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Atrial Fibrillation Awareness – How do we tackle a global epidemic ?

Dhanunjaya Lakkireddy, Andrea Natale

Dear Colleagues

Welcome to the Fall issue of the Journal of Atrial Fibrillation. Thank you for your fight against the global epidemic of Atrial Fibrillation (AF). September was the AF month with several activities organized all over the world. There were educational lectures, awareness walks, yoga sessions and many other activities to raise the AF awareness in the community. A lot of you have been part of this mission with single goal of eliminating AF.

Congratulations are to the Global AF Alliance (GAFA) Foundation, Heart Rhythm Society (HRS) and ACC for launching a very effective AF awareness campaign last month It takes unfettered commitment from all fronts to fight this 21st century epidemic.

While our understanding of AF and its maladies continue to get better the tools to manage them are slowly but steadily improved. AF ablation remains a very important tool in out therapeutic armamentarium. Our ability to tackle non-paroxysmal AF has been limited. In addition to the pulmonary vein isolation several adjunctive strategies have been tested and failed. Complex fractionated electrograms, linear lines, rotor ablation and more have been tried without much success. Our ability to understand the pathophysiology and substrate evolution with the progressive AF will remain the next best hope. Several new options in the form of left atrial appendage (LAA) occluders for anticoagulation eligible high-risk patients have proven to be very promising. The explosion of patient driven diagnostics include Apple Watch have opened gates to the data deluge that we need to figure out now. Like with many other disruptive technologies we need to figure out how to utilize them effectively identifying processes that will continue to improve patient care.

This issue of the journal has several interesting original and review articles worth spending time on. We once again appreciate your support to the journal and look forward to your contributions to the field.

Another big announcement is that I will be signing off as the chief editor of the journal starting November 2018. Dr. DJ Lakkireddy will take over as the next Editor-in-Chief for JAFIB. Dr. Lakkireddy has been the associate editor for all these years and has vast experience in running the journal. There will be a significant revamp in the structure and platform. Your continued support is much appreciated.

contrarian agreed that he will consider ablation if he were to develop symptomatic AF. While meaningful scientific discourse is important, pragmatic approaches to cure diseases is our responsibilities as the takers of the Hippocratic Oath. The full manuscript on this study will hopefully come out soon and address the many unanswered questions..

Best wishes

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Assessment of DNA Damage After Ionizing Radiation Exposure in Patients Undergoing Cardiac Resynchronization Therapy Device Implantation or Atrial Fibrillation Ablation (The RADAR Study)

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Abstract

Background: There is limited data regarding effect of prolonged radiation exposure during electrophysiological (EP) procedures on direct DNA damage. Comet test has shown to assess DNA damage following radiation exposure.

Methods : We performed a single-center prospective observational study assessing direct DNA damage using the quantitative comet assay in patients undergoing cardiac resynchronization (CRT) and atrial fibrillation (AF) catheter ablation procedures. Venous comet assay was performed pre, immediately post procedure and at 3-month duration in twenty-two (N=22) patients who underwent catheter ablation for symptomatic AF and fourteen (N=14) patients who underwent CRT implantation.

Results: The median [interquartile range (IQR)] fluoroscopy time, radiation dose and dose area product (DAP) were 34.3 (27.97 – 45.48) minutes, 853.07 (611.36 - 1334.76) mGy and 16,994.10 (9,023.65 – 58,845.00) UGym2 in the ablation group and 30.05 (18.75 - 37.33) minutes, 345.00 (165.09 - 924.79) mGy and 11,837.20 [7182.67 - 35567.75] UGym2 in the CRT group. When compared with pre-procedure, there was a statistically significant increase in median (IQR) DNA migration on comet assay in the ablation group immediately post procedure [+6.55 µm (0.78, 10.25, p=0.02)] that subsequently decreased at 3 months [-1.00 µm (-2.20, 0.78), p=0.03] but not in the CRT group.

Conclusions: There was a significant increase in DNA damage as detected by comet assay immediately post procedure that normalized at 3 months in patients undergoing AF ablation. Further large prospective studies are warranted to evaluate the impact of this prolonged radiation exposure and DNA damage on long-term follow up.

Introduction

Electrophysiology (EP) procedures such as cardiac resynchronization therapy (CRT) and radiofrequency catheter ablation (RFA) have undergone significant expansion in the last decade and are widely performed for the management of congestive heart failure and atrial fibrillation (AF). Despite, the advent of electroanatomical mapping and 3-D technology both CRT and AF ablation are associated with prolonged procedural and fluoroscopy times, exposing patients and operators to substantial amounts of radiation[1,2]. The estimated effective radiation dose with AF ablation ranges from 15 - 100 milliSievert (mSv) and 2 – 95 mSv with CRT implantation which is equivalent to the radiation dose of 50 – 5000 chest radiographs[3]. Furthermore, cumulative radiation exposure was associated with increased risk of all-cause cancer and mortality in both patient and operators[4,5].

These radiation effects are due to direct and indirect DNA damage by formation of free radicals[6] and through various mechanisms including direct DNA breaks, breaks in cross bridges between DNA and proteins and denaturation of proteins, purines and pyrimidines bases[7]. It is estimated that each Gray unit (1 gray = 1000 mSv) of radiation exposure can cause approximately 20 DNA-DNA cross linkages, 40 double strand breaks, 150 DNA-protein cross links, 160-320 non-double stranded breaks clustered DNA damage, 1000 single strand breaks and >1000 DNA base damage per cell[7-9]. Total accumulated dose of radiation exposure has been associated with chromosomal aberrations due to defective DNA repair and increased risk of carcinogenesis and mutagenesis[7,10].

The blood comet assay is a single-cell gel electrophoresis technique that has emerged as a standard method for assessing direct DNA damage in circulation eukaryotic cells (lymphocytes and monocytes) in subjects exposed to radiation by various cytogenetic,

Key Words

Comet Assay, DNA Damage, Radiation Exposure, Cardiac Resynchronization Therapy, Catheter Ablation, Atrial Fibrillation

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biotechnological and epidemiological studies[11-16]. In this current era of aging population undergoing multiple EP procedures, there is limited data regarding the extent of direct DNA damage from prolonged radiation exposure. The purpose of this study was to estimate the extent of direct DNA damage in patients undergoing two commonly performed procedures (CRT implantation and AF ablation) that requires substantial amount of radiation by using the blood comet assay.

Methods

Study Design

This is a single center, prospective sequential observational study to detect DNA damage occurring from prolonged radiation exposure in patients undergoing AF ablation and CRT implantation by using a blood comet assay. The study included 22 consecutive patients undergoing AF ablation and 14 consecutive patients undergoing CRT implantation. Patient who gave informed consent were enrolled in the study. The study was approved by the local Institutional Review Board. Complete medical history, medications and demographics were extracted from review of electronic medical records.

The study inclusion criteria were age ≥18 years and patients undergoing CRT implantation or AF ablation for standard indications. Exclusion criteria were subjects with any prior radiation therapy, history of cancer, active infection, prior chemotherapy, prior electrophysiological study or cardiac catheterization or CT scans in the last year. Patients with a history of occupational exposure to radiation were also excluded.

The primary end point was assessment of direct DNA damage estimated by distance of DNA migration on the alkaline comet assay immediately post-procedure and at 3-month duration compared with pre-procedure. The extent of DNA damage was assessed by distance of DNA migration (total length of the comet - diameter of the nucleus) on the comet assay using fluorescence microscopy. All patients were followed in clinic at 2 weeks and 3 months' duration

Atrial Fibrillation Ablation

All patients underwent standard catheter ablation procedure for symptomatic drug refractory AF (both paroxysmal and persistent). Briefly, the procedure was performed under general anesthesia using femoral vein access. The procedure required frequent repositioning of the camera between AP (anterior-posterior), LAO (left anterior oblique) and RAO (right anterior oblique) views to locate catheter placement and obtain transeptal access. Two transeptal punctures were made into the left atrium using intracardiac echocardiography, fluoroscopy and electromagnetic mapping system such as CARTO (Biosense Webster Inc.) or the NavX mapping system (St. Jude Medical). A standard Lasso/Pentaray (Biosense Webster Inc., Diamond Bar, California) or Spiral (St. Jude Medical, Minneapolis, Minnesota) catheters were used for mapping the left atrium. A 3.5 mm. open tip- irrigated ablation catheters (ThermoCool, Biosense Webster Inc; Tacticath, St.Jude Medical) was used for ablation. A 3-dimensional geometry of the left atrium was reconstructed using the mapping system. All patients underwent antral pulmonary vein isolation. Additional ablation of the cavotricuspid isthmus, roof line, posterior wall, mitral isthmus line and left atrial appendage ablation was at the discretion of the operator.

Cardiac Resynchronization Therapy

All patients underwent either a denovo CRT implantation or an upgrade for standard indications. The procedure technique was similar in all patients. Briefly, the procedure was performed with moderate sedation and local anesthesia. In patients undergoing denovo CRT – the cephalic vein cut down was performed in all patients for insertion of the right ventricular and right atrial lead while the axillary or subclavian was accessed with a micro puncture needle for implantation of the coronary sinus (CS) lead. A CS venography was performed just prior to cannulation with the CS lead which was inserted by over the wire technique. The procedure was performed under fluoroscopy. Majority of the procedure require AP (anterior-posterior) views but LAO (left anterior oblique) and RAO (right anterior oblique) were frequently used for CS cannulation based on operator preference.

Blood Sampling

A 10 milliliter (ml.) venous blood sample was collected 30 – 60 minutes prior to starting of the EP procedure. The subjects served as their own controls and another 10-ml. blood sample was collected immediately at the conclusion of the procedure and at 3 months follow up. The blood samples were processed in the epigenetics laboratory and blood comet assays were performed on all collected samples.

Laboratory Testing

The technique of alkaline comet assay has been described in great detail previously[13,17]. This technique of assessing DNA damage to cells has been used previously in personnel who were exposed to occupational radiation[16,11]. Venous blood sample has been selected for use in our study since, the average procedure times for EP procedures with conventional modalities is about 142 ± 55.8 minutes and the fluoroscopic time is about 21.2 ± 4.8 minutes. This time would be sufficient to cause irradiation of all the circulating blood cells in the body. The procedure consists of preparation of the buffy coat from the peripheral blood sample. The blood sample is spun at 1500 rpm for 30 minutes and the mononuclear lymphocytes are aspirated from the junction of plasma and lymphocyte preparation media. A microscopic slide was then layered with normal melting point agar (NMPA) and allowed to cool down. In a separate centrifuge tube, the lymphocytes were mixed with NMPA. This mixture was then layered over the agar based glass. A third layer of NMPA was added over the lymphocyte agar layer. The cells were then lysed using a lysis solution. Once the cells lysed, the slide was then run through gel electrophoresis system for 30 minutes. Electrophoresis was performed at 25 V and 300 mA for 20 minutes following which the slides were neutralized with 0.4 M Tris (pH 7.5) and stained with 50 µL of ethidium bromide (20 µg/mL). Slide analysis was performed using a fluorescence microscopy (Olympus. 40x objective lens).

A comet analysis software [CometScore Pro (Tritek Corp, VA)] was used to estimate head diameter (nucleus), comet length and tail length. A total of 100 randomly captured comets from each individual slide were studied and the average of these 100 comets for comet tail length, tail movement, comet head diameter and length of

comet were collected. Despite, several techniques of estimating DNA damage have been previously described including – tail length, head optical intensity, tail distribution moment etc, the extent of DNA damage in this study was assessed by distance of DNA migration (total length of the comet - diameter of the nucleus) on the comet assay using fluorescence microscopy. This technique is a widely accepted method of measurement[18].

[Figure 1 (A,B,C)] demonstrates pre-procedural and post procedural comet assay and how the comet length analysis was performed. Before, after radiation exposure and at 3-month duration the comet parameters were compared. The entire procedure of

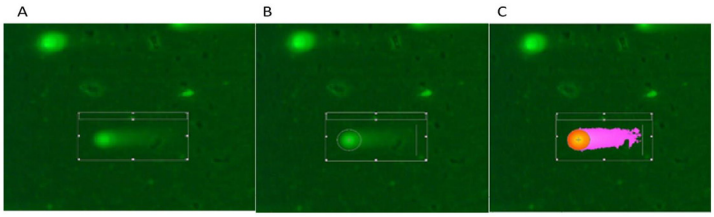

Figure 1: **Figure 1(A,B,C). Figure 1A, 1B, 1C: Fluorescence microscopy images and measurement of comet assay migration using a comet analysis software. A) The automated comet analysis software first randomly identifies a comet B) then estimates the comet head/nucleus and C) then separates the nucleus (red/orange) and the tail (pink) to calculate the comet length which is the difference between the whole comet length and the diameter of the nucleus.**

preparing the comet assay slides and reading was performed at the Center for Epigenetics and Stem Cell Biology at The University of Kansas. To ensure uniformity, the available standardized protocol for blood comet assay was adapted.

Statistical Analysis

Categorical data were represented as counts (percentage) and continuous data as either mean (standard deviation) or median [interquartile range], if assumptions of normality were not met. We compared the baseline characteristics of patients who underwent AF ablation with CRT implantation. Proportions were compared using Chi-square test. Group means were compared using Welch two sample t test, or Fisher exact test as appropriate. For non-normally distributed data, hypothesis testing was performed using Kruskal-Wallis rank sum test. Standardized mean differences between the groups were reported for all the baseline co variates. We calculated the change in comet assay measurement immediately post procedure and at three months follow up from the baseline, for each patient and reported summary statistics as median [IQR] for each cohort (AF ablation & CRT implantation). Hypothesis testing was performed using Wilcoxon signed rank test for paired samples. We used "lme4" package in R to create a linear mixed effects model to investigate within subject variance (Supplementary [Table S1],[Figure S1]). We performed a pairwise correlation plot to examine the relationship between post procedure change in comet assay, age, BMI, procedure time, fluoroscopy time, radiation dose, and DAP to visualize and investigate significant correlations in the entire cohort. We performed linear regression to identify significant predictors of post procedure change in comet assay value. All statistical analyses were performed on mac OS Sierra (version 10.12.6) using R statistical computing program (version 3.3.2; Vienna, Austria).

Table S1: **Linear mixed model fit by REML ['lmerMod'];**

Formula: Comet Assay ~ TIME + PROCEDURE + (1 | PTID); Data: radarData_long REML criterion at convergence: 871.6; Number of obs: 108, groups: SNO, 36

Random Effects:			
Groups	**Variance**	**Std.Dev.**	
PTID	183.9	13.56	
Residual	123.8	11.13	
Fixed effects:	**Estimate**	**Std.Error**	**t value**
(Intercept)	24.7642	2.5651	9.654
TIME1	-0.6874	1.5141	-0.454
TIME2	5.7587	1.5141	3.803
PROCEDURE1	-8.1068	2.5651	-3.16
Correlation of Fixed effects:	**(Intr)**	**TIME1**	**TIME2**
TIME1	0.0000		
TIME2	0.0000	-0.5000	
PROCEDURE1	-0.2220	0.0000	0.0000

Results

Baseline and procedural characteristics

AF ablation group included patients with a mean age of 65.09±9.15 years with a BMI of 31.7±9.4. CRT group included patients with a mean age of 67.8±11.8 years and a BMI of 31±3.9. Patients underwent denovo CRT in 66% and upgrade in 33% of patients. [Table 1] demonstrates the baseline characteristics of patients in both the groups. The median (IQR) fluoroscopy time in AF ablation and CRT group were 34.30 [27.97, 45.48] and 30.05 [18.75, 37.33] minutes respectively.

Comet Assay Testing

[Table 2] demonstrates the comet tail migration measurements before the EP procedure, after and at 3-month duration. Pre-procedural, immediately post – procedure and 3 - month median (IQR) DNA migration in the AF ablation group was 12.55 [8.85, 20.38] µm, 16.70 [12.22, 25.85] and 12.90 [7.25, 19.27] while in the CRT group was 20.70 [13.85, 54.62] µm, 29.66 [13.95, 67.08] and 19.15 [11.38, 39.58] respectively. In the AF ablation group, there was a significant increase (6.55 [0.78, 10.25] µm, p=0.02) in the median comet tail migration measurements pre-procedure vs. immediately post-procedure. Furthermore, the comet migration distance decreased but remained statistically significant (-1.00 [-2.20, 0.78] µm, p=0.03)

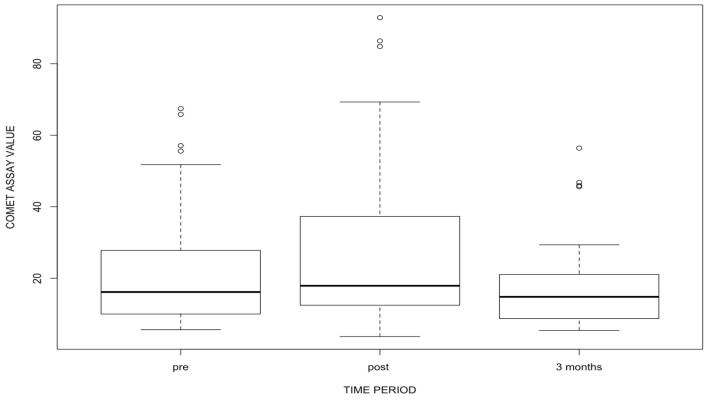

Figure S1: **Box plots demonstrating distribution of comet assay values pre-procedure, post procedure and at 3 months follow up.**

Table 1: Baseline demographics and procedural characteristics of patients in the study. SMD – Standard mean difference, AF – atrial fibrillation, CRT – cardiac resynchronization therapy, IQR – interquartile range.

Baseline Characteristics	AF Ablation (n = 22)	CRT(n = 14)	P value	SMD
Age (Years) (mean [sd])	65.09 (9.15)	67.86 (11.86)	0.436	0.26
Female (%)	6 (27.2)	4 (28.5)	0.8	0.21
Caucasian (%)	20 (90.9)	9 (64.3)	0.125	0.67
Body mass index (mean [sd])	31.74 (9.37)	30.16 (3.98)	0.556	0.22
Hypertension (%)	15 (68.2)	10 (71.4)	1	0.07
Diabetes (%)	6 (27.3)	3 (21.4)	1	0.14
Coronary disease (%)	7 (31.8)	11 (78.6)	0.017	1.07
Myocardial infarction (%)	3 (13.6)	3 (21.4)	0.878	0.21
Coronary bypass surgery (%)	3 (13.6)	3 (21.4)	0.878	0.21
Chronic kidney disease (%)	3 (13.6)	3 (21.4)	0.878	0.21
Heart failure (%)	10 (45.5)	7 (50.0)	1	0.09
Cardiomyopathy (%)				
Ischemic	3 (13.6)	4 (28.6)		
Non-ischemic	7 (31.8)	3 (21.4)		
Sleep apnea (%)	8 (36.4)	5 (35.7)	1	0.01
Chronic obstructive pulmonary disease (%)	3 (13.6)	5 (35.7)	0.253	0.53
Cerebrovascular accident (%)	1 (4.5)	0 (0.0)	1	0.31
History of Alcohol (%)	12 (57.1)	5 (35.7)	0.369	0.44
History of smoking (%)	13 (59.1)	6 (42.9)	0.543	0.33
Procedure time (minutes) (median [IQR])	152.00 [130.00, 200.00]	148.50 [125.75, 191.50]	0.849	0.17
Fluoroscopy time (minutes) (median [IQR])	34.30 [27.97, 45.48]	30.05 [18.75, 37.33]	0.375	0.39
Radiation dose(mGy) (median [IQR])	853.07 [611.36, 1334.76]	345.00 [165.09, 924.79]	0.095	0.92
Dose – Area Product (UGym2) (median [IQR])	16994.10 [9023.65, 58845.00]	11837.20 [7182.67, 35567.75]	0.524	0.28

at 3-month duration when compared with pre-procedure.

In the CRT group, there was a substantial increase (2.43 [- 1.90, 7.11] µm, p=0.17) in median (IQR) comet tail migration immediately post-procedure vs. preprocedural which was not statistically significant. The post procedural comet migration decreased (- 0.70 [- 4.39, 0.62] µm, p=0.17) at 3-months.

We performed a pairwise correlation plot to examine the relationship between post procedure change in comet assay with other variables of interest such as age, BMI, procedure time, fluoroscopy time, radiation dose, and DAP and did not notice any significant correlation when examined in the entire cohort. Linear regression analysis using change in comet assay value as dependent variable also did not demonstrate any significant predictors such as age, BMI, smoking, alcoholism, procedure time, fluoroscopy time, radiation dose and DAP on the outcome.

Discussion

Main findings

In the present study, we investigated DNA damage in a group of 22 patients undergoing AF ablation and another 14 undergoing CRT implantations with no prior significant radiation exposure at a tertiary care teaching hospital. There was a significant increase in

Table 2: Change in comet assay post – procedure and 3 months compared with pre – procedure. AF – atrial fibrillation, CRT – cardiac resynchronization therapy, IQR – interquartile range.

Procedure	Change in Comet Assay	P value
AF ablation (n = 22)		
(Immediate post procedure – pre-procedure)	6.55 [0.78, 10.25]	0.02304
(3 months post procedure – pre-procedure)	-1.00 [-2.20, 0.78]	0.03482
CRT implantation (n = 14)		
(Immediate post procedure – pre-procedure)	2.43 [- 1.90, 7.11]	0.1726
(3 months post procedure – pre-procedure)	- 0.70 [- 4.39, 0.62]	0.1726

comet tail migration immediately post-procedure which normalized at 3-months duration in patients undergoing AF ablation but this change was not statistically significant in patients undergoing CRT implantation.

The comet assay is a well-established molecular technique in biomonitoring and estimation of DNA damage in patients exposed to radiation[11-13,19,20,16]. Singh et al. first demonstrated that comet assay when used under alkaline conditions, it was reported to be more sensitive for detection of alkali labile sites and assess both double- and single-stranded DNA breaks[21]. Comet assay is also one of the measuring techniques of European Standards Committee on Oxidative DNA Damage (ESCODD) and measures DNA breaks allowing fraction of DNA to migrate under electrophoresis towards the anode, forming a comet tail in which the percentage of DNA in the tail reflects the break frequency[16,22]. There are several advantages of assessment of radiation induced DNA damage using the comet assay – First, the test is highly sensitive in detection of radiation induced DNA damage with a reported detection limit of 5 cGy gamma rays in human lymphocytes. Second, the test estimates DNA damage at the cellular level (circulating lymphocyte/monocytes). Third, the test is easy to perform, cost – effective and not time consuming. The possibility that the test may have higher specificity in a subgroup of patients and type of cells remains an area of further investigation[23].

Some studies have reported elevated DNA damage among interventional cardiologists exposed to prolonged and cumulative radiation exposure, suggesting the need for adequate measures to protect and prevent health care personnel who work in areas of prolonged radiation exposure[24]. Another study reported significant DNA damage as measured by increase in comet tail length after a work day of occupational exposure among nuclear medicine and radiology workers[11]. Similarly, there is evidence regarding DNA damage reported in patients undergoing diagnostic and therapeutic radiation testing or interventions[25,26]. It is also estimated that a cumulative dose exposure of 100 mSv may additionally increase the risk of cancer of 1 in 100 patients, this dose can be reached in a patient undergoing 1-2 EP procedures[2].

However, currently there is no data regarding extent of direct DNA damage in patients undergoing EP procedures which require prolong fluoroscopy and radiation exposure. To the best of our knowledge, this is the first study investigating the effects of radiation exposure on direct DNA damage in patients undergoing EP procedures. Although, our results demonstrate that there was a substantial increase in post-procedural DNA migration in terms of absolute distance in patients undergoing both procedures which

reversed at 3-month duration, these findings were only statistically significant in the AF ablation group. The limited power of 14 patients in the CRT group could be a potential explanation for the lack of statistical significance as we observed a similar trend in comet assay values as the AF ablation group. The normalization in comet assay migration at 3 months duration is likely due to process of DNA repair which includes cell cycle arrest, apoptosis etc. minimizing genomic instability[27]. Furthermore, all patients undergoing EP procedures showed large inter-individual variation in comet tail migration that was considered inherently unique to that particular patient. However, the comet tail measurement values pre-and post-procedure were within that particular range for each individual. The amount of radiation exposure observed in this series in somewhat higher, especially in an era of 3-D mapping and intracardiac echo. The reason being - (1) Some patients with persistent AF underwent extensive ablation as described, (2) Anatomical variations observed with coronary venous system and (3) majority of cases were performed by house staff including electrophysiology fellows.

A previous study showed a significant correlation between age and DNA damage as estimated by comet assay in workers with occupational exposure[20]. We performed a pairwise correlation plot to examine the relationship between post procedure change in comet assay and variables of interest such as age, BMI, smoking, alcoholism, procedure time, fluoroscopy time, radiation dose, and DAP and did not notice any significant correlation when examined in the entire cohort. In theory, we expect to notice increased damage form increased radiation dose but did not notice any strong correlation which can be attributed to the small sample size. This difficulty in establishing a correlation between radiation dose and DNA damage with comet assay has been reported previously, especially in cases with modest radiation exposure[28,20,16]. Previous studies have also demonstrated that smoking and alcoholism significantly increases DNA damage in individuals[29,31]. We performed linear regression using change in comet assay value as dependent variable and did not notice any significant predictors of the outcome including age, gender, history of smoking or alcoholism. The small sample size is the likely explanation for the findings.

Limitations

Our study has a few limitations that needs consideration. First, this is a prospective non-randomized study with limited sample size. Second, in spite of the prolonged fluoroscopy exposure, circulating blood cells may have a variable radiation exposure which can impact DNA migration on comet assay. Third, other confounding factors that could impact our results by potentially causing DNA damage and limit the ability for repair include medications, diagnostic testing, endogenous infections and poor nutritional status. Fourth, there is inter-individual variability in DNA migration with the comet assay which is unique for that individual. Fifth, these results do not apply for patients undergoing multiple EP procedures, where cumulative radiation exposure may impact DNA damage. Sixth, we did not assess other described methods such as comet head and tail intensity and tail movement for estimating DNA damage but overall, comet length is a widely-accepted method of estimating DNA damage. Finally, the differences in DNA damage in the AF ablation group cannot rule out the possibility of non – fluoroscopy related damage from the ablation itself, prior cardioversions and antiarrhythmic medications. However, currently there is a lack of data regarding the impact of local ablation on systemic DNA damage, especially in circulating eukaryotic cells as measured by the venous comet assay. Local cardiac comet assay measurements may shed further light into this issue. Despite, the limitations our pilot study provides valuable insights on the effect of prolonged radiation on direct DNA damage in patients undergoing CRT implantation and AF ablation and the continued need for radiation hygiene and protection. Further large prospective studies are warranted to evaluate the impact of this prolonged radiation exposure and ablation procedures on systemic DNA damage in both operators and patients exposed to multiple procedures on long term follow up.

Clinical Implications

It appears that most of the DNA damage in the immediate aftermath of the procedure is self-correcting at 3 months duration in this small group of patients and that there is a lack of permanent damage to the progenitor cells given the relatively short lifespan (few weeks to months) of any individual lymphocyte and monocyte. In the advent of significant DNA damage, some cells continue to persist and undergo mutagenesis resulting in cancer. Even though it is reassuring to see that the impact of fluoroscopy mediated radiation at 3 months it is still very important to minimize the radiation exposure. The ability of the human body to repair/replace cells diminishes with advancing age as it is governed by molecular, biochemical and genetic factors. Hence, these changes can be more profound in older patients undergoing AF ablation and CRT implantation being exposed to radiation exposure, especially those undergoing multiple procedures. Knowledge regarding the extent of DNA damage in patients undergoing electrophysiological procedures is important not only in helping patients make education informed decisions regarding repeat procedures but also the operator to be responsible regarding minimizing radiation exposure. Further studies are required to systematically evaluate the impact of radiation exposure on DNA damage in patients undergoing multiple electrophysiological procedures.

Conclusion

There was a significant increase in DNA damage as detected by comet assay immediately post procedure that resolved at 3 months in patients undergoing AF ablation. Further large prospective studies are warranted to evaluate the impact of this prolonged radiation exposure and DNA damage on long term follow up.

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Acute Pulmonary Vein Reconnection after Ablation using Contact-Force Sensing Catheters: Incidence, Timing, and Ablation Lesion Characteristics

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Abstract

Background: Acute pulmonary vein (PV) reconnection predicts atrial fibrillation (AF) recurrence after ablation. Contact-force (CF) sensing catheters improve lesion delivery. We assessed the incidence, timing, location, and lesion characteristics of acute reconnection after PV isolation with CF sensing catheters.

