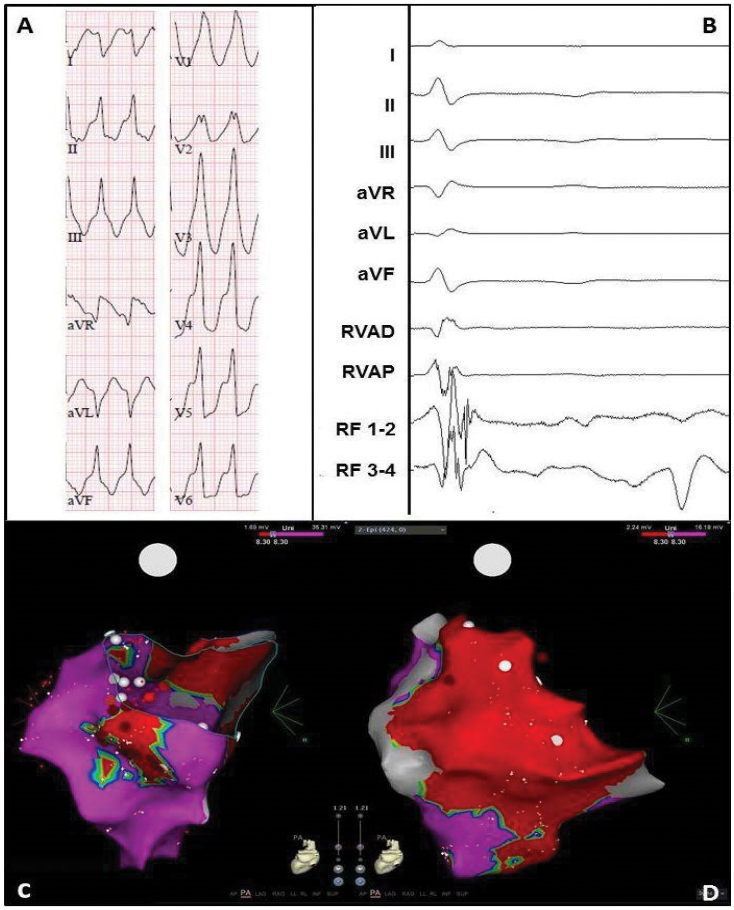

Figure 7: Electrocardiogram and electro-anatomical maps of case 4

A. Twelve-lead electrocardiogram showing a ventricular tachycardia (206bpm) with right bundle branch block morphology, right inferior axis, and positive QRSs in all precordial leads, suggesting origin in the basal lateral wall of the left ventricle. Pseudo delta wave and wide QRS suggest epicardial origin.
B. Epicardial recording obtained in sinus rhythm during the procedure showing local abnormal ventricular activation. RVAD/P = right ventricular apex distal/proximal, RF = radiofrequency.
C. Posterior-anterior (PA) view of the unipolar endocardial voltage map showing a low voltage area inferoposterolateral and lateral basal (area 8/10). Red dots = RF applications.
D. PA view of the unipolar epicardial voltage map showing more extensive low voltages at the lateral basal area 10. Red dots = RF applications.

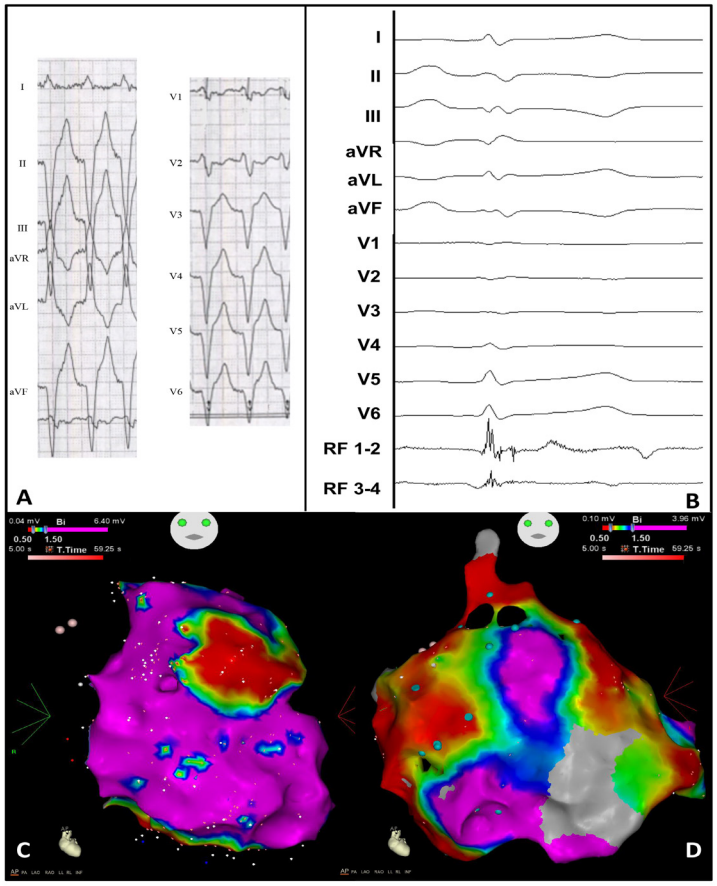

Figure 8: Electrocardiogram and electro-anatomical maps of case 5

A. Twelve-lead electrocardiogram showing a ventricular tachycardia (110bpm) with left bundle branch morphology, superior axis and R/S transition in V3, suggesting origin in mid RV. No specific signs for epicardial origin.
B. Epicardial recording obtained in sinus rhythm during the procedure showing local abnormal ventricular activation. RVAD/P = right ventricular apex distal/proximal, RF = radiofrequency.
C. Anterior-posterior (AP) view of the bipolar endocardial voltage map showing a low voltage area from the basal inferior RV to mid inferior RV and RV outflow tract (areas 13/15-18). Red dots = RF applications.
D. AP view of the bipolar epicardial voltage map showing a more extensive low voltage area consistent with the endocardial map. Red dots = RF applications.

increase. One patient remained in sinus rhythm without, and two with the use of antiarrhythmic drugs.

Surgical and hybrid VT ablation

Since beating heart surgical and hybrid VT ablations are not often performed, studies reporting on these procedures are scarce. In a retrospective multicentre study among 913 VT ablations, Sacher et al. found that 17% of the procedures involved epicardial mapping and ablation[1]. In the vast majority (88%) of epicardial ablation, a percutaneous approach was preferred. A subxiphoidal access, mainly for catheter based mapping or ablation, was only used in 1.5% of the cases, while surgical treatment during concomitant cardiac surgery procedures was even lower (0.7%). Soejima et al. were the first to show that subxiphoidal surgical access provides successful entry for epicardial catheter-based mapping in patients with a failed percutaneous approach[16]. In a population of 444 treated VT patients, Sarkozy et al. reported this approach in 13 patients[17]. However, in only 6% of the total population they were able to successfully ablate the VT circuit epicardially, which is substantially less compared to endocardial circuits. Mathuria et al. reported a case of an epicardial ablation, under direct surgical vision of the epicardium, via a limited anterior thoracotomy by using an unidirectional epicardial bipolar RF device (Coolrail, AtriCure)[18]. Also epicardial VT ablations, under direct surgical vision, using endocardial RF catheters combined with video-assisted mini-thoracotomy and left lateral thoracotomy approaches have been reported[19,20]. Furthermore, one case is described in which both endo- and epicardial mapping and ablation via sternotomy was performed surgically[21]. Michowitz et al. reported on a minimal invasive hybrid VT ablation under direct surgical vision in three patients via limited anterior thoracotomy[22]. Recently Li et al. compared the subxiphoidal and thoracotomy approach with the percutaneous approach, showing no significant difference in complications or outcome[23]. These publications show there are numerous options to perform VT ablation, giving sufficient possibilities for a patient tailored therapy.

Patient selection

It is important to determine which patients might benefit from an epicardial treatment since VT circuits that can be successfully ablated from the epicardium are less common than those that can be addressed from the endocardium. Also, endocardial circuits are seen in 50% of the patients in whom VT was ablated successfully from the epicardium, and additional ablation of the endocardium is often required[17]. Studying 19 patients, Tung et al. demonstrated that percutaneous epicardial in combination with endocardial ablation in patients with ischemic and non-ischemic cardiomyopathy was not superior to endocardial ablation alone after 12 months of follow-up[24]. On the contrary, Di Biase et al. showed in 92 patients that recurrence rates were lower in patients treated with endo- and epicardial ablation compared to endocardial ablation alone during a mean follow-up of 25 months (19% versus 47%)[25].

To date, epicardial ablation is mainly performed after previously failed endocardial ablation, in cases in which the epicardium seems to be the source of VT during endocardial ablation, or in which endocardial access is not possible. It can, however, also be considered to be performed as a first-line epicardial or hybrid VT ablation in patients with high suspicion of an epicardial circuit based on the underlying disease (like in Chagas disease, e.g.)[7,8,26,27]. Sacher et al. observed the highest prevalence of an epicardial substrate in patients with a diagnosis of ARVC (41%), followed by non-ischemic dilated cardiomyopathies (35%) and ischemic heart disease (16%) [1]. Suspicion of an epicardial origin could besides by the diagnosis, also be raised based on the ECG. As Berruezo et al. showed in a population consisting of 65% to 90% ischemic VTs, a VT originating from the epicardium produces a pseudo delta wave that corresponds to widening of the initial part of the QRS-complex[28]. The group of Valles et al. assessed ECG criteria for epicardial origin in a group of non-ischemic VTs and developed a 4-step algorithm[29]. Cardiac MRI can also be helpful in identifying patients with an epicardial substrate (like in case 4 of this report)[30].

Surgical approach

There are several reasons to consider a surgical approach for VT ablation. The most common is failure of a percutaneous approach, which is unsuccessful in 10% of the cases[1]. Another reason could be the anatomy, for example necessity to ablate close to the phrenic nerve or coronary arteries. In the latter case, a surgical approach with direct visualization of the epicardium, allows evaluating whether an epicardial ablation can be performed safely[10]. Here we describe a surgical approach, within the concept of hybrid VT ablation, to perform epicardial VT ablation on the beating heart. Minimal invasive access was obtained via anterolateral mini-thoracotomy at first, to become familiar with the technique, and later via one-sided 3-port thoracoscopy. One case was approached via resternotomy because a sternotomy was performed only a few days earlier.

Literature suggests that a subxiphoidal approach is better for reaching the inferior and infero-lateral areas of the heart[16] . However a lateral thoracoscopic approach not only provides good access to inferior and infero-lateral areas, but also to anterior and apical areas of the heart. In our experience all areas of the heart can be visualised and accessed adequately with a lateral thoracoscopic approach, right or left depending on the target area.

Contrary to other reports, in the current case series endocardial ablation was performed prior to the surgical ablation because of several reasons[1,16,17,22,24]. First, VT induction during thoracoscopic VT ablation should be avoided because of hemodynamics. Second, it was found useful to confirm the endocardial maps obtained during the prior procedures. Last, the surgical procedure could be guided based on the endocardial map, thereby shortening the surgical procedure time.

Advantages and disadvantages of hybrid VT ablation

In our opinion, hybrid VT ablation is superior to endocardial and percutaneous epicardial ablation in a selected patient population as it combines the advantages of endocardial and (thoracoscopic) epicardial ablation techniques. First, endocardial and epicardial high-density mapping can readily map the origin of the arrhythmia. Second, it overcomes the difficulty of making transmural lesions as ablation can be applied from the endocardium as well as the epicardium. This is especially relevant in areas with myocardial scars. Furthermore, direct visualization gives important anatomical

information: the coronary arteries can be located without need for repetitive angiograms, the phrenic nerve can be seen and obviated to avoid damage and potential differentiation between healthy and diseased myocardium might add essential information. Endocardial ablations and percutaneous epicardial ablations necessitate pacing manoeuvres to map the phrenic nerve, and angiography to locate the coronary arteries. Direct visualization also improves catheter stability, which sometimes is difficult in percutaneous approaches, especially when using non-magnetic catheters. Another asset is the possibility to take electrical-anomaly guided surgical biopsies if necessary. Also, working in a hybrid OR has the advantage that complications of the endo- or epicardial approaches can be more easily addressed by two specialties. Furthermore, this set-up allows the application of complimentary techniques to overcome anatomical limitations: while the efficacy of epicardial ablation in the vicinity of the atrio-ventricular annulus is limited, this can be managed endocardially. Last, hybrid ablation could be an attractive solution for lower-volume centers since the surgical access is probably easier for cardiac surgeons than the percutaneous pericardial access is for cardiologists.

The duration of the procedure, which is time-consuming for both the surgeon and cardiologist, and the need for a procedural environment which has to be optimized for both specialties can be experienced as disadvantages of hybrid VT ablation. Further, it potentially comes with more complications since a patient is exposed to the risks of both the endocardial and epicardial procedure, and this procedure might cause more post-operative pain and might require more recovery time compared to endocardial or percutaneous approaches. Managing the periprocedural anticoagulation can also be challenging. However, in our series no complications were seen. Possible disadvantages specifically for the one-sided thoracoscopy approach could be the single lung ventilation and displacement of precordial leads, but in our vast experience with hybrid AF ablation, problems with single lung ventilation rarely have been encountered[31].

Limitations

It cannot be excluded that the previous ablations favourably influenced the outcome of the hybrid ablation.

Conclusions

In this manuscript, we illustrate in a case series of five patients that a hybrid VT ablation, i.e. a combined surgical epicardial and endocardial VT ablation, is a safe procedure with encouraging results. Hybrid VT ablation has several advantages that permit the electrophysiologist and the surgeon to provide an optimal individualized therapy for patients with VTs. It is our opinion that hybrid VT ablation should be considered in the treatment of VTs with a high suspicion of an epicardial origin or in patients where a difficult percutaneous epicardial approach can be expected.

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Predictors of Long-term Outcome in Patients Undergoing a First Repeat Ablation Consisting Solely of Re-isolation of Reconnected Pulmonary Veins

RJuan-Pablo Abugattas[1], Bruno Schwagten[1], Jeroen De Cocker[1], Hugo-Enrique Coutiño[2], Francesca Salghetti[2], Varnavas Varnavas[2], Erwin Ströker[2], Juan Sieira[2], Michael Wolf[1], Pedro Brugada[2], Carlo de Asmundis[2], Gian-Battista Chierchia[2], Yves De Greef[1]

[1] Electrophysiology Unit, ZNA Middelheim, Lindendreef 1, 2020 Antwerp, Belgium.
[2] Heart Rhythm Management Center, Postgraduate program in Cardiac Electrophysiology and Pacing, Universitair Ziekenhuis Brussel–Vrije Universiteit Brussel, Brussels, Belgium.

Abstract

Aim: To define predictors of long-term outcome of a first repeat ablation solely consisting of re-isolation of reconnected pulmonary veins (PVs).

Methods: Three hundred seven patients (age 59 ± 9%, 77% males, non-paroxysmal AF 43%) with recurrent AF after first PVI were studied. Re-isolation of reconnected PVs was guided by a circular mapping catheter and 3D mapping system using RF ablations. A PV was defined as "triggering" in case of spontaneous ectopy or AF paroxysms originating from the PV.

Results: After a mean follow-up of 5.05 ± 2.21 years, 194 (63.2%) patients (73.0% in PAF vs 50.4% in non-PAF, log Rank <0.001) were free from AF. A "triggering" PV was present in 48 (15.6%) during the first PVI and in 52 (16.9%) at repeat. Independent predictors of recurrence were a non-PAF type (HR: 1.814, 95%CI: 1.090 - 3.018, p=0.022) and early recurrence (≤ 3 months) after first PVI (HR: 1.632, 95%CI: 1.091 - 2.443, p=0.017) while a "triggering" PV at first or repeat was a predictor of good outcome (HR: 0.574; 95%CI: 0.344 - 0.959; p=0.034) in the multivariable analysis.

Conclusions: A repeat ablation solely consisting of re-isolation of reconnected PVs results in a high degree of long-term AF freedom, especially in PAF and in case of a PV trigger at index or repeat. Patients with non-PAF or experiencing early AF recurrence after first PVI are less responsive.

Introduction

Electrical isolation of the pulmonary veins (PVs) is now a mainstay AF treatment obtaining single procedure success rates of 60-80% [1-4]. A repeat ablation is however needed in about 30% of patients [1-6].

PV reconnection (PVR) is believed to be the main cause of recurrent AF after an initial successful PV isolation (PVI); this is supported by the finding of at least 1 reconnected PV during repeat ablation in around 80% of patients[2]. Re-isolation of reconnected veins (re-PVI) has shown to further eliminate AF and improve clinical outcome at short- and midterm follow-up. It constitutes therefore the basis of any repeat AF ablation as recommended by the HRS consensus document 2017[4]. Additional ablation strategies beyond PV re-isolation are less well defined at the present time. No data exist at the present time on the long-term outcome of a re-PVI only approach. In view of this, the question arises in which patients a re-PVI only strategy would suffice to prevent future AF recurrences on the long-term and on the other hand in which patients additional 'beyond the PVs' mapping and ablation would be indicated. In the present article, we aim to (i) study long-term outcome of a repeat ablation solely consisting of re-isolation of reconnected PVs and (ii) to define clinical and procedural predictors of outcome.

Key Words

Ablation, Repeat, Atrial Fibrillation, Triggering PV, Re-isolation

Corresponding Author
Juan-Pablo Abugattas,
Electrophysiology Unit, ZNA Middelheim, Lindendreef 1, 2020 Antwerpen, Belgium and Heart Rhythm Management Center, Postgraduate program in Cardiac Electrophysiology and Pacing, Universitair Ziekenhuis Brussel-Vrije Universiteit Brussel, Brussels, Belgium.

Methods

Patient population

In this retrospective, case control study, consecutive patients in the time period from February 2008 to December 2017 from the Middelheim-PVI Registry who underwent a similar ablation trajectory consisting of "PVI only" AF ablation as index procedure and subsequently a "re-PVI only" repeat ablation were analysed.

None of the patients included in the study underwent substrate modification, ablation of complex fractionated electrograms (CFAE) or ablation of non-PV triggers during the index or repeat ablation procedure.

Also, patients presenting with persistent PV isolation at repeat and those with documented or spontaneously occurring atrial tachycardia or flutter requiring additional ablation 'beyond the PVs' were excluded from the study.

Paroxysmal AF (PAF) was defined as AF that terminates spontaneously or with intervention within 7 days of onset. Persistent AF (PersAF) was defined as continuous AF sustained beyond 7 days, long-standing PersAF (LS-PersAF) as continuous AF of more than 12 months duration[4,5].

All patients provided informed consent for the procedure and the study was approved by our local Ethical Committee.

First PVI

The first PVI procedure was performed using different ablation strategies including conventional point-per-point radiofrequency (RF) ablation (CPVI) guided by the Carto system (Biosense Webster, Diamond Bar, CA, USA) in 134 (43.6%) or Ensite system (St Jude Medical, St. Paul, Minnesota, MN, USA) in 37 (12.4%), multi-electrode RF ablation using the PV ablation catheter (PVAC) (Medtronic Inc., Minneapolis, MN, USA) in 84 (27.3%), the high density mesh ablator (HDMA) (Bard Electrophysiology, Lowell, MA, USA) in 34 (11.1%) and cryoballoon ablation (CB) (Medtronic Inc., Minneapolis, MN, USA) in 18 (5.8%). The choice of the technique was at the discretion of the operator. If spontaneous repetitive ectopy or AF paroxysms was observed during ablation, the initiating focus was localized by combining conventional mapping (CS activation pattern) and sequential mapping of the PVs. A pulmonary vein was defined as a "triggering" vein if the earliest local activation was recorded from the PV preceding the onset of the surface P-wave and CS activation. For all techniques, procedural endpoint was defined as LA–PV entry block with elimination of the PV potentials during sinus rhythm and differential pacing.

Re-PVI

All re-PVI procedures were performed using point-per-point RF ablation guided by a circular mapping catheter and the Ensite or Carto system. At baseline, all PVs were mapped sequentially with a circular mapping catheter. In case of repetitive ectopy or short runs of AF, mapping of the initiating focus was done as described above, with in case of a PV origin, defining the PV as "triggering". Subsequently, reconnected PVs were re-isolated by point-by-point RF lesions through localization and closing of conduction gaps at the circumference of the previous ablation circle. Around a confirmed gap, additional RF applications were given for consolidation. In [Figure 1] a representative example of reconnection of a LIPV is given with a conduction gap at the anteromedian region (left panel) and delayed PV potentials (right panel, LIPV pre). Delivery of RF energy at the gap resulted in re-isolation of the LIPV (right panel, LIPV post).

Post-procedural management and follow-up

After the procedure, subcutaneous LMWH was administered to all patients, as well as oral anticoagulation therapy (OAT), either warfarin (target International Normalized Ratio between 2.0 and 3.0) or a NOAC. Antiarrhythmic drugs (AAD) were reinstituted in all patients. After the 1- month blanking period, OAT was continued (unless if a CHA_2DS_2-VASc score of 0) whereas all AAD were invariably stopped, except for beta blocking agents. All patients underwent follow-up (FU) [questionnaire, physical examination, and electrocardiogram (ECG)] at scheduled (every 6 months during the FU) and unscheduled visits (if symptoms). In case of symptoms, the related arrhythmia was documented either by ECG, Holter monitoring (1–7 days), or event recording.

The primary endpoint was the presence of a recurrence, defined as any episode of AF or atrial tachycardia (AT) of at least 30 seconds after re-PVI only ablation respecting a 3-month blanking period[4].

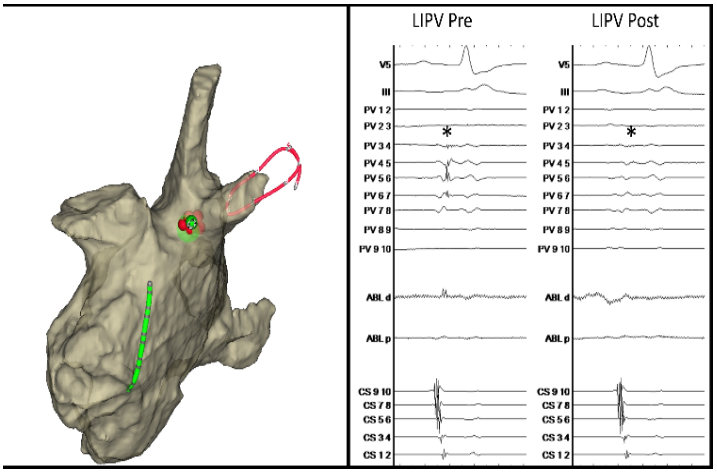

Figure 1: **Left panel: representative LA Ensite map after re-PVI only ablation (left lateral view). A conduction gap (green tag) was identified at the anteromedian site of the prior ablation circle. Additional RF applications were given for consolidation reasons (red tags). Right panel: representative tracings of a re-isolation. Surface ECG leads V5/III and bipolar electrograms recordings of the coronary sinus and a decapolar mapping catheter positioned at the ostium of the left inferior pulmonary vein (LIPV) are shown. Ablation resulted in re-isolation.**

Statistical analysis

Continuous variables are expressed as mean ± SD or median and interquartile range (IQR) and significant differences were analysed by Student's t-test or the Mann–Whitney U test when appropriate. Categorical data are expressed as number and percentages and compared with x^2 test or Fischer's exact test when appropriate. Event-free survival was estimated by Kaplan–Meier method and compared by log-rank test. Hazard ratios (HR) were calculated using Cox proportional hazards models. For the multivariate analysis, variables with a P value greater than 0.10 were removed from the model. All analyses were performed with SPSS Statistics for Windows, Version 24.0.

Results

Baseline population and anatomical characteristics

In the time period of the study, 2045 patients underwent a PVI only index procedure, of these, 437 (21.37%) patients underwent a repeat ablation procedure. In 130 patients either all PVs were found isolated at baseline, or an atrial tachycardia or flutter was present

Table 1: Clinical Characteristics

	Total(n=307)	No Recurrence(n=194 (63.2%))	Recurrence(n=113 (36.8%))	p value
Age (years)	59.03±9.14	59.48±9.03	58.24±9.30	0.252
Gender (Male)	237(77.2%)	152(78.4%)	85(75.2%)	0.529
Non-Paroxysmal AF	133(43.3%)	67(34.5%)	66(58.4%)	<0.001
Left atrial diameter (mm)	42.76 ± 6.69	42.02 ± 6.41	43.94 ± 7.00	0.021
Coronary artery disease	29(9.4%)	18(9.3%)	11(9.7%)	0.895
Dilated CMP	4(1.3%)	2(1.0%)	2(1.8%)	0.582
Valvular heart disease	7(2.3%)	4(2.1%)	3(2.7%)	0.737
Arterial Hypertension	121(39.4%)	73(37.6%)	48(42.5%)	0.402
Diabetes Mellitus	17(5.5%)	10(5.2%)	7(6.2%)	0.701
TIA/CVA	15(4.9%)	10(5.2%)	5(4.4%)	0.775
Endurance sport practice	62(20.2%)	41(21.1%)	21(18.6%)	0.591
Prior flutter ablation	54(17.6%)	30(15.5%)	24(21.2%)	0.200
Tachycardiomyopathy	27(8.8%)	15(7.7%)	12(10.6%)	0.389
Obstructive apnoea	21(6.8%)	11(5.7%)	10(8.8%)	0.287
CHADS2VASC2 ≥ 3 points	32 (10.4%)	21 (10.8%)	11 (9.7%)	0.763
Need for > 1 ECV before first PVI	71(23.1%)	30(15.5%)	41(36.3%)	<0.001
Height (cm)	176.15±8.71	176.03±8.33	176.35±9.36	0.754
Weight (Kg)	85.62±15.53	84.88±14.86	86.88±16.60	0.278
BMI (Kg/m^2)	27.51±4.16	27.33±4.14	27.83±4.18	0.311
Obesity(BMI: Kg/m^2) | BMI: < 30	239(77.9%)	153(78.9%)	86(76.1%)	0.931
Obesity(BMI: Kg/m^2) | BMI: 30 - 35	50(16.3%)	30(15.5%)	20(17.7%)	0.931
Obesity(BMI: Kg/m^2) | BMI: 35 – 39	16(5.2%)	10(5.2%)	6(5.3%)	0.931
Obesity(BMI: Kg/m^2) | BMI: ≥ 40	2(0.7%)	1(0.5%)	1(0.9%)	0.931
BSA (m2)	2.04±0.22	2.03±0.21	2.06±0.23	0.324
Time to first recurrence: median (IQR), months	6.13 (2.79 – 18.17)	6.54 (3.22 – 19.15)	4.73 (2.40 – 15.84)	0.116
Anatomical and Procedural Characteristics				
PV anatomy	4 separate veins	278 (90.6%)	175 (90.2%)	103 (91.2%)
PV anatomy	LCO	24 (7.8%)	14 (7.2%)	10 (8.8%)
PV anatomy	RMPV	4 (2.1%)	4 (2.1%)	0 (0.0%)
PV anatomy LCO + RMPV	1 (0.5%)	1 (0.5%)	0 (0.0%)	0.367
N° of PV's reconnected	1	44 (14.3%)	28 (14.4%)	16(14.2%)
2	78 (25.4%)	52 (26.8%)	26(23.0%)	0.628
3	103 (33.6%)	60 (30.9%)	43 (38.1%)	0.628
4	82 (26.7%)	54 (27.8%)	28 (24.8%)	0.628
LSPV reconnection	182 (64.5%)	117 (65.4%)	65 (63.1%)	0.703
LIPV reconnection	197 (69.9%)	124 (69.3%)	73 (70.9%)	0.630
RSPV reconnection	217 (70.7%)	134 (69.1%)	83 (73.5%)	0.416
RIPV reconnection	220 (71.7%)	141 (72.7%)	79 (69.9%)	0.604
LCPV reconnection	21 (84.0%)	12 (80.0%)	9 (90%)	0.504
Identified PV Trigger at index or repeat	83(27.0%)	62(32%)	21(18.6%)	0.018
Index Ablation method	CPVI	171 (55.7%)	117 (60.3%)	54 (47.8%)
HDMA	34(11.1%)	17(8.8%)	17(15.0%)	0.069
Cryoballoon	18(5.9%)	13(6.7%)	5(4.4%)	0.069
PVAC	84(27.4%)	47(24.2%)	37(32.7%)	0.069

AF: Atrial fibrillation; CMP: cardiomyopathy; BMI: Body mass index; BSA: Body Surface area; PV: Pulmonary vein; LCO; Left common ostium; RMPV: Right middle PV; LSPV: Left superior PV; LIPV: Left inferior PV; RSPV: Right superior PV; RIPV: Right inferior PV; LCPV: Left common PV; ECV: Electrical cardioversion; IQR: Interquartile range; CPVI: conventional pulmonary vein isolation; RF: Radiofrequency; HDMA: High density mesh ablator; PVAC: PV ablation

or documented, requiring additional 'beyond re-PVI ablations. All these patients were excluded from the study. Finally, 307 patients in whom re-PVI only was performed were studied.

The baseline characteristics are presented in [Table 1]. In brief, the mean age was 59.03 ± 9.14 years (male: 77.2%, Non-paroxysmal: 43.3%). 10.4% of the patients had a CHA_2DS_2-VASC score of ≥3 points. The mean LA diameter (LAD) was 42.76 ± 6.69 mm, mean BMI 27.51±4.16 kg/m^2.

Most patients had 4 separate veins (N=276, 89,9%), a minority had respectively a left common ostium (LCO) (N=26, 8.5%), a right middle PV (RMPV) (N=4) or a combination of an RMPV and LCO (N=1).

At baseline, out of 1208 studied PVs, 837 (69.29%) revealed recovered LA–PV conduction with a homogeneous spatial distribution of reconnection in between the 4 PVs: LCPV 21/25 (84.0%), LSPV 182/282 (64.5%), LIPV 197/282 (69.9%), RSPV 217/307 (70.7%), and RIPV 220/307 (71.7%). Reconnection of at least one pulmonary vein being a prerequisite was invariably present in all patients with a mean number of reconnected PVs per patient of 2.73 ± 1.01. A "triggering" PV was observed in 48 (15.6%) at the first PVI and in 52 (16.9%) of re-PVI procedures.

Long term Outcome after re-PVI only

After a mean follow-up of 60.60 ± 26.52 months, 194 (63.2%) patients were free from any recurrence [Figure 2]. The median time to recurrence was 8.84 (IQR: 4.16 – 28.14) months. Patients with PAF had a better event free survival than patients with a non-PAF type (73.0% vs 50.4%, respectively; log Rank <0.001).

Patients who suffered a recurrence had a significantly larger LAD (43.94 ± 7.00 vs 42.02 ± 6.41mm, p=0.021) and more frequently underwent more than 1 electrical cardioversion (ECV) before the first PVI (41 (36.3%) vs 30 (15.5%), p< 0.001). Also, even statistically non-significant, the time to recurrence (TTR) after the first procedure tended to be shorter (4.73 (IQR: 2.40 – 15.84) vs 6.54 (2.79 – 18.17) months; p=0.116) in patients with a recurrence after re-PVI. Other clinical and procedural characteristics were not significantly different between both groups.

Seventy-five out of the 113 (66.4%) patients with a recurrence after re-PVI only underwent a second repeat ablation; of those, 28 (37.3%) patients presented with at least 1 reconnected PV.

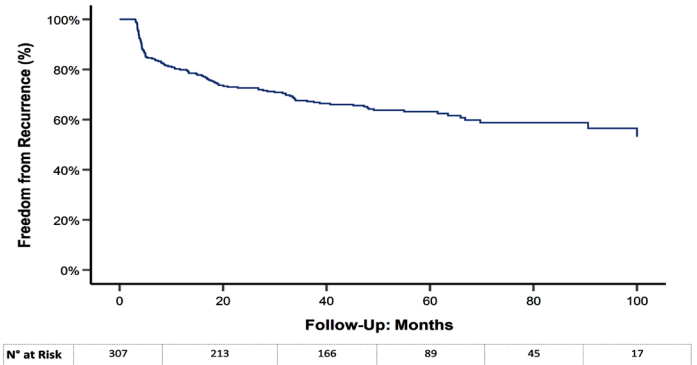

Figure 2: Kaplan-Meier plot representing the time to documented recurrence in the total study population. After a mean follow-up of 5.05 ± 2.21 years, 63.2% patients remained free of AF.

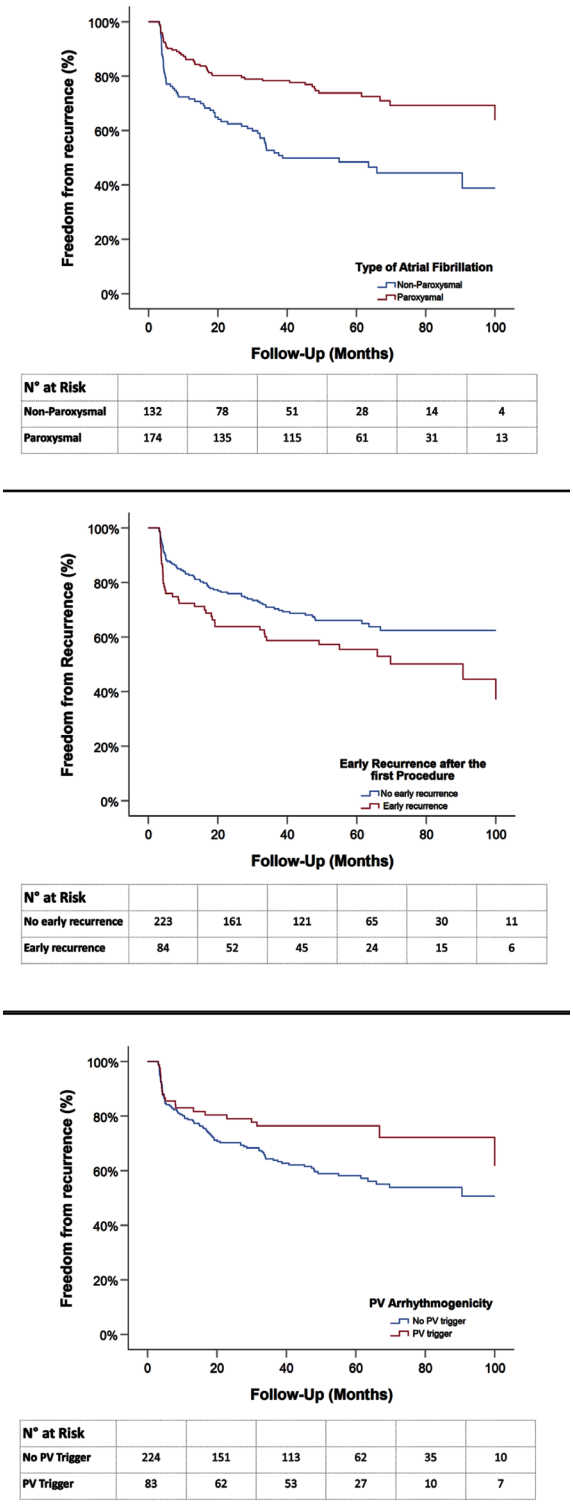

Figure 3: Kaplan-Meier curves representing the time to documented recurrence between PAF and non-PAF patients (upper panel), presence of a PV trigger at index or repeat (middle panel) and early AF recurrence after the first PVI (lower panel) respectively.

Predictors of recurrences

The results of the univariate and multivariate analysis are summarized in [Table 2]. In brief, in the univariate analysis, the LAD (HR: 1.032, 95% CI: 1.003 - 1.062; p=0.032), the need for more than 1 ECV before first PVI to maintain sinus rhythm (SR) (HR: 2.360; 95%CI: 1.605 - 3.470, p<0.001), a non-PAF type (HR: 2.382; 95%CI: 1.633 - 3.475, p<0.001) and a TTR ≤ 3months after the first PVI (index PVI procedure) (HR: 1.512, 95%CI: 1.027 - 2.228, p=0.036) were associated with an increase in the risk of recurrence after re-PVI. On the contrary, the presence of an identified PV trigger (HR: 0.575, 95%CI: 0.358 - 0.925, p=0.022) at first or re-PVI was associated with a better prognosis. Interestingly, neither the number or type of reconnected PVs nor the PV anatomy was predictive of outcome.

In the multivariate analysis, only the non-PAF type (HR: 1.814, 95%CI: 1.090 - 3.018, p=0.022) and TTR ≤ 3 months after the first PVI (index PVI procedure) (HR: 1.632, 95%CI: 1.091 - 2.443, p=0.017) persisted as independent predictors of recurrence while an identified PV trigger (HR: 0.574; 95%CI: 0.344 - 0.959; p=0.034) remained a predictor of good outcome [Figure 3].

Discussion

The main findings of our study are: (1) long-term AF freedom after a repeat ablation solely consisting of re-isolation of reconnected PVs is overall 63.2% going up to 73% in PAF patients, (2) patients with non-PAF and with an early AF recurrence within the first 3 months after first PVI have a higher risk of recurrence while (3) patients with an identified PV trigger at first or repeat PVI have less risk.

Table 2: Univariate and multivariate analysis

	Univariate Analysis			Multivariate Analysis		
	p value	HR	95.0% CI for HR	p value	HR	95.0% CI for HR
Age	0.240	0.988	0.969 - 1.008			
Gender (F=1)	0.563	1.135	0.740 - 1.740			
Coronary artery disease	0.938	0.975	0.523 - 1.819			
Arterial hypertension	0.396	1.176	0.809 - 1.708			
Diabetes mellitus	0.577	1.243	0.578 - 2.672			
TIA /CVA	0.486	0.726	0.295 - 1.786			
Left atrial diameter*	0.032	1.032	1.003 - 1.062	0.426	1.013	0.982 - 1.044
Identified PV trigger at index or repeat	0.022	0.575	0.358 - 0.925	0.034	0.574	0.344 - 0.959
Need for > 1 ECV before first PVI	<0.001	2.360	1.605 - 3.470	0.391	1.249	0.751 - 2.078
Non-paroxysmal AF	<0.001	2.382	1.633 - 3.475	0.022	1.814	1.090 - 3.018
Recurrence ≤ 3 months after the first PVI	0.036	1.512	1.027 - 2.228	0.017	1.632	1.091 - 2.443
LSPV reconnection	0.595	0.897	0.600 - 1.340			
LIPV reconnection	0.990	0.997	0.652 - 1.526			
RSPV reconnection	0.619	1.112	0.732 - 1.688			
RIPV reconnection	0.646	0.910	0.607 - 1.363			
Left sided veins reconnection	0.989	0.996	0.578 - 1.717			
Right sided veins reconnection	0.475	1.244	0.683 - 2.265			
Superior vein reconnection	0.788	0.924	0.518 - 1.648			
Inferior vein reconnection	0.804	1.096	0.533 - 2.252			
Reconnection of all 4 veins	0.237	0.773	0.504 - 1.185			
Reconnection of ≥ 3 veins	0.789	1.053	0.720 - 1.540			
Reconnection of only 1 vein	0.806	1.067	0.637 - 1.788			
Number of PV's reconnected	0.629	0.957	0.801 - 1.144			
Body mass index	0.149	1.033	0.988 - 1.080			

*Increase in risk for every 1 mm increase in the diameter.
AF: Atrial fibrillation; PV: Pulmonary vein; LCO; Left common ostium; RMPV: Right middle PV; LSPV: Left superior PV; LIPV: Left inferior PV; RSPV: Right superior PV; RIPV: Right inferior PV; ECV: Electrical cardioversion; PVI: pulmonary vein isolation; RF: Radiofrequency

Long term Efficacy after re-PVI

To the best of our knowledge, this is the largest study with the longest follow-up evaluating the efficacy and predictors of outcome following a repeat ablation procedure solely consisting of re-isolation of reconnected PVs. In our study, the incidence of a repeat procedure was 21.37% and therefore in line with the 20-40% of patients needing to undergo a repeat ablation due to AF recurrences as stated in the current guidelines[4].

Previous outcome studies after re-PVI based repeat ablations show varying degrees of success at short-and midterm follow-up from 49% up until 76%[6-9]. In 2004, Callans et al. reported data on 74 patients who underwent a repeat procedure using a re-PVI only strategy[6]. After 9.1 ± 6.7 months, freedom from AF was obtained in 44 (59%) patients. In a comparative study between RF and CB in repeat re-PVI only ablations for PAF, 20 out of 34 (59%) RF-treated patients versus 11 out of 29 (38%) CB-treated patients were free from any recurrence after 1 year follow-up[7]. Fichtner et al. compared in a prospective single center study the efficacy of re-PVI only versus re-PVI plus an anterior line[8]. After 12 months, more patients were in sinus rhythm off antiarrhythmic drugs after re-PVI only versus a combined re-PVI plus anterior line (26 of 41 (63%) versus 18 of 36 (50%), p= 0.26)[8]. More recently, De Regibus et al reported the efficacy of the second generation CB for re-PVI[9]. After a mean follow-up of 15 ± 8 months, 76.6% of patients were free from recurrence of AF.

Our results differ from previous studies reporting on a much longer follow-up time of 60.6 ± 26.52 months years and the large number of patients (N 307) all undergoing a similar ablation trajectory (PVI only at index, re-PVI only at repeat). The present study shows that the majority of patients remains AF free using a re-PVI only strategy also on the long-term and supports therefore the primary aim of a repeat ablation to check for PV reconnections and subsequently close reconnection gaps around the previous ablation circle. However, our data also show that despite re-PVI a significant number of patients continue to develop AF recurrences.

Predictors of recurrence

Type of atrial fibrillation

Predictors of AF recurrence as AF type, LA size, early AF recurrence and the duration of AF disease are extensively studied and well known for a first PVI procedure[10,11].Interestingly, some but not all of these predictors could be extrapolated to the present study.AF type continues to be a significant predictor with a clear better outcome of re-PVI only in PAF (73.0%) versus non-PAF patients (50.4%). This finding reflects a higher 'sole' implication of the PVs in PAF, with other mechanisms beyond the PVs being more present in non-PAF patients suggesting the necessity of additional ablation. The latter is however not supported by the STAR-AF II trial showing a similar outcome also after two ablation procedures performed by means of the strategy to what they were initially randomly assigned (only PVI, PVI +lines, PVI +CFAE)[12].

The causative mechanisms of AF recurrence after re-PVI are most probably similar from those described for a first PVI procedure: non-durability of PVI despite re-isolation, the presence of non-PV triggers or a more advanced atrial disease.

Despite re-isolation of reconnected PVs at first repeat ablation, recovery of PV-LA conduction is not an uncommon finding in third and even in fourth ablations. Lin et al analysed 169 patients undergoing 3 or more AF ablation procedures[13]. PV re-reconnection was seen in 156 (92%) with as much as 41% presenting with all 4 PVs re-reconnected. Similar results were reported by Tilz et al[14] with PV re-reconnection found in 77.0%, 28,6% and 0% at the first, second and third repeat procedures. In our study, 75 patients underwent a third procedure and at least 1 reconnected PV was found in 28 patients (37.3%). Our study further highlights the difficulty in achieving durable PVI even after 2 ablations.

As for non-PV foci, the reported incidence has varied between 10 and 28%[15,16]. Although it is assumed that also in non-PAF the PVs harbour the majority of triggers, there is some discrepancy about their prevalence in comparison with PAF patients. Bhargava et al [16] reported a higher prevalence of non-PV foci in patients with LS-PersAF and PersAF than in PAF patients (19.1% and 8.2% versus 2.9% respectively, p<0.001). In contrast, Santangeli et Al[15] elicited non-PV triggers in only 11% of patients with a similar prevalence across the different types of AF (165 (11%) PAF, 54 (11%) PersAF, and 15 (11%) LS-PersAF; p=0.996).

Although evidence shows that not been able to locate and ablate a trigger (PV or non-PV) is associated with a worse outcome[17], a routine search for non-PV triggers was not incorporated in the present study. A future comparative trial between a re-PVI only repeat ablation versus a re-PVI plus actively searching and ablating non-PV triggers could give more insight in the prevalence of non-PV triggers at repeat ablations and differences in outcome.

Poor response to PVI and re-PVI only might also be explained by a more advanced structural atrial disease with enhanced fibrosis and low voltage areas. The presence of left atrial scarring in patients undergoing AF ablation is a known powerful, independent predictor of procedural failure[18].

Not only the presence but also the extent of atrial fibrosis is predictive of ablation outcome. Khurram et al[19] studied the association between late gadolinium enhancement (LGE) in the LA on MRI as a marker of fibrosis and AF recurrence after ablation in a cohort of 165 patients. Regardless of the type of AF, patients with LGE >35% had a higher rate of AF recurrence in the first year after ablation in comparison to patients with LGE ≤35%.

These studies support a more patient-tailored approach to target low LA voltage areas to improve ablation outcomes. Voltage mapping at baseline could have offered an insight to explain outcome after re-PVI only but was not systematically performed.

Time to recurrence after the first PVI

Our data shows that 'early' recurrences (within the first 3 months) are not only strongly predictive of 'late' AF recurrence after the initial PVI but also after a re-PVI only repeat procedure. This strengthens their significance as a marker of non-response to PVI rather than the subsequence of the healing process post-ablation[20,21]. Mechanisms related to ER are the presence of incomplete ablation lesions with early PV reconnection, untreated non-PV triggers, LA enlargement (>40mm), arterial hypertension and permanent AF[22].These 3 later data as markers of more advanced structural atrial disease might suggest that also the presence of atrial fibrosis could be related with the pathogenesis of ERs.

The potential significance of ER as a non-response to PVI is in line with the results of a sub-study of the STAR AF[23] studying the impact of different ablation strategies (only PVI, only CFAE, combined PVI +CFAE) on early and late AF recurrences. Adding CFAE to PVI increased not only long-term success but resulted in rates of ER that were lower than observed with CFAE ablation or PVI alone. This implies that the persistence of non-PV triggers or unmodified arrhythmia substrate after limited PVI could be responsible for ER. Adding CFAE to PVI potentially result in targeting some non-PV triggers or additional substrate modification explaining the lower incidence of ER. The potential relevance of non-PV triggers to explain ERs is further supported by Themistoclakis et al[24] showing that the lack of isolation of the SVC was an independent predictor of ERs after AF ablation.

Identified PV triggers

Our data show that not the number nor the type of PVs found reconnected at repeat but rather the observation of spontaneous electrical activity of the PVs is a key determinant for outcome after re-PVI only repeat. It supports that when a PV trigger is observed at index or repeat ablation most probably the arrhythmia is solely PV-mediated and durable PVI achieved by PVI or re-PVI suffices to achieve a good outcome.

In a previous publication, we described that the presence of a triggering PV during the initial PVI is associated with a higher risk of AF recurrence[25]. The triggering PV as the cause of AF was supported by a 100% reconnection rate with still signs of electrical activity (ectopy, bursts of AF) in 71% at repeat. In line with our study, a re-PVI only strategy was highly successful with long term AF freedom achieved in 22 out of the 25 patients undergoing a repeat ablation.

Our findings highlight therefore the importance of PV triggers during index and repeat procedures as predictor of good outcomes. Unfortunately, spontaneous PV triggering without provocative measures is a rather uncommon finding, and its exact prevalence is not well defined. Valles et al[26] reported spontaneous triggers in 23% of their patients while De Greef et al reported a prevalence of 17%[25]. In the present study, we observed this finding in 15,6% and 16,9% of patients during initial and repeat ablation respectively.

Nowadays, there is no doubt that if a reconnected vein is found, it must be ablated to gain durable and complete disconnection of the PV[27]. However, in our study, a significant number of patients kept having AF recurrences despite re-isolation of reconnected veins. Besides other non-PV causes, the finding that PV reconnection is also frequently observed in patients without clinical AF recurrence[2,28], shows that reconnected PVs can also be a bystander phenomenon. Jiang et al [28], analysed PV reconnections in 32 patients free from AF recurrences at 1-year follow-up. The authors found that 29 of 32 patients (90.6%) presented with at least 1 PV reconnected, and in 10 patients (31.2%) the 4 veins were isolated.

The question therefore remains if the patients who did well after re-PVI only did so due to the achievement of durability of PVI or due to other aspects of the procedure such as, for example, autonomic modulation.

Limitations

Our study has some limitations. First, even though we have a large sample size and our follow–up period is long, it is still a single centre, single arm, retrospective, case control study and is exposed to the biases related to this type of studies. However, the potential selection bias of the criteria determining the choice to do a re-PVI only procedure was minimized given this approach constitutes our standard approach for a first repeat ablation.

Second, contact force sensing ablation catheters, which have shown better isolation rates than standard catheters, were not used in this study. Third, adenosine testing was not performed to search for dormant conduction. Fourth, we do not have information concerning voltage of the LA and consequently the extension of LA scars. Fifth, our follow-up did not include scheduled Holter monitoring, and therefore, asymptomatic episodes of AF may have been missed with a potential overestimation of our success rate. Finally, the lack of knowledge of the status of the PVs after ablation in patients without a clinical recurrence is an important limitation of our study; to overcome this, a new invasive assessment of the PVs would have been necessary, thereby exposing asymptomatic patients to potential complications.

Conclusions

A repeat ablation solely consisting of re-isolation of reconnected PVs has a five-year success rate of 63%, going up to 73% in paroxysmal AF patients. A re-PVI only strategy is particularly efficacious if a PV trigger is observed during first or repeat ablation. Patients with non-PAF and patients with an early AF recurrence during the first 3 months after first PVI tend to respond less well to a re-PVI strategy.

Conflict of interest

Carlo de Asmundis receive compensation for teaching purposes and proctoring from AF solutions, Medtronic, member steering committee ETNA-AF Europe Daiichi Sankyo Europe and research

grants on behalf of the centre from Biotronik, Medtronic, St Jude Medical Abbot, Livanova, Boston Scientific. Pedro Brugada receives fees from Biotronik, Medtronic. Gian Battista Chierchia receives compensation for teaching purposes and proctoring from AF solutions, Medtronic. Other authors: No conflict of interest to declare.

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Protecting the Esophagus from Thermal Injury During Radiofrequency Ablation with an Esophageal Cooling Device

Marcela Mercado Montoya[1], Steven Mickelsen[2], Brad Clark[3], Martin Arnold[4], Joseph Hanks[5], Eric Sauter[6], Erik Kulstad[7]

[1] *Bioengineering Department, Engineering Faculty, Universidad de Antioquia UdeA; Calle 70 No. 52-21, Medellín, Colombia.*
[2] *University of Iowa Carver College of Medicine, Department of Internal Medicine, 200 Hawkins Drive, Iowa City, Iowa 52242 .*
[3] *RRiverside Medical Center: St. Vincent Hospital, 8333 Naab Rd #400, Indianapolis, IN, 46260.*
[4] *University of Erlangen, Department of Cardiology, Ulmenweg 18, 91054 Erlangen, Germany.*
[5] *Riverside Medical Center, Research Department, 350 N Wall St, Kankakee, IL 60901 .*
[6] *A Scientific Venture, Inc., 18140 8th Ave. N, Plymouth, MN 55447 .*
[7] *Department of Emergency Medicine, UT Southwestern Medical Center, 5323 Harry Hines Blvd., MC 8579, Dallas ORCID.*

Abstract

Purpose: We sought to quantify the capabilities of a commercially available cooling device to protect the esophagus from RF injury in an animal model and develop a mathematical model to describe the system and provide a framework from which to advance this technology.

Methods: A series of ablations (10 W, duration 30-45 seconds) were performed directly on exposed swine esophagus. Control ablations were performed with static 37°C water, and treatment ablations were performed with water (range 5°C-37°C) circulating within the device. Mucosal lesions were evaluated visually and with target tissue histology. A mathematical model was then developed and compared against the experimental data.

Results: All 23 ablations (100%) performed under control conditions produced visible external esophageal lesions; 12 of these (52%) were transmural. Under treatment conditions, only 5 of 23 ablations (22%) produced visible external lesions; none (0%) were transmural. Transmurality of lesions decreased as circulating water temperature decreased, with absolute reduction ranging from 5.1% with the use of 37°C water (p=0.7) to 44.5% with the use of 5°C water (p<0.001). Comparison to the mathematical model showed an R^2 of 0.75, representing good agreement.

Conclusions: Under worst-case conditions, with RF energy applied directly to the adventitial side of the esophagus, internal esophageal cooling with an esophageal cooling device provides significant protective effect from thermal injury. A mathematical model of the process provides a means to further investigate this approach to preventing esophageal injury during RF ablation and can serve to guide ongoing clinical investigations currently in progress.

Introduction

Ablation of the left atrium to achieve pulmonary vein isolation (PVI) is a standard therapy in the management of atrial fibrillation; however, esophageal injury is a known potential consequence of this procedure[1,2]. Delivery of the radiofrequency (RF) energy necessary to perform PVI has the potential to cause injury to the nearby esophagus and its associated vagal innervation, with injuries including ulceration, hematoma, spasm, disorders of esophageal motility, and atrial-esophageal fistula (AEF), the latter representing the extreme consequence of esophageal thermal injury due to PVI[1,2]. Esophageal mucosal lesions are the likely precursor to AEF, and esophageal mucosal lesions are commonly found on endoscopy after PVI (with an incidence ranging from 3% to 60%)[3,4].

Luminal esophageal temperature (LET) monitoring is one proposed measure to reduce the incidence of esophageal injury during PVI; however, the success of temperature monitoring has varied widely [5,6] since effective measurement of LET depends on the position of the temperature probe relative to the heated cardiac tissue and also on good contact with the esophageal mucosa[7]. Moreover, the temperature probe used for esophageal temperature monitoring may contribute to a thermal effect and enhance direct tissue heating[8]. Recent data show rates of esophageal lesions in 40% to 50% of patients, regardless of whether a single-sensor or multi-sensor temperature probe is used[3].

Esophageal injury prevention via cooling of the esophagus (primarily with various balloon configurations) has been investigated

Key Words

Atrial Fibrillation, Ablation, Pulmonary Vein Isolation, Esophageal Protection, Radiofrequency Energy, Esophageal Cooling, Finite Element Model, Mathematical Modeling

Corresponding Author
Marcela Mercado Montoya,
University of Antioquia, Bioengineering Department, Calle 70 No. 52-21, Medellin, Colombia

with mathematical modeling, preclinical models, and in the clinical arena, with an abundance of data showing efficacy in this approach[9-16]. The complexity of earlier prototypes, and the workflow disruption inherent in their use, appears to have precluded commercialization of a device leveraging this method. An esophageal heat transfer device (EnsoETM, Attune Medical, Chicago, IL, USA) is available for a variety of patient temperature management needs[17-20]. This device provides a closed-circuit of water flow through a multi-channel 12 mm diameter cylindrical silicone tube placed in the esophagus analogously to a standard orogastric tube, and warms or cools a patient through conductive heat transfer across the esophagus as well as convective heat transfer through the device[17]. The device is used for purposes such as the intentional reduction of patient body temperature below normal, the reduction of patient temperature from hyperthermic levels to normal range, and the prevention of inadvertent perioperative hypothermia[17-20]. Most patients treated with the device are endotracheally intubated; however, placement in sedated patients is also performed successfully. We aimed to quantify the protective effect of this device against thermal injury to esophageal mucosa in an animal model, and to develop a mathematical model that accurately describes the system, allowing further investigation into this approach to esophageal protection.

Material and Methods

Experimental Design

This pilot study was performed under protocol ACD001-IS75 approved by the Institutional Animal Care and Use Committee (IACUC) of American Preclinical Services, Minneapolis, MN. The study utilized methods consistent with current veterinary and USDA standards, with a state-of-the-art, Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International-accredited vivarium. Animal care and handling was in accord with Office of Laboratory Animal Welfare guidance for humane care and use of animals and with regulations outlined in the USDA Animal Welfare Act (9 CFR Parts 1, 2 and 3) and conformed to the conditions specified in the Guide for the Care and Use of Laboratory Animals (National Academy Press, Washington DC, 1996). A swine model was selected due to similarities in size, physiology, and thoracic anatomy to typical adult human subjects undergoing PVI for the prevention of atrial fibrillation.

Procedures

A total of six male Yorkshire swine weighing a mean of 81.5 ± 7 kg, housed on site, were given 12 hours food restriction but free access to water before the intervention. Subjects were medicated with a pre-anesthetic mix of Telazol (tiletamine/zolazepam)/Xylazine 3.5-5.5 mg/kg intramuscularly, endotracheally intubated and anesthetized with 3% inhalational isoflurane (with concentration adjusted as needed to maintain anesthesia). No paralytics were used during any part of the study. Normal saline was instilled at a maintenance rate (2 cc/kg/hr) via ear vein. Continuous cardiac monitoring was performed with a 3-lead EKG rhythm recorder.

Lesion Placement

In each subject, a right lateral thoracotomy was performed to expose a region of esophagus. A series of 6 to 10 ablations, based on esophagus length, were placed directly on the esophagus using a 4mm ablation catheter (Safire 7Fr Quadripolar Catheter, St. Jude Medical, St. Paul, MN) powered by an RF generator (IBI 1500T9 RF, Irvine Biosciences Inc., Irvine, CA). RF energy was delivered via power control mode, holding wattage constant. Room-temperature saline was added to the thoracic cavity prior to performing ablations. Ablation energy was 10W with a 30-45s duration for all but one lesion, where 20W was utilized. The use of 10W represents an equivalent of approximately 30 to 40 W if the additional tissue of atrial wall, pericardium, adipose tissue, etc., was present and the ablation was being performed on the atrial wall and thermal impact measured on the esophageal mucosa. Contact force was measured on the first lesion to gauge pressure requirements, with subsequent lesions performed manually, matching the same level of force by an experienced electrophysiologist physician to achieve 15 g, as the catheter utilized for this study was not a contact-force measuring catheter. Since non-irrigated and non-contact-force sensing catheters are still used by 30% of the writing group of the 2017 HRS-EHRA-ECAS-APHRS-SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation, this first study serves as a reasonable starting point from which to advance knowledge in this important area of patient care[21].

Intervention

The esophageal heat transfer device was placed following standard procedure. Briefly, the device was connected to an external heat exchange unit (either a Medi-Therm III, Stryker Corp., Kalamazoo, MI, or a Thermotek Harmony, Thermotek Inc., Flower Mound, TX, supplying a minimum of 60 L/hour flow rate of water) according to standard procedures, both of which circulate distilled water as the coolant at a temperature range from 4°C to 42°C. After water flow was initiated, the tip of the device was lubricated with a water-soluble lubricant and inserted through the oropharynx into the esophagus to a depth sufficient for the tip to rest beyond the thoracic esophagus (See [Figure 1] for image of the esophageal device). The esophageal heat transfer device is a closed-loop cooling system, in that water does not leave the device but instead circulates in a closed-loop, counter-current configuration. The entire system is designed to utilize servo-mode cooling, which can also be considered a closed-loop feedback

Figure 1: Image of the esophageal heat transfer device.

system; however, for this application, this feature was not necessary, as water temperature was pre-specified and set manually by the operators. Because the esophagus is a flat structure, compressed in the anterior-posterior direction when the patient is supine, firm contact with the anterior aspect of the esophagus occurs once placed into the esophagus. The open central lumen further provides gastric decompression, preventing distention of the esophagus away from the walls of the device. Because the entire length of the device contains water flow, the full length of the esophagus is contacted and cooled equally. Placement in the experimental animals was confirmed by visualization of the device distending the esophagus during entry, and palpation of the device in place once settled. Control lesions were performed with 37°C water held still within the device. Treatment lesions were performed with cooled water (range 5°C-37°C) circulating within the device. Each subject received a combination of control and treatment lesions. The presence of mucosal lesions was evaluated visually after triphenyltetrazolium chloride (TTC) staining and thermal injury depth was measured by target tissue histology, performed by a DVM and Diplomate of the American College of Veterinary Pathologists. Descriptive statistics are reported with comparisons of means via independent sample t-tests.

Modeling

A model was developed utilizing COMSOL Multiphysics software (COMSOL, Burlington, MA, USA), utilizing similar methodology as found in others' work in this area[22,9,23]. Mathematical modeling offers a powerful tool for predicting and confirming the dimensions and characteristics of lesions created under different ablation conditions, and allows evaluation of the impact of different parameters without requiring living tissue for each change in operating parameters of interest[22]. As such, we designed a model based on existing tissue parameters which we could then use to compare the results of the experimental data, and further serve as the basis for modelling of different ablation conditions using esophageal cooling for tissue protection. The 3D computational domain and subdomains were specified as shown in [Figure 2] The RF power was modeled using the Electric Currents interface from the ACDC module included in COMSOL Multiphysics. At the catheter tip boundaries, power (10W) and impedance (from 45Ω to 87Ω) were specified, based on the experimental settings and tissue response. The bottom face of the computational domain was set to ground. The heat transfer was modeled using the Bioheat Transfer interface from the Heat Transfer module included in COMSOL Multiphysics. The heat generation term was defined to be that produced by the RF power, using the coupling interface Electromagnetic Heat Source included in the Multiphysics module. Domain 5, the saline bath, was considered as a non-moving fluid. Further details are included in Supplementary Appendix 1.

Table 1: Outcome as a function of type of procedure.