Methods: Patients undergoing radiofrequency ablation for AF from October 2016 to February 2017 were studied. Assessment for acute reconnection at 20 and 40 minute intervals was performed in each isolated PV. Additional lesions were applied as needed. Lesion location, contact force, power, duration, impedance, and force-time integral values were compared at sites with and without reconnection.

Results: Twenty-two patients (60.6 + 1.8 years; 36.4% female; 27.3% persistent AF; CHA2DS2VASC 1.9 + 0.3) were included. Eighty-eight veins were isolated. Eleven reconnections occurred in 10 patients; 9 occurred by 20 minutes and 2 between 20 - 40 minutes. Most reconnections (6/11) were in the left superior PV. Of 4993 ablation points analyzed, 72 were at acute reconnection sites, and no differences in average contact force (11.4 + 8.1 vs 11.3 + 7.1 gm, p=0.868), power (29.7 + 3.9 vs 29.9 + 4.6 watts, p=0.620), impedance (64.1 + 60 vs 72.5 + 60, p=0.236) and the force time integral (86.9 + 78.8 vs 99.7 + 100 gm/sec, p=0.282) were found.

Conclusion: Acute PV reconnection rates using CF sensing catheters are roughly 12.5%, with the majority occurring within 20 minutes. We found no significant differences in characteristics of ablation points in areas of reconnection. Optimum wait periods after isolation to check for acute reconnection may be as brief as 20 minutes.

Introduction

Catheter ablation is the cornerstone of rhythm management in patients with drug refractory symptomatic atrial fibrillation (AF)[1] Durability of pulmonary vein isolation (PVI) is important to procedural success; both acute and late pulmonary vein (PV) reconnection have been associated with atrial fibrillation recurrence[2,3]. Multiple studies have reported a high rate of PV reconnection within 60 minutes of initial isolation[4-6]. Indeed, it is because of this acute reconnection phenomenon that both the 2012 and 2017 Heart Rhythm Society Expert Consensus Statements on catheter ablation of AF recommend a 20 minute observation period and reassessment of PV sleeve conduction following initial PV isolation[1,7]. Of note, these recommendations were made based on reconnection data obtained during RF ablation with non-force sensing ablation catheters.

Catheter systems capable of providing contact force data likely facilitate improved lesion delivery[8,9] during AF ablation. Whether a 20 minute waiting period and PV reassessment is still needed after initial isolation in the era of force sensing catheters remains largely unanswered. Data regarding PV reconnection patterns in the current era has important clinical relevance, as it may allow for procedures to be simplified and streamlined. In the present study, we aim to assess the incidence and timing of acute PV reconnection during catheter ablation using contact force sensing catheters, and to assess any differences in lesion characteristics at sites of acute PV reconnection in comparison to sites of effective ablation.

Key Words

Contact-Force Sensing Catheter, PV Reconnection, Atrial Fibrillation Ablation

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Methods

Patients undergoing CF-guided catheter ablation for AF at Johns Hopkins Hospital between October 2016 and February 2017 were included in the study as part of a prospective database. All patients included in the current study were undergoing index procedures for either paroxysmal (n=14) or persistent (n=8) AF. All participants signed written informed consent and the study was approved by the institutional review board at Johns Hopkins hospital.

Ablation Procedure

Ablation was performed under general anesthesia, with pre-procedure trans-esophageal echocardiogram done in patients deemed high-risk for LAA thrombus. Femoral site access was obtained with placement of three venous vascular sheaths followed by advancement

of catheters in the coronary sinus and His bundle for measurement of intracardiac electrograms and conduction. Intravenous heparin was administered to maintain activated clotting time (ACT) >350 seconds. After performing a double trans-septal puncture, a Lasso circular mapping catheter (Biosense-Webster, Inc., Diamond Bar, CA) was positioned in the left atrium. An electroanatomic map of the left atrium was obtained using the CARTO System (Biosense-Webster, Inc., Diamond Bar, CA), and superimposed on pre-acquired CAT-Scan or MRI images. A 4mm open-tip irrigated RF Catheter with CF sensor (Thermocool SmartTouch, Biosense-Webster Inc., Diamond Bar, CA) was then positioned in the left atrium: Wide area circumferential ablation of pulmonary veins was performed, with carinal ablation performed between superior and inferior veins, using real-time automated display of RF application points (Visitag; Biosense-Webster Inc.). Visitags were applied with predefined catheter stability settings of range of motion ≤1.5 mm, duration ≥3 s, CF ≥5 g, and tag diameter at 2 mm. Starting energy delivery parameters were 25 Watts on the posterior wall and 35 Watts at other sites. Target contact force was between 10-20g at all sites. Esophageal temperature was monitored with a single sensor temperature probe, with position adjusted based on site of ablation and RF delivery paused if esophageal temperature increased by 0.5C. Electric isolation of pulmonary veins was confirmed by entrance block to individual PVs, assessed by Lasso catheter positioned at the PV antrum.

Assessment for Acute Reconnection

Following confirmation of electrical isolation of a PV, we waited for a period of 20 minutes and assessed for acute reconnection; ablation of remaining PVs was typically performed during that waiting phase. Reconnection at 20 minutes was treated by further spot or segmental ablation until re-isolation was achieved. If no acute reconnection was identified, PVs were reassessed at 40 minutes after initial isolation. In cases where additional RF ablation was required due to reconnection, assessment was performed 20 minutes after repeat isolation. Reconnection observed after a 40 minute waiting period was treated with additional ablation, but delayed reassessment was not performed.

Statistics

Continuous variables are expressed as mean+ SD and categorical variables as percentage. Univariable analysis was done using t-test and chi-squared test where appropriate. P values of <0.05 were considered statistically significant. All statistical analysis was done using the Stata Software (StataCorp, College Station, TX).

Results

Patient characteristics

Twenty-two patients undergoing initial catheter ablation were evaluated for acute pulmonary vein reconnection. Baseline characteristics are outlined in [Table 1]. Mean age was 60.6 + 1.8 years. The cohort included 36.4% women and 27.3% with persistent AF. Mean CHA2DS2VASC score was 1.9 + 0.3 and duration of AF since diagnosis was 2.0 + 0.5 years. Average RF application time was 39.1 + 2.5 mins and procedure time was 222.8 + 6.2 mins.

Acute pulmonary vein reconnection

Each patient in the study had 4 discreet PVs. Of the 88 PVs assessed[11] (12.5%) showed reconnection during the observation window. In 10 patients, 9 PVs reconnected by 20 minutes and 2 between 20 - 40 minutes. Of these, six reconnections (5 at 20 mins, 1 at 40 mins) were in the left superior PV; two reconnections (both at 20 mins) were in the left inferior PV; there was only one reconnection (at 20 mins) in the right superior PV; and two reconnections (1 at 20 mins and 1 at 40 mins) in the right inferior PV. Sites of acute reconnection are presented in [Figure 1].

Table 1: Baseline characteristics of study group

Variable	Study group (n=22)
Age (years)	60.6 + 1.8
Female sex	36.4 %
BMI (kg/m2)	29.6 + 1.4
Hypertension	72.7 %
Diabetes Mellitus	18.2 %
CHF	9.1 %
CAD	9.1 %
PVD	4.6 %
OSA	18.2 %
CHA_2DS_2VASC	1.9 + 0.3
Persistent AF	27.3 %
AF duration (years)*	2.0 + 0.5
LA size (cm)	4.3 + 0.2
LVEF (%)	55 + 1.6
Presenting rhythm AF	27.3 %
RF application time (min)	39.1 + 2.5
Procedure time (min)	222.8 + 6.2

BMI= Body mass index; CHF= congestive heart failure; CAD= coronary artery disease; PVD= Peripheral vascular disease; OSA= Obstructive sleep apnea; CHA2DS2VASC = congestive heart failure, hypertension, age > 75 years, diabetes mellitus, stroke, vascular disease, age 65-74 years, sex category; LA= left atrium; LVEF= left ventricular ejection fraction; RF= radiofrequency. * time since diagnosis of AF.

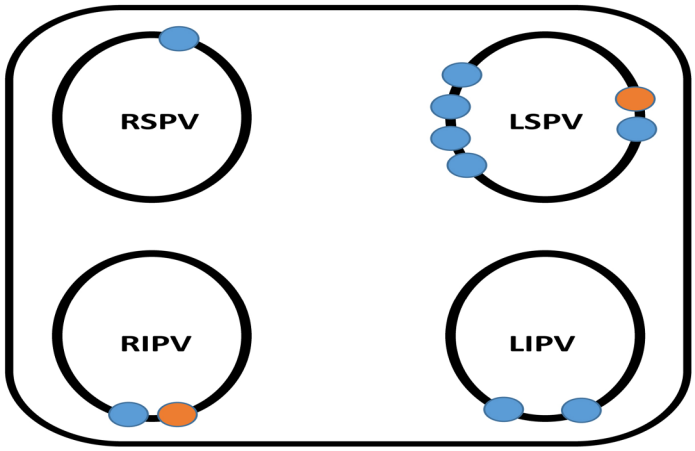

Figure 1: Schematic of the posterior LA, showing sites of PV reconnection occurring 20 minutes after PVI (blue) or between 20 and 40 minutes (orange). LSPV –left superior pulmonary vein; LIPV –left inferior pulmonary vein; RSPV –right superior pulmonary vein; RIPV –right inferior pulmonary vein.

A total of 4993 ablation points were evaluated. Of these, 72 were located in regions of acute reconnection. Comparison of

characteristics of the two different point groups is outlined in [Table 2]. The average contact force (11.4 + 8.1 vs 11.3 + 7.1 gm, p=0.868), power (29.7 + 3.9 vs 29.9 + 4.6 watts, p=0.620), impedance (64.1 + 60 vs 72.5 + 60, p=0.236) and the force time integral (86.9 + 78.8 vs 99.7 + 100 gm/sec, p=0.282) did not show any significant difference.

Table 2: Comparison of characteristics of ablation points in areas with and without acute reconnection

Variable	Reconnected area points (n=72)	Isolated area points (n=4921)	P value[sig < 0.05]
Application Time (sec)	8.9 + 7.0	9.0 + 6.8	0.843
Contact Force (gm)	11.4 + 8.1	11.3 + 7.1	0.868
Temperature (F)	33 + 2.7	33.6 + 2.9	0.077
Power (Watts)	29.7 + 3.9	29.9 + 4.6	0.620
Impedance (Ω)	64.1 + 60	72.5 + 60	0.236
Impedance drop (Ω)	2.9 + 4.2	3.3 + 4.6	0.385
Force time integral (gm/sec)	86.9 + 78.8	99.7 + 100	0.282

Complications

One procedure was complicated by a pericardial effusion that was managed conservatively.

Discussion

In the current investigation we sought to determine the incidence, time course, and location of acute PV reconnection in patients undergoing PVI with force-sensing catheters. In addition, we assessed lesion characteristics including power, contact force, and impedance changes at sites of reconnection and of successful ablation. The principal findings of our study are: 1) Acute PV reconnection occurs at a rate of roughly 12.5% in patients ablated with radiofrequency, CF-sensing catheters; 2) nine of 11 reconnections occurred within a 20 minute waiting period, and 8 of 11 reconnections were at left PV sites; and 3) there were no observable differences in lesion characteristics in areas of acute reconnection when compared to the ablation points in areas without reconnection.

Investigations of PV Reconnection

Acute PV reconnection during PVI is a well-known phenomenon, and has been associated with AF recurrence in long-term outcomes studies[2,3]. Several investigations, including previous work from our institution, have characterized the incidence, time-course, and sites of PV reconnection[4-6]. These studies, largely performed in the era of non-force sensing catheters, showed recurrence rates as high as 50% of all PVs assessed, affecting 93% of patients undergoing ablation. Based on these data, the published Expert Consensus Statements addressing catheter ablation of AF recommend at least a 20 minute observation period followed by reassessment of PV isolation[1,7]. Whether this suggestion is accurate and necessary in the era of PVI with force-sensing catheters is less well established.

Two studies have provided initial data about acute PV reconnection rates using force-guided ablation. In a study by Martinek and colleagues[10], acute PV reconnection rates were compared in patients undergoing PVI using non-force sensing versus force-sensing catheters. The investigators found that on immediate re-assessment of PV isolation (following completion of acute isolation of the last PV targeted), reconnection was reduced from a rate of 36% (in patients ablated with non-force sensing catheters) to 12% (in patients ablated with force-sensing catheters). No data was provided about the time course of reconnection, however. Our results, in terms of the incidence of reconnection, are quite similar (12.5% reconnection rate), but extend the study of Martinek by outlining the time windows during which reconnection was noted. The observation that 9/11 reconnections occurred within 20 minutes, and that 8/11 reconnection sites were located in the left PVs, provides a reasonable guide for limiting reassessment both temporally and spatially.

A second investigation by Haldar and colleagues[11] randomized patients to operators blinded to or informed of contact force during PVI. Reconnection rates were assessed at a single time period (60 minutes). Knowledge of contact force during ablation reduced 1h PV reconnection rates from 21% (blinded group) to 4% (force-guided group). This study, while remarkable for the very low PV reconnection rate observed, does not provide data of the sort provided in the current investigation on rates of PV reconnection versus time. It is knowledge of this kinetics of reconnection, in part, that we think will help inform decision making on when and where to investigate for sites of reestablished conduction following initial vein isolation.

Lesion Characteristics at Reconnection Sites

The idea of the "weakest link" predicting sites of reconnection was described recently in a novel investigation by El Haddad and colleagues[12], who developed an ablation line contiguity index incorporating ablation lesion characteristics (force, time, power) and inter-lesion distance. They found that sites of reconnection were associated with poor lesion depth and lack of contiguous lesion sets. In our investigation we did not find clear differences in the force, time, power, or impedance drop seen in sites of reconnection compared to isolated segments. Visual assessment of Visitag lesions (i.e. algorithm-driven, rather than subjectively applied) on CARTO maps did not suggest discontinuity of lesions in any targeted PV. The fact that lesion characteristics at reconnection sites in our investigation were not quantitatively different from effective ablation sites suggests that other factors (e.g. tissue thickness) may play a role in lesion efficacy.

Clinical Implications

We found that rates of acute PV reconnection were relatively low, occurred typically within a 20m observation window, and were located most often at the left-sided veins. Waiting for 40 minute detected 2.3% (2/88) of additional acute reconnections of the total isolated veins. Based on those observations, a reasonable work flow would be to initially target the left PVs, to then proceed to right-sided PV isolation, and to check the left PVs (only) for durable isolation after completing isolation of the RSPV and RIPV (which presumably will take 20 minutes or more). We propose that if the left PVs are isolated at that point, further assessment may be not necessary. Clearly this approach is worthy of investigation in a prospective, randomized study.

Limitations

This is a single center non-randomized study with a relatively small sample size. Although the total number of ablation points analyzed was fairly large (n=4993), those associated with acute reconnection were much fewer in number (n=72). In this study

pulmonary reconnection was confirmed with entrance block. Adenosine was not used to check for dormant conduction.

Conclusions

Rates of acute PV reconnection during PVI performed with contact force sensing catheters is low, occurs most often within a 20 minute interval, and is typically located at the left PVs. This data suggests that a streamlined approach to PVI, with reassessment of the left PVs at 20 minutes or later after initial isolation, may be feasible. The effect of that streamlined approach on efficiency, safety, and long-term efficacy is worthy of prospective, randomized investigation.

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Remote Monitoring of Atrial High Rate Episodes in Pacemaker Patients. The Rapid Study Design

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Abstract

Background: Remote Monitoring (RM) has been introduced for several years and nowadays most pacemakers are equipped with such a technology. RM can provide early detection of high atrial rate episodes (AHREs) onset and enable prompt medical intervention. However, there are still little data on the clinical reactions triggered by the AHRE detected by RM of pacemaker recipients and on their possible benefit on patients' outcome.

Methods /Design: The RAPID study is a multicenter, prospective, non-interventional study designed to compare the time from onset to first physician's evaluation of AHRE episode with arrhythmic burden ≥5% (72 minutes) for pacemaker recipients without atrial fibrillation history, between patients followed with RM or conventionally with annual in-hospital visits. A total of 98 patients with implanted dual-chamber pacemaker, assigned to RM-OFF or RM-ON according to ordinary clinical site practice, will be followed for a total of 18 months. After the implant, patients will perform their first in-hospital follow-up visit at 1 month and then, in the RM-OFF group, patients will perform an in-hospital FU every 6 months, while in the active group, patients will be continuously monitored via RM until study termination. All AHREs and consequent medical interventions will be collected over the entire study period.

Discussion: The ongoing RAPID study will provide additional information on the role of RM in the management of AHRE detected in pacemaker patients without documented atrial fibrillation history in ordinary clinical practice.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the general population and is associated with an increased risk of stroke and mortality[1-2]. Undiagnosed AF is common as it is often asymptomatic and intermittent[3]. Considering the arrhythmic risk and its consequences, the early detection of AF is of pivotal importance for the optimization of the clinical follow-up and medical therapy. Modern cardiac implantable electronic devices (CIEDs) include detailed algorithms and functions for the accurate detection of atrial high rate episodes (AHREs)[4,5].

In addition, modern CIEDs are equipped with remote monitoring (RM) technology, which provides automatic transmissions of diagnostics and technical data from the implanted devices to the attending physician[6]. RM has been shown to be a safe alternative to the conventional in-hospital visits, especially for low-risk patients, such as pacemaker recipients[7-8]. Despite the latest HRS Expert Consensus Statement which has set a class I recommendation for RM as useful tool for the early detection and quantification of AF [9], there are still few data on the clinical reactions triggered by the AHRE detected by RM of CIEDs and on their possible benefit on patient's outcome. Therefore the role of RM for early detection of significant AHRE is still to be explored and analyzed and is extremely fascinating for its clinical implication.

Key Words

Remote Monitoring, Atrial Fibrillation, Pacemaker, Atrial High Rate Episode.

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Methods/Design

Study Design and Objective

The RAPID Study is a prospective, multicenter, non-randomized, non-interventional study ongoing in three Italian sites that will enroll 98 patients with dual-chamber pacemaker. The objective of this study is to evaluate the time from onset to first physician's evaluation of AHRE with arrhythmic burden ≥5% (72 minutes) in ordinary clinical practice for pacemaker patients without documented AF history and compare it between patients followed with RM or conventionally with annual in-hospital visits. The AHRE burden threshold that constitutes a mandate for anticoagulation is still debated, even if a recent analysis demonstrated that short episodes (<24 hours) had no significant effect on the risk of ischemic stroke[10].

Secondary objectives include: time to first investigator evaluation of AHRE episodes, regardless of its duration, time to anticoagulant therapy onset, time to any medical reaction related to the treatment of new onset atrial arrhythmia, time to cerebral ischemia, and time to first hospitalization due to cardiovascular issues [Table 1].

Table 1: Study objectives and inclusion/exclusion criteria.

Primary objective	-Time from onset to first physician's evaluation of AHRE episode with arrhythmic burden ≥5% (72 minutes) in pacemaker patients followed with RM or conventionally with annual in-hospital visits.
Secondary objective	-Time to first investigator evaluation of AHRE episodes, regardless of its duration;
	-Time to anticoagulant therapy onset;
	-Time to any medical reaction related to the treatment of new AF onset
	-Time to any medical reaction related to the treatment of new AF onset
	-Time to first hospitalization due to cardiovascular issues.
Inclusion criteria	-age > 18 years;
	-Indication to dual-chamber permanent cardiac pacing for sick sinus node dysfunction or atrio-ventricular block
Exclusion criteria	-Ongoing atrial arrhythmia at enrollment;
	-Prior symptomatic or documented AF episodes:
	-Pacemaker replacement or upgrading of previous devices with recorded episodes of AF;
	-Severe valvular disease or valvular prosthesis;
	–Pregnancy;

AHRE = atrial high rate episode.

Investigational centers were selected on the pre-disclosed practice to provide or not pacemaker recipients with RM in order to balance the study arms. Approvals of the local Ethics Committees were obtained for all participating sites. The study started in December 2015 and is expected to last at least 5 years.

Inclusion/Exclusion Criteria

Patients will be enrolled consecutively after providing written consent and fulfilling all the inclusion/exclusion criteria listed in [Table1]. Inclusion criteria include age>18 years, and indication to dual-chamber permanent cardiac pacing for sick sinus node dysfunction or atrio-ventricular block according to the current guidelines[11].

Patients will be excluded in case of ongoing atrial arrhythmia at enrollment, prior symptomatic or documented atrial arrhythmia episodes, pacemaker replacement or upgrading of previous devices with recorded episodes of AHRE, severe valvular disease or valvular prosthesis, and pregnancy.

Implantation and Follow-up

Patients will be screened before undergoing PM implant and will perform an echocardiogram within 3 months prior to implant procedure; patients will participate after having signed the written informed consent before hospital discharge or, alternatively, within 90 days after PM implant, and will receive RM (RM-ON) or not (RM-OFF) according to site standard practice.

Patients in the RM-OFF group will be followed up at 1 month, 6 months (optional), 12 and 18 months with in-hospital visits, while patients in RM-ON group will be visited in-hospital at least at 1 and 18 months. Additionally, patients with RM will be followed remotely and unscheduled in-hospital visits may be triggered by RM alerts. The physician's reaction time to remote notifications was not specified and patients were informed that the data would be evaluated only during office hours on weekdays, as ordinary clinical practice[Figure1]. summarizes the study flow chart.

At every FU visit, all the device diagnostic data and AHRE recordings will be collected in electronic case report forms (eCRFs). In addition, any medical interventions triggered by AHRE episodes, as any adverse event, for both groups will be reported in specific forms. Regular study termination will be at the 18-month follow-up, while premature termination may be due to withdrawal of consent, explantation of device, lost to follow-up or death of patient. AHRE recordings and study endpoints events will be adjudicated by an expert physician blinded to patient's group.

Device Programming

Pacemaker AHRE detection is based on the high atrial rate criterion that will be programmed with a threshold rate of 190 beats/min. AHRE burden, defined as the total time spent in atrial arrhythmias in a single day, is automatically provided by the device, and intracardiac electrogram recordings (IEGM) are stored in the device memory for all AHRE episodes exceeding a duration of 30 seconds. Other settings will be left to the investigator's discretion.

Remote Monitoring System

In the RM-ON group, patients will be provided with RM technology able of daily transmissions (Home Monitoring, Biotronik SE and Co, Germany). Implants, through wide range radiofrequency telemetry, send messages to a patient unit that forwards data to a central server using GSM networks. Physicians have access to this information on protected websites and automatic notifications are triggered by selectable events. The RM notifications for AHRE detection will be set as follows: AHRE burden>5% per 24 hours and long atrial arrhythmic episode>6 hours.

Statistical Consideration and Analysis plan

Standard descriptive analysis will be used for study results and the difference between the areas under the Kaplan-Meier curves will provide an estimate of the expected delay between the episode onset and physician's evaluation for the two groups [Figure 2].

As the primary endpoint is the time to the first ≥5% in 24 hours

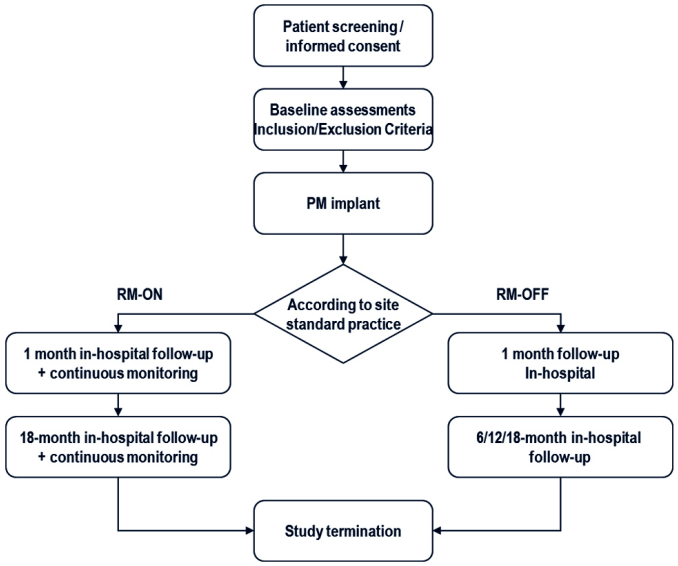

Figure 1: Study Flowchart.

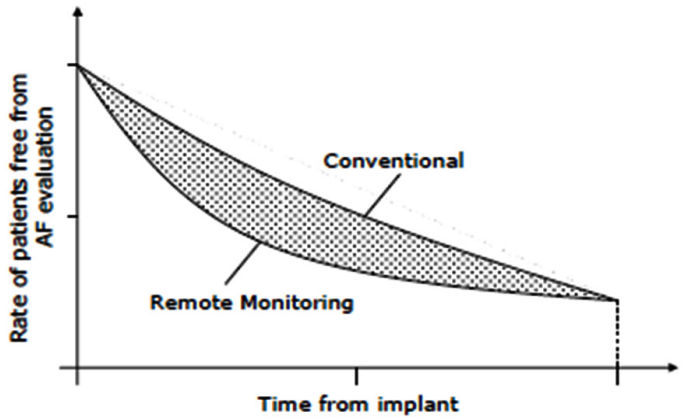

Figure 2: Difference between the areas under the Kaplan-Meier curves will return an estimate of the expected delay between the episode onset and physician's evaluation for the two groups.

(72 minutes) AHRE investigator evaluation, it is expected that its distribution will be skewed and approximately exponential. However, no assumptions have been made on the actual distribution of times, preferring a non-parametric approach (Wilcoxon-Mann –Whitney test). The null hypothesis is that the probability of obtaining a larger value from the RM-OFF group rather than from the RM-ON is 50%. In order to estimate the required sample size to obtain a target statistical power of 80% with an alpha error of 0.05, some assumptions on this probability under alternative hypothesis have been made. Such assumptions depend on the rate of symptomatic atrial arrhythmia episodes and the overall FU duration. Based on available literature[12], the cumulative proportion of patients with AF episode has been considered around 30% at 18 months in an unselected pacemaker cohort; 27% of them with mild or severe associated symptoms and 9% with severe symptoms. It has been assumed that the probability of extracting a longer delay in the RM-OFF group decreased on increasing the rate of symptoms. With these assumptions, the recruitment of 98 patients is needed to reach the required power; such a calculation includes a 10% loss rate.

Discussion

ACIEDs enable continuous monitoring of heart rhythm and have an excellent sensitivity and specificity for AF diagnosis[13]. This increased ability to detect AHREs and the recent evidences of association between such events and stroke risk pose new challenges to clinicians[4,14].

Diagnostic data stored in device memory may become meaningful if they are promptly available to the physician, allowing early detection and possibly preventing severe adverse arrhythmia-related events. In the TRUST study (The Lumos-T Safety Reduces Routine Office Device Follow-up) AF detection was 34.5 days earlier with RM vs standard follow-up (5.5 vs 40 days)[15]. Recently, the SETAM (Strategy of Early Detection of Atrial Arrhythmias with Home Monitoring) study confirmed that remotely monitored patients were diagnosed earlier than for AF, and interestingly found also a reduction of 4 hours/day (18%) in the AF burden when RM was active[16].

Despite these promising results, the evidence of stroke risk reduction with the use of RM is still awaited. The recent IMPACT study (Combined Use of BIOTRONIK Home Monitoring and Predefined Anticoagulation to Reduce Stroke Risk), which randomized 2718 patients with dual-chamber and biventricular defibrillators to start and stop anticoagulation based on RM or conventional in-hospital follow-up (FU), failed to show the superiority of RM[16]. However, the median time from AF occurrence to anticoagulation onset was significantly shorter in the RM group than in the control group (3 days Vs. 54 days, $p<0.001$)[17].

An absence of temporal relationship between arrhythmic event and stroke onset has also been found, atrial arrhythmia may contribute to clot formation in the left atrium but that clot need not embolize during the arrhythmic episode; thus, the atrial arrhythmia may be a risk marker of more severe atrial disease/dysfunction/thrombogenesis potential and/or may be a direct cause. In addition, patients with device-detected AHREs appeared to be at lower risk for stroke compared to patients with overt AF. In patients with $CHADS_2$ score>2, the annualized thromboembolic event rate associated with subclinical AHREs was 2.4% in TRENDS[14] and 2.1% in ASSERT[4], far below from the 4-4.5% annual rate expected in "clinical" AF patients with similar risk profile. As a result the net clinical benefit of anticoagulation may be reduced.

The identification of patients who may benefit from anticoagulation is challenging and combining AHRE burden with CHA_2DS_2-VASC score has been suggested as an appropriate approach to stratify stroke risk. Patients with low CHA_2DS_2-VASC may benefit from anticoagulation if a single AHRE episode exceeds 24 hours; while for patients with a score >2 the anticoagulation could be appropriate start for AHRE lasting > 6 minutes[18,19].

Of note, initiation of anticoagulation was commonly adopted in the recent trials using insertable cardiac monitors, providing a promising methodology for atrial arrhythmias screening in patients without indication to permanent cardiac pacing[20-22].

Several studies such as the ongoing ARTESiA (Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation) and NOAH-AFNET6 (Non-vitamin K antagonist Oral anticoagulants in patients with Atrial High rate episodes) will help to elucidate the use of oral anticoagulation in patients with device-detected AHRE[23,24].

In this complicated scenario the role of RM for early detection of significant atrial arrhythmia is still to be explored and analyzed and it is extremely fascinating for its clinical implication since it may provide additional time to consider how to manage AHRE patients.

An accurate comparison of the delay of significant AHRE detection with standard in-hospital visit with respect to RM should be the first step towards a definite assessment of clinical impact of RM in stroke prevention.

In conclusion, the ongoing RAPID study will provide additional information on the role of RM in the management of AHRE detected in pacemaker patients without documented atrial arrhythmia history

in ordinary clinical practice.

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"Clinical Impact of the Cryoballoon Temperature and Occlusion Status on the Success of Pulmonary Vein Isolation"

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Abstract

Background: Complete occlusion of the pulmonary veins (PVs) with the cryoballoon (CB) is considered to be the crucial factor for a successful PV isolation (PVI). We investigated whether a complete occlusion was indispensable for a successful CB based PVI of every PV.

Methods and Results: TAtrial fibrillation patients (n=123, 97; paroxysmal) undergoing a de novo PVI were enrolled. A total of 477 PVs were analyzed. The occlusion grade (OG) was scored as follows: OG3 (complete occlusion), OG2 (incomplete occlusion with slight leakage), OG1 (poor occlusion with massive leakage). There was no significant difference in the CB temperature (CBT) at all measured time points (from 30 to 120sec after freezing) and nadir CBT between OG2 and OG3 in all PVs except for the right inferior PV (RIPV). The RIPV isolation success rate was significantly lower for the OG2 status than OG3 (97.5 vs. 57.6%; p<0.0001). In contrast, there was not significant difference in the isolation success rate of the other three PVs between OG2 and OG3. In particular, the success rate of the right superior PV (RSPV) isolation was >95% for both OG2 and OG3. Phrenic nerve paralysis (PNP) was provoked during the RSPV isolation in two patients in whom the RSPVs were frozen during OG3.

Conclusions: An OG3 may not always be required for a successful PVI of all PVs except the RIPV. OG2 could have comparable effects as OG3 in terms of a successful RSPV isolation. Not aiming for OG3 for the RSPV may reduce the risk of PNP.

Introduction

Pulmonary vein (PV) isolation (PVI) with a cryoballoon (CB) is widely utilized for treating atrial fibrillation (AF)[1]. When performing a CB based PVI, a complete occlusion of the PV ostia with the inflated CB is considered to be an indispensable factor for creating a continuous circumferential lesion with a high long-term durability for a successful PVI.

PVs often cannot be completely occluded by the CB because of the anatomical shape of the left atrium and PV ostia[2]. In order to obtain a complete occlusion of PVs, we sometimes push the CB deep into the PV ostia or apply the CB slightly inside of the PVs, which may result in increasing the incidence of phrenic nerve (PN) paralysis (PNP). On the other hand, we sometimes can obtain a lower nadir CB temperature (CBT) than we expected and an acute successful PVI in spite of leakage between the balloon surface and atrial tissue, which is an incomplete occlusion. The occlusion grade (OG) is classified according to the amount of leakage of contrast medium through the gap between the CB and PV ostium[3].

One parameter that suggests a good occlusion status is the CBT. A lower CBT indicates a better occlusion, because blood leakage hinders a sufficient temperature drop required for a successful PVI. The time to accomplish a successful PVI and the time for the CBT to reach 10°C have been reported as parameters affected by the OG4. The electrical reconnection rate of the PVs has been reported to be correlated with the completeness of the PV occlusion in the index procedure[4-7]. In all the literature investigating the relationship between the success rate of the PVI and the OG, all four PVs have been analyzed as a whole.

The aim of the present study was to evaluate the occlusion status for each of the 4 PVs separately in terms of examining their relationship to the CBT and PVI success rate. We also investigated whether a complete occlusion of the PV ostium by the CB was indispensable for achieving a complete PVI.

Key Words

Pulmonary Vein Isolation, Cryoballoon, Occlusion Grade, Phrenic Nerve Paralysis

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Methods

From March 2016 to August 2016, consecutive patients who underwent catheter ablation to treat AF with a CB at our institution were enrolled. Patients were excluded if they had thrombi in the LA, uncontrolled thyroid dysfunction, contraindications for

anticoagulation, or an LA anteroposterior diameter of >55 mm. A contrast enhanced cardiac computed tomographic scan was performed before the catheter ablation to assess the LA anatomy and to rule out any intra-cardiac thrombi in all patients. Transesophageal echocardiography was performed in all persistent AF patients to rule out any intra-cardiac thrombi, especially in the left atrial appendage. Anti-arrhythmic drugs were discontinued for longer than 3 half-lives (amiodarone was discontinued for >1 month) prior to the ablation, and all patients were anticoagulated for >1 month.

The study and data collection were performed in accordance with protocols that had been approved by the Human Research Ethical Committee at our institutions.

PV Isolation

Each patient provided written informed consent prior to the ablation procedure. Patients received conscious sedation with dexmedetomidine hydrochloride, which was administered from the beginning of the procedure. The luminal esophageal temperature was measured with a thermocouple catheter inserted through a nostril into the esophagus (Esophaster, Japan-Life-Line, Tokyo or S-CATH, CIRCA, Boston Scientific, Englewood, CO) prior to the ablation procedure to avoid any esophageal thermal injury associated with the cryoenergy application. A single trans-septal puncture was performed with an RF needle (Baylis Medical, Inc, Montreal, QC) under fluoroscopic and intracardiac echocardiographic (AcuNav, Biosense Webster, Diamond Bar, CA) guidance. Thereafter, heparin was administered intravenously to maintain an activated clotting time between 300 and 350 sec during the entire ablation procedure. The arterial pressure was continuously measured directly through the sheath inserted into the femoral artery during the ablation procedure.

The CB Catheter (Arctic Front Advance, Medtronic, Minneapolis) was introduced into the LA through a steerable long guiding sheath (FlexCath Advance, Medtronic, Minneapolis). A 28-mm CB was used in all cases. A mapping catheter (Achieve, Medtronic, Minneapolis) was advanced through the central lumen of the CB toward the PV orifice and introduced into the distal portion of each PV. Then the CB was inflated and advanced to the ostium of each PV in an attempt to obtain a complete occlusion. The OG was assessed according to the grade of retention of the contrast medium injected into the PV through the central lumen of the CB. When we achieved the best OG, cryothermal energy was applied for 180 or 240 sec. A duration of 180 sec was employed in cases when the PVI was successfully accomplished within 60 sec after the start of the freezing or if the balloon temperature reached -40°C within 60 sec as shown in a past report[4]. An acute PV isolation was defined as the complete elimination of the PV potentials recorded by the Achieve catheter during the CB application. If the PV potentials could not be recorded prior to freezing, we manipulated the Achieve catheter so as to locate it at an appropriate position that enabled the recording of the PV potentials. When a successful PVI was not achieved with a single application of the CB, further CB applications (maximum of three times) or irrigated radiofrequency energy (RF) ablation was undertaken as a touch-up ablation.

An electrode catheter was advanced into the superior vena cava for right-sided phrenic nerve (PN) stimulation during the CB ablation for the right-sided PVs. The compound motor action potentials (CMAP) of the diaphragm provoked by PN pacing were continuously monitored during the CB ablation applications for each PV as previously reported[8]. The freezing energy delivery was immediately terminated if the maximum voltage of the CMAP decreased by 30% compared to that before the freezing or weakening of the diaphragmatic excursion was observed.

Occlusion Grade (OG) Evaluation

The degree of the CB occlusion obtained by an injection of 50% diluted contrast medium into the PV was evaluated as: OG3 = complete occlusion (full retention of contrast medium with no visible leakage), OG2 = incomplete occlusion with slight leakage (the shape of the PV could be discerned by the contrast medium), and OG1 = poor occlusion with massive leakage (the shape of the PV could not be confirmed due to immediate flushing of contrast from the PV).

The OG for each PV was evaluated just before the freezing by two fully experienced doctors. The fluoroscopic image analysis used for the OG evaluation was performed at 15 frames/sec and with a normal detailed resolution in the antero-posterior and left anterior oblique projections.

In the case of a massive leakage of contrast medium through the inferior aspect between the CB and PV, a "pull-down" maneuver was utilized to improve the OG[9,10]. In those cases, the OG after the pull-down was adopted for the analysis. The method of the "pull-down" maneuver and evaluation of the OG after that maneuver were as follows: first, we tried to advance the CB on the superior aspect of the PV and started freezing with a massive leakage at the inferior aspect of the PV. Immediately after starting the freezing, we continuously and very slowly injected contrast medium through the central lumen of the CB to prevent blood frozen in that lumen. The CB and FlexCath were pulled down in order to close the inferior gap when the CBT reached -10 °C. The OG can be evaluated by investigating the contrast medium leakage after the "pull-down" maneuver (our experience revealed that the ice cannot be formed in the central lumen until the CBT reaches approximately -10 °C).

When multiple CB applications were performed for a successful PVI, the OG for only the first freezing was analyzed to exclude any cumulative effects provoked by subsequent freezings. The OG of the second and succeeding freezings were not included in the investigation.

Cryoballoon Temperature and Time Parameters

For each PV, the CBT was recorded at 30, 40, 50, 60, 90, and 120 sec from the onset of the freezing. The nadir CBT (NCT) was also noted. Moreover, the time to reach -40 °C of the CBT, time to obtain the PVI, and balloon thawing time (BTT, time for the balloon to return to 20 °C) were also recorded.

Diagnosis of Phrenic Nerve Paralysis

A diagnosis of PNP was made if (1) paralysis of the hemidiaphragm was noted on fluoroscopy during the ablation procedure despite the high-output pacing of the PN, (2) paradoxical movement of the

Table 1: Baseline patient characteristics and the ablation procedure.

Patients (n)	123
Age (years)	65±12
Male gender	107 (87.0%)
Body mass index (kg/m2)	24±4
Echocardiogram	
Left ventricular ejection fraction (%)	64±10
Left atrial diameter (mm)	42±7
Comorbidities	
Hypertension	50 (40.7%)
Diabetes	16 (13.0%)
Previous cerebral ischemia	8 (6.5%)
Heart Failure	10 (8.1%)
Age >75 years	33 (26.8%)
CHADS2 score	1.0±1.0
CHADS2-VASc score	1.9±1.5
Atrial fibrillation	
Paroxysmal AF	97 (78.9%)
Persistent AF	26 (21.1%)

diaphragm during spontaneous respirations was recognized by the fluoroscopy image, and (3) an elevated position of the diaphragm was observed compared to the preoperative state with a chest X-ray on the day after the ablation procedure. Once a diagnosis was established, the patient was closely followed-up with a repeated chest X-ray every month. The normalization of the chest images was considered as a complete clinical recovery.

Follow Up

The patient follow-up was performed through visits in our outpatient department. The referring physician performed a 12-lead surface ECG as well as a 24-hour Holter ECG at 2, 4, 6, and 12 months after the ablation. Any documented episodes of any atrial tachyarrhythmias longer than 30 seconds were considered a recurrence. Patients who underwent a re-do session for the recurrence of any atrial tachyarrhythmias were evaluated. Anti-arrhythmic drugs were discontinued for longer than 3 half-lives (amiodarone was discontinued for >1 month) before the re-do session.

Statistical Analysis

SContinuous data are expressed as the mean ± SD for normally distributed variables. Error bars in all figures represent the SEM. Statistical comparisons were performed using a Student's t-test, Mann–Whitney U-test, Fisher's exact test, or x^2 test, as appropriate. The p-value presented is for a 2-tailed test. A p-value of <0.05 indicated statistical significance. Analyses were conducted using JMP software (version 12.2.0 Scientific Discovery. ™ From SAS).

Results

One hundred twenty-three patients were enrolled. The number of paroxysmal and persistent AF patients was 97 (78.9%) and 26 (21.1%), respectively. The mean age was 65±12 years old and 107 (87.0%) patients were male. The baseline patient characteristics are shown in [Table 1]. In total, 477 PVs were analyzed. Acute success of the PVI was achieved in all patients. Five patients had a left common PV, which was isolated by multiple CB applications with massive leakage on the roof and carina side as reported previously[11]. We excluded those cases from the analysis of this study. In 5 cases, the best occlusion status in the right inferior PV (RIPV) was OG1 in spite of meticulous manipulation of the CB. Those RIPV isolations were performed only by radiofrequency ablation.

The OG and Acute PVI Success Rate

The acute PVI success rate by the initial CB freezing was the lowest for the RIPV (57.6%). The left superior PV (LSPV), right superior PV (RSPV), and left inferior PV (LIPV) were successfully isolated in 81.4%, 91.1%, and 76.3%, respectively. Although an OG3 was obtained in more than 50% of the LSPVs, RSPVs, and LIPVs, in contrast, an OG3 was achieved in only 33.9% of the RIPVs. Moreover, the mean OG was lowest for the RIPV (2.7, 2.5, 2.4, and 1.9 for the LSPV, RSPV, LIPV, and RIPV, respectively [p<0.0001]). Radiofrequency touch up ablation to complete the PVI was required most often for the RIPV (1.7%, 0%, 5.9%, and 20.3% for the LSPV,

Table 2: Acute PVI success rate and OG during the initial CB application.

	Acute PVI success rate	OG (%)	Mean OG		Touch up cases (%)	
		3:88 (74.6)				
LSPV (n=118)	81.4% (96/118)	2:21 (17.8)	2.7		2 (1.7)	
		1:9 (7.6)				
		3:82 (66.7)				
RSPV (n=123)	91.1% (112/123)	2:25 (20.3)	2.5	p < 0.0001	0 (0)	p< 0.0001
		1:16 (13.0)				
		3:67 (56.8)				
LIPV (n=118)	76.3% (90/118)	2:27 (22.9)	2.4		7 (5.9)	
		1:24 (20.3)				
		3:40 (33.9)				
RIPV (n=118)	57.6% (68/118)	2:33 (28.0)	1.9		24 (20.3)	
		1:45 (38.1)				

RSPV, LIPV, and RIPV, respectively [p< 0.0001]). The x^2 was 53.9 for the OG, p<0.0001, with a high count of OG1 in the RIPV contributing the most (20.3) to the x^2 value, then a low count of OG3 in the RIPV (11.9). The x^2 was 47.3 for a touch up necessity, p<0.0001, with a high count of a touch up necessity in the RIPV contributing the most (30.3) to the x^2 value[Table 2].

CB temperature and the PVI Success Rate Between OG2 and OG3

We compared the various parameters between OG2 and OG3. The number of PVs frozen by OG1 was 9/118 (7.6%), 16/123 (13.0%), 24/118 (20.3%), and 45/118 (38.1%) for the LSPV, RSPV, LIPV, and RIPV, respectively [Table 2]. We did not analyze OG1 because the acute PVI success rate of the PVs frozen with OG1 was low for all PVs (LSPV: 44.4%, RSPV: 62.5%, LIPV: 33.3%, and RIPV: 24.4%, average for all PVs: 36.4%).

There was no significant difference in the CBT for the PVs at all time points measured between OG2 and OG3 except for the RIPV. In the RIPV, significant differences in the CBT were observed between OG2 and OG3 at all points after 30 sec [Figure 1].

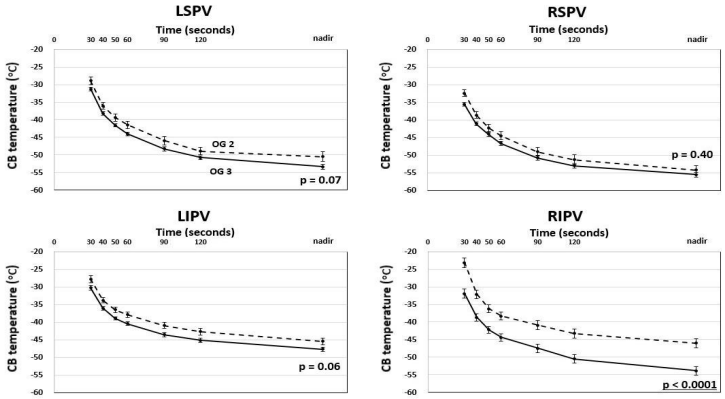

Figure 1: Comparison of CBT between OG2 and OG3 along the time series.

The broken lines and solid lines show the CBTs for OG2 and OG3, respectively, over time from the start of the freeze.

The time to reach -40 °C of the CBT from the onset of the freezing (68±33 vs. 51±29 sec; p=0.034) and BTT (34±16 vs. 51±23 sec; p=0.0003) was significantly different only for the RIPV between OG2 and OG3 [Figure 2A,B].

An average time to obtain a PVI of within 60 sec even with OG2 was observed in all 4 PVs. Significant differences in the time to obtain a PVI were also observed only for the RIPV between OG2 and OG3 (50±18 vs. 28±17 sec; p=0.0065) [Figure 2C].

When comparing the NCT between OG2 and OG3, there was a significant difference in only the RIPV (-54±8 vs. -46±7 °C; p<0.0001). Regarding the other three PVs, the NCTs in OG3 tended to be lower than those in OG2, but there were no significant differences [Figure 3].

The PVI success rate with the initial CB freeze was significantly lower with OG2 than OG3 only for the RIPV (57.6 vs. 97.5%, respectively; p<0.0001). In the other three PVs, the PVI success rate for OG3 tended to be higher than that for OG2, but there were not significant differences. Particularly, the success rates of the RSPV isolation were very close between OG2 and OG3 (95.1 and 96.0 %, respectively) [Figure 3].

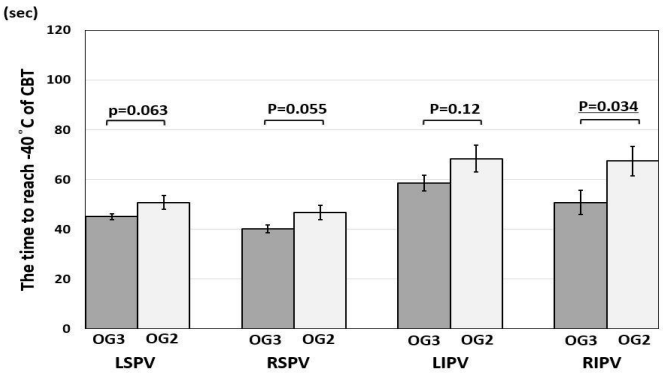

Figure 2A: Comparison of the time to reach -40 °C of CBT between OG2 and OG3

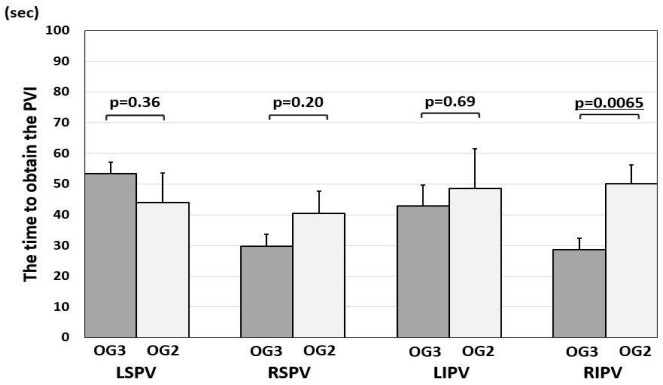

Figure 2C: Comparison of the time to obtain the PVI between OG2 and OG3

Complications

Transient right-sided PNP occurred in three cases (2.4%) during the right-sided PVI (RSPV: 2 patients, RIPV: 1 patient). All three PNP cases occurred during freezing during OG3. The paralyses that occurred during the RSPV freezing resolved after 1 day and 1 month, respectively. That which occurred during the RIPV freezing resolved within a day. A pseudo-aneurysm of the femoral artery occurred in one case (0.8%). No further complications or safety problems occurred.

Follow Up

Twenty (16.3%) patients received a re-do session, which was performed on average 10.5 months after the initial ablation session. The presence or absence of PV reconnections was investigated in 79 PVs of the 20 patients (in one case, the RIPV was isolated only by an RF catheter in the initial session and was excluded from the analysis). PV reconnections were observed in fifteen PVs (19%): LSPV 3/20 (15%), RSPV 1/20 (5%), LIPV 2/20 (10%), and RIPV 9/19 (47.4%).

Fifty-one out of 79 (64.6%) PVs had been isolated by a single freezing application during the first session. Among those 51 PVs, 6 (7.6%) had reconnected by the time of the re-do session (two were LSPVs frozen with an OG3, one was an LIPV frozen with an OG1, and three were RIPVs frozen with an OG1 or OG2 in the initial session). The remaining 28 (35.4%) PVs were isolated by multiple freezings or RF touch-up ablation during the first session. OG3 was never obtained during any PVIs even with multiple freezings. Three

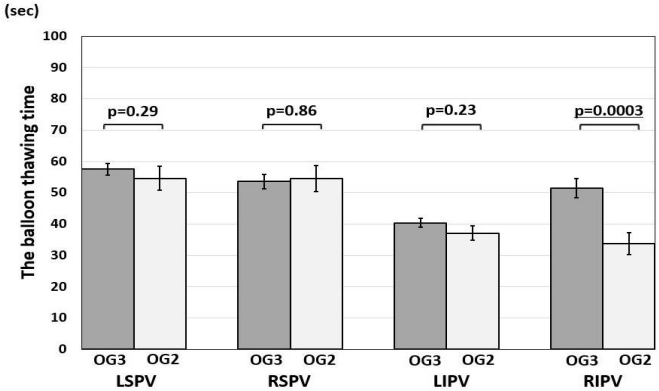

Figure 2B: Comparison of the balloon thawing time between OG2 and OG3

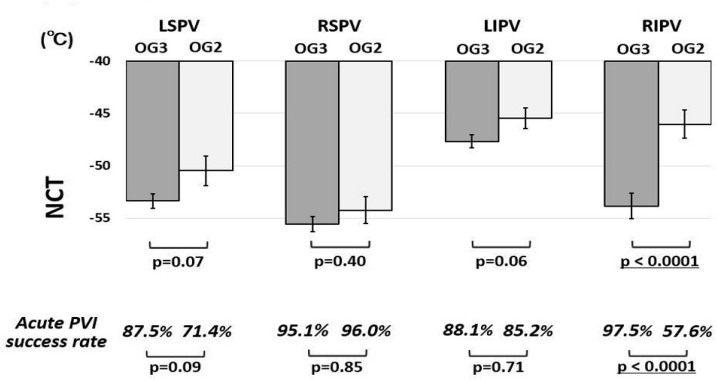

Figure 3: Nadir CB temperature and acute PVI success rate between OG2 and OG3

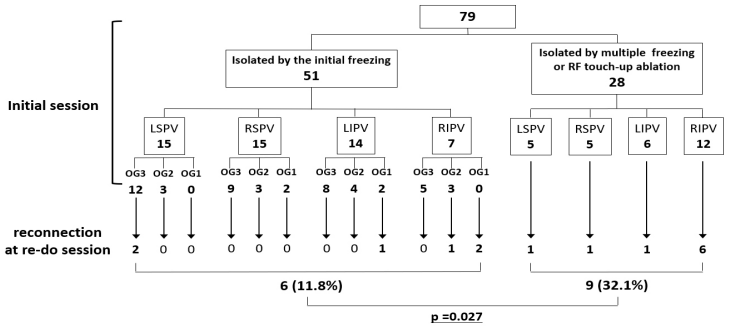

Figure 4: Summary of PVs that could be observed at the re-do session

RIPVs and 1 LIPV were finally isolated by a RF touch-up ablation. A reconnection was observed in 9 (1.1%) PVs (1 LSPV, 1 LIPV, 1 RSPV, and 6 RIPVs) during the re-do sessions. The PV reconnection rate of the two groups significantly differed (p=0.027) [Figure 4].

Discussion

There have been some papers on the OG of CBs. However, all four PVs were analyzed together in the previous reports. To the best of our knowledge, this is the first report of the relationship between the OG and PVI success rate, investigating each PV separately. The major findings obtained from the present study were: (1) the time course of the temperature drop did not differ between OG2 and OG3 for all PVs except the RIPV, (2) the time to reach -40°C, time to the PVI, BBT, and NCT were comparable between OG2 and OG3 for all PVs except the RIPV, (3) an OG3 was not deemed to be indispensable for all PVs except the RIPV in terms of an acute success of the PVI and long-term PVI maintenance, and (4) when the PVI of the RSPV was performed with an OG2, PNP was never provoked.

Many previous reports have stated that it is difficult to obtain a complete occlusion of the RIPV[2,6,12,13]. In a PVI based on the CB, we usually position the CB so that the CB can evenly adhere to the PV orifice. Fürnkranz et al. reported that when CB freezing is performed for the inferior PVs, a central alignment of the CB at the PV ostium is often not possible because the sheath/balloon system must be deflected in order to reach the target structure[14]. In particular, positioning the CB concentrically at the RIPV orifice is more difficult relative to the other PVs because the orifice of the RIPV is close to a portion of the atrial septal puncture.

Although the CBT was recorded 30 ~ 120 sec from the start of the freezing, the CBTs of the three PVs except for the RIPV from 30 seconds did not significantly differ between OG2 and OG3. It was suggested that the ice ball formation could have been accomplished within 30 sec, and eliminated the leak through the gap. Gaps between the PV orifice and CB may be filled with an ice ball formation on the CB surface even if there is a slight leakage of the blood. Gaps may also be sealed, because the CB diameter increases from 26.5 to 28 mm and the internal pressure of the CB also increases from 2.5 to 15 psi during inflation[15]. We believe that it was the reason why there was no significant difference in the PVI success rate between OG2 and OG3 for LSPV, LIPV and RSPV. We speculated that gaps may be too large to be filled by an ice ball formation or a further increase in the diameter of the CB after freezing in the case of the RIPV.

With the RSPV, an NCT between OG2 and OG3 was almost comparable with a p value of 0.4 and had also a similar acute PVI success rate. Sorgente et al.2 calculated the ovality index of the PV ostia (the ratio between the maximal and minimal ostium diameters) from contrast CT. They reported that there was a significant difference in the ovality index between the left- and right-sided PVs (p<0.001) (1.49±0.20 for the LSPV, 1.54±0.16 for the LIPV, 1.14±0.13 for the RSPV, and 1.16±0.13 for the RIPV, respectively). Because the ovality index of the RSPV was low, they speculated that if there was a gap between the RSPV and CB, it would have been relatively even around the CB.

It has been reported that a longer time to the PVI and failure to achieve -40 ˚C within 60 sec independently predicts a late PV reconnection[16]. In this study, when the RSPV was occluded with an OG2, the CBT reached -40 ˚C at an average of 47 sec, and a successful PVI was achieved within 60 sec. The BTT was also similar between OG3 and OG2 (p=0.86). Based on these results, we could expect that an RSPV frozen with an OG2 could have a long-term durability of the PVI equivalent to that of being frozen at an OG34. In fact, 20 patients in whom we performed a re-do ablation, it demonstrated that the PV reconnection rate was low even in PVs that were successfully isolated with a single freezing with an OG2. In other words, the same long-term durability was obtained between the OG2 and OG3. In contrast, the reconnection rate was high in the PVs isolated by multiple freezings, and most of them happened with RIPVs. Regarding the RIPV, a satisfactory long-term durability could not be obtained with the RIPVs despite multiple freezings and devised manipulation of the CB.

When ablating the RSPV with the CB, our results suggested that sufficient injurious effects of the CB could be obtained even with an OG2, and there was less need to manipulate the CB for the purpose of obtaining an OG3. It has been reported that pushing the CB aiming for a complete occlusion can lead to an extension of the anterior surface of the RSPV by 6.3 mm[17]. This RSPV distortion would shorten the distance between the PN and CB, which might result in PN injury. In this study, two of the patients suffering from PNP during the RSPV ablation had been frozen with an OG3. It may be expected that performing the CB ablation with an OG2 rather than an OG3 could reduce the incidence of right-sided PNP.