Group	Number of lesions	Energy (W)	Duration (seconds)	Cooling (yes/ no)	Temperature (degrees C)	Percent transmurality (%)	Std Dev (+/- %)	Significance (P value)	Mean myofiber contraction band necrosis score	Mean submucosal edema score	Mean muscularis mucosa damage score	Mean epithelial damage score
control (45s) (n=8)	8	10	45	no	n/a	79.9	15.7	Ref (45 sec)	3.4	1.3	1.1	0.4
Control (30s) (n=15)	15	10	30	no	na	69.7	12.6	Ref (30 sec)	2.9	0.7	0.3	0.1
37C (45s) 10W (n=2)	2	10	45	yes	37	64.0	10.3	0.20	2.8	0.0	0.0	0.0
37C (30s) 10W (n=1)	1	10	30	yes	37	64.6	n/a	0.70	0.3	0.0	0.0	0.0
30C (45s) 10W (n=2)	2	10	45	yes	30	46.3	12.3	0.02	1.5	0.0	0.0	0.0
10C (45s) 10W (n=2)	2	10	45	yes	10	0.0	n/a	<0.001	0.0	0.0	0.0	0.0
5C (45s) 10W (n=4)	4	10	45	yes	5	44.4	30.4	0.02	0.8	0.0	0.0	0.0
5C (30s) 10W (n=12)	12	10	30	yes	5	25.2	17.1	<0.001	0.7	0.0	0.0	0.0

Score = (0) = None; Score = (1) = Minimal; Score = (2) = Mild; Score = (3) = Moderate; Score = (4) = Severe

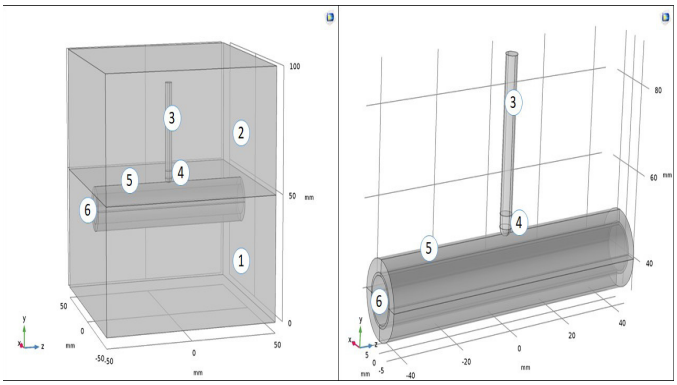

Figure 2: Computational domain used for the mathematical modeling, with the ablation catheter applied directly to the esophagus, and with the cooling device inserted, and with subdomains including: 1) thoracic cavity (average tissue values), 2) saline water, 3) catheter body, 4) catheter tip, 5) esophagus, 6) cooling device

Results

A total of 52 ablations were performed across 6 swine (average mass 81.5 ± 7kg). Six (6) ablations were used to determine experimental parameters. A total of 46 ablations were included for analysis, 23 treatment and 23 control. [Table 1] provides details on all lesions.

All ablations performed under control conditions produced external esophageal lesions; [Figure 3] shows external (adventitial) esophageal surfaces in-vivo, and [Figure 4] (top image) shows ex-vivo, while [Figure 4] (bottom image) shows a representative

esophageal mucosal surface. Transmural lesions extending into the esophageal mucosa were consistently visible on gross examination after 30 seconds of 10W RF energy application in subjects less than 80kg. In subjects greater than 80kg, transmural lesions were obtained in at least 20% of cases with 30 seconds duration and 70% of cases with a 45 seconds duration.

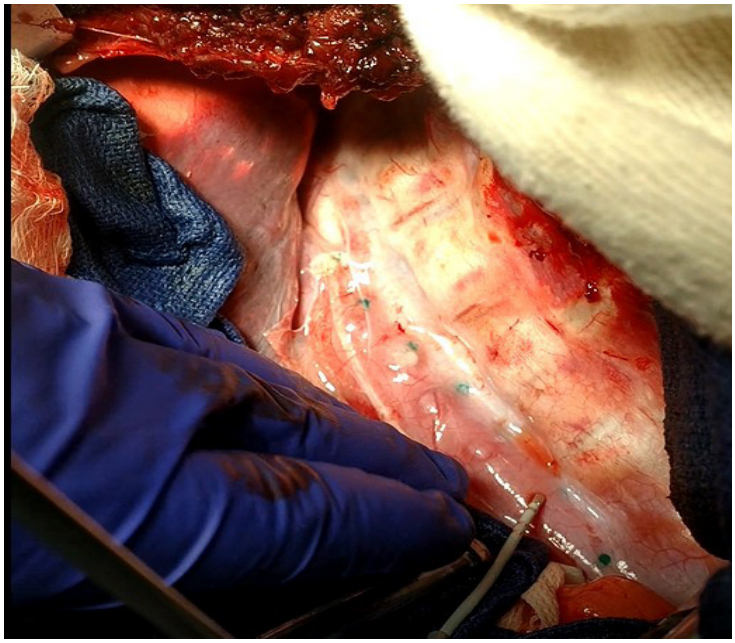

Figure 3: In-vivo ablation application of the device and RF ablation directly on exposed esophagus (shown with normal saline water bath removed for clarity).

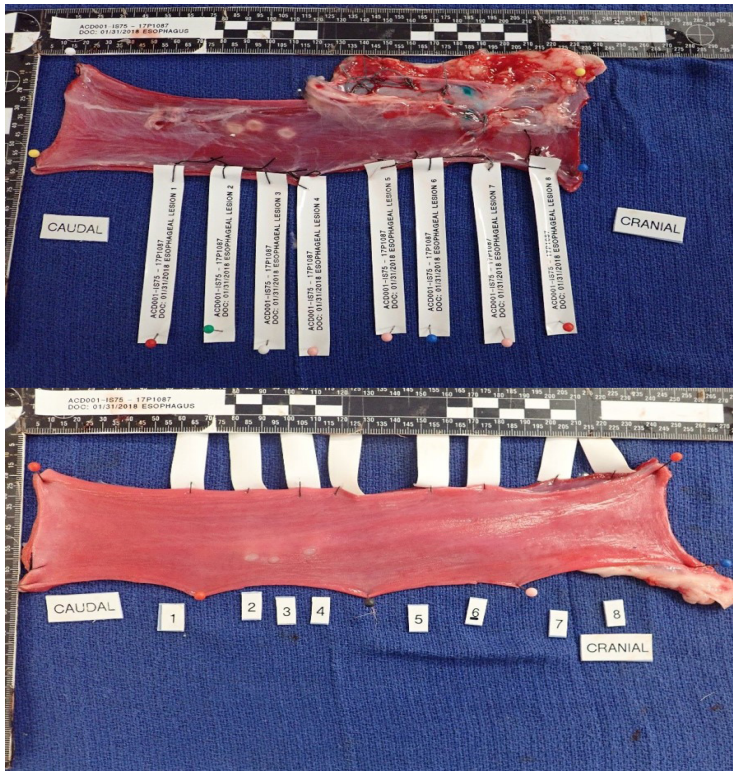

Figure 4: Top image: Sectioned esophagus showing application regions on external surface (lesions visible where no cooling applied, on left half of section). No lesions are visible on surface where cooling was applied with the device (right half of section). Bottom image: Sectioned esophagus showing mucosal surface (transmural lesions visible where no cooling applied).

In contrast, ablations performed under treatment conditions using 10W of RF energy using 37°C, 10°C, or 5°C circulating water, for 30 or 45s duration, did not produce visible transmural lesions and only 6 ablations (25%) produced visible external lesions. Ablations performed during the most aggressive treatment condition (5°C circulating water), did not demonstrate any visible lesions throughout the thickness of the esophageal musculature, including on the external surface of the esophagus at the point of contact with the ablation catheter.

Histopathological evaluation was performed with the measurement method as shown in [Figure 5], in which the maximum lesion thickness was determined, and divided by the maximum tissue thickness.

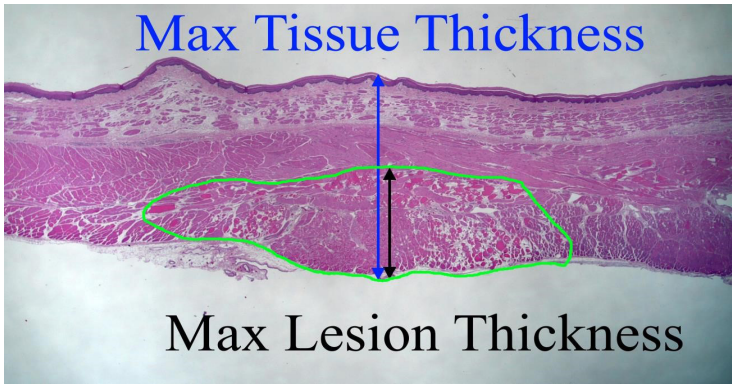

Figure 5: Max Tissue Thickness (in blue) included the entire thickness of the tissue on the slide at the site of measurement. Max Lesion Thickness (in black) included the thickness of the lesion starting at the adventitial connective tissue and going toward the epithelium to the maximum depth of the lesion damage. Measurement lines are illustrated separately for visual clarity but were taken at the same location for data collection to ensure accurate measurements for percentage calculation.

Measurements of lesion thickness confirmed that the percent transmurality of lesions decreased as water temperature flowing through the esophageal heat transfer device was decreased ([Table 1]). [Figure 6] shows a graphical representation of results. The absolute reduction in percent transmurality from control (45 seconds of application) with the use of 37°C water was 16.0% (p=0.2), while the absolute reduction with the use of 30°C water was 33.6% (p=0.02) and the absolute reduction using 5°C water was 35.6% (p=0.02). In the group with 30 seconds of RF application time, the absolute reduction in percent transmurality from control with the use of 37°C water was 5.1% (p=0.7), while the absolute reduction with the use of 10°C water was 69.7% (p<0.001) and the absolute reduction using 5°C water was 44.5% (p<0.001). Mean submucosal edema scores, muscularis mucosa damage scores, and epithelial damage scores likewise decreased with decreases in coolant temperature (and hence increases in heat extraction capacity).

Results of the model output, using tissue parameters as included in the COMSOL Multiphysics software and detailed in the Supplementary Appendix 1, revealed a close correlation to experimental findings, with an R^2 of 0.75. [Figure 6] shows the comparison between experimental and computational data.

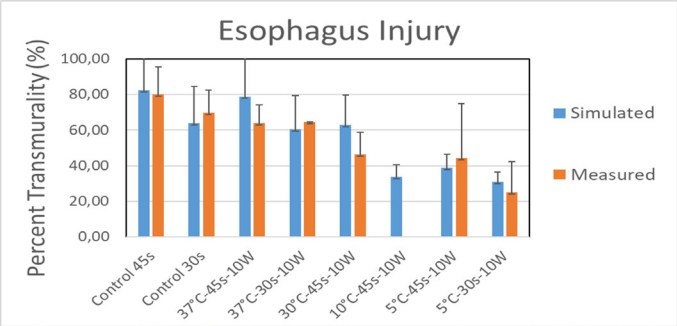

Figure 6: Percent lesion depth (transmurality) for each group of operational parameters, in experimental and modeling conditions.

Discussion

These data suggest a significant protective capability of a new esophageal heat transfer device against esophageal injury from the application of RF energy for ablation, with an accompanying mathematical model of the process developed to allow further investigation into this approach. Using a water temperature of 5˚C supplied to an esophageal heat transfer device by either of two models of heat exchanger, a direct application of RF energy at 10 W for 30 seconds was unable to elicit visual evidence of thermal impact. In contrast, under control conditions without water flow through the device, this same energy resulted in fully transmural lesions visible on gross pathology. Histologic analysis demonstrated a marked reduction in transmurality of lesions with use of the device, and mean submucosal edema scores, muscularis mucosa damage scores, and epithelial damage scores were likewise notably reduced. Even at a coolant temperature of 37˚C, a protective effect was seen, suggesting that the high coolant flow rates obtained with the external heat exchange units (minimum of 60 L/hour) may be an important component of this effect. In comparison, earlier studies of esophageal cooling for thermal protection found generally that efficacy appeared to increase with increasing flow rates, but the range utilized in these earlier studies was typically 25 mL/minute to at most 300 mL/minute, much less than the 1000 mL/minute minimum used in this current study. [Table 2] summarizes these earlier studies

Collectively, these data from prior investigations into esophageal protection via direct cooling suggest that although some efficacy was apparent, a limitation stemmed from the lower, or absent, flow rates of coolant employed. Additionally, it was noted in one paper that the methods previously investigated were somewhat complicated to perform in clinical practice, and thus no follow-up studies were conducted[15]. In contrast, the esophageal heat transfer device evaluated in this study is straightforward to deploy without disruption in typical workflow in the electrophysiology lab. This study did not investigate the potential to protect against injury from cryoablation; however, the device is also capable of warming the esophagus.

A number of clinical studies of this approach are underway, utilizing the device investigated in this study. These include: Esophageal Cooling inRadiofrequency Cardiac Ablation - NCT03481023. Improving Oesophageal Protection During AF Ablation (IMPACT) -NCT03819946, Esophageal Cooling for AF Ablation (eCoolAF) -NCT03691571, Esophageal Cooling inRadiofrequency Cardiac Ablation - NCT03481023, and Esophageal Damage Protection During Pulmonary Vein Ablation. Pilot Study. - NCT03832959. In addition, initial clinical data from a single site using a milder setting of 30˚C water temperature have been presented[24].

Table 2: Summary of prior studies of esophageal cooling during RF ablation.

Modality/ Device	Study Method	Flow Rate	Temperature	Results	Citation
Cooled intra-esophageal balloon	Finite-element mathematical model	N/A	32, 25, and 15 C	Chilling the esophagus minimizes the lesion in the esophageal wall	[9]
Intraesophageal balloon	8 patient clinical study	25 mL/ min	4.5 ± 3.1 C	The intraesophageal balloon successfully lowers luminal esophageal temperature, and might prevent esophageal injury	[13]
Saline filled esophageal balloon	Animal model	Non-flowing	10 C	System was not sufficient to prevent thermal injury	[14]
Cooled intra-esophageal balloon	Agar phantom	25 mL/ min	5 C	A cooled intraesophageal balloon provides effective thermal protection of the esophageal lumen	[10]
Cooled intra-esophageal balloon	Agar phantom	25 mL/ min	37, 23, 15, and 5 C	A cooling balloon gives thermal protection to the esophagus with a minimum pre-cooling period of 2 min and a coolant temperature of 5 C or less	[11]
12 Fr probe with a distal expandable compliant latex sac (up to 3 cm in diameter)	In-vitro and in-vivo animal model	50 to 300 mL/ min	25, 15, 10, and 5 C	Device spares the esophagus from collateral thermal injury with circulating fluid at 5 or 10 C	[12]
Free water instillation	100 patient clinical study	5 mL aliquots	Ice water	Alleviated the severity of esophageal lesions, but did not significantly reduce the incidence	[15]
Free water instillation	318 patient clinical study	10 to 20 mL aliquots	Ice water	Esophageal damage reduced by infusing cooling solution into the esophagus	[16]

Limitations

This study did not utilize a contact-force sensing catheter to measure applied force at each lesion. The first application utilized force measurement with an external gauge, while all subsequent lesions relied on the judgement of an experienced electrophysiologist. Although some variability in contact force is inevitable with this approach, the force was applied directly, without having to navigate through a percutaneous approach with the associated variable resistances through vasculature that would add more variability to the contact force applied. Moreover, a systematic bias is unlikely, and the effect size seen in this approach would likely overwhelm the variability in contact force. Likewise, in lieu of irrigation supplied through the tip of the ablation catheter, saline was used as a water bath during ablations; however, this likely provides a more severe thermal insult to the tissue than would be the case with irrigation. This study did not involve ablation of the atria directly; however, the design that was utilized (ablating directly on the adventitial surface of the esophagus) provided a worst-case model that eliminates confounders such as variations between subjects in location of the esophagus relative to the atria, variations in the amount of interspersed tissue, and variations in atrial wall thickness, all of which would confound the data. An energy level of 10 W was chosen, since the ablations were performed directly on the esophagus. This is equivalent to higher wattages applied to the atrial wall by a factor of 3-4x (due to the significantly greater amount of tissue through which the energy must traverse). Additionally, this study does not address what impact the esophageal heat transfer device may have on the atrial tissue, but the much higher flow rate of blood through the atria is likely to overwhelm the cooling effect such that no significant temperature reduction of the atrial tissue occurs. Mathematical modeling of this is currently underway and further supports this concept. No lesions were identifiable in the region of RF ablations during cooling with 10°C water flow and 45 seconds of duration using 10W of power, which may reflect inadvertent misplacement of sectioning knife for tissue histology, variation in performance of the device, or variation in contact force applied. Finally, protection against AEF using this approach is predicated on the hypothesis that visible lesions on the esophageal mucosa are a precursor to AEF development. Although this hypothesis is generally accepted, additional mechanisms such as delayed ischemic necrosis may potentially play a role in progression to AEF.

Conclusions

Use of a new esophageal heat transfer device resulted in significant protection against esophageal injury from direct radiofrequency ablation. The protective effects seen in these data suggest that this may be an effective approach to the prevention of esophageal injury during RF ablation involving the posterior wall of the left atrium. A mathematical model of the process provides a means to further evaluate and refine this approach to preventing esophageal injury during RF ablation and can serve to guide ongoing clinical investigations currently in progress.

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Robotic Navigation Shows Superior Improvement in Efficiency for Atrial Fibrillation Ablation

Anna Maria Elisabeth Noten[1], Zsuzsanna Kis[1], Ferdi Akca[1], Rohit Bhagwandien[1], Sip Wijchers [1], Sing-Chien Yap[1], Tamas Szili-Torok[1]

[1] *Department of Cardiology, Erasmus MC, University Medical Center, Rotterdam, the Netherlands.*

Abstract

Background: Because of the expanding atrial fibrillation (AF) burden, AF catheter ablation (CA) techniques have to become more efficient. Efficient AF CA procedures are characterized by successful pulmonary vein isolation (PVI) within reasonable procedure time. Currently there are many PVI techniques available and all show substantial improvements over time. However, the magnitude of improvement in procedural efficiency has not yet been compared between different techniques. The aim of this study was to compare efficiency improvement between manually (MAN) guided, cryoballoon (CB) and remote magnetic navigation (RMN) guided PVI.

Methods: A total of 221 patients were included in this retrospective study. Procedural parameters of 115 patients treated with first-generation PVI techniques (MAN-1, CB-1, RMN-1) performed in 2010, were compared to 106 patients who were treated with the latest, second generation techniques (MAN-2, CB-2, RMN-2). Efficiency was characterized by the following parameters: total ablation time, total procedure time, first pass isolation (FPI) (i.e. successful isolation after the first pulmonary vein (PV) encirclement) and touch-up rates.

Results: Every technique showed significant improvement of procedure times from the first to the second generation (P<0.001). In-between second generation techniques, the procedure times were comparable. The greatest magnitude of procedure time improvement was observed within the RMN groups (Δ-180min), which was significantly greater compared to CB (Δ-48 min, P<0.001) and MAN (Δ-98min, P=0.011) groups. The highest FPI rates were observed in RMN-2 (78% and 74%; left and right PVs respectively), which was significantly higher compared to other techniques (MAN-2: 24% and 24%; CB-2: 50% and 48%; P<0.001).

Conclusions: The highest magnitude of efficiency improvement was detected in RMN guided PVI.

Introduction

The atrial fibrillation (AF) prevalence is rapidly increasing[1]. Already 33.5 million patients were diagnosed with AF worldwide in 2013[1]. The AF pandemic constitutes a significant public health problem, as well as it has a substantial financial impact on healthcare. Catheter ablation (CA) has become a first-choice treatment for patients with drug refractory AF[2-4]. Electrical isolation of the pulmonary veins (PVs) is the cornerstone of AF ablation[5,6]. CA procedures have to become more efficient in order to be available for a larger share of the AF population. Efficient AF CA procedures are characterized by successful pulmonary vein isolation (PVI) within reasonable ablation and procedure time. Many PVI techniques are currently available and all experienced substantial improvements over time.

Initially, PVI was performed manually by series of point-by-point radiofrequency (RF) lesions encircling the PVs, which had the inevitable risk of gaps persisting within the ablation lines[4,7]. The efficacy of manual (MAN) guided RF ablation improved significantly with the advent of contact force (CF) sensing catheters, resulting in less recurrence of arrhythmia and significantly shorter ablation times[8]. Besides, single-shot techniques emerged, of which the cryoballoon (CB) is nowadays most frequently used. The CB had the advantage of combining facile positioning and ablation, while decreasing procedure time[4,9,10]. Its disadvantage was the poor adaptation to anatomical variations of PVs[4,11]. The second generation CB exhibited higher freedom of AF within shorter isolation, fluoroscopy and procedure times when compared to its precursor[12]. Subsequently, remote magnetic navigation (RMN) guided ablation was introduced as an alternative RF CA strategy. In RMN, two magnetic platforms are utilized to remotely guide the movement of the ablation catheter by magnetic fields[13,14]. Various publications reported on the benefits of RMN due to precision of catheter movement, its soft tip and its stability, causing superior lesion formation[15] and improved procedural safety[16,17]. However, the disadvantages of RMN guided RF ablation were the prolonged ablation and procedure times and increased operator learning curve[18,19].

Although all techniques underwent progressive improvements resulting in simpler workflow, better efficiency and outcome, there still continues to be an ongoing discussion on which ablation technique

Key Words

Robotic Navigation Guided Ablation, Radiofrequency Ablation, Cryoballoon Ablation, Pulmonary Vein Isolation, Remote Magnetic Navigation Guided Ablation, Atrial Fibrillation

Corresponding Author
Tamas Szili-Torok,
Thoraxcenter, Department of Clinical Electrophysiology, Erasmus MC, Postbus 2040, 3000 CA, Rotterdam, The Netherlands

is preferable. Multiple studies have been published comparing procedural outcome between two ablation techniques[18-23]. However, there is no clear study available that investigates the potential of efficiency improvement of certain techniques. The aim of this study was to compare the advancements of procedural efficiency over time of three different ablation techniques (MAN guided RF, CB and Robotic navigation (RMN) guided RF), to distinguish which technique has highest potential for further efficiency improvement in the future.

Methods

Study design

This study is a retrospective, single-center study, investigating PVI procedures performed with CB, manual guided RF and RMN guided RF. We analyzed and compared procedural efficiency parameters between two generations of each of these three techniques. Procedural efficiency was defined by the following endpoints: total procedure time, total ablation time, first pass isolation rates and touch up rates. Additionally, we analyzed AF recurrence (documented on ECG) and redo procedure rates at 12-months post-procedure, with use of a 3-month blanking period[3].

Study population and data collection

All patients who underwent the first PVI for AF, utilizing the latest available techniques for MAN guided RF, CB or RMN guided RF ablation between September 2016 - July 2017, were selected for analysis (second generation procedures, defined as MAN-2, CB-2 and RMN-2 groups). From January 2010, age and sex-matched controls were selected consecutively for each of the three treatment techniques (first generation procedures, defined as MAN-1, CB-1 and RMN-1 groups). All patients were eligible for AF ablation based on the respective ACC/AHA/ESC Guideline valid at the date of procedure[2,24-26]. Patients with anatomical variants of PVs were valid for inclusion. Patients with intra-cardiac thrombus were contra-indicated for a CA procedure. Patients aged ≤18 years and redo PVI procedures were excluded from study participation. Baseline demographic and clinical characteristics were collected using the electronic health records (Elpado version 2.56.0). Procedural data was derived both from the electronical medical files, as well as from the electronical procedural log files recorded with the EP-workmate™ (St. Jude Medical Inc., St. Paul, MN, USA), the Ensite™ NavX™ (St. Jude Medical Inc., St. Paul, MN, USA), the CryoConsole® (Medtronic, Minneapolis, MN, USA) and the the Odyssey™ Cinema (Stereotaxis Inc., St. Louis MO, USA) systems. Data collection for this study from our registry was approved by the institutional review committee and was carried out in accordance with the ethical principles for medical research involving human subjects founded by Helsinki's declaration. All patients provided informed consent prior the ablation procedure.

Procedural protocols

PV anatomy was evaluated in all patients pre-operatively with a CT-scan. Patients with a left common ostium and/or a PV size >28mm, were scheduled for PVI with RF (either MAN or RMN guided) as standard of care. All procedures were performed under local or general anesthesia. Presence of intra-cardiac thrombus was evaluated at the start of procedure by trans-esophageal echocardiography. All MAN procedures were performed using the EnSite NavX (St. Jude Medical Inc., St. Paul, MN, USA) mapping system. The following catheters were used in the MAN-1 group: the Celsius ThermoCool® 4mm catheter and the Navistar ThermoCool® catheters (Biosense Webster Inc., CA, USA). In the MAN-2 group, all procedures were performed using CF sensing catheters, i.e. the TactiCath™ contact force catheter (St. Jude Medical Inc., St. Paul, MN, USA). Patients in the CB groups were treated with first generation Artic Front® (CB-1 group) or second generation Arctic Front Advance® (CB-2 group) cryoballoon (Medtronic, Minneapolis, MN, USA). RMN procedures were performed using either the Niobe II (RMN-1 group) or the Niobe ES (RMN-2 group) Magnetic Navigation System (Stereotaxis, St Louis, MO, US), with use of the NaviStar RMT ThermoCool catheter (Biosense Webster Inc., CA, US) in both generations. During all PVI procedures, thirty minutes of waiting time were executed as standard of care to identify early PV reconnection. All patients were observed at the intensive care unit or cardiac care unit after the procedure, with continuous hemodynamic, respiratory and ECG recordings. Presence of pericardial effusion was checked in all patients with trans-thoracic echography (TTE) as standard of care.

Remote Magnetic Navigation

The Niobe RMN system (Stereotaxis, Inc., St Louis, MO, USA) is a medical platform designed for electrophysiology and interventional procedures. The RMN system utilizes two permanent magnets, one on each side of the patient, to remotely guide the movement of the distal tip of compatible ablation catheters via magnetic fields. This technique has been described and validated extensively elsewhere[13,14]. In RMN-2 ablation was performed with the following radiofrequency settings: power 45-50 W, temperature 43°C. In all RMN-2 procedures the latest RMN technologic advancements were implemented: the Ablation History feature and the e-Contact module. Ablation History provides a visual display of the history of the catheter's power output and duration of energy application at each location at the map during the ablation. The 'e-Contact module' provides contact feedback, by a visual indicator (starburst) when the catheter tip is in contact with the cardiac tissue.

Definitions

Procedural efficiency is characterized by successful PVI isolation within reasonable procedure and ablation time. Therefore, we analyzed the following procedural parameters: total application duration, total procedure time, PV encirclement times, first pass isolation rate (FPI) and touch-up (TU) rate. Total procedure time was defined as the time from start of the procedure (1st puncture) until the end of procedure (removal of catheters). The PV encirclement time was defined as the start of the first application for either the left or the right sided wide-area circumferential ablation (WACA), until the last application enclosing the vein. In case of CB ablation, encirclement time was calculated as the duration of the first adequate balloon application. First pass isolation (FPI) was regarded when the first PV encirclement or first adequate CB application, resulted in successful PV isolation. If the first encirclement did not result in isolation of the PVs, additional applications were regarded TU. For CB, the second and all additional applications were regarded TU. The PV encirclement time, number of touch ups (TU) and first pass

isolation (FPI) rates were evaluated in second generation procedures only, because of the use of different procedural protocols in the past. When additional ablations of non-PVI triggers were performed, the procedure times were adjusted accordingly, as well as the number of applications and total application duration. The single procedure AF recurrence rates were evaluated. When a redo procedure was performed during the 12 months of follow-up, it was regarded as AF recurrence.

Complications

Major complications were defined as per ISO 14155 definition, as events that led to death, or led to serious deterioration in the health of the subject (i.e. resulted in a life-threatening illness or injury, or a permanent impairment of a body structure or a body function, or in-patient or prolonged hospitalization, or medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function). Minor complications were defined as events that resulted in minimal transient impairment of a body function or damage to a body structure, or which did not require any intervention other than monitoring.

Statistical analysis

Continuous variables were checked for normal distribution with normality plots and the Shapiro-Wilk test. Normally distributed continuous variables were described with mean and standard deviation. Normal distributed continuous variables were analyzed using the 1-way ANOVA. A post-hoc Tukey's honestly significant difference test was performed to investigate significant differences in-between the 6 groups when a significant main effect was present. Continuous variables with a non-normal distribution were described by median and interquartile ranges (IQR). The Kruskal-Wallis test was used to examine continuous variables with a non-normal distribution. Descriptive statistics for categorical data were expressed in absolute numbers with percentages and analyzed using the Chi-square test, or, when appropriate, Fisher's exact test. A 2-sided P-value of <0.05 (2-tailed) was considered significant. Data were analyzed using SPSS 24.0 (SPSS Inc., Chicago, IL, USA).

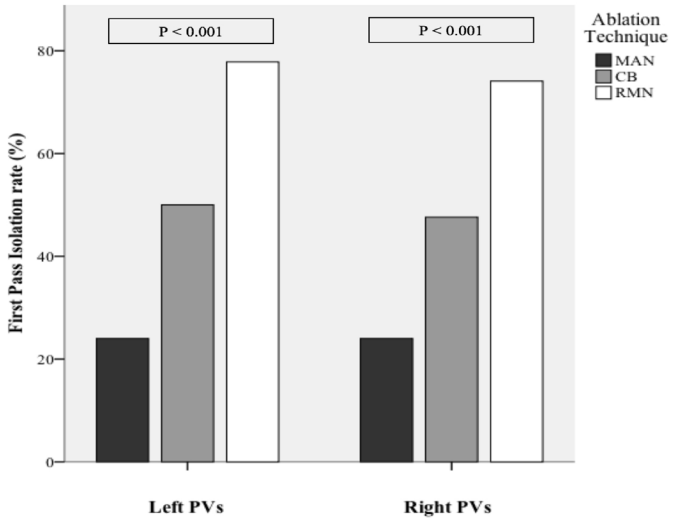

Figure 1: First pass isolation rates - 2nd generation groups only

The first pass isolation rates of the three second generation treatment techniques are displayed in figure 1. First pass isolation (FPI) was regarded when the first ablation encirclement of the PVs or the first CB application, resulted in successful PV isolation. Only second generation groups are displayed, as first pass isolation could only be calculated in these groups.
PVs = pulmonary veins.

Results

Baseline demographic and clinical characteristics

A total of 221 patients were included in this study (MAN-1 n=39; CB-1 n=39; RMN-1 n=37; MAN-2 n=37; CB-2 n=43; RMN-2 n=27). Patient demographic and clinical data are summarized in [Table 1]. Age was significantly different between groups ([Table 1], P=0.009). Post-hoc analysis showed that the only significant difference was found between CB-1 group with a mean of 55.44 ± 9.18 years and MAN-2 group with a mean of 62.36 ± 8.36 years (P=0.022). In both CB groups, significantly more patients with paroxysmal AF were present, as compared to MAN and RMN groups ([Table 1], P<0.001). Treatment with amiodarone was less frequently used in CB and second-generation groups ([Table 1], P=0.002). Prevalence of ischemic heart disease was significantly different between groups as well, which however did not result in a difference in ejection fraction. All patients were treated with anti-coagulation. Vitamin K antagonists were often prescribed in the first generation groups, while direct-acting oral anticoagulants (DOAC) were more prevalent in the second generation groups ([Table 1], P<0.001).