Casado-Arroyo et al. reported the less vigorous wedging maneuver during RSPV freezing was useful to avoid the incidence of PNP15. They recommend the following. First, the inflated CB was positioned with a complete occlusion of the RSPV, then the CB was retrieved to a more proximal position until a small leak was observed. After that, the cryoenergy application was started and the "CB was advanced" aiming for a complete occlusion. The RSPV could be occluded at a more proximal position than the first occlusion because the balloon volume and internal pressure increased during the freezing status as compared to that during the inflated status. However, the final step "advancing the CB" might retain a risk of RSPV distortion and shortening the distance between the CB and PN. Saitoh et al. reported the risk of PNP could be evaluated by the spatial relationship between the CB and cardiac shadow on the fluoroscopic image during the RSPV freezing[18]. Martins et al. analyzed the measured distance between the vertical projection of the distal tip of the SVC catheter stimulating the PN to the distal segment of the CB in the AP view, and related it to the incidence of PNP1. If the risk of PNP is expected to be high before the cryoenergy application starts, aiming for a complete occlusion of the RSPV by pushing the CB might not be necessary.

Limitations

Several limitations to this study should be acknowledged. 1) The OG is a subjective evaluation value. Although we proposed objective criteria for the OG from fluoroscopic imaging, there was the possibility that the interpretation could differ among physicians and medical facilities. 2) These data were an analysis dealing with only anatomically normal PVs and left common PVs, and extremely large PVs were not evaluated. 3) We evaluated the OG only with fluoroscopic imaging. A recent method for assessing the PV occlusion state is with echocardiography and CB pressure wave analyses[19-21]. If those devices had been used in the present study, we might have been able to observe how the PV orifice was occluded, for example, whether the OG2 was occluded by an ice ball formation or not. 4) We evaluated the durability of the PVI only in cases that suffered from AF recurrences. In the future, verification by a large-scale study is desired.

Conclusion

There were no significant differences in the CBT and acute PVI success rate between OG2 and OG3 for the LSPV, LIPV, and RSPV. OG3 should be obtained for a successful RIPV isolation. On the other hand, OG3 was not deemed to be indispensable for a successful PVI especially for the RSPV. An intentional complete occlusion by pushing the CB for the RSPV might not be necessary for preventing the incidence of PNP.

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Contact-Force Guided Pulmonary Vein Isolation does not Improve Success Rate in Persistent Atrial Fibrillation Patients and Severe Left Atrial Enlargement: A 12-month Follow-Up Study

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Abstract

Background: Catheter ablation is a cornerstone treatment strategy in atrial fibrillation (AF). Left atrial (LA) size is one of the contributors in development of AF recurrences. The impact of contact-forced (CF) guided catheter ablation on the success rate of persistent AF patients with severe enlarged LA has not been investigated yet.

Methods: Sixty-six patients with diagnosis of longstanding persistent AF undergoing catheter ablation were enrolled. All patients underwent a standard transthoracic echocardiography according to the guidelines. LA size was considered severely enlarged when LA diameter was ≥ 50 mm. CF catheter ablation with a Tacticath Quartz catheter (St Jude Medical, St. Paul, MN, USA) was used in all patients.

Results: The mean age was 61.9 ± 9.9 years, and LAD 47.8 ± 11.6 mm. Among 66 patients with persistent AF, 32 (48%) patients were diagnosed with AF recurrences. Twenty-eight (42%) patients had severely enlarged LA. The recurrence of AF was comparable in patients with and without severe enlarged LA (47% vs. 42%, p=0.79). The recurrence of AF was lower in patients who underwent CF-guided ablation with a normal LA dimension (36 %, p=0.54). Procedure duration was longer in patients with severely enlarged LA. LA dimension was not significantly different between patients with and without AF recurrence (49.8 ± 7.9 mm vs. 45.9 ± 7.5 mm, p=0.15). LAD and was significantly correlated with the time to recurrence of AF (r:-0.60, p=0.02).

Conclusions: Our preliminary findings have demonstrated that CF guided ablation does not improve the success rate in longstanding persistent AF patients with severe LA enlargement.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in clinical practice with an increased cardiovascular morbidity and mortality[1]. Studies have shown the superiority of catheter ablation compared to medical treatment in patients with refractory symptoms[2]. Despite technological advancements, the recurrence rate of catheter ablation is still high, ranging from 35 to 50%. Patients with persistent AF are more prone to recurrences due to electrical and structural remodeling[3].

Left atrial enlargement has been shown to be associated with an inversed rate of AF recurrence after chemical or electrical cardioversion[4]. Previous studies have shown that an increase in the LA diameter is associated with higher AF prevalence; moreover LA diameter is an independent risk factor in the development of AF, and in determining the long-term outcomes of ablation[5]. The interaction between LA size and AF has been confirmed in many studies, and both conditions mutually exacerbate each other. Therefore, it is important to know whether catheter ablation is useful in treating persistent AF patients with an enlarged LA size. Recently, AF ablation appears to be effective in non-paroxysmal AF patients with severe LA enlargement using non-CF guided catheter. The study also showed that AF ablation is associated with LA reverse remodeling and improvement in LVEF[6].

Contact-force (CF) catheters provide information to the operator to assess the proximity of the catheter to the endocardium. Low CF during pulmonary vein isolation (PVI) has been shown to be a predictor of acute and chronic PV reconnections, and is associated with an increased risk of AF recurrence[7-10]. CF has been shown to improve the durability of the PV isolation and empower the efficacy of catheter ablation[11]. The impact of standard CF parameters using CF guided catheter RF ablation in patients with severe enlarged LA has not been investigated.

Key Words

Atrial Fibrillation, Catheter Ablation, Contact-Force, Enlarged LA

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Materials and Methods

Patient demographics

Consecutive patients from May 2015 to April 2016 with persistent AF who underwent catheter ablation using the non-CF

(Therapy Cool Flex, St Jude Medical, St. Paul, MN, USA) and CF sensing catheters (Tacticath Quartz, St Jude Medical, St. Paul, MN, USA) were enrolled. All patients underwent transthoracic echocardiography (TTE) and cardiac computed tomography (CT) prior to catheter ablation. Persistent AF was defined as an episode of AF lasting between 7 days and 12 months[12]. Patient demographics and medications at the time of the initial ablation were obtained from medical records. Exclusion criteria were defined as follows: patients <18 years of age, prior valvular surgery, severe mitral valve disease, paroxysmal and/or permanent AF, patients with thrombus within the left atrial appendage, and unwillingness to participate in the study. All patients included in the study provided written informed consent for participation in the study. Anti-arrhythmic medications (except amiodarone for a minimum of 4 weeks) were discontinued for five half-lives prior to the procedure. This study was approved by the ethics committee of Kingston General Hospital and Queen's University's Institutional Review Board in Ontario, Canada.

Echocardiography

All patients underwent a transthoracic echocardiography (TTE) with a Vivid E95 machine (GE Healthcare, USA) according to ASE guidelines[13]. The LA size was measured in the short and long-axis parasternal view. LA size was considered enlarged when LAD ≥ 50 mm. Transesophageal echocardiography was performed to exclude any atrial thrombi 24 hours before ablation.

Periprocedural anticoagulation

Patients who were receiving warfarin did not discontinue this prior to the procedure with a target INR of 2.0 and 3.0. Patients on non-vitamin K-antagonists withheld their anticoagulation for 48 hours prior to the procedure. After transeptal access was gained, intravenous unfractionated heparin was administered at 10 to 20 minute intervals to achieve a target-activated clotting time of 300-350 seconds.

Electrophysiology study and Ablation

Patients were brought to the electrophysiology lab in a fasted state, and the procedure was conducted under conscious sedation with intravenous fentanyl and midazolam. Venous access was gained from the femoral veins. Standard intra-cardiac catheters were introduced through the right femoral vein: (1) A decapolar catheter (IBI Inquiry, St. Jude Medical, St. Paul, MN, USA) was positioned in the coronary sinus, (2) duodecapolar catheter (Supreme, St. Jude Medical, St. Paul, MN, USA) was positioned in the right atrium, (3) mapping and ablation catheter (Therapy Cool Flex, St. Jude Medical or TacticathTM Quartz, St. Jude Medical, St. Paul, MN, USA) delivered through a 9 Fr femoral sheath (St. Jude Medical, Minneapolis, MN) (4) A spiral multipolar PV catheter (AFocus II, St. Jude Medical, St. Paul) was placed through the long steerable sheath (Agilis, St. Jude Medical, Minneapolis, MN, and (5) quadripolar catheter (Supreme, St. Jude Medical, St. Paul, MN, USA) placed at the right ventricular (RV) apex. Intracardiac echocardiography (ICE) (ViewFlex XTRA, St.Jude Medical) was used to guide transseptal punctures in some cases. A 3-D reconstruction of the LA and pulmonary veins was created with the use of EnSite VelocityTM system (St. Jude Medical, St. Paul, USA)

AF ablation was performed with a wide area circumferential ablation (WACA) approach. The primary end point was considered as entry and exit block in all PVs. RF was delivered using a 4 mm externally irrigated-tip ablation catheter at a flow of 17-25 ml/min with a power range from 25 to 30 W. For each lesion, CF of at least 10 grams, and lesion duration of 40 seconds were reported as the minimal requirement. In sites with low CF such as LA/LAA ridge, force-time-integral (FTI) > 400 gs was aimed. PV isolation was considered complete when the circular PV potentials were no longer recorded. Acute reconnection was defined as LA-PV conduction spontaneously occurring during a waiting period of 20 minutes following the completion of the PV isolation, or when PV dormant conduction was evoked by an intravenous adenosine.

Follow up

Post ablation, all patients received anticoagulation for at least 3 months and beyond this. Patients were evaluated by 24-h ECG Holter monitoring at 3 months, 6 months, and yearly thereafter. Recurrence was defined as an episode of any atrial arrhythmia lasting more than 30 seconds and occurring at least 3 months after ablation (post-blanking period)[12].

Statistics

Data was collected in an Excel file and imported into IBM SPSS (Version 21 for Windows, Armonk, New York, 2015) for statistical analysis. Data were initially described using means, standard deviations and medians for continuous data, and frequencies and percentages for categorical data. Continuous data was also graphed to assess the underlying distribution. Associations between LAD and continuous data (time to AF recurrence) were assessed using Pearson correlations, with Spearman's-rho correlation in the event of non-normal distributions. The comparison of 4 groups analyzed

Table 1: Demographic and procedural data of patients with persistent AF.

	Overall	Group 1	Group 2	Group 3	Group 4	P-Value
	n=66	n=16	n=16	n=22	n=12	
Age, years	63.5 ± 9.5	63.4±10.2	67.1 ± 7.5	63.8± 11.2	58.3 ± 5.8	0.12
Gender, male	46	8	10	17	11	0.08
BMI, kg/m2	31.6 ± 5.8	31.6 ± 6.4	30.4 ± 5.6	31.3 ± 5.4	34.0 ± 6.0	0.42
DM, n (%)	14 (21)	3 (19)	4 (25)	4 (18)	3 (25)	0.90
HTN, n (%)	46 (70)	13 (81)	9 (56)	15 (68)	9 (75)	0.35
CAD, n	5	1	0 *	1	3 *	0.04
CVA-TIA, n (%)	10 (15)	1 (6)	3 (19)	3 (14)	3 (25)	0.71
SA, n (%)	19 (29)	4 (25)	3 (19)	9 (41)	3 (25)	0.35
CHA2DS2VasC	2.1 ± 1.4	2.0 ± 1.5	2.2 ± 1.4	2.3 ± 1.3	1.7 ± 1.3	0.71
AAD, n (%)	31 (47)	6 (38)	6 (38)	13 (59)	6 (50)	0.44
EF, %	54 ± 10	57 ± 6	59 ± 9	56 ± 12	47 ± 8	0.07
PT, min	288 ± 69	309 ± 55	300 ± 59	265 ± 75	291 ± 82	0.24
FT, min	24 ± 10	26 ± 10	31 ± 15 *	19 ± 14 *	22 ± 8	0.02
Recurrence, n (%)	32 (48)	9 (56)	8 (50)	8 (36)	7 (58)	0.54

* p value < 0.05 Group 1: non-CF and normal LA Group 2: non-CF and severe LA enlargement Group 3: CF and normal LA Group 4: CF and severe LA enlargement
BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; CAD, coronary artery disease; CVA-TIA, cerebrovascular accident-transient ischemic attack; SA; sleep apnea; AAD, anti-arrhythmic drug; EF, ejection fraction; LAD, left atrial diameter; PT, procedure time; FT, fluoroscopy time.

with a one-way ANOVA test, and time to event was assessed using a Kaplan-Meier curve. The association between the presence of enlarged LA and recurrence was assessed using independent samples t-tests, with the Mann-Whitney U test in the event of non-normal distributions. A p-value of less than 0.05 was considered statistically significant.

Results

Sixty-six consecutive patients with persistent AF undergoing catheter ablation for AF were included in this study. Baseline demographics and procedure details are described in Table 1. Baseline LAD was 47.8 ± 11.6 mm, and LVEF was 54 ± 10 % (Table 1). During a follow-up of 12 months after a single ablation procedure, 34 patients (52 %) maintained sinus rhythm.

Analysis of the groups (group 1: non-CF and normal LA, group 2: non-CF and severe LA enlargement, group 3: CF and normal LA, and group 4: CF and severe LA enlargement) revealed that baseline demographic and echocardiographic parameters were comparable among the 4 groups. Patients who underwent CF-guided ablation with a normal LA dimension had lower recurrence rate (36 %, p=0.54). There was no significant difference in the other groups. Procedure duration and fluoroscopy time were shorter in patients who underwent CF-guided versus non-CF-guided ablation [Table 1].

As shown in [Table 2], age, the presence of comorbidities, LVEF, and procedure details were comparable in patients with AF recurrence and severely enlarged LA to those without recurrence. Table 3 shows comparison of patients with and without AF recurrence and normal LA size. AF recurrences were more common in patients who had longer procedure duration (305 ± 75 min vs. 267 ± 63 min, p=0.09) and in females (10 vs. 3, p=0.006) [Table 3].

Table 2: Comparison of patients with severe LA enlargement in terms of recurrence of AF.

	Recurrence	Non-Recurrence	P-value
	n=15	n=13	
Age, years	64.5 ± 7.4	62.0 ± 8.8	0.44
Gender, male	12	9	0.67
BMI, kg/m2	31.0 ± 5.4	33.0 ± 6.6	0.39
DM, n (%)	4 (27)	3 (23)	0.84
HTN, n (%)	10 (67)	8 (62)	0.96
CAD, n	2(13)	1(8)	0.64
CVA-TIA, n (%)	4 (27)	1 (8)	0.33
SA, n (%)	2 (13)	4 (31)	0.36
CHA2DS2VasC	2.4 ± 1.1	1.6 ± 1.4	0.15
AAD, n (%)	4 (27)	8 (62)	0.09
EF, %	49 ± 9	54 ± 11	0.41
LA, mm	54.0 ± 6.3	52.4 ± 6.0	0.49
PT, min	291 ± 84	301 ± 53	0.72
FT, min	28 ± 12	25 ± 13	0.60
CF, n (%)	7 (47)	5 (38)	0.72

BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; CAD, coronary artery disease; CVA-TIA, cerebrovascular accident-transient ischemic attack; SA; sleep apnea; AAD, anti-arrhythmic drug; EF, ejection fraction; LAD, left atrial diameter; PT, procedure time; FT, fluoroscopy time; CF, contact-force.

Table 3: Comparison of patients with non-severe LA size in terms of recurrence of AF.

	Recurrence	Non-Recurrence	P-value
	n=17	n=21	
Age, years	64.4 ± 10.7	63.0 ± 10.7	0.69
Gender, male	7	18	0.006
BMI, kg/m2	32.2 ± 6.2	30.7 ± 5.3	0.42
DM, n (%)	2 (12)	5 (24)	0.41
HTN, n (%)	14 (82)	14 (67)	0.69
CAD, n	1 (6)	1 (5)	0.93
CVA-TIA, n (%)	2 (12)	2 (10)	0.91
OSA, n (%)	4 (23)	9 (43)	0.09
CHA2DS2VasC	2.3 ± 1.5	2.0 ± 1.2	0.62
AAD, n (%)	8 (47)	11 (52)	0.74
EF, %	44.5 ± 3.6	42.7 ± 4.0	0.17
LA, mm	54.0 ± 6.3	52.4 ± 6.0	0.49
PT, min	305 ± 75	267 ± 63	0.09
FT, min	22 ± 8	22 ± 7	0.99
CF, n (%)	8 (47)	14 (66)	0.32

BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; CAD, coronary artery disease; CVA-TIA, cerebrovascular accident-transient ischemic attack; SA; sleep apnea; AAD, anti-arrhythmic drug; EF, ejection fraction; LAD, left atrial diameter; PT, procedure time; FT, fluoroscopy time; CF, contact-force.

Procedural Outcome

Acute procedural success was achieved in all patients. All patients were in sinus rhythm at the end of the procedure. AF terminated to SR or organized atrial tachycardia in 40 patients. SR was achieved by electrical cardioversion in the remaining 26 patients.

Follow up

During a follow-up of 12 months after a single ablation procedure, there were 32 patients (48 %) with AF recurrences. Of those 32 patients, 12 patients underwent another catheter ablation, 8 patients required electrical cardioversion, and the remaining 12 patients were treated with antiarrhythmic treatment. The Kaplan-Meier curve [Figure 1]showed highly significant differences between the four groups in time to recurrence (Log Rank test = 29.9, p<0.001).

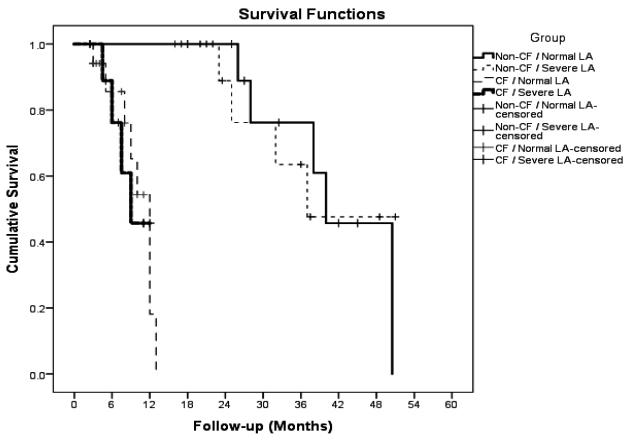

Figure 1: Kaplan-Meier Curve comparing Arrhythmia Free Survival between Groups

Log rank test = 29.9, p<0.001

Discussion

This is the first clinical study where the impact of CF guided catheter ablation was studied in patients with persistent AF and severe LA enlargement. Our findings have demonstrated that CF guided ablation may have a significant impact on the success rate in persistent AF patients with severely enlarged LA but is associated with a lower rate of recurrence in patients with a normal LA size. Procedure duration and fluoroscopy time were shorter in patients with CF-guided ablation compared to those with non-CF catheter ablation.

The interaction between LA size and AF has been confirmed in many studies. Sustained AF results in electrical, contractile, and structural remodeling particularly in patients with persistent AF [14,15]. LA size was found to be a strong predictor of AF recurrences after successful catheter ablation[16]. Maintenance of sinus rhythm (catheter ablation or electrical cardioversion) has been shown to be worse in patients with an enlarged LA [17]. Electrical isolation of the pulmonary veins appears to be an effective treatment for paroxysmal AF[18]. Despite progress in catheter ablation technology, the recurrence rate of catheter ablation is still high and remains around 30-35 % within a year for paroxysmal AF [12]. In patients with the longstanding persistent AF success rate has been shown to be between 52-74 % after 12 months of follow up[16,19,20]. However, the patients included in these studies had a normal LA size. Our results demonstrated a 12 months' success rate of 52 % in persistent AF patients. AF ablation in patients with enlarged LA is highly ineffective and related to a higher rate of failure to keep the patient in SR [21,22].

Catheter ablation in patents with severe LA enlargement has traditionally been challenging. Previous authors have investigated the role of catheter ablation in non-paroxysmal AF patients with severe LA enlargement, and found that radiofrequency ablation of AF is effective, and is associated with LA reverse remodeling and improvements in LVEF[6].

Patients with a larger LA required more ablation and longer durations of ablation in order to complete the ablation. Several techniques and approaches, including using a steerable sheath and better contact force were proposed to improve the outcome in patients with a severely enlarged LA. Very recently, Masuda and coworkers demonstrated the beneficial effects of using steerable sheaths in patients with severe LA enlargement with better outcomes (recurrence rate of 39 %)[23]. The steerable sheath facilitates increased catheter stability and more manipulation, and consequently more adequate lesion formation because of higher catheter-tissue contact. CF technology allows a real-time assessment of the catheter-tissue CF. Low CF during PV isolation is a predictor of acute and chronic PV reconnections, and is associated with an increased risk of AF recurrence[7-10]. In addition, ablation procedures under CF guidance improve the lower recurrence rate of the PV isolation[11]. The clinical outcome of using CF guided catheters in severely enlarged patients has not been investigated very well. In this current study, the recurrence rate of patients with severely LA enlargement undergoing catheter ablation with CF was similar to those without CF (58 % vs. 50 %). Recently, Masuda et al. found that reduced CF in patients with an enlarged LA, and this might explain why a large LA volume was associated with frequent AF recurrences after PV isolation[24]. Schluerman et al. recently studied 25 AF patients undergoing PV isolation with a steerable Agilis sheath, finding that the LA volume did not correlate with the CF[25]. One may question the lower success rate of catheter ablation in persistent AF patients with severely enlarged LA despite technological and procedural developments. This might be explained by evidence of non-PV triggers in patients with persistent AF[26]. In our study cohort, pulmonary veins were targeted in all patients. Several studies have showed that approximately 30% of AF triggers in persistent AF were found to be non-pulmonary venous (non-PV). The most common sites are the superior vena cava, ligament of Marshall, the coronary sinus, crista terminalis, left atrial posterior wall, and the left atrial appendage[27]. Our study did not investigate non-PV triggers.

Limitations

The main limitation of our study is the small sample size. Therefore, we do not emphasize that CF sensed ablation is not effective in severely enlarged LA patients. In this study, we are trying to show that our small sample size did not show any signifcant results, however randomized studies with a larger cohort are needed to validate our findings. LAD may not always accurately reflect LA size because atrial dilatation can be eccentric. Therefore, it would be reasonable to measure left atrial volume and volume index in these patients. We performed 24-h ECG Holter at 3-months, 6 months and 12-months, however the recurrence rate could be underestimated because shorter rhythm monitoring particularly in asymptomatic patients. In addition, we did not assess the difference in terms of durability of PV isolation in the second session, however it is worthwhile to design new follow-up study in order to see this difference.

Conclusions

Although CF guided ablation is a safe approach in persistent AF patients with severe LA enlargement, it does not improve the success rate of catheter ablation. Optimum contact force parameters in persistent AF may not represent the main surrogate for successful outcome.

Conflict of interest and disclosure of funding

All authors declare that, the manuscript, as submitted or its essence in another version is not under consideration for publication elsewhere, and it will not be submitted elsewhere until a final decision is made by the editors of Journal of Arrhythmia. The authors have no commercial associations or sources of support that might pose a conflict of interest. All authors have made substantive contributions to the study, and all authors endorse the data and conclusions. Nevertheless, confirmation of informed patient consent for publication was obtained.

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Compass Mapping, Double Potentials, Activation Patterns Can Identify and Track Rotational Activity Sites in the Left Atrium of Humans with Persistent Atrial Fibrillation

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Abstract

Background: Rotational circuits that occur between bipolar electrodes exhibit double potentials (DPs). It had been previously surmised that rotors could not be electrically tracked directly.

Purpose: Our purpose was twofold; first, to show that the use of compass mapping, one can regionally identify rotational activity; and second, to show that by combining simultaneous compass map recordings, standard narrow-adjacent bipolar, and unipolar recordings, that specific signature recording patterns emerge that allow one to identify the accurate time, location, and path of a rotational mechanism.

Methods: This was an observational study in 20 patients with persistent atrial fibrillation in which the electrode configuration of a circular mapping catheter was changed to wide cross-circle electrode pairing (compass mapping). DPs were recorded and analyzed from 12 left atrial (LA) sites and identified electrical wavefront patterns and direction.A substudy analyzed transitions patterns with simultaneous narrow-adjacent bipolar and unipolar recordings.

Results: Four wavefront patterns were identified: DPs, peripheral waves (PWs), distal peripheral waves and fibrillatory activity. DP wavefront patterns exhibited significantly shorter cycle lengths than PWs in 8 of 12 LA sites. Patients had 2.9± 2.1 regions that exhibited DPs. DPs of varying duration were found, few (25%) were of stable duration and location. Detailed electrical examination at the transition between a PW to a DP identified a highly consistent pattern of simultaneous reversal of activation sequence, a special form of Doppler effect for spiral waves as a rotor passes between 2 electrodes, and a ½ cycle drop-off of activation signals along the line of electrodes.

Conclusions: DP recordings in compass mode can provide a regional assessment for the existence of rotational activity. Simultaneous DP recordings in compass mode, narrow-adjacent bipolar, and unipolar recording provide an accurate assessment of the time, location, and path that a rotational mechanism breaches a perimeter of electrodes. Accurate time, location and path of perimeter breaches can be used to electrically track rotational mechanisms during atrial fibrillation.

Introduction

Twenty years have elapsed since the discovery that most atrial fibrillation is triggered by ectopic beats generated within the ostia of the pulmonary veins[1]. Ablation to electrically isolate these regions has provided a meaningful treatment of this arrhythmia, more so for patients with the paroxysmal than the persistent form[2]. Other ectopic sites[3] and mechanisms[4] may trigger or degenerate into atrial fibrillation. Once initiated, additional mechanisms may maintain and prolong fibrillatory activity. Controversy remains if one or multiple simultaneous sustaining factors are at play. Computational and experimental evidence has provided support for multiple rapid ectopic foci[5,6], multiple random wavelets[7], complex fractionated atrial electrograms[8,9,10] and rotors[11,12].

Key Words

Atrial Fibrillation, Double Potentials, Compass Mapping, Rotor

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Reentry and rotors, both have circular paths of electrical wavefronts. However, they differ significantly when analyzing the central region of that circulation. Reentrant wavefronts move centripetally towards a center that has an unexcitable anatomic barrier or it is functionally refractory[13]. This unexcitable region prevents propagation crossing over to the opposite side that might have disrupted the continuous propagation. In contradistinction, rotor wavefronts spiral centrifugally away from a central core, called a phase singularity. There, at the center, the electrical wavefront shape progressively curves inward to a physical limit preventing advancing into the core[14]. However, since the core region is unexcited, this allows precession (meandering) to adjacent tissue that may too become briefly excitable, but unexcited. Because of the spiral nature of the rotor wavefront, as well as limitations of conduction properties, the cycle lengths measured nearest the core are shorter than adjacent tissue, thus exhibiting a Doppler effect with an approaching core[15,16,17].

Movies of action potential phase changes using voltage-sensitive dyes on in vitro animal models[11,14,18,19] along with computational algorithms[20], provided detailed analysis and description of cardiac

rotor activity during fibrillatory activity. Direct electrode recordings by traditional methods of mapping in humans were deemed too complex to identify potential target areas for ablation[16,21]. Rigorous attempts have been made to recreate the electrical phase analysis (a regional display of action potential phases) in human atria. The action potential phase between electrodes and between splines of a basket catheter was approximated by mathematical interpolation[22]. Phase changes over time that exhibit a spiral movement of an electrical wavefront are considered sites of rotor activity. Ablation within these regions showed initial success for arrhythmia suppression[23,24,25], but has been met recently with far less favorable results[26,27].

Whether an electrical circuit is reentrant[28,29,30] or rotor[31], direct experimental electrical recordings near the center of rotation, or at its pivot point, consistently exhibit double potentials (DPs)[13,28]. DPs have been identified with intracellular electrodes[13], unipolar electrodes[13,28] and bipolar electrodes[29,30]. The DPs have been confirmed to record activation on opposite sides of the electrical circular path[13,28,29,30]. Closer to the center of rotation or near the site of pivot, the DPs appear evenly split[28,30]. DPs, termed inverted double split potentials, were consistently identified at rotor core sites which exhibited highly variable wavefront directions (a higher Shannon entropy,[31]). A bipolar electrode (without regard to alignment) that straddles the center of a rotational electrical mechanism will exhibit two activations (DP) recorded with each one revolution. DPs have also been recorded in various other studies and overall can identify activation on either side of a region of conduction block[32].