Procedural characteristics

Procedural data is depicted in [Table 2] and 3. The mean procedure time significantly differed between the 6 groups ([Table 2], P<0.001). Additionally, significant differences were observed in the number of applications and application duration, with the lowest number of applications noted in the CB groups ([Table 2], P<0.001) and the shortest application durations noted in second generation procedures ([Table 2], P<0.001). The PV encirclement time, number of touch ups (TU) and first pass isolation (FPI) rates were evaluated in second generation procedures only. Encirclement times of left and right sided PVs were significantly different between the three second generation techniques ([Table 3], P<0.001). Interestingly, the first pass isolation rates of the left and right sided PVs differed considerably between the three second generation techniques. The highest FPI rates were observed in RMN-2: 78% for left PVs and 74% for right PVs, while in the MAN-2 group and CB-2 group significantly lower rates were found ([Table 3] and [Figure 1], P<0.001). The TU rates reflected the FPI rates and highlighted a significant difference as well ([Table 3], P<0.001).

Post-hoc analysis

Post-hoc analysis investigated the significant differences in-between groups identified by the one-way ANOVA tests. The mean PVI procedures times were comparable between the second generation groups ([Table 2] and supplemental files). The mean procedure time significantly improved within each treatment technique over time ([Table 2] and supplemental files). The greatest magnitude of improvement of procedure time was observed within the RMN groups (Δ -180min), which was significant higher when compared to CB (Δ -48 min, P<0.001) and MAN (Δ -98min, P=0.011) groups ([Figure 2] and supplemental files). Post-hoc analysis showed that the encirclement time for left PVs was the longest in MAN-2 group

(27 ± 13.76 min), intermediate in RMN-2 (13 ± 5.40 min), while the shortest time was observed in the CB-2 group (6 ± 1.83 min) (MAN-2 vs. CB-2, P<0.001; MAN-2 vs. RMN-2, P<0.001; CB-2 vs. RMN-2, P=0.003). The encirclement times for right PVs showed the same pattern ([Table 3] and supplemental files).

12 month outcomes

Documented AF recurrence rates and redo procedure rates were analyzed for patients with paroxysmal and persistent AF separately. The results are presented in [Table 4]. The overall recurrence rate in paroxysmal AF was 31%, whereas in persistent AF the recurrence rate was 42%. In both paroxysmal and persistent AF, recurrence rates were comparable between groups ([Table 4], P=0.708 and P=0.622, respectively). In patients with paroxysmal AF treated with first generation CB (CB-1), a high redo procedure rate was

Table 1: Patient demographic and clinical data

	MAN-1 (n=39)	CB-1(n=39)	RMN-1 (n=37)	MAN-2 (n=36)	CB-2(n=43)	RMN-2 (n=27)	All patients (n=221)	P-value
Age (years)	59 ±11.2	55 ±9.2A	57 ±9.4	62 ±8.4B	61 ±9.0	62 ±8.9	59 ±9.6	0.009
Female	12 (31%)	10 (26%)	11 (30%)	9 (25%)	7 (16%)	8 (30%)	57 (26%)	0.691
BMI (kg/m2)	28 ±4	27 ±4.0	28 ±4.5	27 ±4.7	27 ±3.2	28 ±3.0	27 ±4.0	0.733
AF duration (years)	2 (1 - 6)	2 (1 - 3)	3 (1 - 7)	3 (2 - 6)	3 (1 - 6)	3 (1 - 6)	1 (2 - 6)	0.056
Paroxysmal AF	26 (67%)	36 (92%)	18 (49%)	28 (78%)	39 (91%)	14 (52%)	161 (73%)	<0.001
Previous EP procedure (No PVI)	7 (18%)	5 (13%)	3 (8%)	8 (22%)	6 (14%)	5 (19%)	34 (15%)	0.629
Hypertension	13 (33%)	14 (36%)	14 (38%)	17 (47%)	21 (49%)	7 (26%)	86 (39%)	0.367
Hyperlipidemia	9 (23%)	7 (18%)	4 (11%)	7 (19%)	13 (30%)	6 (22%)	46 (21%)	0.422
Diabetes Mellitus	5 (13%)	3 (8%)	5 (14%)	2 (6%)	2 (5%)	2 (7%)	19 (9%)	0.640
Ischemic HD	8 (21%)	0 (0%)	4 (11%)	1 (3%)	4 (9%)	5 (19%)	22 (10%)	0.019
Dilated CMP	2 (5%)	0 (0%)	2 (5%)	0 (0%)	0 (0%)	0 (0%)	4 (2%)	0.169
OSAS	0 (0%)	3 (8%)	3 (8%)	2 (6%)	4 (9%)	0 (0%)	12 (5%)	0.311
CVA / TIA / PE	7 (18%)	1 (3%)	3 (8%)	1 (3%)	3 (7%)	4 (15%)	19 (9%)	0.102
CHA2DS2-VASc 0	12 (31%)	19 (49%)	12 (32%)	11 (31%)	15 (35%)	8 (30%)	77 (35%)	0.507
CHA2DS2-VASc 1	9 (23%)	12 (31%)	16 (43%)	13 (36%)	13 (30%)	7 (26%)	70 (32%)	0.491
CHA2DS2-VASc ≥2	18 (46%)	8 (21%)	9 (24%)	12 (33%)	15 (35%)	12 (44%)	74 (34%)	0.315
Beta-blocker	14 (36%)	21 (55%)	21 (57%)	21 (58%)	16 (37%)	14 (52%)	107 (49%)	0.162
Amiodarone	13 (33%)	5 (13%)	17 (46%)	9 (25%)	7 (16%)	2 (7%)	53 (24%)	0.002
Flecainide	8 (21%)	7 (19%)	7 (19%)	13 (36%)	13 (30%)	7 (26%)	55 (25%)	0.411
Sotalol	9 (23%)	6 (14%)	5 (14%)	7 (19%)	12 (28%)	7 (26%)	46 (21%)	0.598
Calcium antagonist	2 (5%)	3 (8%)	4 (11%)	0 (0%)	4 (9%)	2 (7%)	15 (7%)	0.515
Anticoagulation								
None	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.000
VitaminK antagonist	36 (92%)	39 (100%)	37 (100%)	15 (42%)	18 (42%)	11 (41%)	155 (71%)	<0.001
DOAC	3 (7%)	0 (0%)	1 (3%)	21 (58%)	25 (58%)	16 (59%)	65 (30%)	<0.001
EF (%)	45 ±15.7	62 ±10.8	57 ±12.8	60 ±14.9	58 ±8.6	55 ±11.4	57 ±13.0	0.056
EF ≥55%	27 (69%)	34 (87%)	23 (68%)	29 (81%)	39 (91%)	22 (82%)	174 (80%)	0.065
EF 45 - 54%	9 (23%)	3 (8%)	6 (18%)	5 (14%)	3 (7%)	2 (7%)	28 (13%)	0.196
EF 30 - 44%	2 (5%)	2 (5%)	3 (9%)	2 (6%)	1 (2%)	3 (11%)	13 (6%)	0.716
EF <30%	1 (3%)	0 (0%)	2 (6%)	0 (0%)	0 (0%)	0 (0%)	3 (1%)	0.185
LA volume (ml)	87(67-103)	78 (65-89)	88(55-110)	79 (64-98)	76 (63-97)	92(67-108)	83 (65-100)	0.686
LA size (mm)	45 ±6.6	42 ±5.4	43 ±6.5	43 ±8.1	42 ±5.5	42 ±5.1	43 ±6.3	0.289

All continuous variables represent mean ± standard deviation and were analyzed with the one-way ANOVA. For variables with a significant ANOVA test, post-hoc analysis by Tukey's honestly significance difference test was performed. The significant relations found with the post-hoc analysis are marked by letter annotations. Labeled means in a row with a different letter annotation differ significantly. All categorical variables represent count (percentage) and were analyzed using the Chi-square test. When variables do not have a normal distribution, the median (IQR) is given and these were analyzed using the Kruskal-Wallis test. BMI = body mass index, AF = atrial fibrillation, EP = electrophysiology, PVI = pulmonary vein isolation, HD =heart disease, CMP = cardiomyopathy, OSAS = obstructive sleep apnea syndrome, CVA = cerebrovascular accident, TIA = transient ischemic attack, PE = pulmonary embolism, DOAC = direct acting oral anticoagulation, EF = ejection fraction, LA = left atrium.

Table 2: Procedural data

	MAN-1 (n=39)	CB-1 (n=39)	RMN-1 (n=37)	MAN-2 (n=36)	CB-2 (n=43)	RMN-2 (n=27)	All patients (n=221)	P-value
Procedure time (min) *	251 ±89.4 A	197 ±78.0 C	293 ±65.1 A	153 ±52.0 B	150 ±32.1 B	113 ±48.1 B	184 ±83.4	<0.001
Number of applications *	57 (41-77)	10 (8-13)	87 (56-122)	39 (27-53)	8 (6-11)	17 (15-25)	16 (9-48)	<0.001
Application duration (sec) *	1814 (1319-2284)	3253 (2667-4026)	2396 (1789-3135)	1522 (1244-2089)	1445 (1197-2012)	1568 (1211-1844)	1845 (1331-2681)	<0.001
Additional ablations (non-PVI triggers)	12 (31%)	7 (18%)	20 (54%)	16 (43%)	0 (0%)	15 (56%)	70 (32%)	<0.001

[Table 2] shows procedural data. When additional ablations (non-PVI triggers) were performed in addition to PVI, the presented procedure times, number of applications and application durations were corrected for this. All continuous variables represent mean ± standard deviation and were tested with the one-way ANOVA. For variables with a significant ANOVA test, post-hoc analysis by Tukey's honestly significance difference test was performed. The significant relations found with the post-hoc analysis are marked by letter annotations. Labeled means in a row with a different letter annotation differ significantly. Labeled means in a row with a common letter annotation are not significantly different. See the supplemental files for the detailed post-hoc analysis results. All categorical variables represent count (percentage) and were tested using the Chi-square test. When variables do not have normal distribution, the median (IQR) is given and these were analyzed using the Kruskal-Wallis test. * When additional ablations of non-PVI triggers were performed, the procedure times, number of applications and total application duration were corrected accordingly. PVI = pulmonary vein isolation.

detected (42%), which was significantly higher compared to the other groups (P=0.004). Moreover, the CB redo procedure rate improved significantly from first to second generation (CB-1 42% vs. CB-2 21%, P=0.005). No significant improvements over time were observed in-between first and second generation MAN and RMN.

Complication rates

Complication rates are shown in [Table 5] Total complication rates were higher in first generation procedures as compared to second generation procedures: 21% vs. 9% (P=0.010). In-between the three second generation treatment techniques, no significant differences were found (P=0.784), as well as in-between the three first generation techniques (P=0.662). The minor complication rate exhibited the same configuration, with significant improvement over time from first generation (16%) to second generation procedures (5%) (P=0.008). The major complication rate was comparable between first and second generation procedures (5% vs. 4% respectively, P=0.606). The majority of minor complications were access site complications not requiring intervention (N=10; 5%) and minor pericardial effusion not requiring intervention, noted during routine post-operative evaluation with TTE (N=7; 3%).

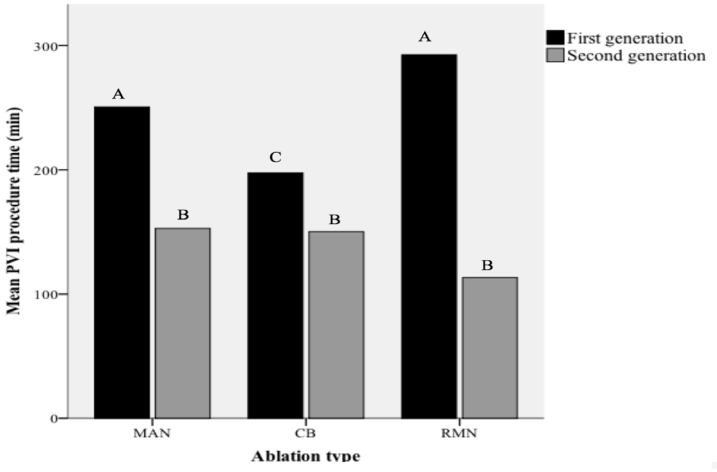

Figure 2: Mean procedure time

Figure 2 demonstrates the mean procedure time of the first and second generation treatment techniques. Mean procedure times were analyzed with the one-way ANOVA, which demonstrated a significantly different distribution in general (P<0.001). Results of the post-hoc analysis by Tukey's honestly significance difference test are marked by letter annotations. Labeled means with a different letter annotation differ significantly. Labeled means with a common letter annotation are not significantly different.
PVI = pulmonary vein isolation

Procedure and ablation times

The study by Kataria et al evaluated long-term outcome data of 336 patients undergoing PVI with MAN and RMN guided RF[22].

This is the first clear study to compare the improvement of efficiency of three recognized treatment modalities of CA for AF: MAN guided RF, CB and RMN guided RF ablation. In accordance with other studies, all ablation techniques exhibited significant improvement of efficiency over time. However, the major finding of

Table 3: Procedural data of second generation procedures

	MAN-2 (n=36)	CB-2 (n=43)	RMN-2 (n=27)	All patients (n=221)	P-value
Left PVs encirclement time (min)	27 ±13.8 A	6 ±1.8 B	13 ±5.4 C	13 ±10.9	<0.001
Left PVs FPI rate	6 (24%)	21 (50%)	21 (78%)	50 (38%)	<0.001
Left PVs TU done	19 (76%)	21 (50%)	6 (22%)	83 (62%)	<0.001
Left PVs TU number	3 (0.5 - 7)	0.5 (0 - 2)	0 (0 - 0)	2 (0 - 4)	<0.001
Left PVs TU duration (sec)	64 ±66.4 A	229 ±322.3 B	37 ±78.4 A	413 ±558.7	0.002
Right PVs encirclement time (min)	28 ±15.3 A	5 ±2.0 B	13 ±7.3 C	13 ±12.0	<0.001
Right PVs FPI rate	6 (24%)	20 (47%)	20 (74%)	48 (36%)	<0.001
Right PVs TU done	19 (76%)	22 (52%)	7 (26%)	85 (64%)	<0.001
Right PVs TU number	2 (0.5 - 4.5)	1 (0 - 2)	0 (0 - 1)	2 (0 - 3)	<0.001
Right PVs TU duration (sec)	81 ±108.3	184 ±235.6	96 ±197.3	317 ±398.2	0.096

[Table 3] depicts procedural data of second generation procedures. All continuous variables represent mean ± standard deviation and were tested with the one-way ANOVA. For variables with a significant ANOVA test, post-hoc analysis by Tukey's honestly significance difference test was performed. The significant relations found with the post-hoc analysis are marked by letter annotations. Labeled means in a row with a different letter annotation differ significantly. Labeled means in a row with a common letter annotation are not significantly different. See the supplemental files for the detailed post-hoc analysis results. All categorical variables represent count (percentage) and were tested using the Chi-square test. When variables do not have normal distribution, the median (IQR) is given and analyzed using the Kruskal-Wallis test. PVs = pulmonary veins, FPI = first pass isolation, TU = touch up.

Table 4: 12-month outcomes

Paroxysmal AF	MAN-1 (n=26)	CB-1 (n=36)	RMN-1 (n=18)	MAN-2 (n=28)	CB-2 (n=39)	RMN-2 (n=14)	All patients (n=161)	P-value
AF recurrence	8 (31%)	14 (39%)	7 (39%)	6 (21%)	11 (28%)	4 (29%)	50 (31%)	0.708
Redo procedure	4 (15%)	15 (42%)	3 (17%)	1 (4%)	8 (21%)	1 (7%)	32 (20%)	0.004
Paroxysmal AF	**MAN-1 (n=26)**	**CB-1 (n=36)**	**RMN-1 (n=18)**	**MAN-2 (n=28)**	**CB-2 (n=39)**	**RMN-2 (n=14)**	**All patients (n=161)**	**P-value**
AF recurrence	6 (46%)	1 (33%)	9 (47%)	4 (50%)	1 (25%)	4 (31%)	25 (42%)	0.880
Redo procedure	1 (8%)	1 (33%)	2 (10%)	0 (0%)	1 (25%)	2 (15%)	6 (10%)	0.622

[The documented AF recurrence rates and redo procedure rates 12-months following the PVI procedure are presented in [Table 4]. Results were analyzed for patients with paroxysmal AF and patients with persistent AF separately. Analysis was performed using the Chi-square test. ECG = electrocardiogram

this study is that the magnitude of procedure time improvement was most explicit in RMN guided RF CA procedures. The progress made in robotic navigation guided CA has resulted that nowadays ablation and procedure times are comparable with CB and MAN guided CA. Furthermore, the RMN guided RF CA has the highest potential for future advance.

Table 5: Complication rates

1st generation procedures	MAN-1 (n=39)	CB-1 (n=39)	RMN-1 (n=37)	Total (n=115)	P-value
All complications	10 (26%)	7 (18%)	7 (19%)	24 (21%)	0.662
Major complications	2 (5%)	3 (8%)	1 (3%)	6 (5%)	0.620
Minor complications	8 (21%)	4 (10%)	6 (16%)	18 (16%)	0.457
2nd generation procedures	**MAN-2 (n=36)**	**CB-2 (n=43)**	**RMN-2 (n=27)**	**Total (n=106)**	**P-value**
All complications	4 (11%)	3 (7%)	2 (7%)	9 (9%)	0.784
Major complications	1 (3%)	2 (5%)	1 (4%)	4 (4%)	0.909
Minor complications	3 (8%)	1 (2%)	1 (4%)	5 (5%)	0.437
All procedures	**1st generation (n=115)**	**2nd generation (n=106)**	**Total (n=221)**	**P-value**	
All complications	24 (21%)	9 (9%)	33 (15%)	0.010	
Major complications	6 (5%)	4 (4%)	10 (5%)	0.606	
Minor complications	18 (16%)	5 (5%)	23 (10%)	0.008	

Major, minor and total complication rates are visualized in [Table 5]. Percentages represent occurrence within procedure type. Comparison within first generation procedure types and within second generation procedure types was performed, as well as comparison between all first generation and between all second generation procedures. Analysis was performed using the Chi-square test.

The investigators observed a significantly higher mean procedure time in the RMN group, when compared to the MAN group. Also, a significant difference in mean ablation time was found in favor of the MAN group. Similar results of higher procedural time of RMN guided RF ablation, in comparison to MAN guided RF ablation, were also described by Miyazaki et al. and Arya et al. and found in two meta-analyses[18,19,27,28]. A mean CB procedure time of 124 ± 39 minutes was observed in the Fire and Ice trial [23], whereas the current study noted a higher mean CB procedure time. This could be attributed to the standard 30 minutes of waiting time which is performed in all procedures in our center as standard of care. Moreover, due to the retrospective nature of our study with consecutive enrollment, procedures were sometimes performed by less experienced electrophysiologists.

To the best of our knowledge, no clear studies comparing the advancements of efficiency of three CA modalities (MAN, CB and RMN) have been performed. We found a significant improvement of both procedure and ablation times within each treatment modality over time, highlighting the technological advances made in each of them. The higher procedural time in the RMN guided RF ablation found in previous studies, was attributed to the additional time required to set up the navigational system, positioning of the patient and time required for placing the circular mapping catheter into different veins. In the present study, a notable evolvement of RMN procedure times was observed, which now makes procedure times comparable with CB. These advancements could be attributed to the use of a dedicated EP lab for RMN procedures, where the EP staff has a broad experience using the RMN hard- and software, as well as in positioning of the patient. Second, RMN guided PVI was performed only by highly experienced electrophysiologists, whereas in CB procedures less experienced electrophysiologists were sometimes performing the procedures. Third, multiple improvements were implemented to the RMN Niobe ES system, which for instance significantly improved the response time (defined as time of vector movement by the operator, until movement of the magnetic field) [29]. Moreover, we introduced a new ablation strategy in the RMN-2 group, implementing the latest technological advancements made in RMN guided RF CA. With the use of the 'Ablation History feature' and contact feedback by the 'e-Contact module', a new ablation approach for RMN guided PVI was designed: the 'Continuous Dragging' technique. While ablating, the catheter is dragged around both ipsilateral PVs by wide area circumferential ablation (WACA) with help of the e-Contact and Ablation History feedback, using high power settings. It was attempted to interrupt ablation as least as possible. Only after completing the encirclement of either right or left sided PVs, electrical isolation was evaluated. If necessary, additional touch ups were performed to acquire PV isolation. This approach resulted in our opinion, in an efficient and safe RMN guided PVI procedure.

First pass isolation

First pass isolation (FPI) was defined as the first encirclement (WACA) resulting in successful PV isolation. FPI in CB was regarded when the first cryo-application resulted in successful PV isolation. Interestingly, a high rate of FPI was observed in the RMN-2 groups, which in our belief, is an affirmation of our new RMN ablation strategy. In CB-2, the first adequate application did not

often result in successful isolation. However, when first pass isolation in CB occurs, the procedure is much shorter than other techniques. In our opinion, this emphasizes the convenience of CB ablation, but also its susceptibility to anatomic variants of PVs. Where CB and manual ablation catheters are still confined to uni- or bidirectional movement using pull wires[30], magnetic navigation ensures enhanced maneuverability of the ablation catheter that makes reach of difficult anatomical structures possible[13,31]. Therefore, in our opinion RMN is the preferential technique for ablation of anatomical variants of PVs.

12-month outcomes

Whereas the highest efficiency improvement was detected in RMN, the highest efficacy improvement was observed in CB. Although the current study was designed to evaluate procedural efficiency, we also observed a significant improvement of the CB redo procedure rates over time, which correspond with literature[12]. The efficacy improvement was not detected to such extent in the other techniques. In our opinion, this is because first generation MAN and RMN techniques already had acceptable long-term outcomes.

Complication rates

Numerous studies reported on complication rates of CA ablation techniques for AF, but data comparing three techniques is limited. A large meta-analysis by Cardoso et al[32] evaluated complication rates between CB and MAN guided RF CA. CB ablation was associated with a lower incidence of pericardial effusions or tamponade, but with a higher rate of transient phrenic nerve palsies. The Fire and Ice trial found a comparable primary safety endpoint between CB and MAN guided RF (a composite of death, cerebrovascular events or serious treatment related adverse events)[20]. Shurrab et al observed a non-significant overall complication rate between MAN guided PVI and RMN guided PVI procedures[27]. However, the meta-analysis by Proietti et al investigating MAN and RMN guided PVI, revealed that major complications were rare, but significantly different between MAN 5% and RMN 2% groups (OR 0.41, 95% CI 0.19 - 0.88, P=0.02)[28]. Both studies observed a significantly lower rate of significant pericardial complication in RMN guided ablation[27,28]. Unfortunately, the literature does not yet report a comparison between the three treatment techniques performed here. The present study, observed no significant improvement of major complications over time. The number of patients in this study however, may not be powered to detect a difference in major adverse events. Nevertheless, minor complication rates improved significantly over time between first and second generation procedures, accentuating advances in technology and operator experience.

Limitations

The techniques presented in this study, seem to have different learning curves. In our believe, it takes more time to master RMN and MAN ablation techniques, whereas CB ablation technique is most easily adopted. The present study is a retrospective, single-center study investigating an average cohort of patients who underwent CA for AF. The study aimed to investigate as many patients possible per group, but still only an average of 37 patients per group was included. Unfortunately, FPI and TU rates and encirclement times could only be evaluated in second generation procedures. In first generation procedures, different ablation strategies were used as standard of care, which made the data incomparable (e.g. in CB-1 group a standard of two applications per PV were performed regardless of electrical isolation). Prospective studies comparing the efficiency and outcomes of the three treatment modalities, as well as the presented new ablation strategy for RMN guided PVI, are desired to clearly define the role of RMN in CA of AF.

Conclusions

The highest magnitude of procedural efficiency improvement, as defined by procedure times, ablation times and first-pass isolation rates, was detected in RMN guided PVI. Because of the technical advances made in the robotic navigation ablation technique, it has become as efficient as CB and MAN guided PVI. The efficiency evolution observed in RMN guided PVI, highlights that this technique has most potential for future advance.

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Supplemental Material

Table 1: Post-hoc analysis of procedure time (min)

Procedure	Number	Mean	SD	Compared to procedure type	P-value
MAN-1	39	251	89.41	CB-1	0.018
				RMN-1	0.256
				MAN-2	<0.001
				CB-2	<0.001
				RMN-2	<0.001
CB-1	39	198	77.96	MAN-1	0.018
				RMN-1	<0.001
				MAN-2	0.046
				CB-2	0.033
				RMN-2	<0.001
RMN-1	37	293	65.14	MAN-1	0.256
				CB-1	<0.001
				MAN-2	<0.001
				CB-2	<0.001
				RMN-2	<0.001
MAN-2	36	153	52.09	MAN-1	<0.001
				CB-1	0.046
				RMN-1	<0.001
				CB-2	1.000
				RMN-2	0.141
CB-2	43	150	32.13	MAN-1	<0.001
				CB-1	0.033
				RMN-1	<0.001
				MAN-2	1.000
				RMN-2	0.212
RMN-2	27	113	48.10	MAN-1	<0.001
				CB-1	<0.001
				RMN-1	<0.001
				CB-2	0.212
				MAN-2	0.141

Table 1 presents results of the post-hoc analysis of procedure time. Post-hoc analysis was performed by the Tukey's honestly significance difference test as part of the one-way ANOVA to investigate the in-between relationships between the 6 ablation techniques.

Table 2a: Post-hoc analysis of encirclement time of left PVs

Procedure type	Number	Mean (min)	SD	Compared to procedure type	P-value
MAN-2	36	28	13.76	CB-2	<0.001
				RMN-2	<0.001
CB-2	43	5	1.83	MAN-2	<0.001
				RMN-2	0.004
RMN-2	27	13	5.40	MAN-2	<0.001
				CB-2	0.004

Table 2a presents results of the post-hoc analysis of the mean encirclement time of left PVs. Post-hoc analysis was performed by the Tukey's honestly significance difference test as part of the one-way ANOVA to investigate the in-between relationships between the 3 second generation ablation techniques. PVs = pulmonary veins

Table 2b: Post-hoc analysis of encirclement time of right PVs

Procedure type	Number	Mean (min)	SD	Compared to procedure type	P-value
MAN-2	36	28	15.27	CB-2	<0.001
				RMN-2	<0.001
CB-2	43	6	1.83	MAN-2	<0.001
				RMN-2	0.003
RMN-2	27	13	5.40	MAN-2	<0.001
				CB-2	0.004

Table 2b presents results of the post-hoc analysis of the mean encirclement time of right PVs. Post-hoc analysis was performed by the Tukey's honestly significance difference test as part of the one-way ANOVA to investigate the in-between relationships between the 3 second generation ablation techniques. PVs = pulmonary veins.

Table 3: Post-hoc analysis of TU application duration of left PVs

Procedure type	Number	Mean (min)	SD	Compared to procedure type	P-value
MAN-2	36	65	66.37	CB-2	0.026
				RMN-2	0.911
CB-2	43	229	322.28	MAN-2	0.026
				RMN-2	0.003
RMN-2	27	37	78.40	MAN-2	0.911
				CB-2	0.003

Table 3a presents results of the post-hoc analysis of the touch up application duration of left PVs. Post-hoc analysis was performed by the Tukey's honestly significance difference test as part of the one-way ANOVA to investigate the in-between relationships between the 3 second generation ablation techniques. TU = touch up. PVs = pulmonary veins.

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Clinical and Procedural Effects of Transitioning to Contact Force Guided Ablation for Atrial Fibrillation

Daniel R. Frisch[1], Sean J. Dikdan[1]

[1] *Thomas Jefferson University Hospital, Division of Cardiology, 111 S 11th St, Philadelphia, PA 19107.*

Abstract

Background: A major innovation in atrial fibrillation (AF) ablation has been the introduction of contact force (CF) sensing catheters.

Objective: To evaluate procedural and clinical effects of transitioning to CF-guided AF ablation.

Methods: Consecutive AF ablation patients were studiedduring the period of time of transitioning from a non-CF to CF sensing catheter. Procedural data recorded was total radiofrequency time, time to isolate the left pulmonary veins (LPVs), and time to isolate the right pulmonary veins (RPVs). Clinically, the 3 and 12-month maintenance of sinus rhythm was noted and compared by: paroxysmal vs. persistent AF; CT scan LA volume more or less than 150 cc; CHA_2DS_2VASC more or less than 2; and LVEF more or less than 55%. Safety data was recorded as well.

Results: Total ablation times were shorter (113 vs.146 min, p=0.011)when using the CF catheters compared to non-CF ablations. This was driven by a decrease in both LPV (46 vs.72 min, p<0.001) and RPV time (54 vs. 75 min, p=0.002).The use of CF catheter did not change the overall percentage of patients in sinus rhythm at 3 and 12-months of follow up. However, sinus rhythm was more frequent at 12 months with CF ablation in patients with a LA volume of more than 150 cc when compared to non-CF ablation (84.6% and 52.4%, p=0.03). There was no difference in outcomes with stratification by CHA_2DS_2VASC score or LVEF. No significant difference in complications was noted.

Conclusions: For AF ablation, the initial use of CF-sensing technology reduced procedure times with similar overall sinus rhythm maintenance at 3 and 12 months. CF improved 12-month outcomes in patients with an enlarged LA.

Introduction

Electrical pulmonary vein isolation (PVI) for atrial fibrillation (AF) is an established and effective therapy[1]. Clinical trials have demonstrated that an ablation strategy is generally superior to antiarrhythmic medications for the treatment of AF[2]. Radiofrequency energy is the most common energy source used for ablation and is often delivered in a point-by-point fashion around the pulmonary veins. The original, non-irrigated catheters, recorded the temperature via a thermistor at the tip of the catheter and measured impedance changes over the duration of ablation. Later, irrigated catheters were introduced for improved ablation efficacy and safety[3]. A limitation of irrigated catheters is the inability to measure the temperature at the tissue level of ablation due to the intentional cooling effect of the irrigant on the catheter's thermistor. The next major innovation in ablation technology, which was approved by the FDA in 2014, was the ability to measure catheter-tissue contact force (CF) in real-time and to use that information to guide ablation. BiosenseWebseter's Smarttouch catheter was approved on February 25, 2014 and St. Jude Medical's TactiCath was approved on October 27, 2014[4,5]. The use of contact force-guided ablation has been demonstrated to reduce ablation gaps and improve ablation effectiveness[6,7,8].

Key Words

Atrial Fibrillation, Ablation, Contact Force

Corresponding Author
Daniel R. Frisch,
925 Chestnut Street Mezzanine Philadelphia, PA 19107

Once the CF catheters were approved at our institution we adopted them into use for pulmonary vein isolation in place of the irrigated, non-CF ablation catheters used previously. As with any new technology, there was a requisite period of introduction and transition. The purpose of this observational study was to assess the impact of the single variable of incorporating CF technology on procedural and clinical characteristics at the time of transition to this technology. The hypothesis was that the introduction of CF technology would improve both procedural and clinical aspects of PVI. We expected that cases would take less time, require less ablation, have fewer complications, and have better clinical outcomes with CF technology. The other aspects of ablation, including the ablation strategy, the personnel (a single attending electrophysiologist working with one of three fellows depending on the academic year), the other recording catheters, and the workflow remained the same.

Methods

This retrospective review included the period of time from July 2013 through November 2017, which was the time frame for collection and follow up of 112 paroxysmal and persistent atrial fibrillation patients referred for ablation. Patients eligible for this study included consecutive patients who had undergone their first AF ablation with CF catheters and the consecutive group of patients who underwent their first AF ablation before CF catheters were available. Exclusion criteria included patients who underwent ablation for arrhythmias other than AF or who presented for a repeat procedure.

Procedural and clinical characteristics were collected from our institution's electronic health record. Of the initial 112 patients designated for inclusion in the study, 51 patients underwent non-CF ablation and 61 underwent CF ablation; 7 patients in the non-CF group and 10 in the CF group were excluded from analysis because AF ablation was not performed or the presentation was for a repeat ablation procedure. The data were collected and stored securely in a password-protected database. The study was approved by our institutional review board.

Catheter Ablation Procedure

All patients were referred for catheter ablation of AF and provided written informed consent in accordance with institutional policy. Antiarrhythmic medications other than amiodarone were stopped three days before the procedure. In brief, femoral venous access was obtained and a multipolar catheter was placed in the coronary sinus and a diagnostic intracardiac ultrasound catheter (5.5 to 10 MHz; AcuNav; Biosense Webster, Diamond Bar, California) was placed in the right atrium. Two atrial transseptal punctures were performed, and an ablation catheter and a circular mapping catheter (Spiral; St. Jude Medical) were advanced into the left atrium. Three-dimensional electroanatomic mapping was performed using the Velocity system (St. Jude Medical).

All pulmonary veins were routinely isolated, typically as a pair. Ablation was performed in the carina between ipsilateral veins if isolation could not be achieved with wide area encirclement. Radiofrequency ablation was delivered with a 3.5-mm open-irrigated tip catheter or a 3.5-mm open-irrigated CF sensing catheter (TactiCath; St. Jude Medical, St.Paul, MN). For LA volumes exceeding 150 cc by cardiac CT a TactiCath 75 was used, and for a volume less than 150 cc a TactiCath 65 was used[9]. With the non-CF catheter, radiofrequency was routinely delivered to lesions for 30 to 60 secondsto achieve a decrease in impedance of at least 5 to 10 Ohms at the ablation site. With the CF sensing catheter, ablation was performed with a flow of 17 cc/minute, power 20-25 watts, a goal of 10-40 g per lesion, and a goal of 400-500 g seconds per site (typically a lesion size index 4.5-5.5). Successful PVI was defined by the loss of all pulmonary vein potentials (entrance block) and failure to capture the left atrium when pacing from sequential bipoles of the circular mapping catheter placed at the ostium of each pulmonary vein (exit block). Attempts at reinduction with burst pacing were performedand recorded.

The rationale for the use of CF catheters and the working parameters that we chose were determined by a number of published investigations. The first was the 2012 TOCCATA study, which was primarily a safety study for right and left atrial ablation using the same CF ablation catheter used in our study[10]. Investigators identified a force >100 g as a risk for perforation, which occurred in one patient. The EFFICAS I trial (2013) was designed to assess CF (using the TactiCath ablation catheter) and the ability to predict ablation gaps during ablation for AF[11]. The operators were blinded to the contact force data. The results established that a minimum CF (<10 g) and minimum force-time integral (FTI; <400 gs) were predictors of gaps in the ablation lesion set. To achieve durable lesions and to obtain a successful PVI, a target CF of 20 g was recommended, with an absolute minimum CF of 10 g and an absolute minimum FTI of 400 gs per individual ablation lesion. The SMART AF trial (2014) was designed for safety and effectiveness of the SmartTouch catheter[6]. In this trial, when the CF was between "investigator selected working ranges" >80% of the time, outcomes were 4.25 times more likely to be successful. In 2015, the EFFICAS II, which was designed based on the findings in EFFICAS I with unblinded operators using TactiCath, found that a CF of 20g and a minimum FTI of 400 gs reduced ablation gaps. The investigators found that fewer lesions were required, and lower fluoroscopy times were achieved with these parameters[12]. Finally, the TOCCASTAR study (2015) randomizedCF vs. non-CF for paroxysmal AF and looked at 1 year AF freedom after ablation (n=300) using TactiCath[7]. The authors noted that when optimal CF was used (≥90% of the lesions with a CF ≥10 g) outcomes were better (76% v. 58%) and fluoroscopy and ablation times were less. Support for the use of ablation catheters with CF parameters are supported by national guidelines[13].

Follow up

Patients in this practice tend to remain within the health system. These patients were followed up periodically with routine office visits at up 1, 3, 6, and 12 months and both in between visits and beyond 12 months if there was a reportof symptoms. Standard electrocardiography was performed at each follow-up visit to assess AF status. Mobile cardiac outpatient telemetry monitors were used if indicated clinically. Phone calls and emails were encouraged with any symptoms. At 12-month follow up, data was able to be collected on 30 patients in the non-CF group and 38 patients in the CF group.

Study Endpoints

The primary procedural endpoints were total radiofrequency time, time to complete isolation of the left pulmonary veins, time to complete isolation of the right pulmonary veins, and inducibility to AF, atrial flutter, or other arrhythmias. The primary clinical endpoints were the presence of AF during the first 3 and first 12 months. Recurrence of AF was defined as 30 seconds or more of symptomatic or asymptomatic AF after ablation regardless of the pre-procedural burden or the patient's perception of improvement after the procedure.

Results

Baseline characteristics of the 95 included patients did not show any significant differences [Table 1]. The sample was predominantly men around the age of 60. Persistent AF comprised a larger proportion of the sample (60%)than paroxysmal AF.

Procedural Results

For the procedural analysis, data was complete for 86 patients. In each of the categories measured, there was a reduction in procedural time and total radiofrequency application time when a CF catheter was used [Table 2]. Theuse of a CF catheter significantly reduced the mean total ablation time by about 33 minutes (1 hour and 53 minutes compared to 2 hours and 26 minutes, p=0.011). LPV and RPV times were both significantlyshorter in the CF ablation group

as well[Figure 1]. There was no difference in the ability to reinduce-sustained atrial fibrillation, non-sustained atrial fibrillation, or other arrhythmias between catheter types [Table 3].

Clinical Results

We chose 2 time points to evaluate for AF recurrence: 3 months—frequently considered the blanking period—and 12 months after ablation. No differencein the percentage of patients in sinus rhythm was detected between the CF and non-CF groups (74.5% and 68.2%, respectively; p=0.50) at the 3-month follow up period [Table 4a]. The overall 12-month incidence of sinus rhythm was also not significantly different [Table 4b]; [Figure 2]). Subgroup analysis done at 12-month follow up showed that sinus rhythm was more frequent with CF compared to non-CF in patients with an LA volume greater than 150 cc compared (84.6% and 52.4%, respectively; p=0.03). There was no difference in outcomes with stratification by CHA_2DS_2VASC score or LVEF.

Table 1: Patient demographics and baseline data

	Contact Force (N=51)	Non-Contact Force (N=44)	p-value
Age, years mean (STD)	60.7 (9.8)	60.3 (8.8)	0.60
Male gender, no. (%)	40 (78.4)	29 (65.9)	0.13
Paroxysmal AF, no. (%)	21 (41.2)	17 (38.6)	0.48
CHA_2DS_2-VASc score median (IQR)	1 (1-2)	2 (1-3)	0.24*
Anti-arrhythmic drug use, no. (%)	16 (31.4)	10 (22.7)	0.24
Anticoagulation use, no. (%)	24 (47.1)	23 (52.3)	0.38
3D LA volume, mL	162.3 (39.9)	165.6 (46.3)	0.26
Left Ventricular Ejection Fraction, %	56.6 (13.3)	55.0 (15.8)	0.29

* The nonparametric Wilcoxon rank-sum test was used to analyze CHA_2DS_2-VASc score, as median instead of mean were being compare.

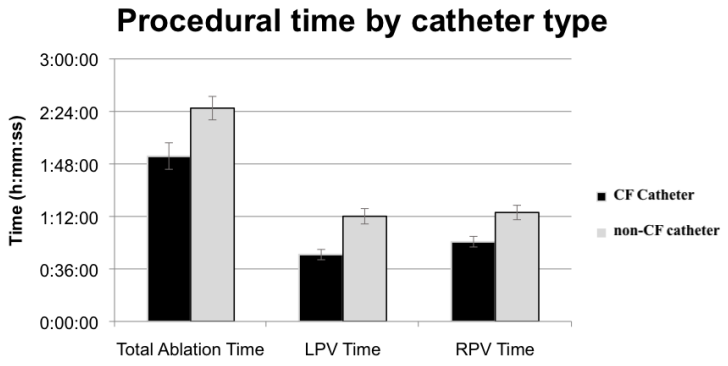

Figure 1: Graph of total, left pulmonary vein, and right pulmonary vein ablation time by catheter used.

Table 2: Procedural Times. Independent two samples two-tailed t-test of left, right, and total ablation time by catheter used.

	Total Ablation Time		LPV Time		RPV Time	
	Contact Force	Non-Contact Force	Contact Force	Non-Contact Force	Contact Force	Non-Contact Force
N	47	39	47	40	47	39
Mean	1:53:24	2:26:16	0:45:51	1:12:07	0:54:41	1:14:43
STD	1:03:38	0:51:11	0:24:44	0:33:55	0:25:28	0:31:33
p-value	0.011		<0.001		0.002	

* All comparisons were found to be statistically significant.

Safety Results

Overall, there was no observed increase in complications with the introduction of CF ablation. Pericardial effusion with or without the need for pericardiocentesis occurred in 3/45 = 7% of patients prior to the introduction of CF catheter and in 1/52 = 2% of the patients who underwent ablation with a CF catheter (p=0.24). There were no strokes, deaths, bleeding episodes requiring transfusion, esophageal injuries, or phrenic nerve injuries in either group.

Table 3: Arrhythmia Inducibitily. Independent two samples two-tailed t-test of left, right, and total ablation time by catheter used.

	Contact Force (N=46)	Non-Contact Force (N=37)	Chi-squared	P value
Non-inducible	21	13	0.094	.30
AF	6	8		.33
Non-sustained AF	2	3		.47
Typical AFL	17	9		.22
Atypical AFL	0	4		.02

* Inducibility testing was not performed on 2 patients in the Contact Force group and 3 patients in the non-Contact Force group. These are excluded.
** Bonferroni correction method was used to correct for multiple comparison post-hoc (adjust p-value=0.05/5= 0.01). No significant differences were found.

Table 4a: Clinical Outcomes. Patients in sinus rhythm after 3-months based on disease characteristics and catheter used.*

		Contact Force (N=51)	Non-Contact Force (N=44)	P value
Overall patients in sinus rhythm, % (n)		78.4 (40)	68.2 (30)	0.26
Type of AF	Paroxysmal	71.4 (15)	70.6 (12)	1.00
	Persistent	83.3 (25)	66.7 (18)	0.22
LA volume, cc	≥ 150	76.9 (20)	61.9 (13)	0.34
	< 150	80 (20)	73.9 (17)	0.74
CHA_2DS_2VaSc score	≥ 2	82.6 (19)	64.0 (16)	0.20
	< 2	75.0 (21)	73.7 (14)	1.00
LVEF, %	≥ 55	78.4 (29)	80.0 (24)	1.00
	< 55	78.6 (11)	42.9 (6)	0.12

* Chi-square used for overall analysis while fisher's exact test used for subgroup comparisons as some cells contained numbers <10

Table 4b: Clinical Outcomes. Patients in sinus rhythm after 12-months based on disease characteristics and catheter used.*

		Contact Force	Non-Contact Force	P value
Overall patients in sinus rhythm, % (n)		74.5 (38)	68.2 (30)	0.50
Type of AF	Paroxysmal	61.9 (13)	82.4 (14)	0.28
	Persistent	83.3 (25)	59.3 (16)	0.08
LA volume, cc	≥ 150	84.6 (22)	52.4 (11)	0.03
	< 150	64.0 (16)	82.6 (19)	0.20
CHA_2DS_2VaSc score	≥ 2	73.9 (17)	64.0 (16)	0.54
	< 2	75.0 (21)	73.7 (14)	1.00
LVEF, %	≥ 55	73.0 (27)	73.3 (22)	1.00
	< 55	78.6 (11)	57.1 (8)	0.42

*Chi-square used for overall analysis while fisher's exact test used for subgroup comparisons as some cells contained numbers <10

Discussion

The intent of this study was to quantify the impact of the

introduction of CF technology at the time of transition to this technology on procedural and clinical aspects of PVI. The ablation strategy, techniques, and workflow were the same but the catheter, specifically the ability to measure CF, was different. This strategy minimized confounding by other variables (e.g. changing the ablation strategy, the ablation modality, or the primary operator).

The main findings in this study of transitioning to the use of contact force catheters for atrial fibrillation ablation are that (1) procedure times, ablation times, and time to pulmonary vein isolation is reduced

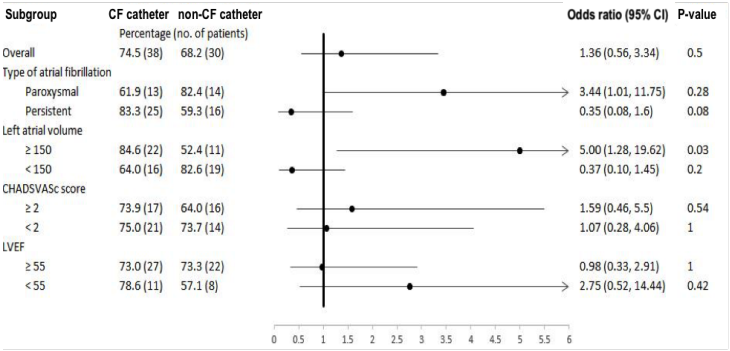

Figure 2: **Forest plot comparing patients in sinus rhythm at 12 months based on catheter used and atrial fibrillation characteristics.**

when contact force catheters are used; (2) clinical outcomes are similar, and perhaps improved in patients with large LA volumes; and that (3) complications rates were not increased.

As is the case with introduction of many new technologies, a learning curve is often required to become comfortable and demonstrate proficiency, thus maximizing the benefit of the innovation. Clearly, if new technology is difficult to use or if it is associated with complications it is unlikely to succeed. With the introduction of the contact force parameter there was a novel ablation parameter to follow. At times the tactile feel of the catheter would be discordant to the measured force. That is, the feeling of "heavy" force sometimes equated to a low force readings and vice versa. Confidence in the contact force recordings and calibration sometimes meant deciding which parameter (tactile feel or recorded force) represented the optimal ablation scenario. Because of this unfamiliar dilemma due to inexperience, we were reminded of the so-called "July phenomenon" (when there is a perceived decrease in the quality of health care at the start of the North American academic year for medical training) [14]. Although the July phenomenon has been largely refuted,an abundance of evidence that "surgeon volume" matters across a range of operations including electrophysiology procedures[15,16].

We found that, somewhat paradoxically, the initial use of a new ablation catheter improved procedural time and some effectiveness endpoints immediately, without the benefit of a large volume of cases. This reassured us about any concerns we had about slowing our workflow. Measuring contact force added usable information to the ablation strategy, and it also reduced ablation times, which ultimately improved workflow. The decreased procedural duration times were apparent almost immediately with adoption the contact force technology. Prior studies have shown a decrease in procedural time, but without differentiating between LPV and RPV times[17,18].

Our study found that patients with large LA volumes (which we defined based on a previous investigation)undergoing AF ablation with a CF catheter were more likely to remain in sinus rhythm at 12 months[9]. This difference was driven by two CF patients converting to sinus between the 3 and 12 month period and two non-CF patients who convert from sinus back to AF in the same time period.One long term study has shown PV reconnection in both CF and non-CF ablated patients owing primarily to the RPV that negated a significant difference in atrial arrhythmia free survival[19]. CF ablation has been shown to improve outcomes in patients with paroxysmal AF in large studies[20-22] and subsequent research on persistent AF has shown a benefit as well[23]. Patients with exclusively persistent AF and large LA enlargement, however,have been shown not to have an increase in sinus rhythm at 12 months[24]. Our analysis did not compare these two covariates directly, and it is possible that the advantage seen in our study was due to patients with large LA volumes and specifically paroxysmal AF.

Our complication rates were low in both arms, and similar to those of other studies involving CF ablations[23,24]. Larger studies with longer follow up have seen a reduction in complications with CF ablation so it is possible that we lacked significant enough power to detect a difference in complication rate[24].

This study has several limitations. First, the sample size is small. Despite initially selecting 112 charts, only 68 patients who met inclusion criteria completed their 12-month follow up. The patients lost to follow up appear in proportion between both the CF and non-CF group, but nevertheless this may result in unintended selection bias. Second, despite outpatient telemetry monitoring and regular electrocardiography it remains possible that patients had recurrences that asymptomatic and unrecorded. Third, subgroup analysis was not performed on procedural outcomes. Certain patient characteristics may have impacted procedural times. Finally, mean times to perform each AF ablation were reported. Changes in procedural time may have occurred towards the end of the CF group as the operator became more familiar with technology.

Conclusions

For atrial fibrillation ablation, introduction of CF-sensing technology reduced procedure times with similar overall sinus rhythm maintenance at 12 months. Notably, CF improved 12-month outcomes in patients with an enlarged left atrium.

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"AF HeartTeam" Guided Indication for Stand-alone Thoracoscopic Left Atrial Ablation and Left Atrial Appendage Closure

Sacha P. Salzberg[1], Thomas Zerm[4], Christophe Wyss[3], David Hürlimann [3], Ivano Reho[3], Georg Noll[3], Maximilian Y. Emmert[2], Roberto Corti[3], Jürg Grünenfelder[3], Wim-Jan van Boven[1]

[1] *H1Heart and Rhythm Center, Zurich, Switzerland*
[2] *University Heart Center Zurich, UniversityHospital Zurich, Zurich, Switzerland*
[3] *HeartClinic, Klinik Hirslanden, Zurich, Switzerland*
[4] *Albertinen Krankenhaus, Hamburg, Germany*

Abstract

Background: Traditional surgical treatment for patients with atrial fibrillation (AF) is performed via sternotomy and on cardiopulmonary bypass. It is very effective in regard to rhythm control, but remains unpopular due to its invasiveness. Truly endoscopic AF treatments have decreased the threshold for electrophysiologists (and cardiologists) to refer, and the reluctance of patients to accept a standalone surgical approach. Practice guidelines from around the world have recognized this as an acceptable therapeutic approach. Current guidelines recommend the HeartTeam approach in treating these complex AF cases. In this study we report our experience with AF HeartTeam approach for surgical stand-alone AF ablation.

Methods: The AF HeartTeam Program began in 2013, patients qualified for inclusion if either of the following was present: failed catheter ablation and/or medication, not suitable for catheter ablation, contraindication to anticoagulation, or patients preferring such an approach. All patients with a complex AF history were assessed by the AF HeartTeam, from which 42 patients were deemed suitable for a totally endoscopic AF procedure (epicardial ablation and LAA closure). Endpoints were intraoperative bidirectional block of the pulmonary veins and closure of left atrial appendage confirmed by transesophageal echocardiography (TEE). Post discharge rhythm follow-up was performed after 3 and 12, 24 and 36 months. Anticoagulation was discontinued 6 weeks after the procedure in patients after documented LAA closure.

Results: In total 42 patients underwent the endoscopic procedure (Median CHA_2DS_2-VASC=3 (1-6), HAS-BLED=2 (1-6)) for paroxysmal (15/42) and non-paroxysmal AF (27/42) respectively. Bidirectional block was obtained in all patients and complete LAA closure was obtained in all but one Patient on TEE (41/42). In one patient the LAA was not addressed due to extensive adhesions. Two patients underwent median sternotomy because of bleeding during the endoscopic surgery early in the series. There were no deaths. Procedure duration was a median of 124min (Range 83-211) and duration of hospitalization was median of 5 days (Range 3-12). During 36 months follow-up survival free of mortality, thromboembolic events or strokes was 100%. Twelve month freedom from atrial arrhythmia off anti-arrhythmic medication was 93% and 89% for paroxysmal and non-paroxysmal patients respectively. 6/42 patients who had an AF recurrence during the follow-up underwent touch-up catheter ablation.

Conclusions: Atrial fibrillation heart team approach provides excellent outcomes for patients with AF. This approach is beneficial for patients after failed catheter ablation or not candidates for such and offers a very effective mid-term outcome data. In addition to effective rhythm control the protective effect of epicardial LAA closure may play an important role in effectively reducing stroke. The creation of an AF HeartTeam as recommended by the guidelines insures unbiased therapies and provides access to this minimally invasive but effective therapeutic option for AF patients.

Introduction

Atrial fibrillation (AF) is a very common arrhythmia with increasing incidence and disease burden[1,2]. Rhythm control strategies are manifold varying from electrical cardioversion, anti-arrhythmic pharmacologic therapy, catheter (endocardial) ablation (CA), surgical AF (epicardial) ablation, and hybrid approaches[2]. Self eased diagnosis and patient empowerment will lead to a significant increase in AF diagnosis and awareness[3]. Since the development of the Maze procedure by James Cox in 1982 the role of surgical ablation has become more and more important in the treatment of atrial fibrillation (AF)[4]. As such concomitant surgical ablation of AF at the time of mitral valve surgery has a class Ia indication in the most recent guidelines[2]. Recently catheter based pulmonary vein isolation has established itself as the first line of invasive therapy to treat paroxysmal AF[2]. However, it is apparent that some patients with paroxysmal AF fare less well than others. Certain risk factors for worse outcome are well known, such as duration of atrial fibrillation, extent of left atrial dilatation and left atrial fibrosis. Results of catheter ablation for the persistent forms of AF remain suboptimal[5]. It

Key Words

Atrial Fibrillation, Ablation, Left Atrial Appendage, Catheter Ablation

Corresponding Author
Sacha P. Salzberg,
Heart & Rhytm Center,
Bellariastreet 38, CH 8038 Zurich, Switzerland

is established that in the setting of non-paroxysmal AF pulmonary vein isolation is not sufficient[6] and this is why more extensive lesions obtained with an epicardial approach may provide more durable results as the LAA is also targeted [7] during this procedure[2,8,9]. And finally the latest guidelines recommend the creation of AF HeartTeams to pose the indication for complex ablations[8]. In our clinic we applied the HeartTeam approach from our TAVI practice to the field of complex AF ablations and report our results herein.

Material and Methods

This is a prospective registry approved by the local institutional review board. All patients included in this study provided an informed consent prior to surgery.

Patient selection

The Atrial Fibrillation Heart Team Program began in 2013 and since then a total of 69 patients have been evaluated for an ablation procedure. Referrals for AF ablation were accepted from primary care doctors, cardiologists and from within our clinic. Self-referrals from patients directly were also accepted after screening of their medical history. Patients with paroxysmal AF and no additional risk factors or not requiring discontinuation of anticoagulation were triaged to catheter ablation as a first line of therapy. All other patients were considered for the endoscopic procedure. Most common inclusion criteria were: failed catheter ablation, or not suitable for such and patients with contraindication to anticoagulation. We did also take into consideration patient's choice for such a procedure after informed consent about both therapies. Contraindications for the endoscopic procedure were previous cardiac or thoracic surgery, severely impaired pulmonary capacity and/or contraindication for endotracheal intubation and poor mobility.

AF HeartTeam

Our institutional AF HeartTeam is an interdisciplinary team composed of several specialists who have no competing financial interest in the treatment of any given patient, identical to the TAVI board. Specialists composing this AF HeartTeam are: non invasive Cardiologist, interventional cardiologists, electrophysiology/device specialist, cardiac surgeon with AF experience and a nurse involved in patient care. All patients are discussed after a first consultation and prior to them receiving an appointment for any procedure. [Figure 1] depicts patient flow.

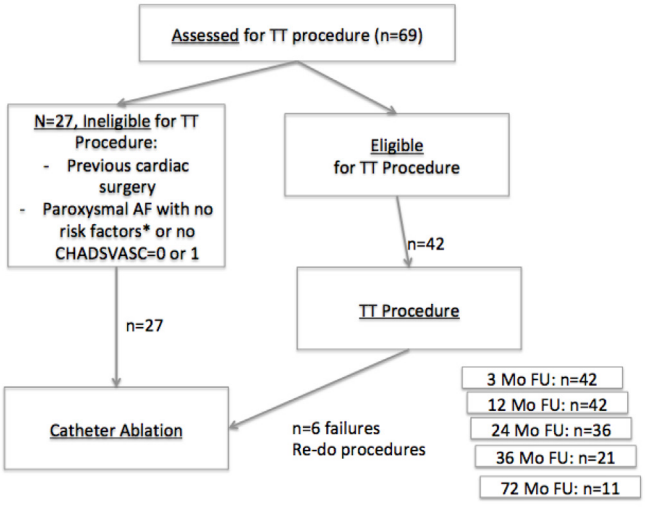

Figure 1: Patient flow directed by the AF Heart team

Preoperative Workup

Preoperative workup is composed of pulmonary function testing, 9-day/Holter/ECG, cardiac CT to assess anatomy of the left atrium and the LAA. All patients had echocardiographic evaluation. The presence of significant risk factors for coronary artery disease, or a high calcium score on cardiac CT, mandated diagnostic coronary angiography.

Surgical Procedure

Surgery was performed by two dedicated AF surgeons (SPS and WJvB). The patient was prepared in suppine position with the patient draped for a median sternotomy. Cardio pulmonary bypass was always on standby. Double lumen endotracheal tube, central venous line and arterial line were used in all. All patients underwent intraoperative transesophageal echocardiography (TEE) to assess the left atrial appendage in particular by a cardiologist. The procedure, has previously been described[10], it is begun on the right side with the insertion of 3 ports, one 5mm and two 12mm Ports. CO_2 insufflation is used to displace the mediastinum and lung. The pericardium is opened 1cm dorsally to the phrenic and 2 stay sutures are applied. In cases of prior ablation the bipolar pen is used in the sensing mode (Isolator Transpolar Pen™, Atricure, Westchester (OH), USA) to assess entrance and exit block over the pulmonary veins. After which the oblique and transverse sinus are opened. The transverse sinus is then dissected all the way to the left atrial appendage (LAA). With the GlidePath™ Dissector (Atricure, Westchester (OH), USA) the right pulmonary veins are encircled and then ablated with the bipolar radiofrequency clamp (Isolator Synergy Clamp™, Atricure, Westchester (OH), USA). Energy application was done (7-16 Applications) several times until the tissue impedance as measured on the ablation console dropped in under 5 seconds. Once the ablation procedure complete entrance and exit block were confirmed with the bipolar pen (Isolator Transpolar Pen™, Atricure, Westchester (OH), USA) in pacing/sensing mode, the pericardium was closed, chest tube were inserted and the procedure repeated on the left side in the same manner. In all patients a connection from the left superior pulmonary vein to the base of the LAA was also done with the bipolar pen prior to addressing the left atrial appendage. Finally the left atrial appendage was addressed in all. The first 20 patients underwent left atrial appendage resection with a stapler (Endo GIA™ Reinforced Reload with Tri-Staple™, Medtronic, Mineapolis (MN), USA). After this we used the Atriclip Pro2 Device (Atricure, Westchester (OH), USA) which can be inserted through a port. The Stapler and Atriclip were only deployed when adequate closure was documented on TEE with a stump less than 1.0cm in all. A chest tube was inserted on the left side. The patients were extubated in the Operating Room and transferred thereafter. [Figure 2] depicts a schematic of the used lesion set in the patients. We assessed all LAA prior to incision to screen for LAA Thrombi. LAA closure was confirmed by Transesophageal echocardiography (TEE) in all patients.

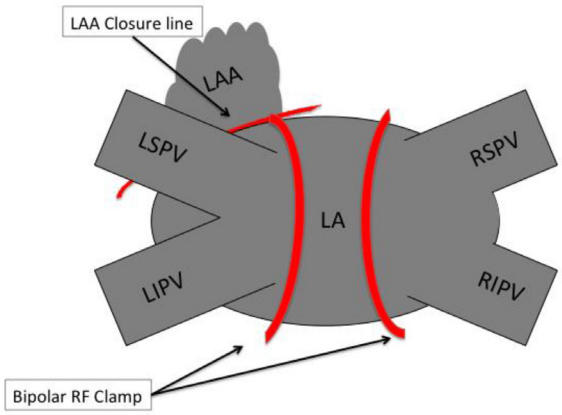

Figure 2: Schematic description of the lesion set used during the TT procedure.

Postoperative Management

Postoperative management was conducted on an individual level, with increased experience by the entire team the threshold to no longer transfer patients from the operating room to the intensive care unit (ICU) decreased. Either in the ICU or the wake-up ward, the chest drains were removed rapidly (2h postoperatively) followed by a chest x-ray. Transfer to the regular ward with telemetry was then done. Patients were ambulating on the day of surgery. Anticoagulation management was tailored individually. Patients with Coumadin were kept on an INR 2-3 and Coumadin was not discontinued. Patient not on anticoagulation were given only sub-cutaneous low molecular weight heparin 6h postoperatively and then anticoagulated for 6 weeks. Patients on NOAC where discontinued according to our institutional policy and guidelines. Postoperatively on Day one LMWH was given and on day 2 NOAC was reinstated for 6 weeks.

Antiarrhythmic medications were only given when severe arrhythmias were present postoperatively. In cases where hemodynamic compromise was severe; readmission to the ICU with IV Amiodarone and/or DC electroconversion was instituted.