We hypothesized that changing the pairing of the narrow adjacent electrodes along a circular mapping catheter to that of cross-circle pairing could provide stable, regional recordings such that the operator could identify the time and place that a rotor entered the perimeter of that region. This cross-circle arrangement of bipolar electrodes creates an electrical compass. If a rotor or rotational mechanism moves toward the perimeter of a circular catheter, stable single wavefronts or peripheral waves (PWs) ought to be recorded with each rotation. However, if a rotor, that has its plane of rotation parallel to the plane of the recording catheter, meanders or precesses across the perimeter of the circular mapping catheter, then the PWs should immediately transition into recording DPs. In addition, rotor precession in and out of the compass perimeter might provide directional and possibly direct location information as to where the rotor entered and exited. Such a method might utilize direct recognition of alternating double potentials as sites of rotational activation rather than relying on proprietary computation, interpolation, and animated movies.

Methods

Study Population

Twenty-two consecutive patients with symptomatic persistent atrial fibrillation (> 1week duration or required cardioversion to regain sinus rhythm) were admitted for ablation. Two patients had a prior ablation with pulmonary vein isolation (PVI). The average age of patients was 65 ± 8 years, 15 male and 7 female. The average duration of atrial fibrillation was 7.5 ± 6.2 months. Cardiac structure and function assessment show large LA diameter (4.5 ± 0.6 cm) and mild LV dysfunction (LVEF 48 ± 12 %). The average CHADS2VA2Sc score was 2.3 ± 1.0. Nineteen patients had a diagnosis of hypertension, 4 patients with diabetes, and 1 patient with a prior stroke. Each patient signed a written informed consent of the research protocol that was approved by our local institutional review board. All patients underwent a transesophageal echocardiogram one day prior to procedure to exclude a left atrial thrombus. Patients remained on their prescribed oral anticoagulation without cessation. Previously prescribed antiarrhythmic drugs except amiodarone (n=9) were discontinued 5 half-lives prior to their ablation. Patients completed their procedure in the post absorptive state under general anesthesia. Standard access of catheters was performed through femoral and right internal jugular vein access. All research protocol mapping was completed prior to standard pulmonary vein (PV) isolation. PV isolation of all 4 veins was achieved in every patient. AF was terminated in 1 patient during PVI alone. All other patients underwent additional ablation lines (roof line, mitral isthmus, tricuspid isthmus, and/or appendage) with goal of achieving sinus rhythm. If AF organized to an atrial flutter or tachycardia, then this mechanism was also targeted for ablation. In another 7 patients, AF terminated with additional lines. If further mapping and ablation did not terminate into sinus rhythm, then electrical cardioversion was performed. Ablation was performed with a 3.5 mm irrigated tip catheter (Thermocool, Biosense-Webster, Diamond Bar, CA). Ablation energy used was 25 W along the posterior wall and 30-35 W elsewhere. All electrogram cycles, vector analysis was completed off-line and could not be used to help target ablation.

Compass Mapping Technique

Experimentally, rotors in animals with atrial fibrillation can control a surrounding tissue area up to 5cm^2[33]. A circular mapping catheter (LassoTM, Biosense Webster, Diamond Bar CA, USA) encircles an area of 3.14 cm^2 and was used to systematically map, record and analyze 12 specific regions of the LA [Figure 1]. To identify and examine rotational activity with the characteristic double potentials, the bipolar electrode input configuration from the standard adjacent narrow pairing of electrodes was changed in the software electrode parameters in the recording workstation (Cardiolab, GE Medical, Milwaukee, WI, USA). An electrode was paired with the electrode

Table 1: Electrode configuration of cross-circle bipolar pairings to create compass recordings.

			Inputs	
Catheter	**Lable**	**Type**	**+**	**-**
Coronary Sinus	CS 1,2	Bipolar	2	1
	CS 3,4	Bipolar	4	3
	CS 5,6	Bipolar	6	5
	CS 7,8	Bipolar	8	7
	CS 9,10	Bipolar	10	9
Circular Mapping	Ls 1,2	Narrow Bipolar	12	11
	Ls 3,4	Narrow Bipolar	14	13
	N 11,19	X-Circle Bipolar	21	29
	NW 9,17	X-Circle Bipolar	19	27
	W 7,15	X-Circle Bipolar	17	25
	SW 5,13	X-Circle Bipolar	15	23
	S 12,20	X-Circle Bipolar	30	22
	SE 10,18	X-Circle Bipolar	28	20
	E 8,16	X-Circle Bipolar	26	18
	NE 6,14	X-Circle Bipolar	24	16

directly across the circle, 8 such pairings (using electrodes 5 - 20) were made moving around the circle [Figure 2A]. [Table 1] provides the electrode pair configuration. Electrode pairs (1,2), and (3,4) remained configured as narrow pairs to provide very specific local electrical information while simultaneously recording regional wide cross-circle bipolar recordings. All recordings were made at gain

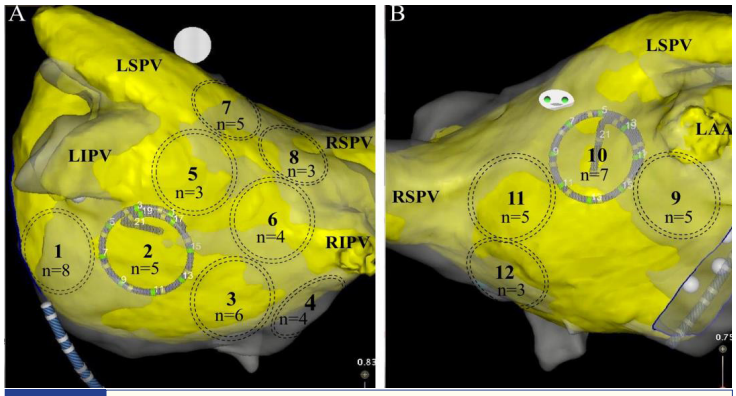

Figure 1: **Left atrial sites of recording (LA). A. Posterior view of LA. Recording sites 1-8. Site 1: left lateral atrial wall; site 2: left inferior postero-lateral; site 3: left inferior postero-medial; site 4: left postero-septal; site 5: Left inferior pulmonary vein (LIPV) posterior wall ostia; site 6: Right inferior pulmonary vein (RIPV) posterior wall ostia; site 7: Left superior pulmonary vein (LSPV) posterior wall ostia; site 8: Right superior (LSPV) posterior wall ostia. B. site 9: left anterolateral adjacent to left atrial appendage (LAA); site 10: roof at LSPV; site 11: roof at RSPV; site 12: left antero-septal.**

At each site, identified by dashed circles, DPs were observed by n number of patients.

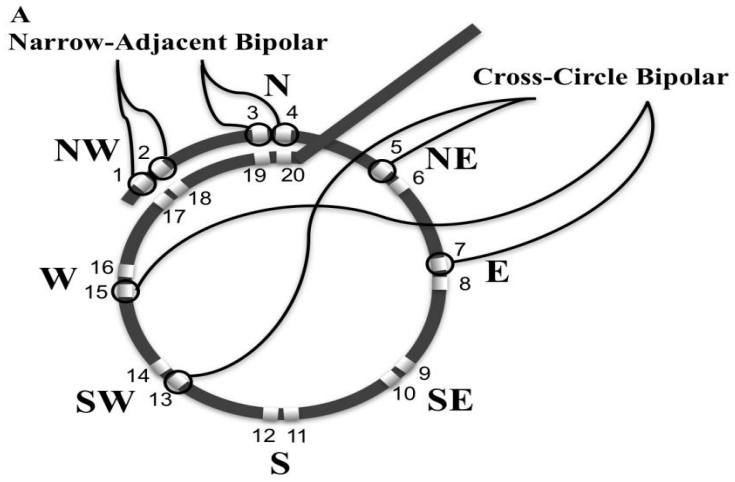

Figure 2A: **Electrode pairing configuration to create compass-mode recording. A. Schematic of circular mapping catheter bipolar electrode configurations. Narrow-adjacent bipolar electrode pair included (1,2) and (3,4). Cross-circle bipoles are arranged in a compass-mode configuration North or N = bipolar electrode pair (11,19) , NW = bipolar electrode pair (9,17) ; W = bipolar electrode pair (7,15); SW = bipolar electrode pair (5,13); S = bipolar electrode pair (12,20); SE = bipolar electrode pair (10,18); E = bipolar electrode pair (8,16); and NE = bipolar electrode pair (6,14).**

of 500 with low pass and high pass filters set at 30 Hz and 500Hz respectively. The cross-circle pairing created an electrical compass and were labelled the 8 cardinal points of a compass (N, NE, E SE, S, SW, W, and NW). Looking down the barrel of the shaft where the catheter turns perpendicular to the shaft is designated North. The East direction is designated 90 degrees moving clockwise around the compass. Sliding the thumb lever up moves the catheter downward or to the south. With a 90-degree bend toward the south, rotating the handle clockwise moves the compass to the west.

The electrode configuration setup results in a rising slope activation electrogram with an approaching electrical wavefront from that specific cardinal point direction. Compass directional information was confirmed with a 3-dimensional high density activation map that was created in sinus rhythm of the right atrium [Figure 2B,Figure 2C]. The circular mapping catheter was placed just inferior to the sinus node along the lateral wall with East electrode of the compass closest to the sinus node. Note that a large broad wavefront propagates past electrodes parallel to wavefront direction, whereas activation perpendicular to the wavefront is very short.

A rotational circuit, whether rotor or reentry within the perimeter of the circular mapping catheter would be expected to exhibit double potentials of alternating slope [Figure 3]. A rotational circuit outside the perimeter should result in a wavefront that passes through the perimeter with a single activation pattern that identifies the wavefront direction as it passes under the circular catheter.

All patients were mapped while in atrial fibrillation prior to ablation. In one patient (patient #2), at the time of catheter entry, despite multiple aggressive pacing techniques, AF could not be induced into sustained epochs long enough to adequately map. His mapping data was not included in the analysis. Another patient (patient # 20) was in an atypical perimitral flutter at the start of the case. He was mapped while in atypical flutter and this information will likely be submitted as a case study. His data is not included along with the other 20 patients.

A LA 3-D atriography image (Philips, EP Navigator) was created in each patient just prior to induction of anesthesia. The 3-D map was merged into Carto Biosense Workstation. After transseptal puncture the circular mapping catheter was placed into the LA. The catheter was positioned at each of 12 locations of the LA. Just prior to the recording at each LA site, electrode numbers 1,2, were confirmed to be aligned with electrode 17, 18 to maintain consistent circle size. This properly oriented all electrodes as a compass. Sixty second recordings were completed from each of the LA sites. In a substudy, simultaneous unipolar and narrow adjacent bipolar electrode recordings were obtained in the last 5 patients with either jpg or mp4 files. These recordings were synchronized to the recordings on the GE workstation by placing 3-5 V-paced beats at the start and end of each one-minute epoch.

Wavefront Activation Pattern Definitions

Activation patterns of the areas mapped by the circular catheter were analyzed off-line, cycle by cycle. In [Figure 4A], and similar to what others describe[34,35], but with the addition to DPs, we designated patterns of activation as either DPs, PWs, distal peripheral waves (DSPW), or fibrillatory conduction (Fib). PWs were designated if at least 5 sequential cycles recorded a similar morphology and wavefront direction and separated between cycles with quiescent electrical activity. Cycle measurements continued until there was a sudden change in waveform morphology or direction. Cycle lengths continued to be measured for that epoch pattern if there was as shift

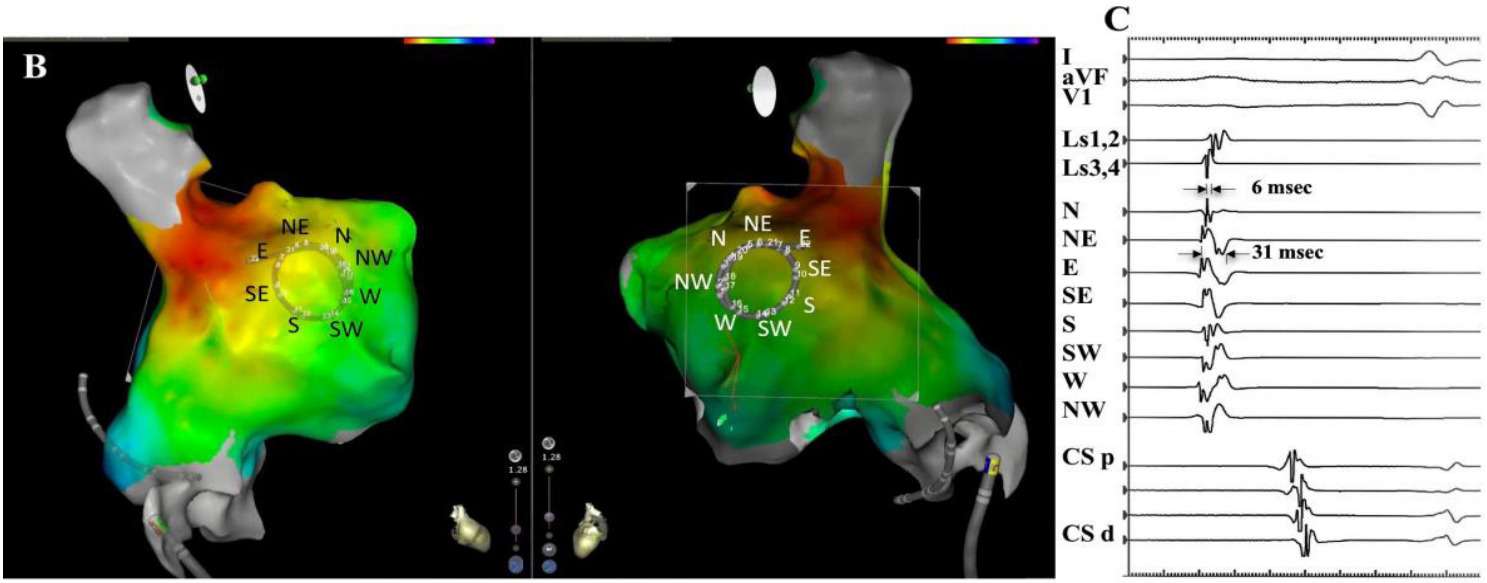

Figure 2B,2C: Electrode pairing configuration to create compass-mode recording.B.3-D electroanatomic map identifies sinus node region in red external perspective on left, internal perspective on right. East electrode (E) is closest to sinus node. C. Recording of electrical wavefront with circular catheter placed at lateral wall of right atrium in sinus rhythm. Top 3 recordings are surface leads 1, avF, and V1. The next two traces are recorded from narrow adjacent pairs (1,2) and (3,4). The next 8 traces record form the 8 cross-circle bipolar electrodes as configured in 2A. The last 5 traces record activation from the coronary sinus catheter (CS) from proximal(p) to distal (d). Atrial wavefront originating from sinus node moves across recording region of circular mapping catheter that records in compass mode with the E direction showing the largest, broadest activation. Perpendicular to this direction, N and S directions show smallest and narrowest activation.

to an adjacent compass direction sources, as what might be expected during precession (meandering) of a possible rotor core (i.e., N=> NE). CL measurements ended for this event if the shift was not to an adjacent directional vector (i.e., N=> SW). Similar to PWs, a DSPW identified regions where cyclic wavefronts had similar morphology and direction for at least 5 cycles, but at least one additional wavefront,

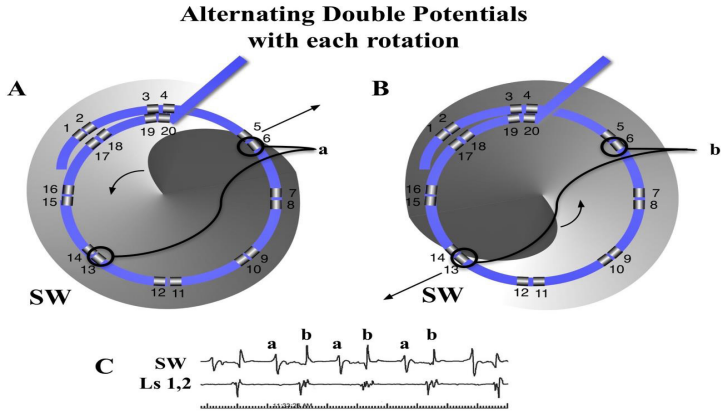

Figure 3A: Diagram of a counterclockwise rotor that exhibits DPs of alternating slope in compass-mode mapping. The gray spiral rotor has its advancing head at darkest gray curve. Arrow showing wavefront spiral direction) with core near the center of circular catheter with wavefront passing opposite sides of the compass. A. The wavefront spiral passes electrode 6 of the cross circle bipolar pair (6,13), SW on compass. The SW tracing shows a positive deflection. B. One half cycle later, the wavefront spiral passes the electrode 13 of the cross-circle bipolar pair (6,13). The SW tracing now shows a negative deflection since the wavefront is in the opposite direction compared to ½ cycle earlier.C. The 2 tracings below show the recordings from the SW direction with alternating DPs, while only single activation wavefront is recorded from the narrow-adjacent bipolar pair (1,2).

a secondary wave, that prevented an isoelectric phase between cycles of the primary wavefront. The secondary wavefront(s) could not have a 1:1 association with the cycle lengths of the primary wavefront. Double potentials (DPs) were designated as a wavefront pattern within the region that displayed two distinct wavefront activations. The primary and secondary wavefronts maintained a 1:1 correlation of cycle lengths. To minimize chance of nonrotational causes or competing adjacent cyclic mechanisms of DPs, 5 cycles were required to be categorized as a DP. DPs were described in more detail; having alternating or same slopes, or if cardinal point activations were sequential in time or almost simultaneous (a vertical alignment in time). DPs had to be displayed in at ≥ 2 cardinal directions. Fibrillatory activity was designated for the rest of the disorganized activity recorded that did not fulfill the criteria as discussed above. Cycle lengths, number cycles, total duration, wavefront direct of each pattern were recorded over the minute. Transitions between each type of activation pattern were also tabulated.

To assess inter-observer variability, all double potential sites classified by the primary investigator was reassessed by a second observer (H.Y.) All were confirmed as double potentials, six differed as to the duration of DPs, none more than 2 rotations. Final duration of these patterns was determined by mutual consensus.

Analysis of Transitions between Double Potentials and Peripheral Waves

Simultaneous unipolar, narrow bipolar, and wide cross-circle electrodes were recorded during this transition in 4 patients analyzing a total of 28 rotational events at the transition. The 5th patient had perimitral flutter. The presence of a rotational activation, parallel to the plane of endocardial surface, was defined similar to Ghoraani et al.[36]. We utilized the criteria of sequential activation along the 16

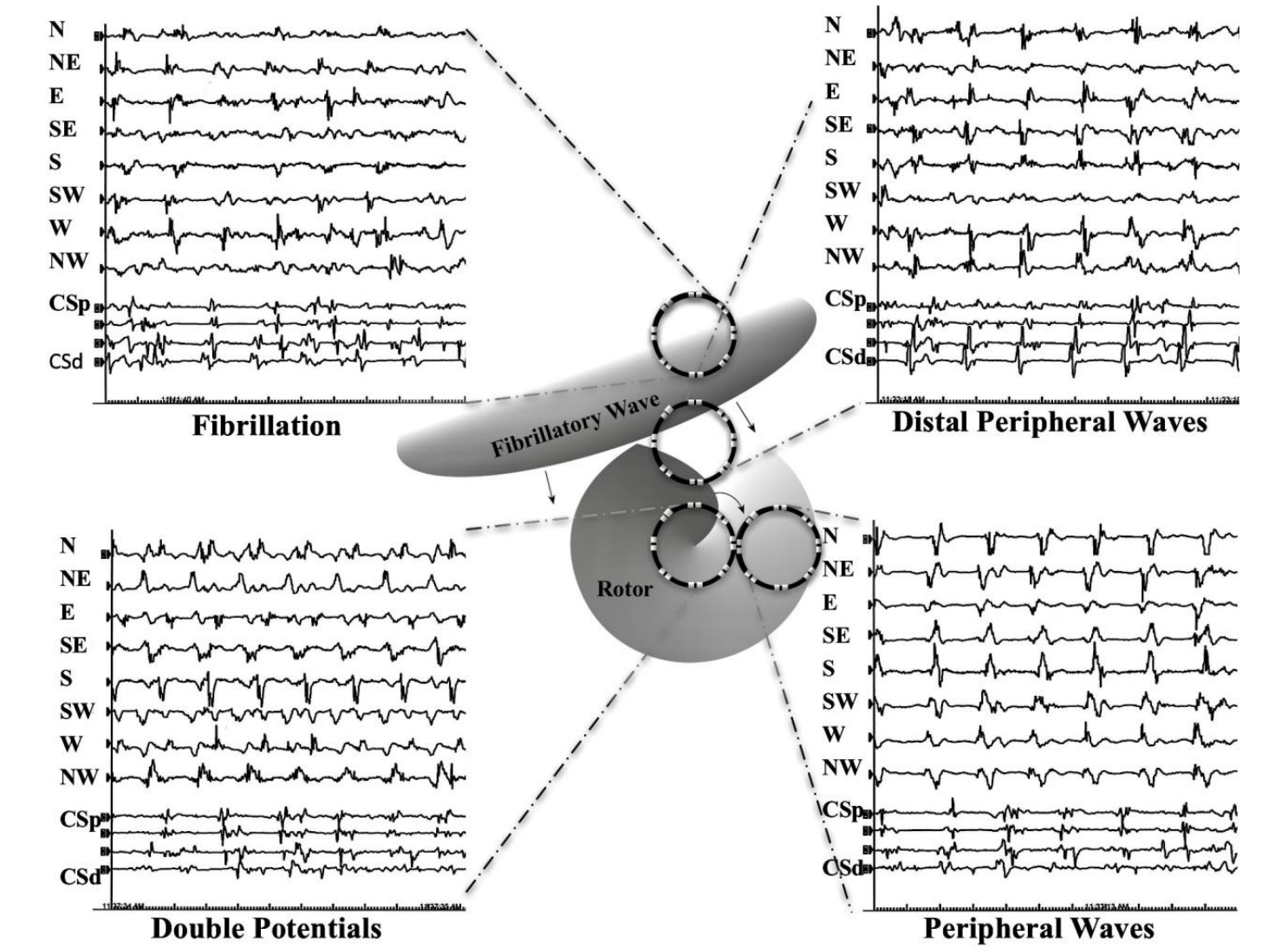

Figure 4A: Diagram of wavefront patterns defined in Methods of compass recordings in different areas over or near a rotor. Each of the 4 recordings show the cardinal compass recordings in the top 8 traces with the next 4 traces recorded from the coronary sinus catheter (CS) from proximal (p) to distal (d). At the top left, fibrillatory (Fib) activity is seen throughout all 8 cardinal directions. At the top right, distal peripheral waves (DSPW) exhibits a cyclic pattern is seen with gradually changing morphology with additional wavefront activation between the primary cyclic activations. The bottom right shows a peripheral wave (PW) that exhibits a cyclic pattern and stable morphology with almost no activation signals between cycles. The bottom left shows the circular catheter that directly overlays a rotor and would show double potentials (DPs) in many, if not all cardinal directions.

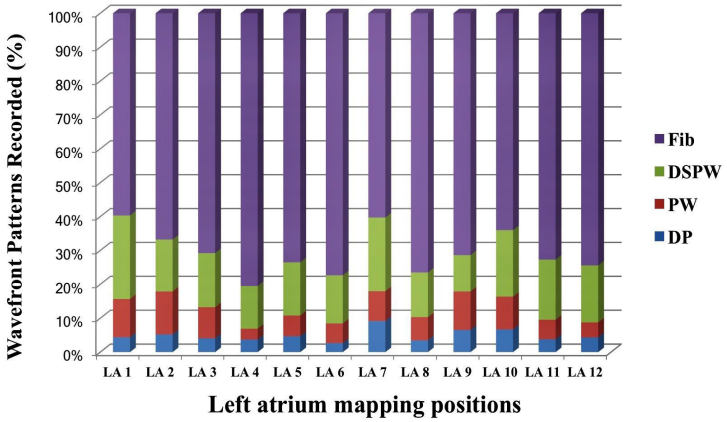

Figure 4B: Shows cumulative data wavefront patterns over 20 patients in the 12 different LA sites. LA site #7 (LSPV ostia) and site #10 (roof) showed highest percentage of DPs

electrodes around the perimeter of the circular catheter, where head-meets-tail, and ≥2 rotations. We added further stipulation that the time gap between any 2 adjacent electrodes was ≤ 50% of the cycle length, as will be discussed below. Two separate recording systems were required to confirm DPs by compass and unipolar recording. Additional data of from the narrow adjacent bipolar recordings allowed simultaneous verification of local activity at the N and NW compass poles [Figure 2A].

Statistical analysis

Data were expressed as mean ± SEM and were compared between study groups with the use of one-way ANOVA. Probability value of $P<0.05$ were considered statistically significant.

Results

Compass mapping utilizing cross-circle paired electrodes identified

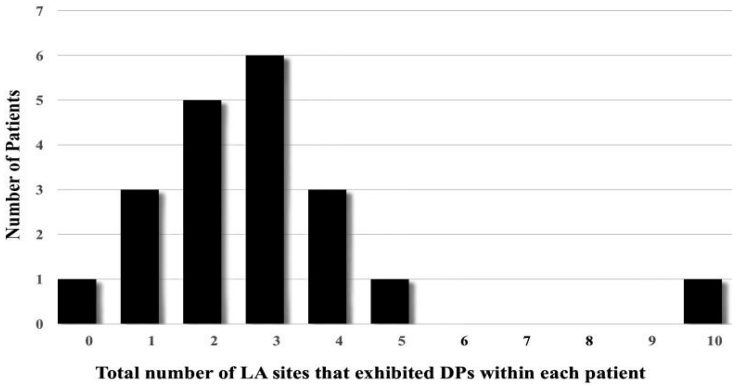

Figure 5: Number of LA sites that exhibited DPs within each patient. One patient showed no DPs at any of the 12 LA sites recorded. At the other extreme, one patient had 10 of 12 LA sites exhibit DPs. The average number of LA sites that exhibited in a patient DPs was 2.9 ± 2.1.

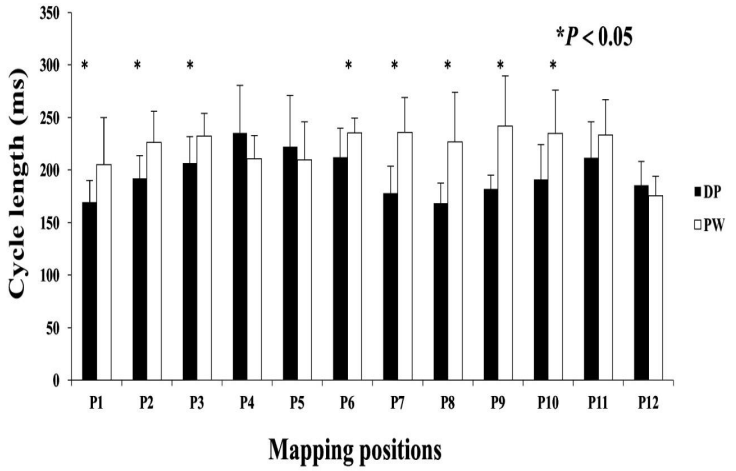

Figure 6: DPs and association with Doppler Effect. Compass mode mapping exhibits a PW across the region of recording, the CL shortens as a rotational mechanisms precess into that region. Each LA site was matched paired with PW to DPs. DPs showed significantly shorter CL compared to PWs at LA sites 1,2,3,6,7,8,9,and 10.

rotational activity whether from microreentry or rotor activity in the recognizable form of double potentials. A total of 235 sites utilizing the compass mapping method recorded regional AF out of a possible 240 sites. A stable position with good electrode contact was maintained for the 60 seconds of recording at each of the sites. Anatomic constraints, a thin flat atrial chamber, prevented stable recordings from sites 4,7,8,9 from patient # 5, site 8 from patient #8.