Follow-up

Long-term rhythm follow-up was obtained in all patients (100% Complete). As per clinical standard all patients were seen by the referring cardiologists (or at our clinic) after 3, 12, 24 and 36 months. Clinical evaluation, echocardiography and Holter and/or 9 Day EKG (Bodyguardian, Preventice) were performed either at our clinic (9day Holter) or by the referring cardiologists (24h Holter). During follow-up if the patient had an AF recurrence antiarrhythmics were started and a DC electroconversion was organized. If this failed a re-

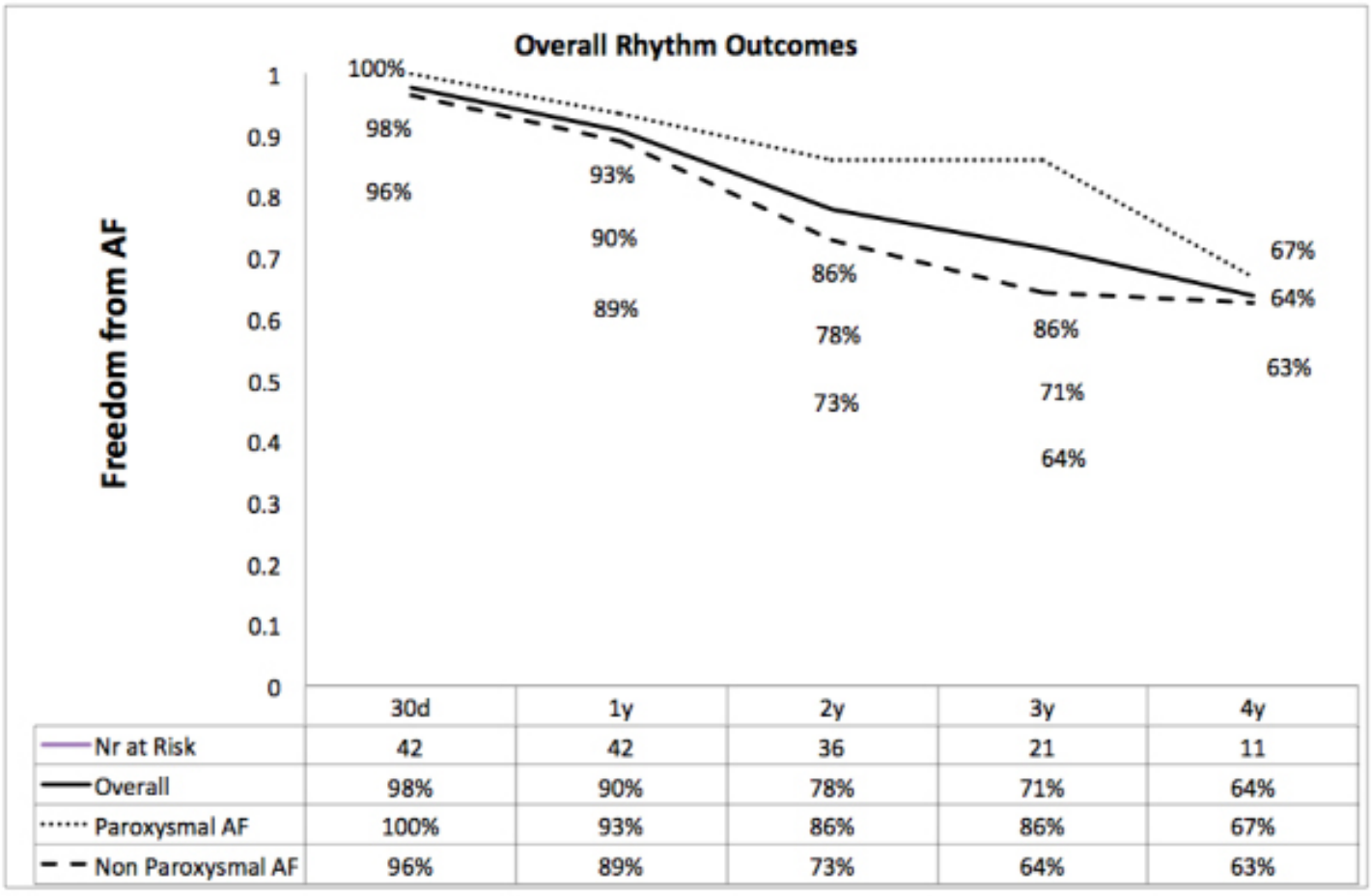

Figure 3: Rhythm outcomes.

Table 1: Patient Demographics

n=	42
Age (y)	65 +/- 7
Gender (M)	14 (54%)
HTN	32 (76%)
DM	13 (31%)
CAD	12 (29%)
Stroke/TIA	4 (10%)
CHF	6 (19%)
CHA_2DS_2-VASc	median 2 (R: 0-4)
LVEF (%)	60 (40-77)
LA Diameter (mm)	48+/-10
LAVI (ml/m2)	34+/-6
Medications:	
Beta-Blocker	26 (62%)
Ca-Antagonists	7 (21%)
Cordarone	9 (23%)
Marcoumar	14 (33%)
NOAC	24 (57%)
no Anticoag	4 (10%)
Aspirin	10 (38%)
Paroxysmal AF	15/42
Non Paroxysmal AF	27/42
	mean +/- stdv

LVEF=Left Ventricular Ejection Fraction, LA=Left Atrium, LAVI=Left Atrium Volume Index

ablation by catheter was discussed with the patient and the referring cardiologist.

Results are reported according to the Guidelines for reporting data and outcomes for the surgical treatment of atrial fibrillation[11].

Results

Patient selection

Out of 69 patients evaluated, a total of 42 patients (Median CHA_2DS_2-VASC=3 (1-6), HAS-BLED=2 (1-6)) were treated (15 paroxysmal AF, 27 non-paroxysmal AF). [Table 1] depicts general patient's demographics ablated in this series. The 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation[9] and the 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS[8] where applied for patient selection. A total of 5 patients (12%) with paroxysmal AF and no prior catheter ablation were included after discussion in the AF HeartTeam.

A subset of 17 patients despite paroxysmal AF were not deemed suitable for catheter ablation by the AF HeartTeam and addressed for catheter ablation at our institution. Reason for this was mainly patient choice as these patients presented already with the desire not to undergo catheter ablation. The second reason was the ability to discontinue oral anticoagulation after the thoracoscopic ablation

Table 2: Preoperative Atrial Fibrillation

	Paroxysmal (n=15)	non Paroxysmal (n=27)
Duration (years)	3.7 ± 3.5	4.4 ± 4.6
no Ablation	15 (100%)	7 (26%)
CA 1	5 (33%)	10 (37%)
CA 2	6 (40%)	8 (30%)
CA 3+	4 (27%)	2 (7%)

CA=Catheter Ablations

Table 3: Postoperative Outcomes

Outcomes	Perioperative	Follow-up
Sternotomy	2	0
Bleeding*	2	0
Intubation > 6h	1	0
Stroke/TIA	0	0
Pacemaker	0	1
MACCE	1	0
Pleural Effusion	2	7 (16%)
Pleurodhesis	0	1
Death	0	0

MACCE=Major Adverse Cardiac and Cerebrovascular Event

Table 4: Rhythm Outcomes

	Paroxysmal (n=15)	Non Paroxysmal (n=27)
Freedom from AF off AAD	93%	89%
Follow-up (months) Median(range)	15 (11-43)	16 (11-43)
DC Electroconversion (during Blanking P.)	5	10 (37%)
re-Ablation - Right	0	1
re-Ablation – Left + Right	1	4
NOAC during FU	1	4 (15%)

AAD=Antiarrhythmic Drugs

procedure because the LAA is managed. All patients were highly symptomatic and/or had intolerance to antiarrhythmic medications. In addition patient's choice played an important part in decision-making. [Table 2] shows Atrial Fibrillation characteristics.

Operative details

All procedures were performed successfully. No mortality occurred in this series. Median duration of the procedure was 124 minutes (Range 83-211). Pulmonary vein isolation was successful in 41 patients (98%). In one patient a bleeding occurred during lumitip encirclement of the left pulmonary veins. The procedure was aborted and the patient came back after 3 months for a redo thoracoscopic pulmonary vein isolation on the left side – this time successful. All 42 patients (100%) received a connecting line to the left atrial appendage. LAA closure was successful and complete 40 patients, while one 1 patient had an insufficient LAA closure due to technical problems during application and in one patient with severe adherences LAA amputation with the stapler was not attempted.

All but one patient were extubated in the Operating theatre. One patient showed prolonged effect of sedatives and was extubated 5h postoperatively and discharged to the regular ward the next day.

The first 20 patients spent the first night in the intensive care unit (ICU) thereafter all patients were individually assessed for the intensive care unit or just to transit through the wake-up ward. Median duration of stay in the ICU and Recovery-Ward was 18h (Range 2-72) and 4h (Range 3-48). Chest-tubes were removed shortly after arrival in the intensive care unit /wakeup ward, after chest X-ray Patients were transferred to the regular ward on the same day in some, or on postoperative day one. A summary of the postoperative Outcomes is depicted in [Table 3].

Complications

Conversion to a sternotomy was necessary in 2 patients. In one case it was due to bleeding from a tear in the right upper pulmonary vein during encircling with the dissector. In the second case this occurred in a patient with severe scoliosis while inserting the bipolar clamp. Both cases were managed without cardiopulmonary bypass and had an uneventful postoperative course leaving the hospital after 5 and 8 days in sinus Rhythm. In one patient a bleeding occurred during encircling of the left pulmonary veins. In a second patient on postoperative day 1 a hematothorax occurred which required placement of a drain. One patient suffered ECG changes on the regular ward on postoperative day 1. Emergency PCI was performed on a LAD occlusion. Pleural effusions was a "common" postoperative problem. Effusion was managed conservatively with diuretics. When the chest X-rax prior to discharge demonstrated effusion a pleural ultrasound was performed for quantitative evaluation. In patients with >500ml a thoracentesis was performed. In one patient who developed chronic pleural effusions, which did not disappear despite pharmacologic management and several thoracentesis a pleurodhesis was necessary 18months out.

Cardiac Rhythm Outcomes

During the early postoperative period Direct-Current (DC) cardioversion was aggressively performed in all patients, when AF recurrence was symptomatic or a hemodynamically relevant. This occurred in 13 patients once, in 1 Patient three times and in 1 patient four times. After DC Conversion pharmacologic treatment with Amiodarone and/or Betablockers was started. Overall 9 Patients (21%) required antiarrhythmic medication after hospital discharge for atrial arrhythmias. A total of 6 patients (14%) required a redo procedure for AF recurrence. [Table 4] shows Rhythm status at Follow-up.

Follow-up

Median follow-up was 20 Months (11-43). During follow-up no mortality, thromboembolic events, TIA or stroke occurred. Overall (12 month) freedom from AF and antiarrhythmic medication was 93% and 89% for paroxysmal and non-paroxysmal patients respectively.

In the paroxysmal AF group, one patient had a symptomatic atrial arrhythmia recurrence after 18 month, which required a catheter ablation. This was due to a peri-mitral flutter and a reconnection of the right inferior pulmonary vein. In addition left sided substrate modification and a right sided cavo-tricuspid-isthmus line were performed. Only one patient with paroxysmal AF remained under oral anticoagulants due to an incomplete LAA closure with a CHADSVASC score of 3.

In the non-paroxysmal group overall 5 patients (12%) required a redo procedure. This was due to pulmonary vein reconnection and mitral isthmus flutter. Despite optimal LAA closure 15% of patients remained under oral anticoagulation with NOACS.

Discussion

This is the first study that highlights the role of an AF HeartTeam Program (AFHTP) in appropriately utilizing both catheter and minimally invasive surgical ablations in the management of AF. Our study shows that AFHTP can yield excellent patient outcomes for patients with improved communication between cardiologists and cardiac surgeons.

Too often, surgeons and electrophysiologists work in silos taking care of the same problem. With increased communication between specialists and increased awareness about quality and outcomes the surgical community has slowly begun to embraces the HeartTeam as it has become evident from the TAVI HeartTeams and team assessment of coronary artery disease.

The results for the surgical approach when randomized to either catheter or totally thoracoscopic ablation demonstrated a high rate of freedom of AF at 12 months, 77 vs. 42% in favor of the thoracoscopic procedure[12]. Other studies have shown a 2-year success rate of 70–80% for preventing AF recurrence in these complex patients[13]. Furthermore the relatively high complication rate initially described in the FAST trial[12] was demonstrated to become significantly lower in a very recent report by Vos et al.[14]. Over a period of 11 years in a dedicated AF center n=558 patients underwent thorascopic ablations, the freedom from complications was 89% and 97% for complications with life-long affecting consequences[15].

We believe that the surgical procedure comes with some advantages which are: bipolar RF as energy source, large antral epicardial bites isolation, inclusion of the entire epicardial fat pads and the ganglia within the wide antral ablation, and most importantly electrical isolation the LAA by amputation. The importance of this is confirmed by interesting EP data on targeting the LAA during first time catheter ablation[16]. As we have demonstrated, the Atriclip exclusion of the LAA leads to it's electrical silencing[17].

The most recent guidelines ESC suggest that a dedicated AF Heartteam setting and integrated AF care chain may be crucial for good outcomes[8]. Our's is the first report of such an integrated care chain.

Anticoagulation management after ablation procedures is directed by the guidelines[8]. However LAA closure plays a crucial role in this setting, as this is done as an add-on to the ablation procedure. Though the interventional cardiology literature suggests that we can discontinue anticoagulation when the LAA is closed[18], after ablation

procedures the recommendation is different[8]. Anticoagulation in this setting is to prevent thromboembolism from thrombi accumulating on the endocardial ablation lines due to the transmural nature of the epicardial ablation. However we believe that in the presence of LAA closure the risk of such thromboemboli is lower. There is currently some evidence indicating that the LAA closure line may present a thrombotic surface and that LAA closure in itself might warrant oral anticolagulation during a limited period. Further insight in this matter is necessary. In accordance to the guidelines referring doctors are reluctant to discontinue oral anticoagulation despite documented epicardial LAA closure. In a series of 291 Atriclip patients, Caliskan et al demonstrated that in a sub-group of 166 patients with no oral anticoagulation during benefited from a relative risk reduction of 87.5% with an observed ischemic stroke-rate of 0.5/100 patient-years compared with what would have been expected in a group of patients with similar CHA_2DS_2-VASc scores (expected rate of 4.0/100 patient-years). This is where endoscopic ablation techniques offer safe[15], effective[12] and durable[13] results, hence providing an additional option in the therapeutic armamentarium of invasive AF therapies. In addition to effective rhythm control, left atrial appendage (LAA) closure diminishes stroke risk and affords the possibility to discontinue anticoagulation. Together, these latter two factors potentially provide improved long-term survival not attainable with catheter ablation alone. This is an important factor in favor of the endoscopic treatment option as the epicardial techniques provide safe, effective and durable left atrial appendage closure[19].

The Star AF II demonstrated an absence of reduction in the rate of recurrent atrial fibrillation when either linear ablation or ablation of complex fractionated electrograms was performed in addition to pulmonary-vein isolation in patients with persistent AF[6]. Based on this and our experience, we believe that obtaining bidirectional block over all pulmonary veins is the cornerstone of any ablation procedure. Isolation from the epicardium, through the fat to the endothelium is done with very effective energy delivery. In fact the only energy source to have proven transmurality is the bipolar clamp[20].

Thoracoscopic ablation could be the first line of therapy due to the nature of transmural lesions on the left atrium leading to a high success rate of pulmonary vein isolation.

From recent studies[21] it appears that up to 20% of pulmonary veins seem isolated when measured with the pen, but when more sophisticated EP tools are used there appears to be a significant amount of incomplete lesions. This again leads to another argument in favor of a combined EP/surgical approach.

Limitations of this study are that we were not able to compare catheter ablation to thoracoscopic ablation. This was not the scope of the work as we believe that these therapeutic pathways are complimentary.

Conclusions

In patients who have either failed catheter ablation or not candidates for such, evaluation by a multidisciplinary HeartTeam can lead to effective combined therapy. Thoracoscopic bipolar ablation is safe and effective. In addition to effective rhythm control the protective effect of LAA closure decreases the risk of stroke significantly.

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Incomplete Endothelialization of Watchman™ Device: Predictors and Implications from Two Cases

Sharan Prakash Sharma[1], David Singh[2], Dean Nakamura[2], Rakesh Gopinathannair[1], DhanunjayaLakkireddy[1]

[1] *Kansas City Heart Rhythm Institute and Research Foundation, Overland Park, KS*

[2] *The Queen's Medical Center, Honolulu, Hawaii*

Abstract

Left atrial appendage occlusion (LAAO) is a promising alternative for stroke risk reduction in patients with non-valvular atrial fibrillation who are not suitable for long-term oral anticoagulation (OAC). Current practice mandates use of post-procedural OAC for 45 days after WatchmanTM placement duringwhich complete device endothelialization is expected to occur. However, most of theevidence supporting this strategy stem from animal studies. Incomplete device endothelialization are often encountered after 6-weeks of procedure and its therapeutic implications are less clear. Here, we present two cases of incomplete endothelialization after 1.5- and 2-year of Watchman implantation. In one of the cases, we believe thatan eccentric mitral regurgitation jet caused shearing force on the Watchman device and impeded with normal endothelialization. In the other case, we found a device related thrombus possibly favored by prothrombotic environment created by lack of endothelialization. Further studies are warranted to find predictors and better diagnostic tool of LAAO endothelialization.

Introduction

Atrial fibrillation (AF) is the most common cause of stroke. Oral anticoagulation (OAC) is used to mitigate stroke risk in patient with non-valvular AF[1]. However, a significant number of patients cannot be started on OAC due to bleeding complications. Percutaneous left atrial appendage occlusion (LAAO) has emerged as a potential option for such group of patients. Post-LAAO anticoagulation is maintained until device endothelialization. However, there is no systematic human study on device endothelialization and currently recommended OAC strategy mainly stem from animal evidence. There can be variability in endothelialization of the devices and delayed or lack of endothelialization of devicesare often encountered. There are no standard techniques to ensure device endothelization and little is known about the predictors of delayed endothelization after LAAO.

Here we present two cases of delayed endothelialization after watchman device and discuss potential mechanisms.

Cases

Case 1

A 70-year-oldwoman with diabetes, hypertension, moderate to severe mitral regurgitation(MR) and persistent atrial fibrillation had a history of recurrent gastrointestinal bleeding. As she was not a good candidate for long-term oral anticoagulation, she underwent Watchman device implantation. Adequate deployment of the device was confirmed both by transesophageal echocardiography (TEE) and Fluoroscopy using the PASS criteria (Position, Anchoring Size, and Seal). No residual flow into the appendage was observed by TEE at the conclusion of the case. She received warfarin and aspirin for 6 weeks after the procedure. TEE at 45 days after the procedure showed good device apposition and no evidence of thrombus or device leak. She was then treated with aspirin and clopidogrel for the next 6 months followed by aspirin therapy alone thereafter. TEE after a year post-procedure did not reveal any thrombus or device leak. Patient developed severe symptoms from MR and needed open mitral valve replacement surgery 1.5 years after watchman procedure. Intraoperatively, on visual inspection of the Watchman device the cardiac surgeon noted that there was complete lack of endothelialization [Figure 1]. A jet of blood stream from posterior mitral leaflet was seen to hit the left atrial appendage on the echocardiogram.

Case 2

A 57-year-old man with a history of permanent AF and lower GI bleed while on warfarin. underwent implantation of a 30 mm WatchmanLAAO device. Adequate deployment of the device was confirmed both by TEE and fluoroscopy using the PASS criteria. There was no leak and an inferior shoulder noted was deemed to be acceptable with respect to the device's final position. The patient was maintained on warfarin and aspirin therapy following the procedure for 45 days.Follow up TEE after approximately 45 days following implant revealed no thrombus on the device or residual leak.

Key Words

Atrial Fibrillation, Oral Anticoagulation, Left Atrial Appendage Occlusion.

Corresponding Author

DhanunjayaLakkireddy,
Executive Medical Director & Professor of Medicine University of Missouri Columbia
The Kansas City Heart Rhythm Institute (KCHRI) @ HCA MidWest
12200, W 106th street, Overland Park Regional Medical Center
Overland Park, KS 66215

Warfarin was stopped, and the patient was placed on clopidogrel 75 mg daily in addition aspirin 81 mg daily. Follow up TEE at 1-year revealed stable device position, no leak or thrombus on the device. clopidogrel was discontinued, and the patient was maintained on ASA therapy. Two years after the procedure the patient underwent a transthoracic echocardiogram that revealed a large thrombus along the superior and lateral region of left atrium as well as the surface of the Watchman device. A TEE was performed that confirmed a large mass, consistent with thrombus, that appeared to originate at the center of the Watchman device and extended along the wall of the Left Atrium. The patient was initially restarted on warfarin therapy with (target INR 2.5-3.5). When this failed to resolve the thrombus, aspirin 325 mg daily, and clopidogrel 75 daily were added. Several months later, the patient developed acute lower gastrointestinal bleeding and warfarin, aspirin and clopidogrel were discontinued. The patient underwent surgical removal of the LAA thrombus, the Watchman device, and excision of the LAA. Gross inspection of the Watchman device revealed patchy and incomplete endothelization of the device [Figure 2]. The patient recovered from the surgery without incident and is doing well.

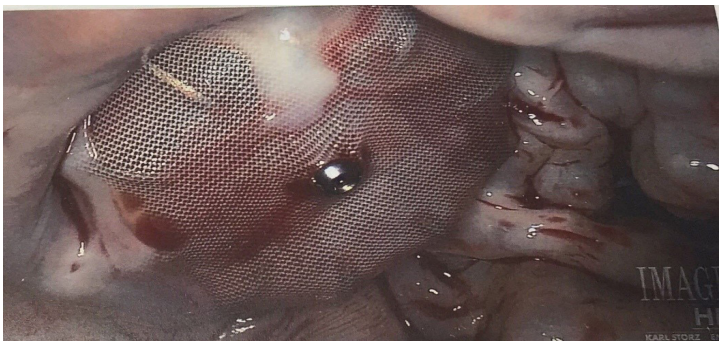

Figure 1: Intraoperative picture showing complete non-endothelialization of Watchman device after 1.5 years of implantation. Patient had severe posterior mitral regurgitant jet hitting on the Watchman device

Discussion

LAAO is being increasingly used for stroke risk reduction in patients not suitable for long term oral anticoagulation. It is important to understand the endothelialization process in these devices as it has clinical implications in the management of these patients.Here, we report two cases of incomplete endothelialization after more than 1.5 year of watchman LAAO. While the cause of delayed endothelialization in one is less clear we hypothesized that chronic force from posterior mitral regurgitant jet into the watchman could be the significant contributor in the other case.

Most of the information about endothelialization of LAAO devices stem from animal studies.In animal studies, LAAO devices have been found to undergo complete endothelialization in 3 months[2]. Except for a few case reports, there are no systematic studies about endothelialization in human.Massarenti et al reported a case of incomplete endothelialization that was observed after 10 months of Watchman implantation in a patient with hereditary hemorrhagic telengectesesia. Patient had stroke with device and when the device was analyzed,incomplete endothelialization was noted[3]. Another report from Canada reports a post mortem finding of incomplete endothelialization of Watchman device in a patient with multiple thromboembolic events[4]. Another report describes a direct visualization of an area of incomplete endothelialization of Amplatzer Cardiac Plug by a cardiac surgeon during open heart surgery for CABG after 1.5 years[5]. More publications exist in the sphere of Amplatzer Septal Occluder (ASO). Animal studies on ASO showed that it gets endothelialized in 3 months[6]. However, many human studies have found incomplete endothelialization of septal occluder device on autopsy or surgery after 5 months to 7 years post implantation[7–12]. Such discrepancy in endothelialization of endovascular devices between animals and humans clearly point to the presence of different regeneration mechanisms and calls for systemic studies in humans.

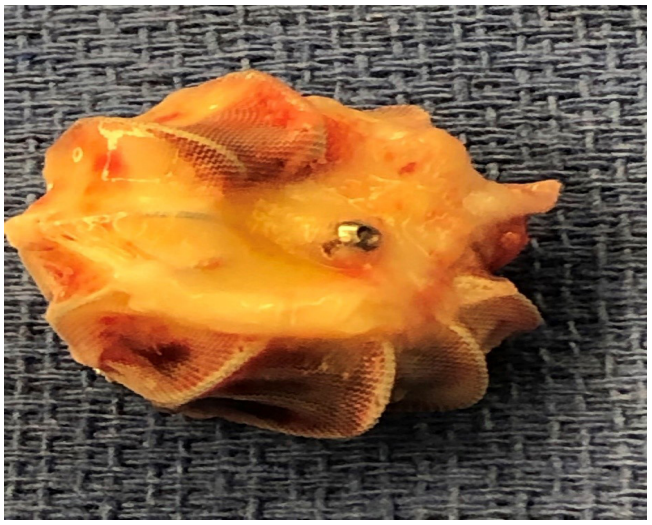

Figure 2: Gross inspection of Watchman device that was removed after 2 years of implantation. It shows a large area of non-endothelialization

Clinically, it is important to clearly understand the process of endothelialization for better management of LAAO patients. Postprocedural antithrombotic therapy largely prevents thrombus formation until endothelialization is complete. Incomplete endothelialization could provide a persistent prothrombotic surface for thrombus formation.Delayed device surface healing could potentially be related to thrombus formation that accompanies any device implantation(13). Device related thrombus (DRT) formation may be related to degree of LAAO device endothelialization[14].

There is no standard test to determine the degree of endothelialization of LAAO devices in current practice. In a study by Granier et al, incomplete endothelialization was defined as residual permeability on cardiac computed tomography without peridevice leak on TEE at follow-up[15]. Using such definition, they found 61% of the implants to have incomplete endothelialization after the mean follow up of 10 ± 6 months. Behenes et al recently presented a standardized cardiac computed tomography angiography (cCTA) protocol for systematic follow-up and comparison of patients after LAAO device implantation. They have proposed a protocol to correlate contrast enhancement with degree of endothelialization after LAAO device placement. Complete neo-endothelialization is characterized by the absence of contrast enhancement within the LAA without any peri-device leak.Contrast enhancement in the LAA of less than 50 Hounsfield units compared to the left atrium suggests incomplete

neo-endothelialization while equal contrast enhancement in both LAA and Left atrium signifies no or very early endothelialization[16]. However, it is unknown at this time, if cardiac CT would provide additional benefits over standard TEE after LAAO. Nevertheless, growing interest in the use of alternative imaging modalities after LAAO may be able to provide with better test to assess neoendothelialization after endocardial LAA closure devices.

In addition to the need of better diagnostic tool for detecting device endothelialization, understanding factors associated with device endothelialization is equally important. The optimal neoendothelialization of any implanted cardiac device might largely depend on the internal milieu such as hemodynamics ofthe heart and endothelial function. Dysfunctional endothelial cells due to abnormalities in transforming growth factor-B in a patient with hereditary telengectesia has been a putative cause of incomplete endothelialization that was observed 10 months after a watchman implant[3]. The high shear force near vascular stenotic area is known to affect cellular adherence and cause deleterious effects on endothelial cells[17]. Similarly, turbulent blood flow caused by high velocity regurgitant jet has been known to invoke spatial and temporal disorganization that can thwart normal compensatory endothelial realignment[17]. It is our speculation that turbulent flow caused by posterior MR jet might have impeded normal endothelialization in response to LAAO device in our first case. Granier et al had found patients with incomplete endothelialization tended to be more likely to have diabetes (36% vs 11%) and permanent AF (57% vs 22%), and to have been implanted with larger devices (86% vs 44%)[15].

Conclusion

Incomplete endothelialization of LAAO devices are often encountered clinically. There is paucity of understanding regarding the causes of incomplete endothelialization. Incomplete endothelialization may provide a persistent prothrombotic surface for thrombus formation and may warrant prolonged anticoagulation use post-implant. Based on our case, we hypothesize that MR could be one of the predictors of delayed endothelialization. The predictive factors associated with delayed endothelialization should be determined in a large prospective cohort.

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Bipolar Voltage Mapping for the Evaluation of Atrial Substrate: Can We Overcome the Challenge of Directionality?

Takanori Yamaguchi[1], Akira Fukui[2], Koichi Node[2]

[1]*Department of Cardiovascular medicine, Saga University, Saga, Japan.*

[2] *Department of Cardiology and Clinical Examination, Faculty of Medicine, Oita University, Yufu, Japan.*

Abstract

The relationship between atrial fibrosis and atrial fibrillation (AF) has been proven. Patient specific substrate ablation targeting fibrotic tissue estimated by bipolar voltage mapping has emerged as an alternative strategy for additional substrate modification beyond pulmonary vein isolation. The primary mechanism of a low-voltage electrogram has been suggested to be atrial fibrosis, however, no direct correlation between histological fibrosis and low-voltage zone has been confirmed. Furthermore, the definition of low-voltage zone is still controversial, and bipolar voltage amplitudes depend on multiple variables including electrodes orientation relative to direction of wavefront, electrode length, interelectrode spacing, and tissue contact. The aim of this article is to review the role and limitation of voltage mapping, and to share our initial experience of a newly released grid-pattern designed mapping catheter to make the voltage mapping more reliable to guide patient specific AF ablation.

Introduction

The initiation and maintenance of atrial fibrillation (AF) requires triggers and an atrial substrate, and AF often progresses from trigger-driven arrhythmias to more substrate-dependent arrhythmia. Haissagurre et al [1] demonstrated in their seminal work that ectopic beats from the pulmonary vein trigger AF, and thereafter, electrical isolation of the PV has been developed as a cornerstone therapy for AF ablation[2]. However, pulmonary vein isolation (PVI) alone has demonstrated a 60 to 80 % of sinus rhythm maintenance rate in paroxysmal AF and 50 to 60 % in non-paroxysmal AF patients [2,3] . To improve the outcomes, several techniques to modify atrial substrate has been vigorously developed especially in non-paroxysmal AF patients. Linear ablation and ablation of complex fractionated electrograms have been recognized as a conventional substrate modification[2]. However, the STAR-AF II trial (Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial Part II) demonstrated no reduction in AF recurrence rate when either empirical linear ablation or ablation of complex fractionated electrograms was performed in addition to PVI[3]. This study suggests that more patient-specific substrate modification is needed to improve ablation outcomes.

Atrial fibrosis and atrial fibrillation

AF is associated with structural, electrical, and contractile remodeling of the atria. Development and progression of atrial fibrosis are the hallmark of structural remodeling and are considered to be the substrate for AF perpetuation[4]. Shortening of action potential duration characterize electrical remodeling. Animal models of AF demonstrated early recovery of electrical remodeling after sinus rhythm restoration,[5] however, structural remodeling has been suggested to persist in the long term[6]. At sites of atrial fibrosis, collagen deposition and proliferation of fibroblast and myofibroblasts arises. Atrial fibrosis produces the substrate to promote AF by interrupting fiber bundle continuity, causing local conduction disturbances, and promoting anisotropic conduction[7]. AF is also facilitated by shortening of action potential duration resulting from the electrophysiological effects of fibroblasts and myofibroblasts[8]. In addition, myofibroblasts are also known to elicit ectopic activity, potentially providing triggers for reentry formation[9]. Human histology data show that increased amounts of atrial fibrosis are found in the atria of AF patients[10-13]. In post-mortem atrial tissues, the amount of atrial fibrosis was significantly correlated with presence of AF and duration of arrhythmia[11]. Even in patients with lone paroxysmal AF, atrial septal biopsies have revealed inflammatory infiltrates consistent with myocarditis and fibrosis[12]. These experimental and clinical studies proved a positive correlation between atrial fibrosis and AF.

Accurate and reliable detection and quantification of atrial fibrosis could help to choose an appropriate strategy for treatment of AF. Late gadolinium enhancement magnetic resonance imaging (LGE-MRI) has been developed to visualize and quantify extent of atrial fibrosis, [14,15] providing indirect evidence of fibrosis in the left atrium. Although significant advancements have been made in this technology, many significant controversies and limitations remain, including limited spatial resolution to detect fibrotic tissue in thin

Key Words

Atrial Fibrillation, Catheter Ablation, Fibrosis, Low Voltage

Corresponding Author

Takanori Yamaguchi,

Department of Cardiovascular medicine, Saga University, 5-1-1 Nabeshima, Saga, Japan.

atrial wall coupled with motion or flow artifact, non-reproducibility in different centers, high inter-observer variability, and no standardized image acquisition protocols and image processing techniques[16]. Furthermore, LGE-MRI is available only in limited research centers. Another method to estimate fibrotic burden in atria is peak-to-peak bipolar voltage mapping using three-dimensional electroanatomic mapping (EAM) systems, which have been developed and widely used in clinical practice to guide ablation and mapping catheters. EAM identifies and quantifies the presence of low-voltage zone (LVZ) in the atria, the amount of which is strongly related to AF recurrence after PVI[17,18].

Definitions of low-voltage zone in the atria

The primary mechanism of a low-voltage electrogram has been suggested to be atrial fibrosis. Low-voltage electrograms have been reported to come from diverse mechanisms[19-22] and may reflect poor tissue coupling, discontinuous conduction, and non-uniform anisotropic tissues caused by fibrosis. However, no direct correlation between histological fibrosis and LVZ has been confirmed. The definition of LVZ still remains controversial, mainly due to lack of histological examination. Sanders et al[24,25] created electroanatomical maps of the RA either with distal coronary pacing or in sinus rhythm in their work to investigate electrophysiological substrate in the right atrium (RA) for AF in humans with congestive heart failure and sinus node diseases. In this work, they initially characterized electrically silent areas (scar) defined by the absence of recordable activity or a bipolar voltage amplitude ≤0.05 mV; and low-voltage areas defined by contiguous areas of bipolar voltage ≤0.5 mV. Based on these reports, Verma et al.[17] defined pre-existent left atrial scarring as an absence of voltage or a bipolar voltage amplitude ≤0.05 mV and low-voltage "abnormal" areas as an amplitude ≤0.5 mV recorded during sinus rhythm. This seminal work first demonstrated that pre-existent left atrial scarring, identified by electroanatomic mapping, is a strong independent predictor of recurrence after PVI. Subsequently, Lo et al.[26] also defined LVZ as ≤0.5 mV based on the report by Sanders et al., in their work investigating progressive remodeling of the atrial substrate in patients with AF recurrence after AF ablation. The same group[27] also investigated biatrial substrate properties in AF patients using the same definition of "scar" and LVZ as report by Verma et al. [17] Thereafter, the cut-off value of 0.5 mV for the definition of LVZ has been historically used by other researchers.

However, electrophysiological and histological evidence of the cut-off value for the definition of LVZ has been still lacking. Miyamoto et al. [28] reported that the local conduction through the LVZ defined as <0.5 mV during sinus rhythm was significantly delayed compared with that through the non-LVZ. On the other hand, the local conduction through the LVZ defined as 0.5–0.75 or 0.75-1.0 mV was similar to that through the non-LVZ. In addition, a complex electrogram morphology of fractionated or double potentials was more frequently found in the LVZ defined as <0.5 mV compare with the non-LVZ. These findings suggest that the LVZ defined as <0.5 mV would reflect region with significant fibrosis which cause slow conduction due to interruption of fiber bundle continuity [29]. Masuda et al [30] reported that LVZs defined as < 0.5 mV are associated with high inducibility of atrial tachyarrhythmias after PVI, suggesting LVZ defined as < 0.5 mV works as arrhythmogenic substrate.

Clinical evidence of the impact of LVZ defined as <0.5 mV during sinus rhythm on outcomes after PVI also has been reported. Yamaguchi et al. [18] compared the long-term outcomes after PVI alone in patients with LVZs defined as <0.5 mV and those in patients without LVZs. An atrial tachyarrhythmia free-survival rate after PVI alone was significantly lower in patients with LVZs, and the extent of the LVZ was identified to be an independent risk factor of AF recurrence after PVI alone. Masuda et al.[31] also revealed that the presence of LVZ defined as <0.5 mV predicts AF recurrence in patients with paroxysmal AF as well as those with persistent AF. Lin et al [32] established the definitions of LVZ as 0.1-0.4 mV and transitional zone (TZ) as 0.4-1.3 mV. In their study, 13 patients without any cardiovascular risk factors, who were supposed to have "normal" LA, were analyzed. In this population, 95% of all bipolar electrogram signals were >0.38 mV. Therefore, the upper limit cutoff of the LVZ was defined as 0.4 mV. In patients with persistent and long-standing AF, 95% of complex electrograms defined as ≥three positive or negative distinct peaks and electrogram duration ≥50 ms were distributed in areas with the bipolar voltage <1.32 mV. As such, the transitional zone was defined as bipolar voltage between 0.4 and 1.3 mV. Chen, one of the authors, described in his nice review article regarding scar homogenization, "Theoretically speaking, diseased atria are not only "black and white" with a clear line; therefore, setting LVZ as the profound scar and TZ as the moderate fibrotic area is more reasonable." [33]. Vlachos et al [34] also reported that the existence of LVZ in the LA defined as <0.4 mV more than 10% of the total LA surface area, detected through high density voltage mapping (median number of 2,485 points), predicts arrhythmia recurrence after PVI for paroxysmal AF using defined as <0.4 mV.

Oakes et al [13] described the utility of delayed-enhancement MRI in detecting fibrosis in the LA, and reported that an increased amount of LA wall enhancement is strongly associated with recurrence after PVI. The researchers also confirmed a good correlation between enhancement on LGE-MRI and low-voltage regions defined as <0.5 mV on electroanatomic map (R^2 = 0.61). Subsequently, the same group provided histological evidence of fibrotic remodeling based on 14 surgical biopsy specimens taken from nine patients with AF and one non-AF patient. LA wall biopsies demonstrating tissue fibrosis were correlated with regions of LA wall enhancement on LGE-MRI, whereas normal biopsy tissue matched with non-enhanced regions, suggesting the accuracy of LGE-MRI in detecting fibrosis. The DECAAF multicenter, and prospective study demonstrated that among patients with AF undergoing AF ablation, atrial fibrosis estimated by LGE-MRI was independently associated with the likelihood of AF recurrence[15]. Several studies comparing EAM derived low-voltage areas and LGE-MRI have been reported. Lim et al. summarized the relationship between voltage map and DE-MRI in their editorial comment, however, the threshold of bipolar voltage and DE-MRI methodology are heterogeneous [35].

Spatial distribution of LVZ, LGE, and fibrosis

LVZs defined as < 0.5 mV during SR are identified about 30% in patients with persistent AF [18,36,37] and 15% in patients with paroxysmal AF [31]. We categorized patients into Stage I to Stage IV according to the extent of %LVZ ([Figure 1]), and reported that LVZ extent is still a strong predictor for recurrence even after LVZ

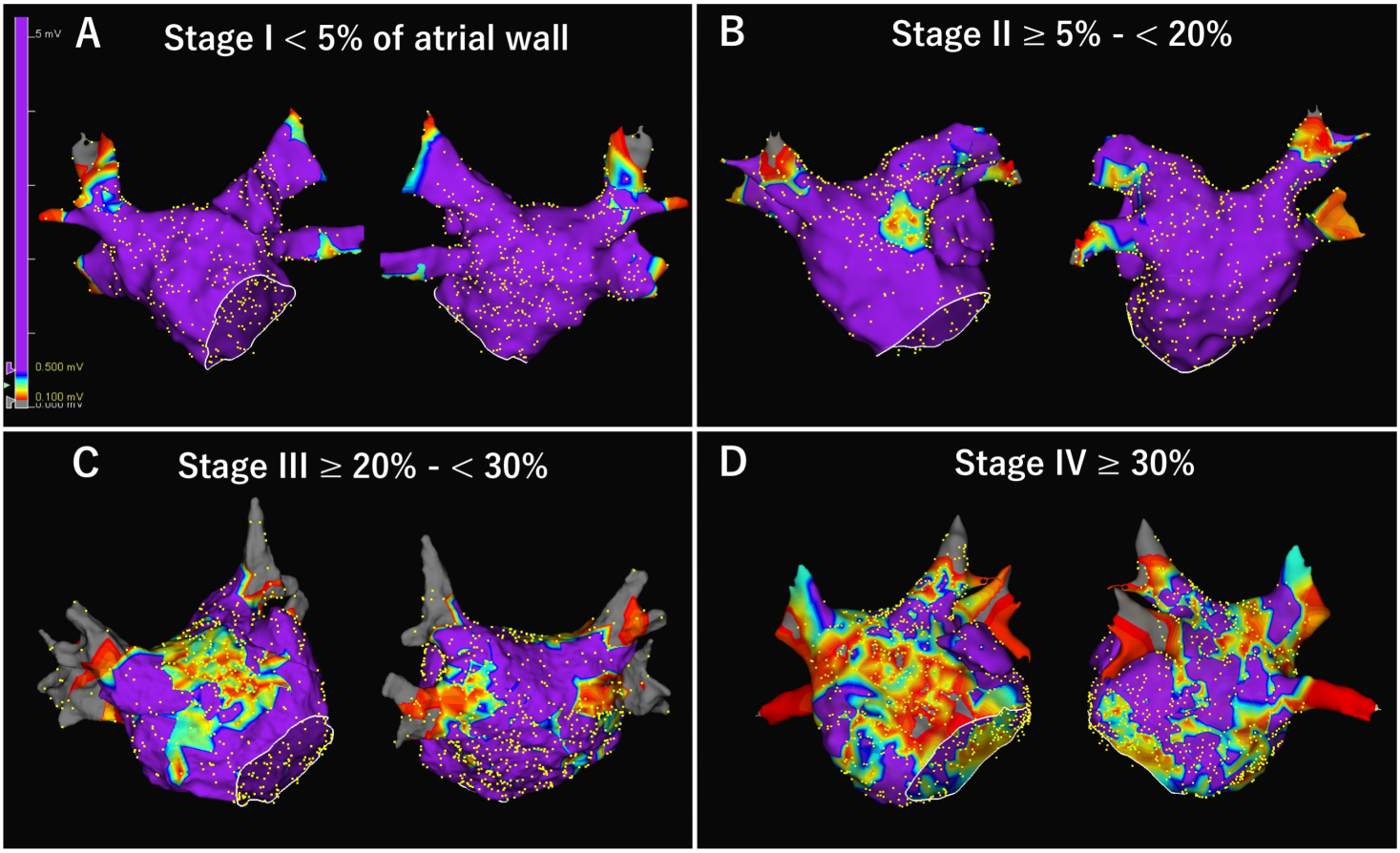

Figure 1: **Four stages of left atrial (LA) low-voltage zone (LVZ). After obtaining LA and pulmonary vein geometry, high-density bipolar voltage map was created during sinus rhythm using a 20-pole circular mapping catheter with a 1-mm electrode length and 2-mm interelectrode spacing (Reflexion HD™; Abbott). LVZ and electrical scar was defined as < 0.5 mV and < 0.1 mV during sinus rhythm, respectively. Total %LVZ area was calculated as the percentage of LA surface area excluding the PV antral region, LAA orifice, and mitral valve, and LVZ was subsequently categorized as stage I (<5%), II (≥5% to <20%), III (≥20% to <30%), and IV (≥30%) according to previous publication.[37]**

homogenization[37]. The spatial distribution of LVZs is related to the extent of LVZ. LVZs were most frequently identified at the anterior wall, septum, and roof, and posterior wall. However, LVZs were less frequently identified at the inferior wall and lateral wall. Only patients with extensive LVZ (Stage IV) have LVZs at the inferior and lateral wall ([Figure 2]). On the other hand, Higuchi et al.[38] from Utah group reported that LGE was most frequently identified in the lateral, inferior, and posterior wall. There is a great discrepancy in spatial distribution of LGE by DE-MRI and LVZ. From histological perspective, Platonov et al [11] reported that in postmortem atrial tissue analysis, the extent of fibrosis did not differ among the 5 sampling locations in the atria including crista terminalis, Bachmann's bundle, inferior PV, posterior LA, superior PV. Although anterior wall and atrial septum, which is most frequent site of LVZ, was not examined, this study proved that fibrosis progression is more ubiquitous process. Schreiber et al. recently reported that the success rate of PVI and box isolation of fibrotic area (BIFA) was lower in severe fibrotic atrial cardiomyopathy (FACM class III and IV) than in mild-to-moderate FACM (class I and II), which is consistent with our study. Furthermore, the maximum LA voltage reduced over the FACM classes, which is consistent with the histological examination report by Platonov et al.[11] Because both voltage mapping and DE-MRI have important limitations in imaging for atrial fibrosis, histological validation is necessary to reveal the relationship between fibrosis extent and specific spatial distribution in LVZ and LGE.

Efficacy of Voltage-based AF ablation

Improved outcomes may be possible with patient-specific substrate modification targeting atrial fibrosis as estimated by voltage mapping. Recently, there is increasing evidence of the efficacy of voltage-based AF ablation predominantly in non-paroxysmal AF patients[36,37,39-45]. The hypothesis is that performing substrate ablation, based on the individual patient's location and extent of LVZ, in addition to PVI would improve outcomes, while no substrate modification would be necessary in patients without LVZ. However, most studies were small and/or non-randomized observational assessments. Recently, Yang et al.[46] reported the results of a multicenter, randomized study that compared substrate modification targeting LVZ and conventional stepwise approach after PVI and found similar success rates at 18 months, with lower procedure and fluoroscopy durations and shorter energy delivery time in the former group. Importantly, over 50% of nonparoxysmal AF patients did not need further ablation beyond PVI, which is consistent with the previous study results[36,37,39-45]. Kircher et al [47] also reported the efficacy of voltage-guided ablation in a randomized single-center study. A large, multicenter randomized trial, START Trial (Substrate Targeted Ablation of Persistent Atrial Fibrillation Trial) designed to assess the safety and efficacy of left

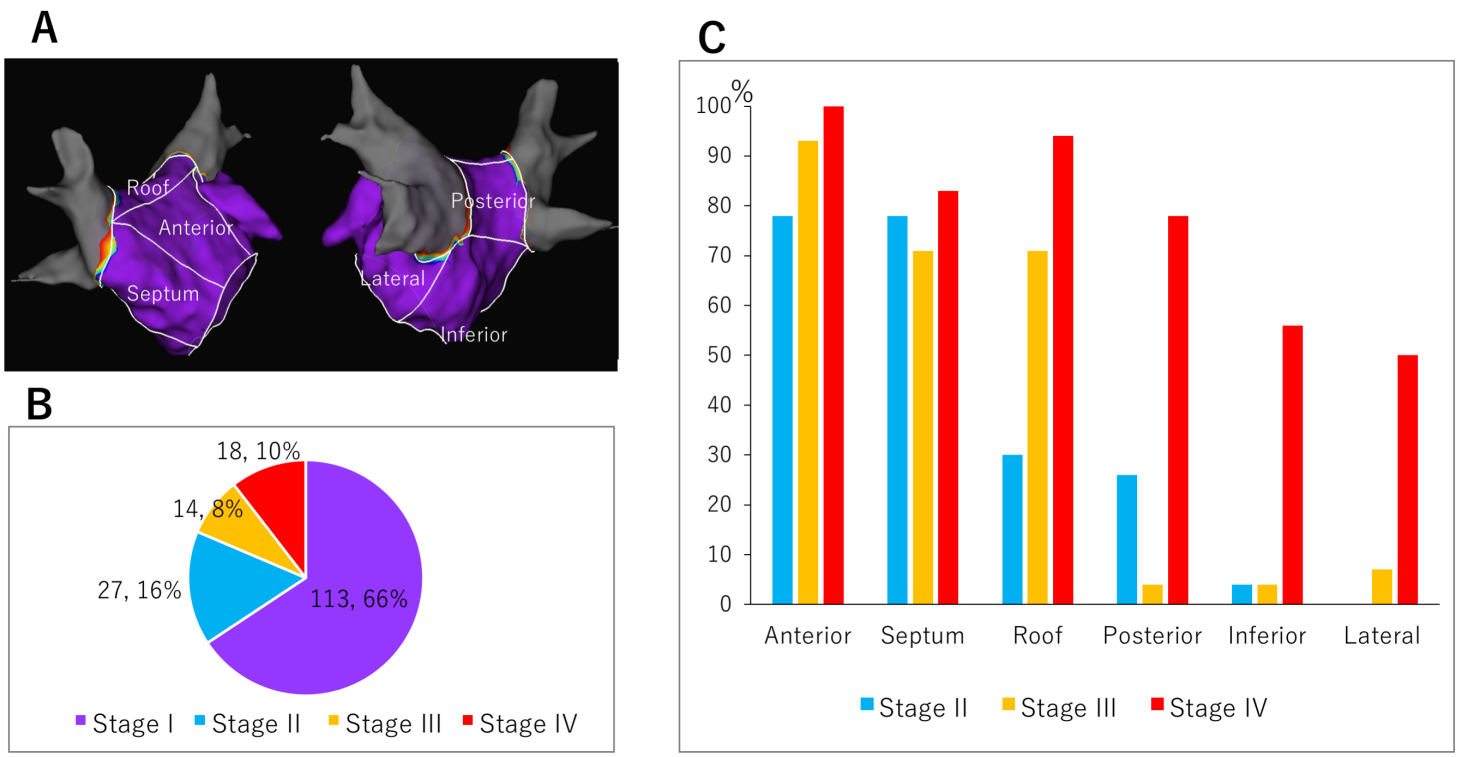

Figure 2: **Spatial distribution of left atrial (LA) low-voltage zone (LVZ). (A) LA was divided into six segments (anterior, septal, roof, posterior, inferior, and lateral wall) to describe LVZ distribution. (B) Percentage of patients classified into each stage among 172 persistent patients were shown. (C) Spatial distribution of LVZ in each stage. LVZ was frequently identified in the anterior wall, septum, and roof in Stage II and III. LVZs at inferior and lateral wall were less frequent and identified almost exclusively in patients in Stage IV (extensive LVZ). Graphs are created from the data in the previous publication (supplementary [Table 1], Yamaguchi et al. J Cardiol. 2018; 72: 427-433.)**

atrial voltage-based ablation (PVI plus LVZ homogenization Vs. PVI alone in patients with LVZ), is ongoing (https://www.umin.ac.jp/ctr/index.htm, UMIN000022119), which will provide further insight into this strategy. [Figure 3] shows an example of homogenization of LVZ identified during sinus rhythm. Jadidi et al[42] and Yagishita et al[48] defined LVZ as <0.5 mV during AF, and reported the efficacy of voltage-based ablation based on the definition. However, bipolar voltage depends on the direction and complexity of the wavefront propagation. Therefore, an accurate measurement of the bipolar voltages during AF may be chagellnging due to the temporal variation in the voltages.

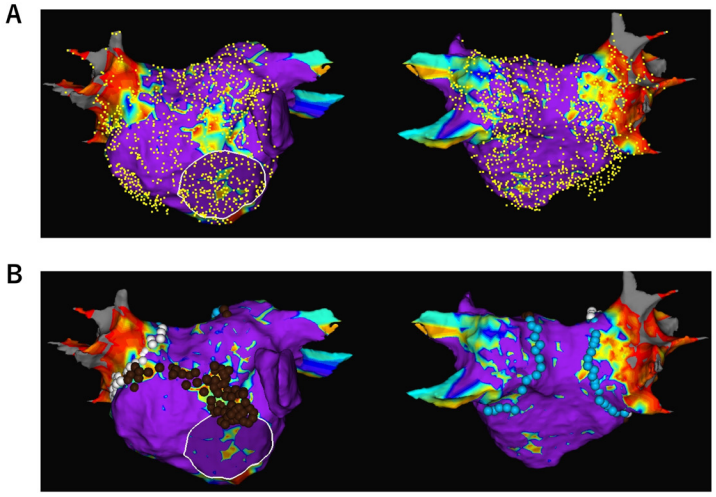

Figure 3: **An example of newly appeared low-voltage zone (LVZ) in a 76-old-year male during a redo procedure for recurrence of persistent AF. A left atrial (LA) voltage map was created using a circular mapping catheter during sinus rhythm. No prior substrate ablation was performed and no LVZ was identified at the index procedure 2 years prior. LVZ was identified at the anterior wall and the septum. Pulmonary vein (PV) reconnection was also identified in the left inferior PV. LVZ homogenization at the anterior wall and septum, as well as wide antral PVI, was performed. To prevent atrial tachycardia due to a narrow isthmus between the homogenized area and PVI line, strategic linear lesions were placed to create an anterior mitral line.**

Limitations of voltage map

It is important to consider which factors determine bipolar electrogram amplitude. Bipolar electrograms are the difference in voltage between two unipolar electrograms that are recorded at two closely spaced electrodes, providing sharp and high frequency signals, and used as a good indicator of local timing of near field. However, there are many variables that can influence the electrogram amplitude. Anter and Josephson nicely summarized those variables in their editorial commentary[49]. The variables are (1) activation vector; (2) angle of incidence; (3) recording electrode size; (4) interelectrode spacing; (5) tissue contact; (6) filtering; (7) mapping density; (8) mapping resolution. Voltage map during sinus rhythm changes in response to the change of activation wavefront. [Figure 4] shows an example of influence of activation direction on bipolar voltage map and wave propa-

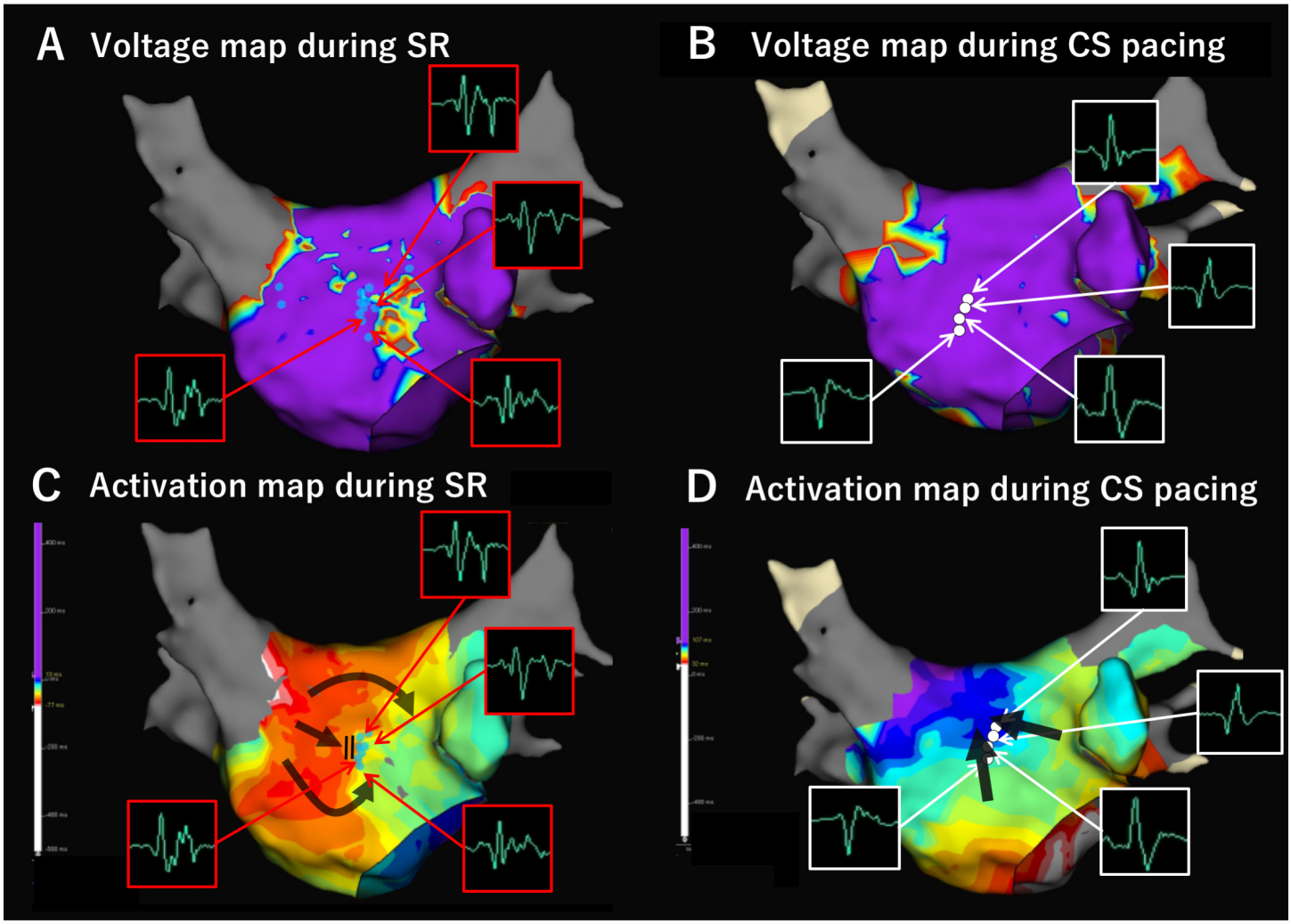

Figure 4: **Activation direction of wavefront influences bipolar voltage and conduction velocity. Left atrial (LA) voltage map was created using circular mapping catheter (CMC, Reflexion HD) both during sinus rhythm (SR) and distal coronary sinus (CS) pacing in a patient with persistent AF. LVZ defined as <0.5 mV was identified at the anterior wall during SR (A), while it disappeared during CS pacing (B). Conduction block and/or delay as well as fractionated potentials observed during SR along the LVZ disappeared during CS pacing (C, D). Figure modified from Fukui A. et al. Heart Rhythm, S322, Vol. 15, No. 5, May Supplement 2018.**

gation[50]. The voltage map was created by circular mapping catheter (CMC) during sinus rhythm. An LVZ defined as <0.5 mV was identified at the anterior wall and conduction delay was also observed through the LVZ, while the LVZ and conduction delay disappeared during CS pacing, suggesting unidirectional block at the LVZ.

A New HD Grid mapping catheter in voltage mapping

Dependence of the orientation of electrode catheters relative to the propagating wavefront is one of most important disadvantage of bipolar recordings [49,50]. When the activation wavefront moves parallel to the electrode pair, there is a maximum difference between the unipolar electrogram recorded for the distal and the unipolar electrogram recorded for the proximal electrode, which results in maximum bipolar amplitude between the two electrodes. On the other hand, when the activation wavefront moves perpendicular to the electrode pair, both electrodes record the similar unipolar signals. Therefore, there will be minimum to no difference in the unipolar signals, resulting in a bipolar electrogram that may cause a false low-voltage.

A recently released Advisor™ HD Grid mapping catheter (HD Grid, Abbott) has a unique grid-pattern design, consisting of 16 electrodes of 1-mm length across 4 splines with equidistant 3-3-3 mm spacing allowing bipole recording along and across the splines [Figure 5]. This mapping catheter was designed to reduce the variability in bipolar electrogram characteristics associated with different orientations of the electrodes relative to the wavefront. Bipolar electrograms both along and across the spline can be recorded. The potential of this catheter can be maximized when used in conjunction with the EnSite PrecisionTM System Best Duplicate algorithm. When multiple points are obtained within every 1 mm sphere of space, this algorithm selects mapping point with the largest voltage and with timing near the timing average. In addition, the HD Wave Solution accounts for directionality taking voltage recordings only from orthogonal bipoles and only keeping the highest amplitude point. Multiple configurations are possible, at our center we leveraged a configuration that collected 9 Best Duplicates for each saved map point.

[Figure 6] shows a good example of difference in bipolar voltage

amplitude with different electrodes orientation relative to activation direction. Some of bipoles of the CMC were placed perpendicular to the wavefront and the bipolar amplitude was very low (0.05 mV). On the other hand, when HD Grid was placed at the same position and the bipoles along the spline were parallel to the wavefront, the bipolar amplitude was normal (1.79 mV). LVZ at the right atrial posterior wall identified using the CMC disappeared when HD Grid was used.

[Figure 7] and [Figure 8] show comparisons of voltage maps during sinus rhythm between CMC and HD Grid catheters in different patietns. [Figure 9] shows voltage maps in a redo session of the patient represented in [Figure 8]. In both cases, HD Grid decreased the extent of LVZ. Importantly, conduction delay or block was observed along the LVZ identified by HD Grid. For the patient in [Figure 8] and [Figure 9], the LVZ at the anterior wall was revealed to be a cause of atrial tachyarrhythmia recurrence. [Figure 10] shows comparison of voltage map during AF and high RA pacing. In this comparison, HD Grid drastically reduced the extent of LVZ during AF. These examples suggest that HD Grid can overcome directional sensitivity and can exclude false low-voltage, and can detect AF substrate more accurately, which leads to more effective voltage-based ablation strategy, although difference in interelectrode spacing may influence the voltage amplitudes and clinical studies are needed to evaluate the clinical impact of this technology.

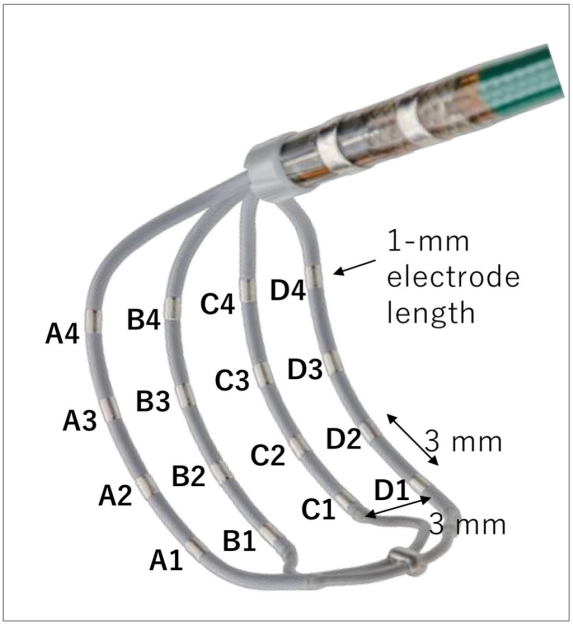

Figure 5: **Electrode configuration of a mapping catheter with grid-patterned design (Advisor™ HD Grid Mapping Catheter, Abbott)**

Conclusions

Patient specific substrate ablation targeting fibrotic tissue estimated by bipolar voltage mapping is a promising alternative strategy for additional substrate modification beyond PVI, although more clinical evidence should be accumulated. However, consideration must be given to the fundamental mechanism and potential limitations of bipolar voltage mapping. Dependence of the orientation of electrode pairs on the catheter relative to the wavefront is one of the most important disadvantages. Our initial experience of a newly developed grid-pattern designed mapping catheter may overcome this limitation and make the voltage map more accurate, thereby impacting ablation strategies; however, further studies are needed.