Distribution, Prevalence and Cycle Lengths of Wavefront Patterns

[Figure 4B] shows distribution of wavefront patterns seen at each of the 12 locations. Highest percentage of DPs were located at Position #7 (9.2%), at the posterior wall just outside the left superior PV. Figure 1 shows how many patients (n) exhibited DPs at a recorded LA site. Most frequent sites exhibiting DPs included left lateral wall, roof, LSPV and RIPV (n = 8,7,5,5 respectively). A measure of local stability of the DP is the duration of epochs, for continuous number of cycles of DPs prior to transitioning to a different wavefront pattern. Duration was separated into bins of cycle #s. Most abundant were DP# 5-10 cycles (n=82), then > 20 cycles (n=38), followed by 11-15 cycles (n=37), and 16-20 cycles (n=16). Average cycle lengths

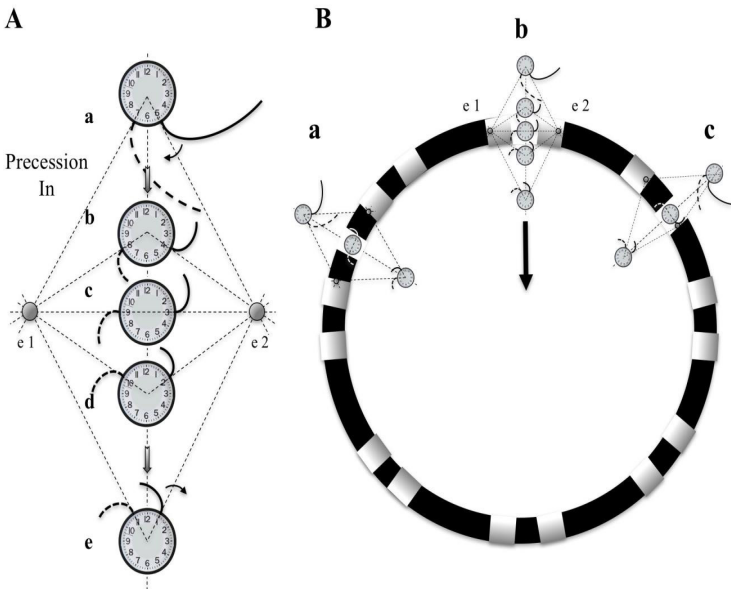

Figure 7: Diagram of differential Doppler effects on electrodes with precession past electrodes. A. A rotor diagrammed as a clock hand circulating clockwise moves on a path that bisects electrode 1 and 2. Electrode 2 is on the side of the rotor which the wavefronts are moving forward, parallel to the precession path. Electrode 1 is on the other side of the rotor which the wavefronts are also parallel to the path of precession but in the opposite, or backward direction. Initially (position a), a spiral wave will transmit a wavefront signal at electrode 2 at 5 o'clock followed shortly by the wavefront signal reaching electrode 1 at 7 o'clock. A moment later (position b), with the rotor closer to the electrodes, the wavefront reaches electrode 2, earlier in time, at 4 o'clock (Doppler compression with a shorter CL), while reaching electrode 1, later in time, at 8 o'clock (Doppler expansion with a longer CL). When the rotor reaches a point directly between electrodes 1 and 2, the wavefront reaches electrode 2 at 3 o'clock and then electrode 1, a full ½ cycle later, at 9 o'clock. If the rotor were to stay at this position, DPs that are fairly equally separated in time would be expected, (see Movie 1). The process continues as the rotor reaches position d and e. When reaching these positions there is a reversal of sequence, activation at electrode 1 followed shortly by activation at electrode 2. B. Diagram of three paths that a rotor can breach the perimeter of the circular catheter, between 2 pairs of narrow-adjacent bipolar electrodes (a), between 2 electrodes of a narrow-adjacent pair (b), or directly under an electrode (c).

(CLs) of consecutive DPs were compared between bins of 5-10 cycles (CL = 192.9 ± 34.5 msec), 11-16 cycles (CL = 182.8 ± 31.4 msec), 16-20 cycles (208.9 ± 36.7 msec) and > 20 cycles (199.3 ± 46.2 msec). Epochs exhibiting consecutive DPs of 11-15 cycles had significantly shorter CLs from epochs lasting 16-20 cycles (p =0.02) and epochs lasting longer than 20 cycles (p =0.04). Long continuous DP epochs were rare to be recorded (n=11 for 10-20 sec; n=3 for 20-30 sec; n=1 for 30-40 seconds, n=1 for > 60 seconds). Only 2 patients (Pt #19 and Pt#22) showed 2 LA sites with DPs recorded for >30 seconds. Marked variation is seen between patients in the site location, number of locations and stability. The average number of LA sites that exhibited DPs in a single patient was 2.9 ± 2.1 with a large range (0-10, [Figure 5]). Patient # 14 showed no DPs at any of the 12 LA positions. Only highly disorganized activity with only 1.8 seconds of PWs were recorded from position 1, with all other measurements showed either a DSPW pattern or Fib. At the other extreme, patient #16 had 10 of 12 LA sites exhibit DPs, with the longest total duration identified at LA site #1 for 17.8 seconds. Of

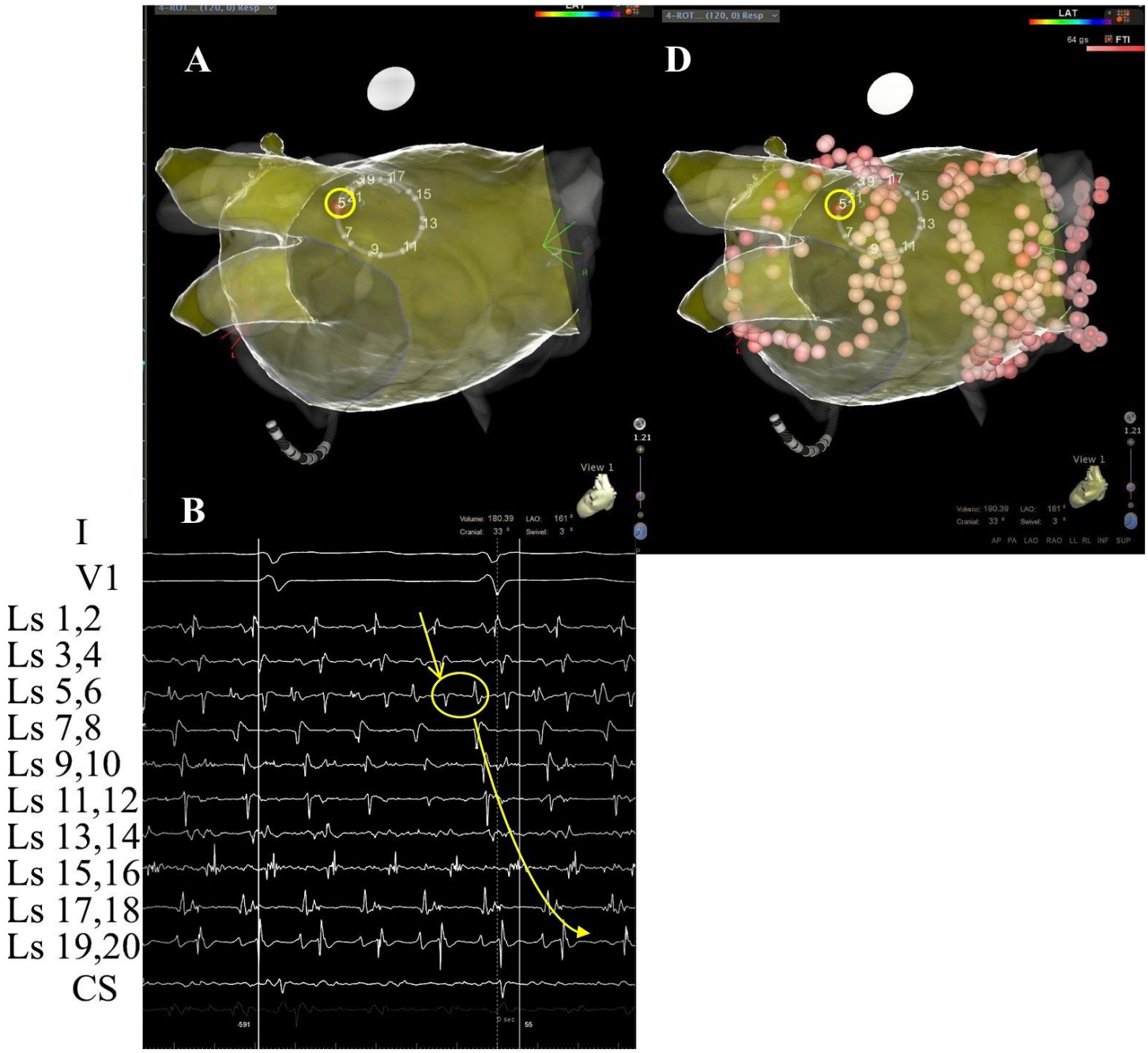

Figure 8 A B & D: **Rotational mechanism at perimeter of circular catheter. A. 3-D anatomical map with transparent position of circular catheter placed at LA site 7 in patient #18. B. Top 2 tracings show surface leads I and V1. Next 10 tracings show narrow-adjacent bipolar electrode recordings around circular catheter, then unipolar electrodes followed by coronary sinus (CS) proximal (p) and distal (d). The last trace shows recording from CS catheter. Yellow circle shows position of electrode 5 at site of DPs as seen throughout recording of bipolar pair (5,6). D. Superimposed ablation lesions compared to location of relatively stationary rotational mechanism. Electrode 5 is well within the lesion set to isolate the left PVs.**

interest, in the 9 patients that had been on amiodarone there was no significant difference of the cycle lengths of DPs compared to the 11 patients not exposed to amiodarone (188 ± 32 msec vs 191 ± 35 msec, respectively).

Cycle lengths of Waveform Patterns and Evidence for Rotor Doppler Effect

Many DPs were preceded and or followed by a short period of a PW pattern. Measuring CL at this transition commonly exhibited a shortening of CLs, or Doppler effect on the compass recordings until DPs were manifest. The opposite was noted moving from DPs to PW. The CL of DP wavefront patterns were evaluated in a matched pair comparison to the CL of PWs from the same LA site [Figure 6]. Eight of 12 LA sites showed a significantly shorter CL for DPs compared to PWs. DP cycle lengths did not show a significant difference at any of the 12 LA sites when compared to DSPW.

Transitions

Recording the transitions between DPs and PWs were most

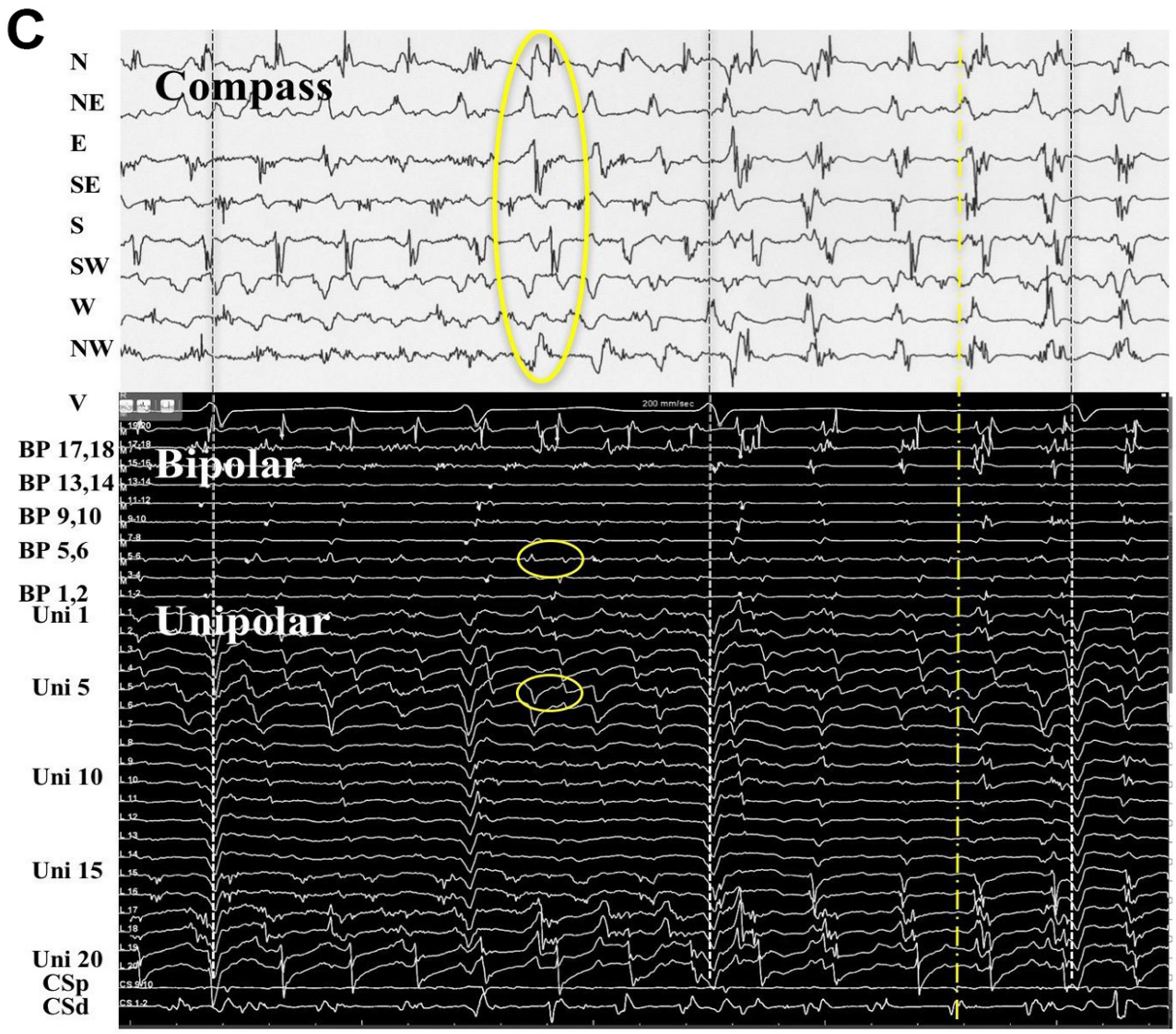

Figure 8 C : Simultaneous recordings at LA site #7 from top: compass map (top 8 recordings), V1 surface recording used to synchronize all recordings with grey-white dashed lines, middle: narrow-adjacent bipolar (middle BP pair 10 recordings), unipolar (bottom Uni 20 recordings) around catheter and then coronary sinus (CS) proximal (p) and distal (d). The yellow circles show simultaneous DPs in unipolar 5, narrow-adjacent bipolar 5,6, and throughout compass recordings. The yellow dashed line shows the rotational mechanism precessing out away from perimeter of circular catheter as DP pattern switched to PW on compass, bipolar, and unipolar recordings, while the sequential activation gives way to a more vertical alignment. Note that location is corroborated by the largest amplitude, earliest positive deflection occurs at NE – E direction which is exactly where electrode pairs (5,6) reside.

instructive. It might be expected that an approaching rotor prepares or clears the tissue ahead of it by organizing it into PWs prior to precessing into that region. In the 173 recordings of DPs, there was a transition from a PW pattern (n=26, 15.0%), DSPW (n=88, 50.9%) and Fib (n=59, 34.1%). Once in DP, there was a transition to PW (n=27, 15.6%), DSPW (n=69, 39.9%) and Fib (n=77, 44.5%).

In Depth Analysis of DP Transitions and New Relative Doppler Effect Physiology

Perimeter Breach, activation Sequence Reversal, Compression and Expansion Doppler Effects

Transitions to and from DPs and PWs were analyzed with simultaneous recordings in compass mode, narrow-adjacent bipolar and unipolar recordings. A diagram is presented first to demonstrate hypothetical geometric and time dependent changes of electrode recordings as a rotor passes between a pair of electrodes [Figure 7A]. A rotor, represented as a clock hand moving clockwise lies just outside the perimeter of the circular catheter. The wavefront generated from the rotor crosses the two electrodes (e2 and then e1) at times 5 and 7 o'clock respectively. As the rotor moves along a path that bisects e1 and e2. The timing of activation at these electrodes moves in opposite direction. The e2 activation signal occurs progressively earlier in the rotation cycle, while the e1 activation signal occurs progressively later. The time lapse between activation signals from e2 and e1 lengthens. If the rotor were to sit at the midpoint between the 2 electrodes, then the time separation between the 2 electrodes would be ½ of a full rotation. If e1 and e2 are electrodes of a bipolar recording, then the activation recordings would result in alternating double potentials (movie1, and [Figure 7B]). This leads to an important finding that the narrow-adjacent bipolar recordings can detect crossing the perimeter

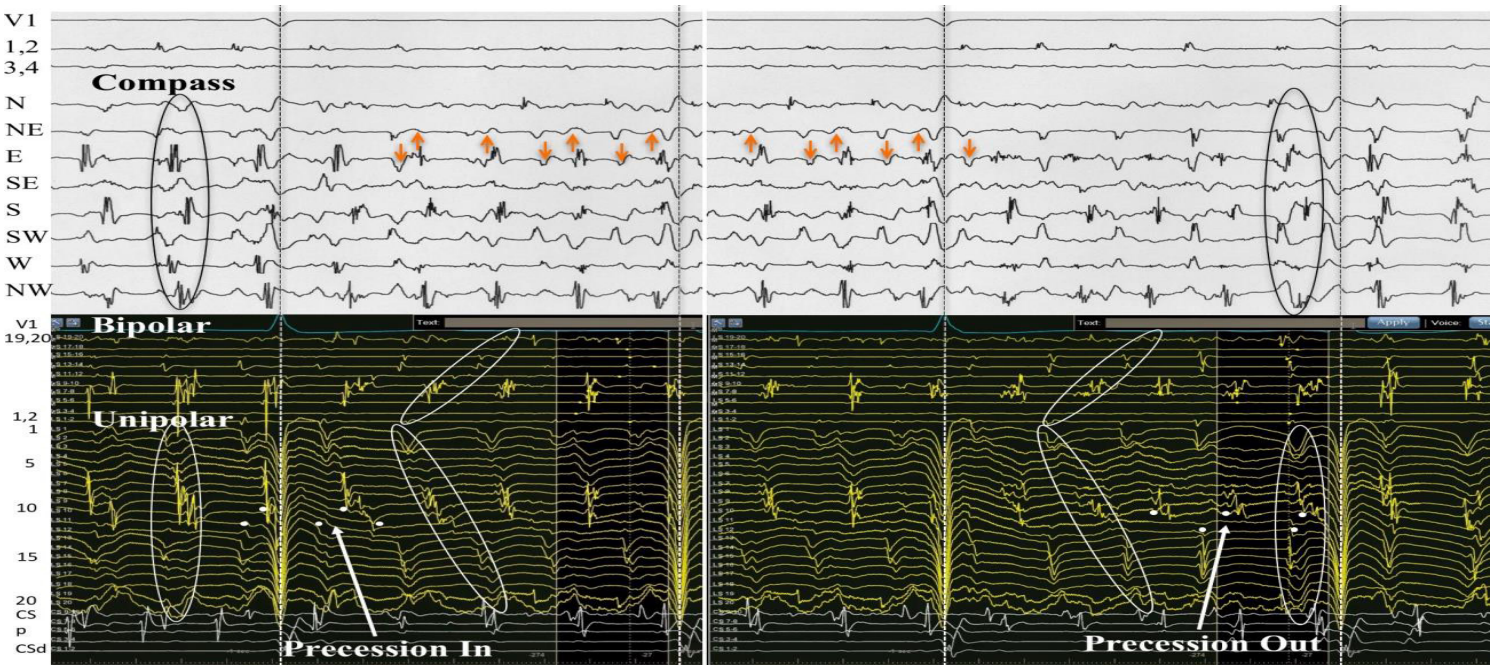

Figure 9:

A rotor precessing in and out of a circular perimeter of electrodes. Simultaneous methods of recordings were performed at LA site #9 from patient # 21. From top: Surface lead V1, narrow-adjacent bipolar pair 1,2 and 3,4, compass recordings (next 8 recordings), narrow-adjacent bipolar pairing 1-20 electrodes, unipolar recordings 1-20, and coronary sinus (CS) tracings proximal (p) to distal (d). Initial wavefront pattern is a PW on compass recordings (black vertical oval) with fairly vertical alignment of bipolar and unipolar recordings. As rotor precesses passed the perimeter, alternating DPs (gold arrows) develop throughout compass recordings while a sequential alignment (slanted white circles), head-meets-tail of narrow-adjacent bipolar and unipolar recordings. A ½ cycle drop off occurs between electrodes 11 and 12. A Doppler compression of wavefronts occur at electrode 12, while there is a Doppler expansion at electrode 11. White dots show the moment that the 1/2 cycle drop off occurs when the vertical alignment switches to sequential alignment and reversal of activation sequence. The narrow-adjacent bipolar recording shows a DP as the rotor passes between the 2 electrodes. The right-hand portion of the figure shows the opposite movement of the rotor passing between electrode 11 and 12. The rotor continues to spin with the same direction. Sequential activation with a slanted head-meets-tail alignment are identified by white slanted circles. As expected the rotor precessing in the opposite direction of between the same electrode pair exhibits a Doppler compression of wavefronts at electrode number 11 while electrode 12 receives a Doppler expansion of wavefronts (white dots). A DP appears at the narrow adjacent bipolar recording of 11,12 at the moment of ½ cycle drop off occurs and when the PW pattern appears on the compass recordings (black vertical oval). Grey to white dashed lines synchronize unipolars to compass recordings.

by a transient DP in that specific pair just as the cross-circle pairing detects that a rotor has moved within the perimeter. Importantly, once the rotor has moved within the perimeter of the circle, the time gap between the e1 and e2 electrodes would be less than ½ the CL.

In patient #18, at LA position #7, rotational activity was noted to be slowly transitioning from the perimeter with DPs on all 3 forms of recordings (compass, narrow-adjacent bipolar, and unipolar, [Figure 8] to a position outside of the compass, generating a PW [Figure 8C]. The PW, identified by the vertical yellow dashed line on the right, shows a wavefront that has earliest activation at electrodes 5,6 at the NE compass point. Two cycles earlier than the yellow line, the largest gap in time is seen on unipolar 6. Note the drop of ½ of the signals from electrodes 6 through 20. This position site as seen in[Figure 8AandFigure 8D], was incorporated within the ablation line that circumnavigated the left PVs. Isolation was achieved, Afib persisted. Just prior to completion of the right PV isolation line, AF terminated. This patient has remained arrhythmia free for 22 months. Our simulation of the activation sequence of a rotor is taken further and breaches a line of electrodes or a perimeter of electrodes around a circular catheter (Movie 2 and Movie 3). This slow-motion identifies an expected pattern of activity that would be specific to a rotor or any rotational mechanisms that moves completely to the other side of the recording line. If a rotor close to the line of electrodes moves along a path towards the midpoint of 2 electrodes, then relative Doppler compression of wavefronts are expected on the electrode receiving the forward moving waves that are parallel to this path. A relative Doppler expansion of wavefronts are expected on the second electrode that is on the opposite side of the rotor. This second electrode receives the backward moving wavefronts relative to the precession direction. At this moment of transition a PW with mostly vertical alignment of activation signals becomes slanted or sequential in alignment where head-meets-tail. That transition, that breach, occurs at the site between the 2 electrodes that exhibit maximal Doppler compression and maximal expansion of wavefronts. This occurs at the moment that activation sequence reverses in direction (movie2 and movie3). Whether precession occurs past a line of electrodes, or along the perimeter of a circle, that transition pattern of Doppler compression and expansion is the same. The progressive delay in activation at the 2nd electrode along with the simultaneous changes in all the other electrodes along the line, results in a unique pattern of activation change that we label as the ½ cycle drop-off. This position and moment in time of sequence reversal, puts a very specific location of the center of rotation. The ½ cycle drop-off would be unique to a rotor or a microreentrant mechanism, since it requires the entire circular path to have crossed the line between the 2 electrodes.

Recordings from patient #21 at position 9 [Figure 9A and Figure 9B]) shows simultaneous compass, narrow-adjacent bipolar and unipolar recordings of a transition from a PW to DP and then back to PW. At the moment of wavefront pattern transition occurs in compass mode, the unipolar activation pattern shows the Doppler compression and expansion at poles 12 and 11 respectively, while the same bipolar pair (11,12) exhibit DPs. The ½ cycle drop-off occurs above electrode 10. The opposite transition occurs with precession out from the circle. This pattern repeated a total of 5 times during the 1 minute of recording.

Back and Forth Rotor Precession

Even though we did not have simultaneous unipolar recording of patient #16, the simultaneous narrow-adjacent bipolar recordings from the free end of the circular catheter (Ls1,2) and (Ls3,4) were available to observe. A special transition occurred to and from PW and DP on the compass and ultimately provided a rare look at rotor precession ([Figure 10A, Figure 10B and Figure 10C]). The simultaneous DPs at the narrow-adjacent pair Ls3,4 coincided with the DPs on the compass in the wider cross-circle (N-NE direction) which is orthogonal to Ls3,4. When the DPs move (presumably the site of the rotor core) to narrow-adjacent pair Ls1,2, the DPs in the compass mode record a transition of the wavefront pattern to PWs. The rotor moved along the line of the catheter, back and forth between narrow-adjacent pairs Ls1,2 and Ls3,4 and exhibited twelve transitions in the first twenty-three seconds of recording, each time coinciding with simultaneous transitions in the compass. The repetitive electrical activation pattern was confirmatory that a rotor precessed back and forth at this location. Bipolar pair Ls1,2 must lie just exterior to the perimeter since when DPs occurred here at this narrow-adjacent pair, only PWs were being recorded on the compass. The equally separated DPs recorded from Ls1,2 are consistent with a rotor just outside the perimeter of the compass. The compass mode recording provides location verification that the rotor exists very close to the perimeter (maximal and earliest positive deflection at the N direction) exactly where these narrow-adjacent pairs of electrodes are located. As soon as the DPs move to bipolar pair Ls3,4 there is a simultaneous switch to DPs within the compass and loss of DPs at bipolar pair Ls1,2. Each transition showed a gain of DPs at one bipolar pair with a simultaneous loss of DPs at the other bipolar pair. This provided a critical form of proof of rotor activity without need to annihilate the rotor. In addition to the remarkable repetitive recording patterns, this recording allowed a unique opportunity to analyze the behavior, morphology and patterns of a rotor (Fig 10B and 10C). The electrogram recordings exhibited discreet DPs while at other times, there was a transition to one component of the DP

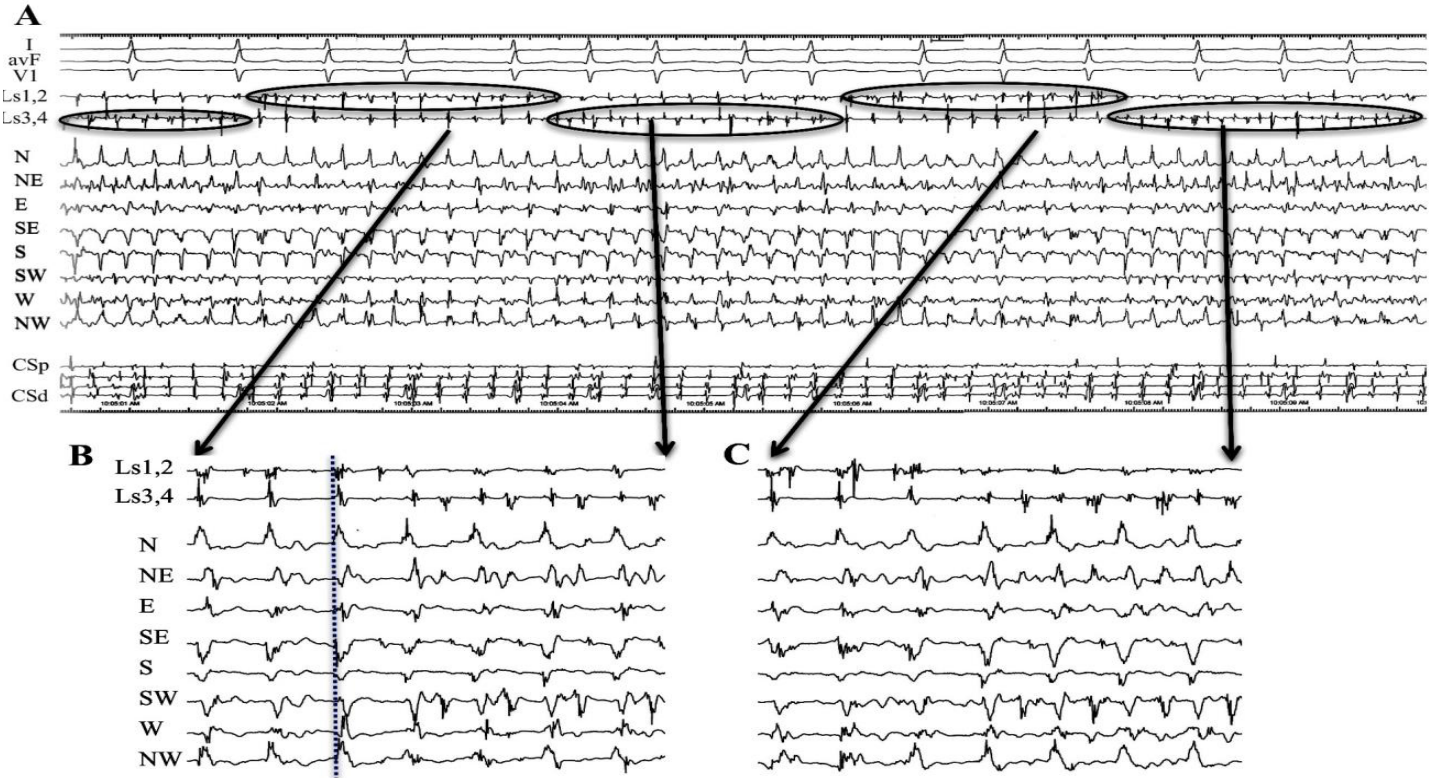

Figure 10: Precession of a rotor along a line of electrodes passing back and forth at perimeter at LA site #7 from patient #16. A. Recordings from the top are surface leads I, avF and V1, narrow adjacent bipolar electrode pairs Ls1,2 and Ls 3,4, Compass recordings, and coronary sinus (CS) proximal (p) to distal (d). Simultaneous narrow-adjacent pair of electrodes record DPs between electrode pair Ls1,2 with immediate shift to pair Ls3,4. Each time that DPs appears (top ovals) at bipolar pair Ls1,2, a PW is observed on the compass. As the rotor precesses to the bipolar electrode pair Ls3,4 as seen at the bottom ovals, a DP wavefront pattern is seen throughout compass recordings consistent with rotor within the perimeter. B,C. Expanded version of two of these transitions are seen below. Electrode pairs Ls1,2 and Ls3,4 are the free end the circular catheter. Wavefront pattern transitions between DP and PW occurred 12 times in 23 seconds. At each moment of transition, there was a simultaneous transition in which the local DP recorded, switched back and forth between narrow-adjacent pair Ls1,2 and Ls3,4. This observation can be explained by electrode pair Ls3,4 at a position just within the perimeter of the cross-circle pairs, while the electrode pair Ls1,2 lies just outside the perimeter. Further evidence of rotor at this site is the simultaneous PW pattern which exhibits largest amplitude, broadest span and earliest positive deflection at the North cardinal point where bipolar electrode pair Ls3,4 resides.