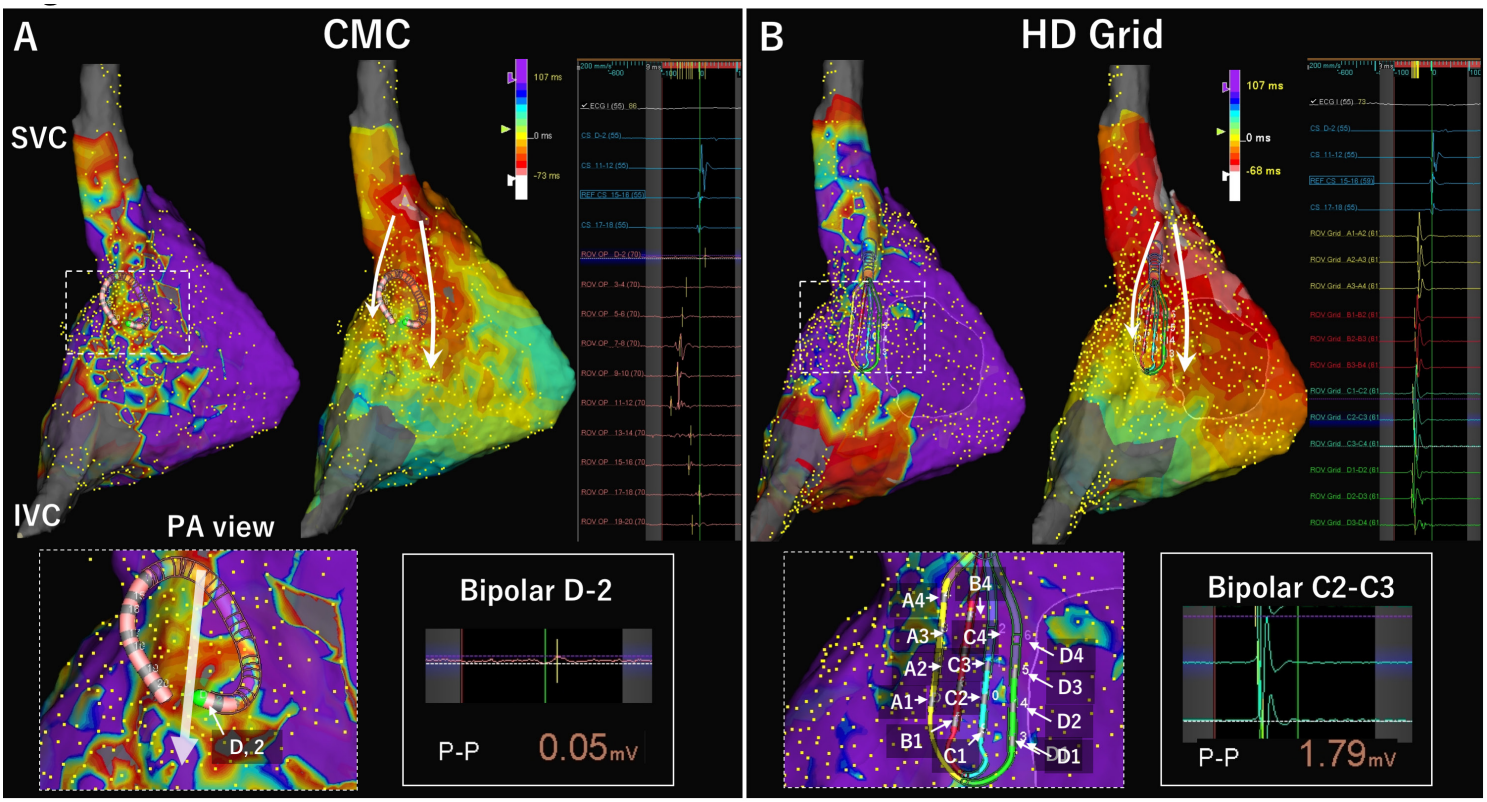

Figure 6:	**Difference in bipolar voltage amplitude with different electrode orientation relative to activation direction. Right atrial (RA) bipolar voltage maps during sinus rhythm were compared between a conventional circular mapping catheter (CMC) with a 1-mm electrode length and 1-mm interelectrode spacing (Inquiry™ Optima™; Abbott) and a mapping catheter with grid-patterned design (Advisor™ HD Grid Mapping Catheter, Abbott). Low-voltage zone (LVZ) and scar was defined as <0.5 mV and <0.1 mV during sinus rhythm, respectively. The internal and external projection of the geometry's electrical information was strictly set at 4 mm, and mapping catheters were introduced via a steerable long sheath (Agilis™, Abbott). Bipolar electrograms were filtered by a band pass to frequencies between 30 to 500 Hz. Timing of local activation was automatically set at the initial deflection using EnSite Precision™ System. (A) A LVZ was identified at the RA posterior wall along the crista terminalis when a 20-pole CMC used. White arrows in the activation maps show the activation direction. The enlarged map shows the electrode orientation relative to activation direction. The bipolar D-2 was placed perpendicularly to the wavefront, and the bipolar signal shows a peak-to-peak amplitude of 0.05 mV. (B) The LVZ disappeared when the HD Grid catheter was used. In this map, all bipole pairs along spline only (12 pairs) were used (so-called Standard configuration). Electrode numbers of the HD grid were shown in the enlarged map. In this position, all of the bipolar pairs were placed parallel to the wavefront. The bipole C2-C3 located at the same position with bipolar D-2 of the CMC in figure A shows an amplitude of 1.79 mV. Note that activation sequence map is also more organized in the HD grid map compared to the CMC map probably because of more accurate detection of initial deflection due to higher amplitudes in the HD grid map.**

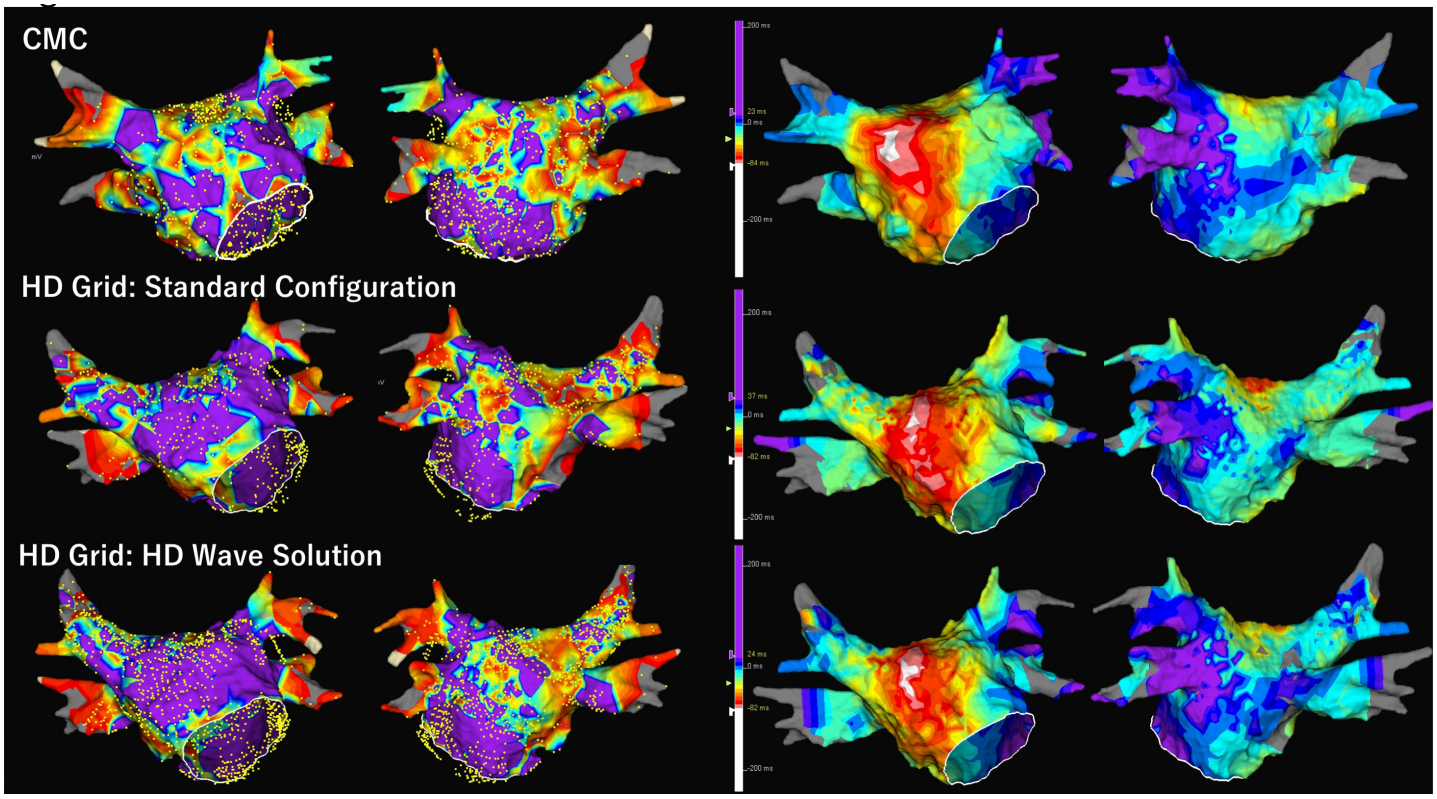

Figure 7:	A comparison of voltage maps obtained during sinus rhythm between a circular mapping catheter (CMC, Reflexion HD) and a HD grid catheter in a 65 year old male with paroxysmal AF. No prior ablation was performed. Geometry creation and voltage mapping of the LA was separately performed during sinus rhythm (SR) using CMC and HD Grid. Voltage map by CMC shows extensive low-voltage zones (LVZs) at the anterior wall, septum, and roof, and the posterior wall (46% of LA surface) (Upper panel). Another voltage map was created by HD Grid during SR. Standard Configuration map using all bipole pairs down the splines only with 12 bipolar sets shows decrease of LVZ extent to 31% of LA surface, especially at the anterior wall (middle panel). Interestingly, the HD Wave Solution using only orthogonal bipoles further decreased the LVZ extent to 18%. Of note, the LVZ at the anterior wall completely disappeared.

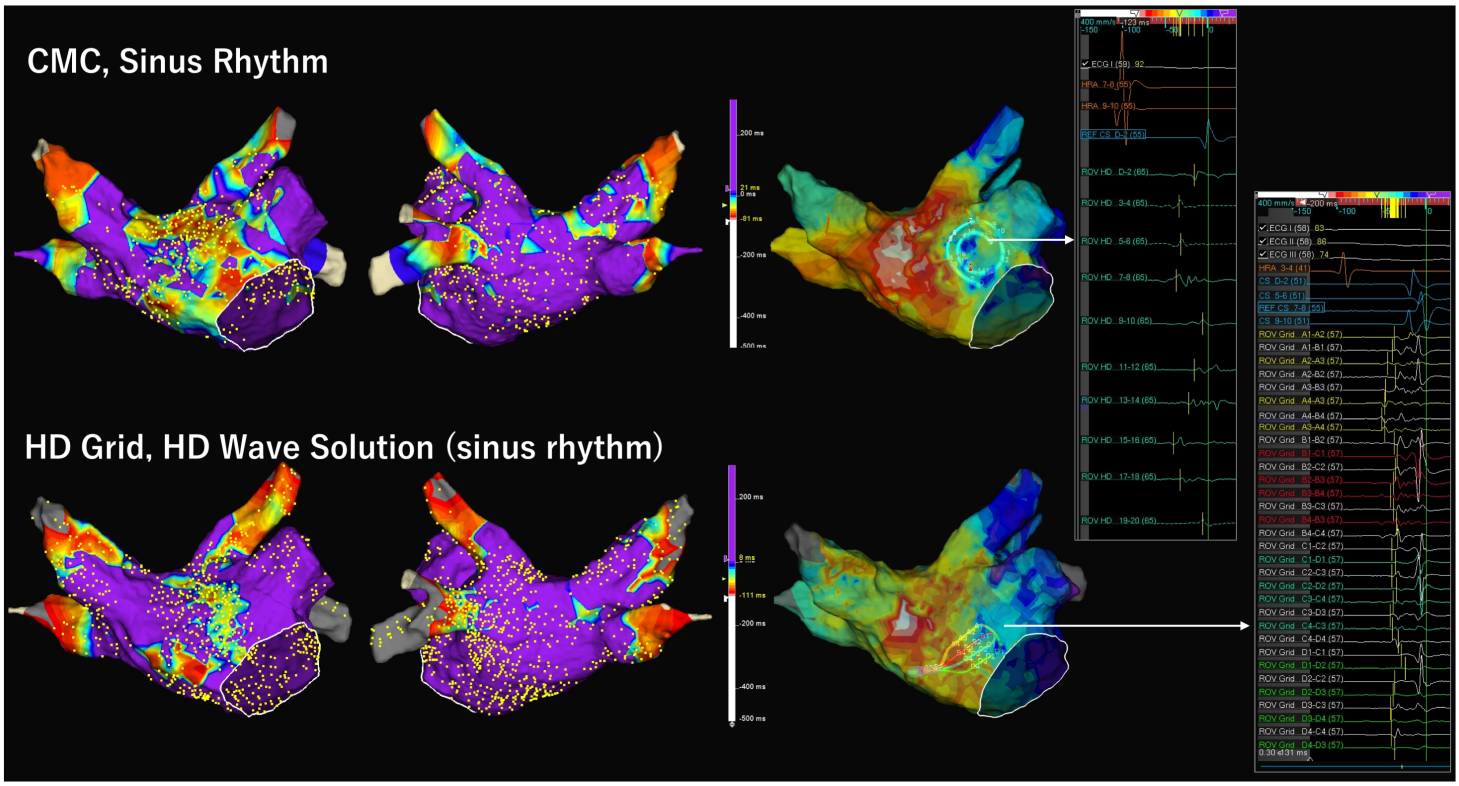

Figure 8:	A comparison of voltage maps during sinus rhythm (SR) between a circular mapping catheter (CMC) and a HD grid catheter in a 75 year old female with persistent AF. No prior ablation was performed. Voltage map of the LA was separately created during SR using CMC and HD Grid. LVZ was defined as <0.5 mV and scar as <0.1mV. Voltage map by CMC shows extensive low-voltage zones (LVZs) at the anterior wall, septum, and the roof (20% of LA surface) (Upper panel). Another voltage map created by HD grid using HD Wave Solution shows smaller extent of LVZ (9% of LA surface). Activation sequence maps show conduction slowing at the sites with LVZ detected by HD Grid in both maps. Bipolar electrograms obtained by each mapping catheter at the slow conduction zone were shown. This patient underwent pulmonary vein isolation alone in the first session.

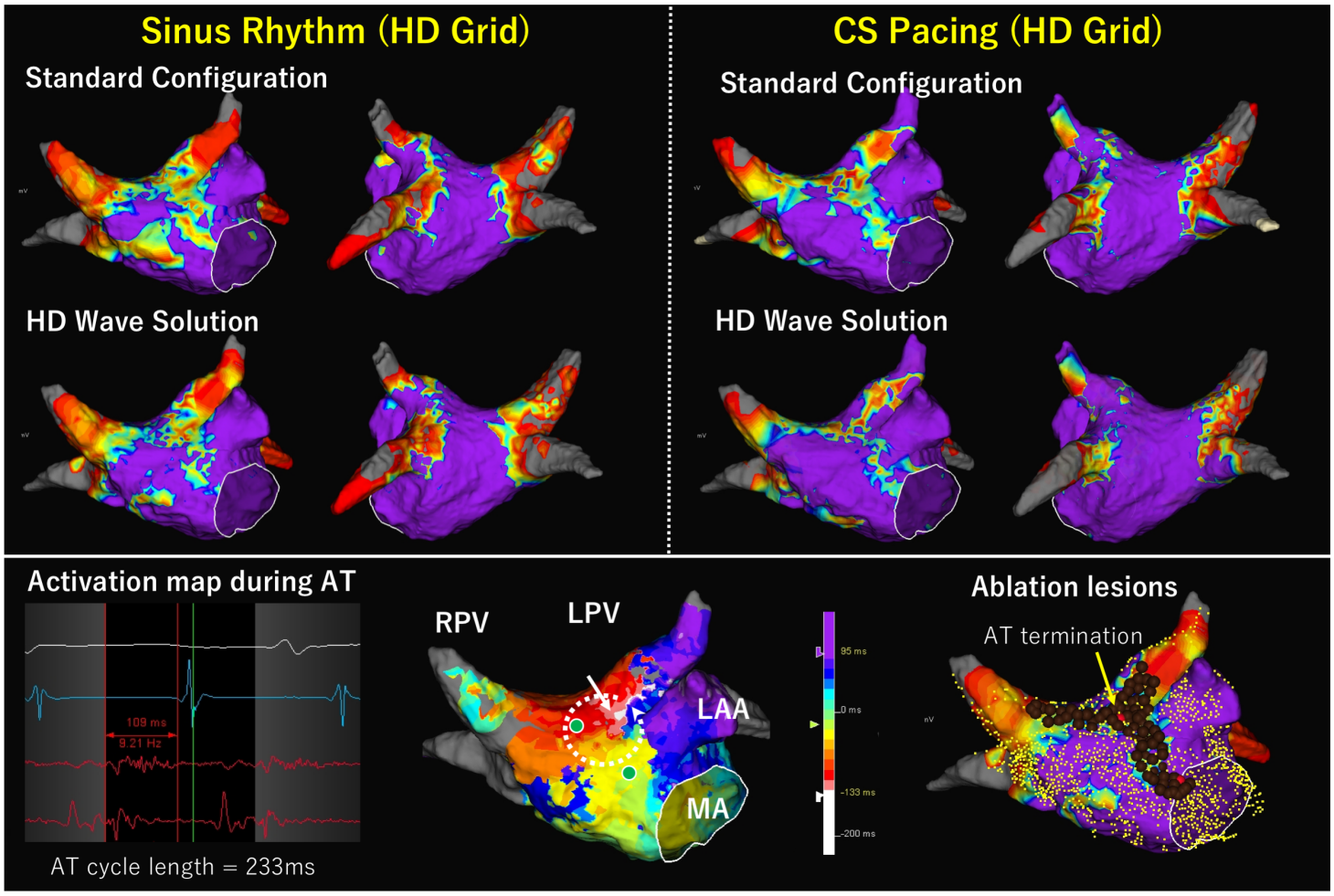

Figure 9: A comparison of voltage maps between during sinus rhythm (SR) and during distal coronary sinus pacing (CS pacing) both created by HD Grid catheter in a 75 year old female with cardioversion and drug refractory repeated recurrent atrial tachycardia (AT). This is the same patient described in [Figure 8]. No prior substrate ablation was performed in the index procedure. Redo procedure was performed 30 days after the index procedure. Voltage mapping of the LA was separately performed using HD Grid during SR and during CS pacing. LVZ was defined as <0.5 mV and scar as <0.1mV. The upper left panel shows voltage maps during SR with Standard Configuration and with HD Wave Solution. The upper right panel shows voltage maps during CS pacing with Standard Configuration and with HD Wave Solution. Voltage map during CS pacing shows less LVZ extent than that during SR both in Standard Configuration and HD Wave Solution. In addition, the voltage map during SR with HD Wave Solution was comparable to that during the index procedure ([Figure 8]) except for pulmonary vein antral lesions. Lower panel shows activation sequence map during AT (cycle length 233ms), which revealed counter-clockwise rotation at the anterior wall. Post-pacing interval was identical to the AT cycle length at the sites with green dot. The AT was successfully terminated at the site indicated by the yellow arrow and red tag, which showed continuous fractionated potential lasting 109 ms. Thereafter, perimitral AT and roof reentrant AT were also induced. LVZ homogenization resulted in creation of anterior mitral isthmus line and roof line. A conduction gap identified at the anterior carina of left superior pulmonary vein was also ablated. Finally, non-inducibility of any tachycardia during isoproterenol infusion was confirmed.

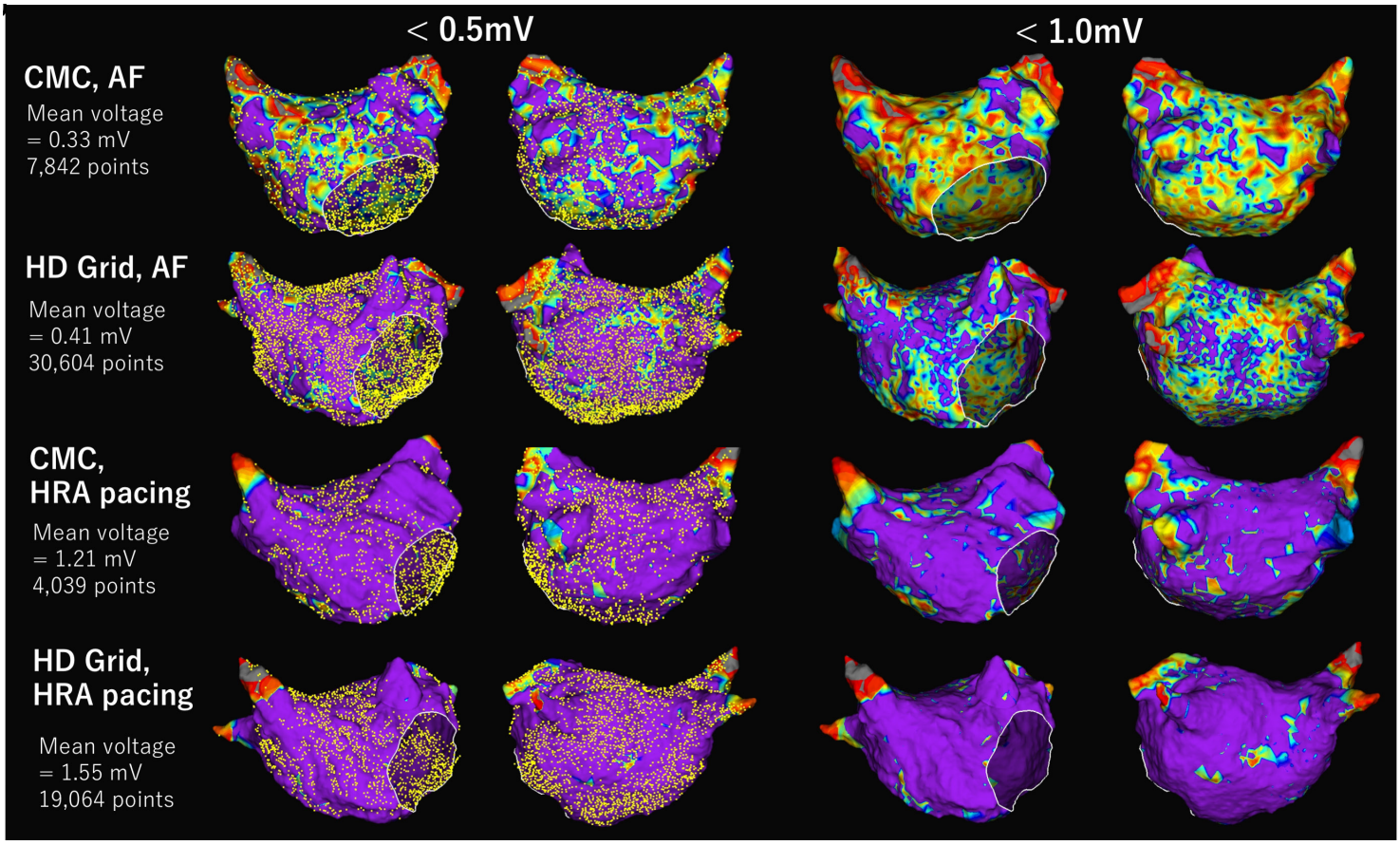

Figure 10: Comparison of high-density voltage map in the left atrium (LA) during atrial fibrillation (AF) and high right atrium (HRA) pacing using circular mapping catheter (CMC) and a grid mapping catheter in a different voltage threshold of <0.5mV and <1.0mV in a 63 years old male with long-lasting persistent AF. For voltage mapping during AF, a peak-to-peak bipolar voltage was collected in a roving acquisition time interval of AF cycle length (160 ms) using HD Wave Solution, and ultra-high-density mapping was performed for 10 minutes for each voltage map. Using CMC, about 8,000 mapping points were obtained. With the threshold of <0.5 mV, LVZ was observed diffusely but predominantly in the anterior wall. With the threshold of <1.0 mV, the whole LA was covered by LVZ. On the other hand, using HD Grid, over 30,000 mapping points were acquired in the same mapping time (10 minutes). Only limited LVZ was observed at the posterior wall at the threshold of <0.5 mV, and diffuse but less extent of LVZ was observed at <1.0mV compared to CMC. The mean voltage was higher in the HD Grid map (0.41 ± 0.28 mV vs. 0.33 ± 0.14 mV). Voltage map during HRA pacing (120 beats per minute) at the site close to sinus node was also created. With the threshold of <0.5 mV, LVZ was not identified using both CMC and HD grid. With the threshold of <1.0 mV, only patchy LVZs were identified in both mapping catheters. The mean voltage during HRA pacing was also higher in the HD Grid map (1.56 ± 0.80 mV vs. 1.21 ± 0.19 mV).

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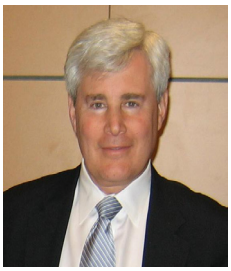

Dr. James A. Reiffel, MD

Professor Emeritus of Medicine at Columbia University College of Physicians and Surgeons; and, Attending Physician [Emeritus] at Presbyterian Hospital in New York City; Department of Medicine, Division of Cardiology, Section of Electrophysiology.

Dr. Noel G. Boyle, MD, PhD

Professor of Medicine,
Director of Cardiac EP Fellowship Program,
UCLA Health System and David Geffen School of Medicine at UCLA

Dr. Serkan Cay, MD

Dr. Serkan Cay is an associate professor of Cardiology at the University of Health Sciences, Ankara, Turkey. He received his M.D. from Hacettepe University and eventually became cardiology specialist at the cardiology center of Yuksek Ihtisas Heart-Education and Research Hospital in 2007. After his 5-year career as a specialist there, Dr. Cay became an associate professor at the cardiology center of Yuksek Ihtisas Heart-Education and Research Hospital in 2012. In addition to teaching, Dr. Cay is a member of Division of Arrhythmia and Electrophysiology. He currently resides in Ankara with her wife and their 2 children. He can be contacted at cayserkan (at) yahoo (dot) com.

Dr. Vedat DAVUTOGLU, MD, PhD

Mustafa Yildiz is working at the Deparment of Cardiology at Istanbul University Cardiology Institute, Istanbul/Turkey. Having completed M.D. at School of Medicine, Gazi University, Ankara/Turkey in 1995. He specialized in Internal Medicine, Cardiology and Physiology (Ph.D.). His major research areas are cardiac electrophysiology and ablation, interventional cardiology, cardiovascular physiology, exercise physiology, cardiac imaging (especially real-time 3D transoesophageal echocardiography) and cardiovascular Biomedical Engineering.

Dr. Ashraf Alqaqa, MD, FACC

Dr. Farhad Farokhi received his medical degree from the Kansas City University of Medicine & Biosciences. He finished his internal medicine residency at the Grandview Hospital in Dayton, OH. He currently holds board certification in Cardiovascular Disease and Clinical Cardiac Electrophysiology from the American Osteopathic Board of Internal Medicine, Internal Medicine from the American Osteopathic Board of Internal Medicine, and Echocardiography from the American Society of Echocardiography. Dr. Farokhi's clinical interests include Atrial Fibrillation, Catheter Ablation, Ventricular Arrhythmia, and Left Atrial Appendage Closure (LARIAT).

Dr. Hickey

Dr. Hickey is an Associate Professor of Nursing at Columbia University Medical Center and holds a joint appointment in the Division of Cardiology (electrophysiology) as both a family and adult nurse practitioner. Her interdisciplinary research, clinical practice and scholarship is focused in the areas of cardiac genetics, the clinical care of those with chronic cardiac conditions and arrhythmias, and the prevention of sudden cardiac death. Her current grant awards include a R01 from the National Institute of Nursing Research (iHEART) focusing on arrhythmia telehealth monitoring in those with atrial fibrillation, her newly awarded (multiple-PI) P30 award with Dr. Suzanne Bakken is focusing on improving symptom self-management for underserved populations with or at risk for chronic health conditions.

Dr. Hussam Ali, MD, FESC

University Master in Cardiac EP & Pacing. EHRA Certified Electrophysiology Specialist (ECES1, ECES2). Current affiliation: Cardiac Electrophysiologist, Arrhythmia & EP Unit II, Humanitas Gavazzeni Clinics, Bergamo (BG), Italy. Major interests: catheter ablation and arrhythmia mapping, WPW, pacing maneuvers, subcutaneous ICD.

Dr. Stefan Peters, MD

St.Elisabeth Hospital gGmbH Salzgitter, Germany.

Dr. Atul Verma, MD

Electrophysiologist Dr. Atul Verma has been awarded the first ever Southlake Regional Health Centre Research Award of Excellence.

Dr. Aleksei Kulikov, MD

Cardiologist-Interventional Arrhythmologist in Russian Cardiology Research and Production Complex. His interests are in the field of electrophysiology, arrhythmology, implantable electronic devices, sudden cardiac death, cardiomyopathies and syncope. Prior research on atrial fibrillation and ways of its surgical treatment.

Dr. Tobias Haber, MD

Electrical Engineer and deputy director of Peter Osypka Institute for Pacing and Ablation at Offenburg University of Applied Sciences, Germany. Actually his postgraduate research focusses on engineering solutions for educational simulations on electrostimulation and radiofrequency-ablation and provides trainings for medical engineering students, fellows and practicing physicians. This work was awarded by the German Association for the Promotion of Science and Humanities as innovation in university education.

Dr. Justin Hayase, MD

Fellow in Cardiovascular Medicine,
UCLA Health System and David Geffen School of Medicine at UCLA