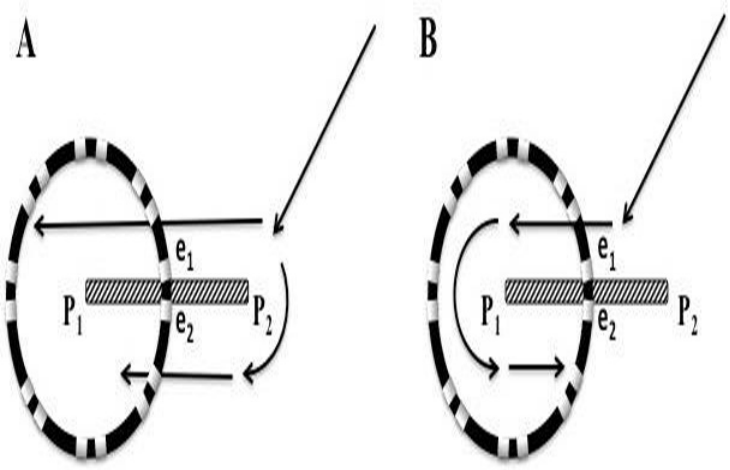

Figure 11: Wave propagation near a scar. A. A circular mapping catheter lays across a scar (stippled line) on atrial tissue. The scar crosses between electrodes e1 and e2. The electrical wavefront splits into two wavefronts at the end of the scar at pivot point 2. The wavefront delay underneath the scar would result in DPs between the top and bottom half of the compass. B. The electrical wavefront passes along one side of the scar and pivots around the other end of the scar P1, circling back underneath the scar. This too would result in DPs recorded in compass mode

being more uniform while the other became highly fractionated as in complex fractionated atrial electrograms (CFAE). Since the complexity appeared to be asymmetric, far more complex on one of the double potential components, it suggested that the rotor core might be directly beneath just one of the electrodes. If the rotor is in fact moving down the line of electrodes, then the core would be recorded passing beneath. The multicomponent complex fractionated electrogram exists throughout this recording and meets criteria to be considered as a CFAE[9]. CFAEs may be nonspecific but no one knows if that specificity increases when the CFAE is one component of a DP.

Of the 28 rotational events (56 transitions) identified by sequential activation around the 16 electrodes, 26 had both precession into and out of a PW pattern. Each of the other 2 events had sequential activation preceded by fibrillatory wavefront patterns. Once in a sequential activation, the wavefront pattern transitioned to a PW. 54 out of 56 transitions (96%) each showed the ½ cycle drop off pattern. Seven of these epochs were less than the 5 cycles to be considered by our definition of a DP pattern on compass mapping. An additional 2 events had sequential activation but were at the perimeter with sequential activation (i.e. [Figure 8B] and [Figure 8D]), with 50% of CL between 2 adjacent electrodes with DPs noted at that electrode location (both unipolar and narrow-adjacent bipolar). 16 of the 43 DP epochs (either sequential, n=22; or vertically aligned, n=21) recorded in compass mode had either a sequential unipolar activation or a perimeter activation pattern for a positive predictive value of 37%. Sequential activation of DPs in compass-mode (less than a 50% time gap between all cardinal directions) was seen in 22 of the compass-mode recordings resulting in a positive predictive value of 73% of sequential unipolar activation. None of the vertically aligned DPs in compass mode showed sequential activation in the unipolar recordings.

Ablation Results

Ablation data is presented anecdotally. This was a pilot observational study to determine usefulness of DPs in compass mode and in typical narrow adjacent electrode separation to determine regions of rotational activity and to identify electrical patterns of activation directly that will be useful in newer mapping systems. DP data was evaluated retrospectively and assessed off-line. Ablation at sites of rotor activity was only due to it being discovered that that site was incorporated into ablation lines. Patient 18 had the stable rotor at the posterior wall adjacent to the ostia of the LSPV as discussed above. Eight of 20 patients had AF terminate during ablation of PVs with or without additional lines. Fifteen patients are arrhythmia free, five of whom required a 2nd procedure, and one while on additional flecainide. The other five patients with recurrence opted for AVNode ablation with permanent pacemaker implantation.

Discussion

Long term successful treatment of persistent AF by ablation remains elusive. If ablation is to be effective, then improved mapping methods, identification of maintenance mechanisms, and ablation site strategies must all become more accurate. It has been previously suggested that direct electrically mapping of rotors would be nearly impossible due to meandering of the rotating core along with constant changing of electrical waveforms. It has long been known that a rotational mechanism that has a pivot point or its center of rotation between 2 electrodes will exhibit DPs[28,29]. Therefore, we used the premise that by setting up a perimeter of electrodes, that specific patterned activation wavefronts could detect when the center of rotation crossed the perimeter (a perimeter breach). Important detailed analysis along the perimeter can specifically locate the core at the time of the breach.

Time, location, and path are essentials to proper targeting. In addition to rotational mechanisms, DPs can occur if the wavefront is split at a pivot point such as at the end of a scar. However, there are important activation characteristics of DPs that should allow the operator to discriminate whether the cause of the DPs is from a rotational mechanism versus a scar.

Assessing techniques with other standard mapping catheters, it was surmised that only non-meandering rotors could be localized in the mere happenstance that the catheter lay directly over the rotor[37]. A rotational wavefront, with its center of rotation between a bipolar electrode pair, will record DPs whether the mechanism is reentry or rotor[28,29,31]. DPs would be expected to be recorded at a pivot point, or surrounding the center of rotation in any 3-dimensional plane. Some rotors can electrically control local tissue with stable centrifugal spiral waves having diameters as great as 6 cm[34]. Modification of bipolar electrode pairing to a cross-circle arrangement provides an immediate compass-like assessment of a 3 cm^2 region. A rotational mechanism with its center within the perimeter would be expected to exhibit DPs around the compass and potentially alert the operator to look more closely at this region for specific activation patterns that identify rotor location. We set out to prove that one could identify not only regionally locations of rotational activity, but that specific reproducible patterns of activation unlocked the puzzle as to precisely

where and when a rotor moves passed a line of electrodes.

We studied LA sites to detect DPs within 12 specific locations. The circular catheter provided consistency in electrode contact stability, reliable electrode separation distances (regardless of LA size), and ability to record from nearly all areas of the LA. Clearly, we were disadvantaged by the inability to record from all regions of the LA simultaneously. Analyzing the 1 minute epochs, cycle by cycle, allowed us to observe patterns of activation and precession that were consistent with other investigator descriptions[34,35]. Presence or absence of DPs provided statistical information regarding that specific region. However, patient # 6 provided some important insight into the duration of recordings. In the minute that we recorded from LA position #8, the entire minute exhibited only fibrillatory activity. Just prior to moving the catheter to the next LA position, DPs emerged and a full second minute was recorded, but not included in the statistical analysis. In that 2nd minute, seven epochs of DPs were recorded ranging from 866 msec to 9152 msec (5 to 49 rotations). DPs, PWs, DSPWs and Fib were recorded representing 38.4 %, 5.6%,5.5%, 50.5% respectively. This begs the question then, how much time is adequate to record? Studies using different methods, different catheter types, utilized different epochs of analysis. Only 2.5 seconds were recorded from sites in a circular catheter study of activation sequence[36], 4 seconds by basket catheter use in CFAE[24], 5 seconds in a point by point catheter tip measurement for dominant frequency[17,38], 8 seconds in a Pentaray study of Shannon entropy[31], 10 seconds in an epicardial high density electrode plaque[34], 1 minute in basket catheter phase map[39], and 5 minutes using a spiral catheter to measure CFAE[17]. We clearly have an incomplete and inconsistent picture of persistent afib.

Results from the substudy identified a new physiologic form of the Doppler effect that is unique for wavefronts emitted from rotors. Typically a Doppler effect is defined as the change in frequency or wavelength noted when the source of the wave is moving relative to the observer[40]. However, in this human physiological example of a source emitting a cyclic wavefront, the wavefront is not a simple periodic wave transmitted radially, but it is a moving rotor core emitting a spiral wave. The observers, in this case, are two adjacent electrodes along the perimeter of a circular catheter, and the core of the spiral wave approaches and moves along a path between them. Initially, with the core near the circular catheter, the compass recording mode identifies a PW that is transmitted across the circle. As the rotor core moves along a path directly between the 2 consecutive electrodes, both sense the activation wavefront nearly simultaneously with e2 slightly ahead of e1 (position a and b of Figure 7A). In the explanatory figure 7, movie numbers 2 and 3, and actual real human recordings in [Figure 8] and [Figure 9], the changes in CL as recorded by two electrodes as the rotor approaches and moves passed, depend upon which side of the rotor that the electrode sits. The electrode on the side of the rotor that receives the activation of forward moving wavefronts (e2 in Figure 7A), there is a decrease in the CL, a higher frequency, as the rotor approaches, as would be expected in a typical Doppler effect.

However, on the other side of the rotor (where e1 sits in[Figure 7A]), the wavefronts are moving less directly forward and therefore as the rotor approaches, it takes progressively longer for each subsequent wavefront to reach e1 than it does to reach e2. Thus, the Doppler effect at e1 is less than e2. We believe this is first description of this special form of Doppler effect and is critical to the understanding of activation sequence changes observed with a moving rotor passed stationary electrodes. The change in timing of activation between these 2 electrodes is a result dependent upon the electrode's relative position to the spiral wave. The electrode receiving the forward moving wavefronts as the core moves forward exhibits a relative compression (a shorter frequency) of cycle lengths compared to the electrode on the opposite side of the core which exhibits a relative expansion (a longer frequency) of cycle lengths. At the moment that the rotor core is directly between the 2 electrodes, at the perimeter, the wavefronts are moving in directly opposite directions. These wavefronts are separated in time by one half of the cycle length, creating the DP when the e1 and e2 are configured in a bipolar mode. As the core continues moving passed e1 and e2, to a position within the circle of the electrodes, then there is an immediate reversal in activation sequence (e1 ahead of e2). To reverse activation sequence there is a loss of activation in ½ the electrodes (½ cycle drop-off, movies 2, 3, and [Figure 9]).

In a simplified overall view, the compass-mode recordings show when a rotor moves from outside the perimeter of the circular catheter to somewhere within the perimeter by the transition from a PW pattern of activation to sequential DPs around the compass points. The unipolar and narrow-adjacent bipolar electrodes identify where specifically that the rotor core passes between 2 electrodes along the perimeter. DPs are exhibited between only one set of narrow-adjacent pairs along the perimeter at the moment the core is between these 2 electrodes (i.e., e1 and e2 of [Figure 7A, Figure 8]). A moment later when the core is inside the perimeter, DPs are then exhibited when looking at a bipolar pair of electrodes that is perpendicular or cross circle in compass-mode.

The relative Doppler compression-expansion pattern along with the ½ cycle drop-off pattern at the time of reversal of activation sequence was observed in 54 of 56 unipolar transitions (96%) from either the vertical time alignment of activation into sequential activation around the circle (PW to DP in compass mode) or transition from unipolar sequential activation into vertical activation (PW to DP in compass mode). The electrode positions where there is a Doppler compression immediately adjacent to the electrode that exhibits the Doppler expansion is also the electrode site that exhibits the ½ cycle drop-off when looking at all the electrodes around the perimeter. This is the site exactly where the rotor just passed. If a rotational mechanism exists with its plane of rotation parallel to the endocardial surface and the circular recording catheter, then there are 3 pathways that the rotational mechanism may enter the perimeter of the compass; between 2 electrodes of a narrow-adjacent bipolar pair; between 2 pairs of adjacent pairs (pattern similar to unipolar recordings of all electrodes around circle); or directly under an electrode. We showed examples in actual human recording of all 3 transitions across the perimeter. In a previous study[36], the authors also used a circular catheter and confirmed that sequential activation around the circle of electrodes was indicative of rotor activity within the circle. Although not discussed, it should be noted at the transitions into sequential activation around the circular catheter, the

½ cycle drop-off described here, also can be observed in their Figures 3,4, and 5. These details become very important in distinguishing sources and patterns of DPs.

Other than rotational wavefronts, DPs can be observed when recording over scars. [Figure 11] shows diagrammatically that an electrical wavefront can move one of two ways around a scar. First, the wavefront could split into 2 waves, one with slight delay and travel on both sides of the scar. Second, the wavefront could turn at the pivot point at the end of the scar and move backwards along the opposite side of the scar. Both would cause delay in activation at opposite sides of compass catheter, creating DPs.

Important differences are immediately evident when comparing DPs from a continuous rotor with a precessing core versus a scar. First, the scar is immobile and the DP pattern would therefore be fairly uniform over time. DPs created by a delay of activation along one side of a scar [Figure 11A], would be expected to be more vertically aligned in time, not sequential around the circle. In either example of [Figure 11], there would be no transition from PW to DPs, there would be no reversal of activations sequence, no transient DP at the perimeter breach site, and no ½ cycle drop-off pattern when observing all the electrodes. In addition, recordings along scars typically have either little or no voltage. Therefore, recordings of DPs from a rotor moving along a line of narrow-adjacent bipolar electrodes (as seen in Figure 10) might never occur because of a scar. DPs from a scar might be confused from DPs from a rotor that is anchored to one particular spot. However, there would still be an expected shorter CL as one approaches the core of a rotor. One would not see a change in CL as one approached a scar. Lastly, the DPs of a rotor even if stationary, would be sequential activation around the cardinal compass points, and the time separation between activation between any 2 adjacent cardinal direction or any 2 consecutive unipolar electrode must be less than 50% of the CL. Only at the perimeter, the wavefront has 1/2 rotation through all the electrodes and the 2nd half of the rotation moves all the way around until reaching the perimeter of electrodes once again. A reentrant circuit around a scar that traverses one part of the circular catheter may show similar DPs to that of a rotor. No Doppler effect would be expected. Whether mechanism is reentrant or rotor in this case is moot, as this region of tissue would be a target for ablation.

If we assume that sequential unipolar activation, head meets tail with a time gap of ≤ 50% of the CL is indicative of a rotational mechanism, then the DPs recorded in compass mode of any alignment (vertical or sequential) only had a positive predictive value (PPV) of 37%. Separating out the vertically aligned DPs, the PPV of DPs observed sequentially around the compass points improved to 73%. Importantly, none of the vertically aligned DPs in compass mode showed unipolar sequential activation. Thus, vertically aligned DPs in compass mode recording may be a result of wave propagation around a scar, or possibly even from a rotor that its plane of rotation is perpendicular to the tissue recording plane. The fact that a rotor core could be recorded moving down a line of electrodes [Figure 10] with DPs only observed between 1 bipolar pair separated by only 2 mm, suggests that the rotor core was < 2mm. Average atrial muscle thickness has been measured by MRI at 2.37±0.74 mm[41], so all rotors might not have a rotational plane that is parallel to the endocardial surface, and in theory, may even change axis or flip poles over time.

We did not statistically study CFAE sites, but we repeatedly observed their appearance in our study. CFAEs have been recorded at sites of wavefront curvature (pivot points), but may also occur in regions of slow conduction[42]. CFAEs were studied with Shannon entropy [31], during phase mapping[24], and epicardial mapping[34], none of which showed close correlation with sites thought to be important to target for ablation. As was observed in several patients, CFAE was often seen as one of the components of DPs in the narrow-adjacent bipolar electrode pair at the precession breach site, with a rare continuous recording at a breach site in patient #16 Figure 10. The fact that the CFAE migrated as a component of the DP is especially interesting. CFAEs also appeared in other electrode recordings at a significant distance from the breach site. A future study might assess whether CFAE as a component of a DP to be a more specific signature of a rotor core.

The time perspective of direct electrical rotational epochs however should not be lost when comparing these results to indirect interpolated phase mapping. Narayan et al.[24], has described rotors as being stable lasting at least tens of minutes and precessing within regions of 2-3 cm2. The circular catheter used in our study has a 3 cm2 area of coverage. Detailed off-line compass recordings, cycle by cycle, and more refined narrow-adjacent bipolar and unipolar recordings found long running epochs but these were quite rare. Only 5 patients (25%) showed epochs lasting 20 seconds or greater. Yet, similar to their study, we found between 2-3 LA (2.9%) sites per patient that showed evidence of rotational activity. However only 2 patients (10%) had DPs recorded for > 30 seconds, and only 1 patient exhibited DPs for the entire minute. Our findings of very frequent short rotational epochs are consistent with more recent investigations[34,35,36,43].

We used a circular mapping catheter, but we expect than any shape with a perimeter of electrodes would show the same activation pattern changes as a rotor passes from one side to the other. With all 3 tracking requirements (time, position, and path) met, new recording, tracking and targeting strategies can now be devised. Scaling up with automated software using simultaneous highly dense electrode maps might now provide the ability to identify and track directly (without interpolation) rotor locations over longer times. Three important phases of a rotor life-cycle could be investigated as possible customized target sites of ablation. On-line tracking should provide the ability to precisely identify unique or common atrial tissue sites that spawn rotors (sites of wavefront vortex shedding), common paths of meandering or precession, or common sites of anchoring. Targeting any one or a combination of these 3 sites might improve arrhythmia-free duration endpoints. Scaling up with automated software using simultaneous highly dense electrode maps for longer recording periods for on-line analysis that can recognize DPs, reversal of activation patterns, migration of DPs, will require significant software development and testing. Once completed, direct electrical mapping and ablation studies could be compared in a randomized study against interpolation mapping and ablation methods.

Limitations

DPs were examined from cross-circle compass mode, narrow-adjacent bipolar, and unipolar recordings focusing on rotational mechanisms and transition pattern of activation. We only recorded from the LA, therefore we do not know if longer duration rotor activity from the right atrium would have impacted the prevalence of rotor sites. We did not analyze for possible ectopic sites of activation and this would have been recorded as PWs. Whether PW was a result of an ectopic focus or from a nearby rotor will be a subject of future investigations. We utilized a circular catheter that we purposely kept the same dimensions to provide consistent cardinal directions of a compass. A rotor with a smaller radius of wavefronts that morphed into fibrillatory activity would have been detected as a DSPW. A smaller size catheter may have improved detection, but we would have lost tissue coverage. We did not record simultaneously from all left atrial sites, it is not known if this would result in under or overestimation of rotor activity. Finally, our recording figures, as in all publications, were selected with the least noise, best amplitudes. There is a selection bias on these figures by all authors to convey their clear thoughts and results to the reader. Therefore, in real-time, the recording of short epochs, pattern recognition, perimeter breaches, all would be present and gone, literally in the blink of an eye. Reliance on current computer interpolating algorithms may be premature. Mapping and targeting AF remains at its infancy.

Conclusions

Our methods of studying DPs provided the ability to have stable local contact, high electrode resolution, and consistent shape, that allowed us to recognize electrical patterns of rotational mechanisms during atrial fibrillation. These recordings, we believe, are the first to identify specific electrical patterns of rotor activity and behavior as it breaches a line or perimeter of electrodes. By our findings, we also believe that now have the fundamental tools to electrically map and track rotor activity directly without need for interpolation. This study was conducted using standard recording methods but it required very time-consuming off-line analysis. Technological improvements with better high dense electrode resolution will be needed to create higher quality, efficient mapping techniques. Since stable rotors of long duration, limited precession appears to be rare (5-25%), then at the current state of technology, the compass map method might be used to quickly survey the atrium. Compass mapping might allow for time and cost efficient targeting of the more rare low-hanging fruit without need of proprietary software and basket catheters.

The frequent short duration epochs of rotational activity with precession requires a paradigm shift in thought, investigation, and ablation strategies. Without more detailed mapping, our current methods used for ablation in patients with persistent AF is more a "whac-a-mole™" technique on a klinko™ game. Now with the building blocks to electrically record directly rotor location and path by using the electrodes as sensors of a perimeter breach, specific customized maps could be created. More importantly, the life-cycle of a rotor could now be assessed from the time of spawning of vortex shedding to migration, to anchoring, to its final demise. In 2 patients of detailed unipolar and narrow-adjacent bipolar recordings, sequential activation was not preceded by precession from a PW and appeared to emerge from fibrillation. If this was a site of vortex shedding, then a preceding Fib recording directly into sequential activation, head-meets-tail, might identify common sites of rotor births. Ablation sites of regions of vortex shedding might be as important as the ablation lines used to isolate sites of ectopic impulses, or sites of rotor anchoring. In addition, studies are needed desperately to evaluate directly different ablation patterns on atrial tissue substrate and its effect on rotor precession[44]. The goal of ablation should be to optimize conduction with least destruction.

Movie 1. Slow motion activation patterns as a rotor is positioned directly on the perimeter between a narrow-adjacent pair of electrodes. Two activations occur with each rotation, creating double potentials.

Movie 2. Slow motion activation patterns of a rotor precessing passed a line of electrodes. Doppler compression, expansion, reversal of activation and the ½ cycle drop off.

Movie 3. Slow motion activation patterns of a rotor precessing passed a perimeter of electrodes. Doppler compression, expansion, reversal of activation and the ½ cycle drop off.

Disclosures

D S Rubenstein received a consulting a fee from BioSense Webster.

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Atrial Fibrillation and Objective Sleep Quality by Slow Wave Sleep

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Abstract

Background: Self-reported poor sleep quality has been suggested in patients with AF. Slow wave sleep (SWS) is considered the most restorative sleep stage and represents an important objective measure of sleep quality. The aim of this study was to compare quantity of SWS between patients with and without AF.

Methods and Results: We included patients with and without a documented history of AF by reviewing clinically indicated polysomnography data from a single sleep center. Patients on medications with potential influence on sleep architecture were excluded. Logistic regression was performed to determine the association between AF and SWS time (low vs. high) adjusting for age, gender, body mass index, and sleep apnea. In a 2:1 case-control set-up, a total of 205 subjects (139 with AF, 66 without AF) were included. Mean age was 62 (SD: 14.3) years and 59% were men. Patients with AF had lower SWS time (11.1 vs. 16.6 min, p=0.02). In multivariable analysis, prevalent AF was associated with low SWS independent of sleep apnea and other potential confounders (OR 2.5 [1.3, 5.0], p=0.006). Limiting the analysis to patients whose total sleep time was greater than 4 hours (by excluding N=31) resulted in more robust results (OR 3.9 [1.7, 9.7]. p=0.002).

Conclusions: AF is associated with more impaired sleep quality as indicated by lower quantity of SWS. More studies are needed to explore the mechanistic interactions between AF and sleep.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia with a growing public health burden. AF increases the risk of hospitalization, cardiovascular morbidity and mortality, and impairs quality of life[1]. Among many established risk factors of AF, obstructive sleep apnea (OSA) has drawn significant attention as a potentially modifiable risk factor. In comparison, other aspects of sleep such as sleep quality have rarely been studied in relation to AF[2]. Poor subjective sleep quality has been reported in patients with AF[3,4]. However, objectively measured sleep characteristics of patients with AF remains unclear.

Slow wave sleep (SWS) is an electroencephalogram-defined low frequency sleep state constituting about 10-20% of sleep and is considered to be the most restorative sleep stage. This proportion of SWS decreases with aging and can be affected by various central nervous system (CNS) medications. Both SWS proportion and quantity also partly depend on total sleep time. Therefore, the lack of SWS is an objective marker for poor sleep quality. SWS is also considered cardio-protective characterized by a predominantly parasympathetic state[5,6]. While the associations of SWS or sleep architecture as a whole in cardiovascular health remains unclear, there have been suggestions that reduced SWS may be associated with increased cardiovascular risks[7,8]. For example, a recent community-based study showed that low quantity of SWS was associated with AF independent of OSA severity, signaling an implication of sleep architecture in AF[9]. The current investigation therefore attempts to validate these findings and perform additional sensitivity analyses in a real world sleep clinic patient cohort. In this study we tested the hypothesis that patients with AF would have poorer quality of sleep as characterized by a lower quantity of SWS compared with those without AF.

Key Words

Atrial Fibrillation, Sleep Apnea, Slow Wave Sleep

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Methods

Study design and Subjects

Using an unmatched 2:1 case-control study design, we selected patients with and without AF referred to a single academic sleep center for diagnostic polysomnography (PSG). Consecutive patients with AF were identified from electronic health records retrospectively between January 2010 and December 2017 (a 7-year period) wherein detailed PSG data were available.

Consecutive patients without AF were identified retrospectively between July 2017 and December 2017 (a 6-month period). This 6-month period was chosen in order to have a similar number of non-AF patients because a recent report found AF prevalence among sleep clinic referred patients to be 6.5%, and the true prevalence estimated to be about 8% after taking into account underestimation error (thus 8% of the 7 year period was 6 months)[10]. The diagnosis

of AF was confirmed by individual chart review by investigators. For patients with AF, the timing of AF diagnosis preceded that of PSG. Given the possible impact of benzodiazepines or Gamma-aminobutyric acid analogs (GABA) on sleep architecture, patients on these medications were excluded[11,12]. Patients who were receiving continuous positive airway pressure therapy were also excluded. The study was approved by the institutional review board at the University of Virginia (Charlottesville, VA, USA).

Sleep Study Data

Overnight PSG was performed employing the standard channels recommended by the American Academy of Sleep Medicine (AASM) and data were processed with Embla Sandman Elite software (Natus Medical Incorporated, California, USA)[13]. Sleep stages (N1, N2, N3 (or SWS)), and rapid eye movement (REM) sleep) were expressed both as absolute times in each stage and proportion of the sleep period (%) in each stage. N3 (SWS stage) was determined if more than 20% of an epoch consisted of slow wave activity defined by at least 75 microvolt amplitude in frequency of 0.5-2 Hz [Figure 1]. The arousal index was defined as the number of arousals per hour. Sleep efficiency was calculated by dividing the PSG-based total sleep time (TST) by the total time between sleep onset and lights on. The apnea hypopnea index (AHI) was defined as the number of apnea and hypopnea events divided by TST and expressed as the number of events per hour. Apnea was defined as a reduction in air flow greater than 90% of the pre-event baseline, and occurring for longer than 10 seconds using a thermocouple signal. Hypopnea events were recorded when the amplitude of the nasal pressure flow signal decreased by more than 30% of the pre-event baseline for longer than 10 seconds; only hypopneas with at least 4% O2 desaturation were included in the AHI. AHI greater than 15 /h was considered clinically significant OSA.

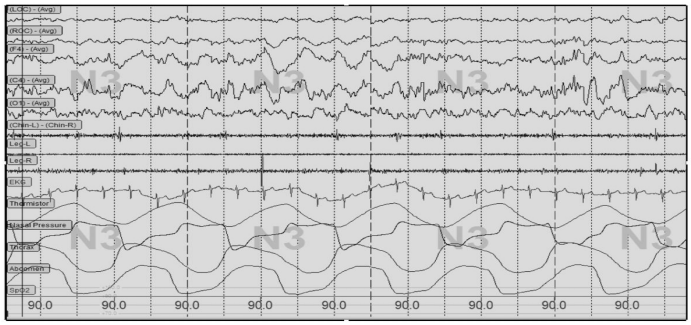

Figure 1: **Illustration of slow wave sleep on polysomnography montage.**

Note slow (delta) wave activity characterized by high amplitude (>75 microV) and frequency of 0.5-2 Hz amplitude shown on frontal and central electroencephalogram leads (F4, C4).

Covariates and Clinical Information

Demographic information (age, gender), body mass index (BMI) and medical history (hypertension, diabetes, heart failure and stroke) were collected from electronic health records. Detailed medications lists were also reviewed with particular attention to CNS-active agents including benzodiazepines, GABA agents, as well as antidepressants, all of which can potentially affect SWS. Echocardiographic finding of left ventricular ejection fraction (LVEF) from the closest timing to PSG were also recorded.

Statistical Analysis

Baseline characteristics were stratified into low vs. high SWS time patient group based on the median value for those with and without AF. Either unpaired t test or Mann-Whitney test (for nonparametric distribution) was used to compare continuous variables between the two groups. For categorical variables comparison, either Chi-square or Fisher's exact test was used as appropriate. Unconditional logistic regression was performed for the outcome of SWS above the median value (high SWS). Predictor variables included prevalent AF at the time of the sleep study. Due to a highly skewed distribution of SWS with many patients with little amount of SWS, we categorized SWS into low vs. high groups based on the median value. Sleep efficiency and arousal index categories classified by respective median values were assessed as secondary predictors. Age, gender, BMI, and OSA were included in the model as covariates. Analysis was then performed after excluding patients who were on any CNS-active medications including tricyclic antidepressants and serotonergic antagonists[14]. Other sensitivity analyses included limiting the cohort to a TST of greater than 4 hours. Values were expressed as mean (SD) unless specified otherwise. For all analyses, a two-tailed p value less than 0.05 was considered significant. All analyses were performed using SAS software v. 9.2 (SAS Institute Inc. Cary, NC, USA).

Results

A total of 205 patients including 139 patients with AF were eligible for the study. Among the 139 subjects, 28 had persistent or permanent AF with the rest having paroxysmal AF. During the sleep study, 19 patients were in AF during the study (for either part of the study or for its entirety). The overall cohort was characterized by middle-aged patients (mean age: 63 years, male: 59%) with a high burden of cardiovascular risk factors (Table 1). OSA was common with greater than half of the patients having an AHI>15/hr. Average TST was 283.1 (106.1) minutes. Average SWS amount and SWS % were 12.9 minutes (15.5) and 5.1 % (7.8), respectively.

When categorized by the amount of SWS time, patients with low SWS were older and had lower BMI, LVEF, and a higher prevalence of AF (78.4 vs. 57.3%, p=0.001) [Table 1a]. Patients with low SWS exhibited a higher severity of OSA by AHI but not by mean O2 saturation. Those with low SWS also had a higher arousal index and lower sleep efficiency.

When categorized by presence or absence of AF, patients with AF as compared to those without were older and less likely hypertensive. BMI and the prevalence of OSA were similar between the two groups. Those with AF also had lower SWS time (11.1 vs. 16.6 min,

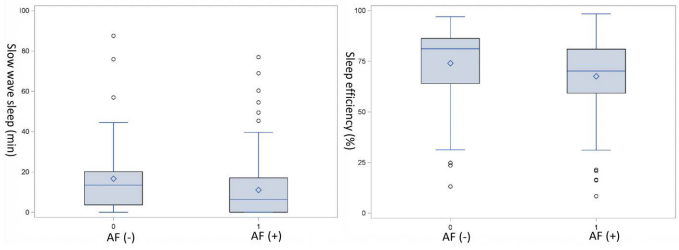

Figure 2: **Box plot. Distribution of slow wave sleep (SWS) time and sleep efficiency in patients with and without atrial fibrillation (AF).**

Table 1A: Characteristics of study participants by slow wave sleep

	Total (N=205) Mean (SD) or Number (%)	Low SWS (N=102) Mean (SD) or Number (%)	High SWS (N=103) Mean (SD) or Number (%)	P value
Age (yrs)	62.9 (14.4)	65.4 (14.0)	60.5 (14.4)	0.01
Gender (Male)	120.0 (58.5)	66.0 (64.7)	54.0 (45.0)	0.07
BMI (kg/m2)	34.2 (8.5)	32.9 (6.9)	35.3 (9.7)	0.04
LVEF	52.6 (11.1)	50.6 (12.3)	54.7 (9.2)	0.01
AF	139.0 (67.8)	80.0 (78.4)	59.0 (57.3)	0.001
HTN	106.0 (51.7)	49.0 (48.0)	57.0 (55.3)	0.30
DM	85.0 (41.5)	40.0 (39.2)	45.0 (43.7)	0.52
Stroke/TIA	16.0 (7.8)	10.0 (9.8)	6.0 (5.8)	0.29
SSNRI	33.0 (16.1)	13.0 (12.8)	20.0 (19.4)	0.19
TCA	6.0 (2.9)	4.0 (3.9)	2.0 (1.9)	0.45
CHADS2	2.0 (1.3)	2.2 (1.9)	1.9 (1.2)	0.09
OSA	118.0 (57.6)	71.0 (69.6)	47.0 (45.6)	0.001
AHI (/hr)	25.7 (23.9)	31.9 (24.3)	19.6 (21.9)	<.0001
Mean O2 Sat(%)	94.4 (2.6)	94.1 (2.4)	94.7 (2.8)	0.11
TST (min)	283.1 (106.1)	264.2 (110.4)	301.9 (98.6)	0.01
AI (/hr)	30.1 (27.2)	35.8 (30.6)	24.4 (22.2)	0.006
SE (%)	69.7 (18.5)	66.4 (20.8)	72.9 (15.3)	0.01
SWS (min)	12.9 (15.5)	2.1 (2.9)	23.5 (15.6)	NA

AF, atrial fibrillation; AHI, apnea hypopnea index; AI, arousal index; BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; LVEF, left ventricular ejection fraction; OSA, obstructive sleep apnea; SE, sleep efficiency; SSNRI, Serotonin–norepinephrine reuptake inhibitor; SWS, slow wave sleep; TCA, tricycle antidepressants; TIA, transient ischemic attack; TST, total sleep time. For continuous analysis, unpaired t test performed except for AHI (Mann Whitney test was performed). For categorical analysis, Chi square test used except for Stroke/TIA (Fisher's exact test).

p=0.02) and lower sleep efficiency (67.6 vs. 74%, p=0.02) ([Table 1b], [Figure 2]). Multivariable logistic regression analysis showed that prevalent AF was associated with low SWS independent of OSA

Table 1B: Characteristics of study participants by AF (atrial fibrillation)

	No AF Mean or Numbe(N=66)	AF Mean (SD) or Number (%) (N=139)	P value
Age	57.2 (16.0)	65.7 (12.7)	<.0001
Gender(Male)	33.0 (50.0)	87.0 (62.6)	0.09
BMI (kg/m2)	35.2 (8.6)	33.6 (8.4)	0.21
LVEF	54.5 (9.8)	51.8 (11.5)	0.12
HTN	51.0 (77.3)	55.0 (39.6	<.0001
DM	27.0 (40.9)	58.0 (41.7)	0.91
Stroke/TIA	4.0 (6.1)	12.0 (8.6)	0.59
SSNRI	14.0 (21.2)	19.0 (13.7)	0.17
TCA	2.0 (3.0)	4.0 (2.9)	0.95
CHADS2	1.7 (1.2)	2.2 (1.3)	0.01
OSA	81.0 (58.3)	37.0 (56.1)	0.76
AHI (/hr)	25.4 (27.4)	25.9 (22.2)	0.96
Mean O2 Sat (%)	94.8 (2.6)	94.2 (2.6)	0.19
TST (min)	295.7 (114.9)	277.1 (101.5)	0.24
SWS (min)	16.6 (17.3	11.1 (14.3)	0.02
AI (/hr)	33.0 (31.5)	28.7 (24.9)	0.29
SE (%)	74.0 (18.8)	67.6 (18.0)	0.02

AF, atrial fibrillation; AHI, apnea hypopnea index; AI, arousal index; BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; LVEF, left ventricular ejection fraction; OSA, obstructive sleep apnea; SE, sleep efficiency; SSNRI, Serotonin–norepinephrine reuptake inhibitor; SWS, slow wave sleep. TCA, tricycle antidepressants; TIA, transient ischemic attack; TST, total sleep time. For continuous analysis, Unpaired t test was performed except for AHI and SWS (Mann Whitney test was performed). For categorical analysis, Chi square test used except for Stroke/TIA (Fisher's exact test).

and other potential confounders (OR 2.5 [1.3, 5.0], p=0.006) [Table2]. In this model, OSA was also associated with low SWS. Exclusion of OSA from the model did not significantly change the association between AF and low SWS (OR 2.3 [1.2, 4.4], p=0.01). Addition of either sleep efficiency or arousal index to the model yielded similar results (arousal index in the model: OR 2.8 [1.4, 5.6], p=0.003; sleep efficiency in the model: OR 2.5 [1.3, 4.9], p=0.008). Similarly, results remained comparable when patients taking any CNS active medications (by excluding N=38) were excluded (OR 2.9 [1.4, 6.2], p=0.007). A sensitivity analysis based on patients whose TST was greater than 4 hours (by excluding N=31) resulted in a stronger association between AF and low SWS (OR 3.9 [1.7, 9.7]. p=0.002). A model with SWS % as an outcome yielded similar, albeit slightly less robust, results compared with SWS (OR 2.1 [1.1, 4.0], p=0.02). Multivariable analysis designating other sleep quality metrics as secondary outcomes failed to show an independent association between AF and low sleep efficiency (OR 1.8 [0.9, 3.4], p=0.09) or arousal index (OR 1.0 [0.5, 2.1], p=1.0).

Table 2: Multivariable analysis of predictors of low slow wave sleep time

Variable	OR [95% CI]	P value
BMI (per 1 kg/m2)	0.97 (0.9,1.0)	0.14
Age (per 1 year)	1.0 (0.99,1.03)	0.47
Gender (Male vs. Female)	1.1 (0.6,2.1)	0.75
AF (vs. no AF)	2.5 (1.3,5.0)	0.006

AF, atrial fibrillation; BMI, body mass index; OSA, obstructive sleep apnea

Discussion

In this sleep clinic cohort consisting of patients undergoing clinically-indicated PSG, we found SWS quantity was significantly lower in patients with AF as compared to those without. This finding was independent of potential confounding factors such as age, body habitus, gender, and OSA that are known to be associated with both AF and SWS[14-17].

This represents one of the first in depth examination of the association of AF with objectively measured sleep characteristics in real world clinical practice. We primarily focused on SWS, as this represents the most restorative sleep stage. The majority of studies linking sleep and AF association have focused heavily on the sleep disordered breathing component (e.g. OSA). In contrast, there is a paucity of studies examining qualitative aspects of sleep in relation to AF. A recent survey-based study found that patients with AF report shorter sleep duration and poorer sleep quality compared with age-matched subjects without AF. Interestingly, among the patients with AF, those who underwent successful cardioversion and maintained sinus rhythm had improved sleep quality at 6 months whereas those who had recurrence of AF did not[3]. Another study found that up to about half of AF patients reported poor sleep quality, and the prevalence of poor sleep quality increased incrementally with greater AF symptom severity[4]. While these studies were all based on self-reported sleep quality questionnaires (both using the Pittsburgh Sleep Quality Index inventory), one community-based study assessed objective sleep quality metrics, including SWS quantity, arousal index, and sleep efficiency found a dose dependent inverse association between SWS quantity and AF highlighting the potential association of the sleep architecture in the pathogenesis of

AF[9]. Furthermore, a recent study by Christensen et al. found that sleep disruption was a predicter of AF before and after adjusting for OSA and other confounders, and in the subset of 1127 that had PSG, every standard deviation decrease in REM sleep quantity was associated with an 18% higher risk of developing incident AF[18]. In this context, the current study was intended to examine whether real-world sleep clinic patients with AF would have more impaired sleep quality as measured by SWS.

In this sleep clinic cohort, patients with AF exhibited more impaired sleep quality as indicated by lower quantity of SWS compared with those without AF. This difference in SWS amount persisted after controlling for potential confounders. Various sensitivity analyses revealed that AF was associated with approximately 2-3 times higher odds of having low SWS time. Exclusion of patients with 'any' CNS active medications did not alter the results. Since shorter sleep duration and longer wake after sleep onset time, owing to an unfavorable sleep environment during in-lab sleep study setting, can curtail SWS time and, in turn, impact the results, we repeated the analysis excluding patients who achieved less than optimal TST (less than 4 hours). By limiting our analysis to this group of reasonable TST, we uncovered an even stronger association (OR ~4). This suggests that AF's association with low SWS may be even stronger in a usual sleep setting beyond the sleep lab environment where TST is expected to be much longer. Given OSA's negative effect on SWS time via sleep disruption, it is not surprising that OSA was also independently associated with low SWS[15]. However, we did not find any evidence of a confounding effect of OSA on the association between AF and SWS considering the minimal difference in the results with or without OSA in the model. Similarly, we did not find any association of other sleep quality measures including sleep efficiency or arousal index on with AF and SWS. Furthermore, in a secondary analysis, we did not find any independent association between AF and sleep efficiency or arousal index, other key sleep quality metrics commonly obtained from PSG.

SWS is a sleep stage characterized by substantial presence of electroencephalographic slow wave activity and is the deepest sleep state with the highest arousal thresholds. As such, SWS is considered the most recuperative sleep period and is often indicative of high quality sleep[19]. Well-described SWS rebound after either total sleep or selective SWS deprivation implies that SWS is subject to a highly regulated homeostatic process. While our understanding of the functional role of SWS is still very limited, SWS has been implicated in neurocognitive and autonomic regulation[20]. In fact, SWS is considered to be cardio-protective sleep state characterized by decreased sympathetic and increased parasympathetic tone. In this context, it is noteworthy that an imbalance in the complex interplay between sympathetic and parasympathetic activity has been implicated in the pathogenesis of AF[21]. Although we are unable to suggest any causality, given the design of the study, a few theories can be postulated based on our findings. First, consistent with our overarching hypothesis of this study, AF may influence sleep quality as previously suggested by other self-report-based studies. Increased sympathetic tone, or other comorbidities such as depression and anxiety, commonly found in patients with AF, could lead to poor quality of sleep[22,23]. Decreased SWS has been reported in patients with depression[24,25]. Conversely, it can be viewed that decreased SWS and a subsequent reduction in the cardio-protective state may play a role in the pathogenesis of AF. Finally, decreased SWS may be a simple marker of underlying autonomic dysfunction or other unknown substrates for electrophysiological dysregulation including AF. In this regard, one may speculate whether the decrease in SWS with aging plays any role in the increasing risk of aging-related AF.

Another important aspect of sleep quality is its implication on cognitive function[26]. SWS loss is linked to impaired memory consolidation[27,28]. On the other hand, a number of studies have demonstrated a higher risk of cognitive decline in patients with AF independent of stroke[29,31]. Although the mechanism behind this association remains unclear, findings of this study raises a question whether sleep quality, specifically SWS, may have any pathophysiological role in linking AF with cognitive decline[32]. Similarly, SWS may have implications in the AF-stroke relationship. Future studies on SWS's impact on stroke may offer more insights into a potential role of SWS in mediating the risk of stroke in AF.

A number of limitations need to be considered in our study. Although the timing of AF diagnosis preceded that of the sleep study, our study is inherently cross-sectional by nature. Findings of the sleep study do not represent an event or outcome but likely stable sleep traits. Therefore, causality cannot be assumed. Because only small portion of patients were in AF during the sleep study, a subgroup analysis to determine the impact of nocturnal AF rhythm (vs. non-AF rhythm) was not feasible. However, it is our opinion that the association found in our study (SWS quantity and AF) is predominantly related to the underlying pathophysiology or substrate of AF rather than to the AF rhythm by itself. Similarly, because of a small proportion of patients with permanent / persistent AF, analysis based on the subtype was not feasible. A prospective examination of the relationship would be valuable in the future. Although in-lab PSG is considered the gold standard method of objective sleep evaluation, one time PSG performed in the sleep lab environment (vs. home) may not represent true sleep architecture. Self-reported sleep quality metrics would have provided more insights into the understanding of our findings as it is unclear how the difference in SWS is reflected in subjective perception of sleep quality, which may be important by itself. However, it is well described that sleep quality is a complex construct and is difficult to measure, with prior studies showing that subjective sleep quality has poor correlation with objectively measured sleep quality[33,34]. Thus, the focus of this study was on objective PSG measures. The adoption of forthcoming wearable sleep technologies capable of accurately capturing sleep architecture over longer periods of time may allow us to yield more valid and robust analyses in this regard.

In conclusion, in a sleep clinic setting, patients with AF spent less time in SWS during sleep compared to those without AF, and this association was independent of OSA and other risk factors. Further studies investigating the clinical significance of these findings is warranted.

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Successful Percutaneous Closure of Traumatic Right Ventricular Free Wall Rupture Using Amplatzer Vascular Plug Devices

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Abstract

Ventricular free wall rupture (VFWR) is a rare entity and is mostly related to post myocardial complications usually involving left ventricle. In traumatic chest injuries, the right ventricle (RV) is more commonly involved due to its anatomic and structural vulnerability, as in our case. Survival, although rare, has almost always been secondary to urgent surgical repair, which is the current standard of care for such cases. However, extremely tenuous hemodynamic parameters preclude urgent surgical interventions in most of these cases. Surgical repair was considered to have prohibitive risk in our case also due to multiple comorbidities. Our case offers a unique perspective into the feasibility and safety of percutaneous closure of VFWR with devices such as Amplatzer Vascular Plug (AVP) II under transesophageal echocardiography (TEE) and angiographic guidance in patients who survive VFWR. The lack of randomized evidence to standardize the duration and regimen of antiplatelet therapy following placement of these devices is to be noted.

Introduction

Traumatic ventricular free wall rupture (VFWR) has a reported incidence of 0.3%-1.1 %. Most often VFWR is related to post myocardial infarction (MI) complications and usually involves left ventricle[1,2]. However autopsy results on chest trauma patients report a much higher incidence (35%-60%), indicating immediate fatality of myocardial ruptures in most cases[3]. Reported mortality rates range from 30%-80%, especially in acute traumatic cases[4,5]. Emergent surgical intervention is an important predictor of outcome. However, extremely tenuous hemodynamic parameters preclude urgent surgical interventions. We report a case of traumatic VFWR successfully repaired percutaneously with multiple Amplatzer Vascular Plug (AVP II) devices.

Case

An 80 year old man with prior coronary artery by-pass grafting (CABG) was admitted with a blunt cardiac injury with VFWR confined to the right ventricle (RV) apical segment and contained by an apical sac (28 mm x39 mm x 54 mm), thereby preventing tamponade [Figure 1-A and B] [Figure 2-A and B]. The defect was single (10 mm x 10 mm) and no specific fenestrations were noted. Given the presence of multiple comorbidities including pulmonary contusion, multiple spinal fractures and a prior sternotomy, surgical repair was considered to have prohibitive risk and a percutaneous closure was performed.

Key Words

Leak, Repair, Angiography, Sac, Chest Trauma

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Bilateral common femoral venous accesses (14-French (F) on the right for device delivery and 6F on the left for pigtail catheter for RV angiography and angiographic visualization of the defect) were obtained[Figure 3A-I and II]. Intra-procedurally, a ventricular septal defect closure device was found to be disproportionately small compared to the defect. A 10-F Amplatzer delivery system was advanced into the right atrium over a 0.035 J wire. We then advanced a 0.035 wire into the right ventricle over which a 5F angled Glide catheter was advanced. A 0.035 Storq wire was used to access the RV apex and subsequently track the delivery system over the latter. A 22 mm AVP II device was deployed. This appeared to occlude the defect to a significant extent with moderate residual leak. We redirected the 5F angled Glide wire micro catheter system over a 0.035 Storq wire and successfully delivered a 12 mm AVP II device followed by a third 14 mm AVP II device adjacent to the initial device. Following device deployment, there was near complete resolution of the leak into the apical sac as noted based on transesophageal echo (TEE) and RV angiography using the pigtail catheter [Figure 3B]. Immediate post-procedural TEE and 1-day post procedural echo confirmed successful closure and the absence of more than a trivial leak into the apical sac. The patient remained hemodynamically stable throughout the procedure. Considering the high bleeding risk of our patient with multiple injuries, aspirin 81 mg daily was preferred for antiplatelet therapy. Seven days after successful closure of the pseudoaneurysm, the patient developed fatal respiratory failure from significant pulmonary contusions, multiple rib fractures while on aspirin mono therapy. Aspirin was discontinued 3 days after the procedure in view of worsening respiratory failure due to concerns of expansion of pulmonary contusions. However, 2-D echocardiography performed 1-day prior to death demonstrated normal biventricular function and no evidence of thrombus formation at the site of AVP deployment

after aspirin discontinuation. Color Doppler confirmed the absence of significant residual flow or enlargement of the pseudoaneurysm.

Discussion

In traumatic chest injuries, the RV is more commonly involved due to its anatomic and structural vulnerability[4]. VFWR results in severe hemorrhage into the pericardial space leading to cardiac tamponade. Survival, although rare, has almost always been secondary to urgent

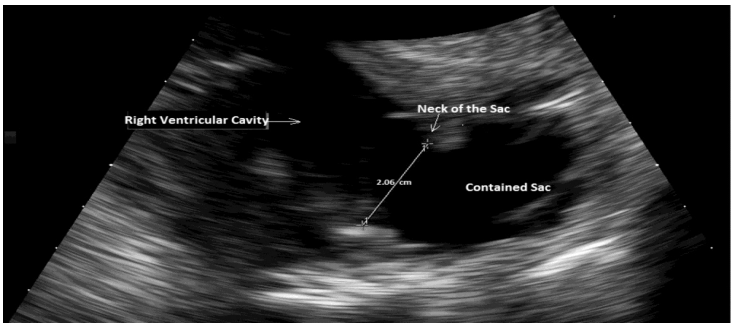

Figure 1A: Transesophageal Echocardiography (TEE) images showing right ventricular rupture with a "contained sac"showing the neck of the sac measuring around 2 cm.

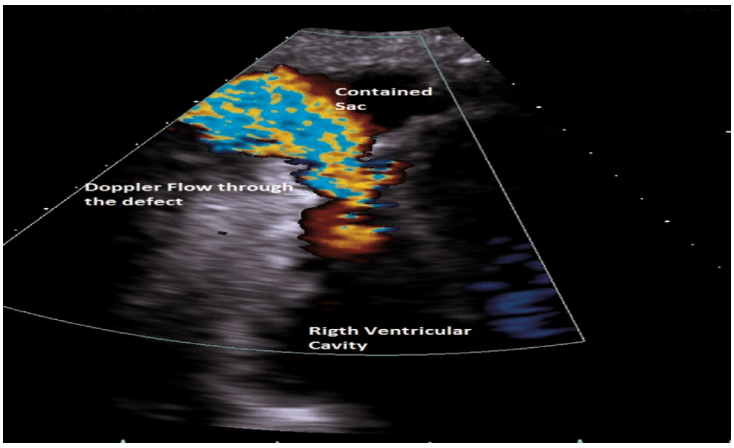

Figure 1B: Transesophageal Echocardiography (TEE) images showing right ventricular rupture with a "contained sac" showing the Doppler flow through the defect.

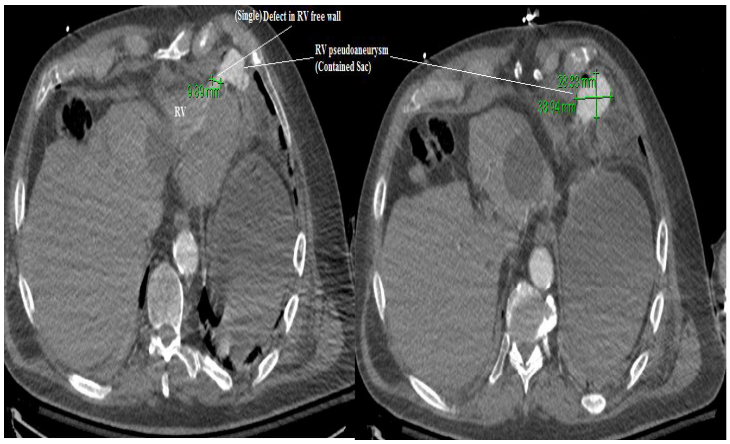

Figure 2A: Contrast computerized tomography (CT) images in the coronal (2-A) planes demonstrating the traumatic RV pseudoaneurysm.

RV-Right ventricle

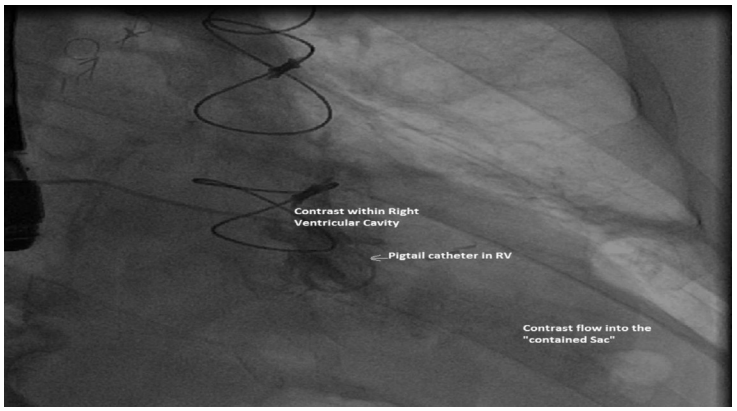

Figure 3A-I: Illustrating the angiographic visualization of the right ventricle and the "contained sac". showing contrast leakage from right ventricular cavity through the defect into the "contained sac".

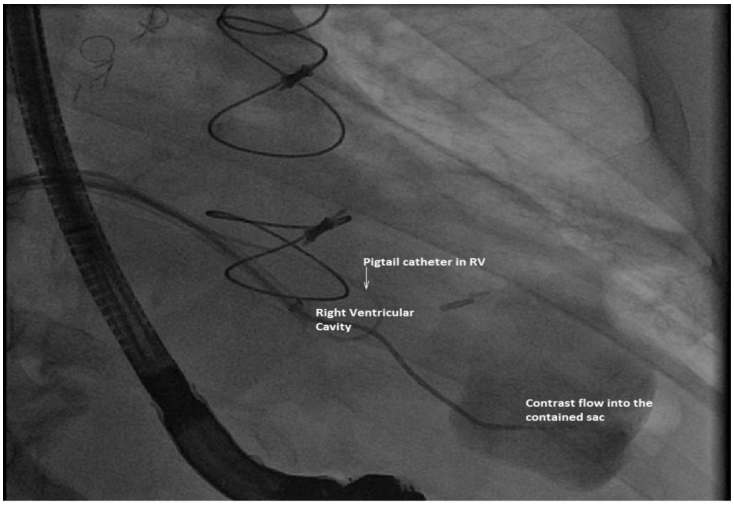

Figure 3A-II: Illustrating the angiographic visualization of the right ventricle and the "contained sac". showing contrast leakage from right ventricular cavity through the defect into the "contained sac".

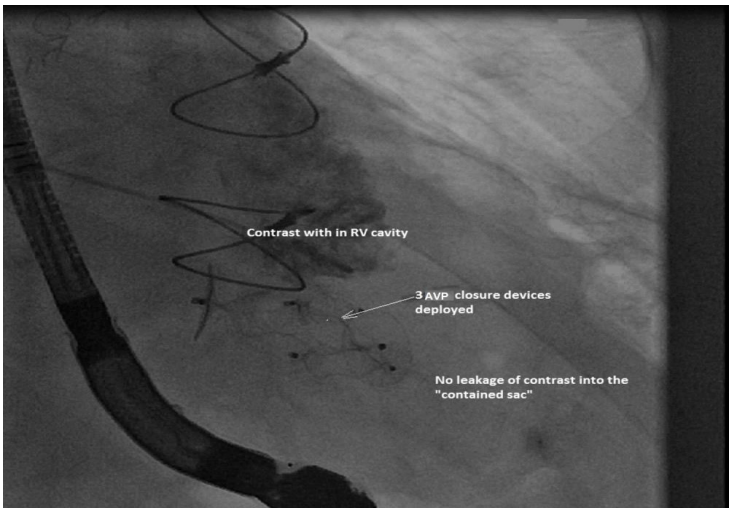

Figure 3B: Illustrating the angiographic visualization of the right ventricle and the "contained sac". 3B-showing 3 AVP (amplatzer vascular plug) II closure devices deployed with no leakage of contrast into the "contained sac".

surgical repair. Previously, patients who survived were reported as having subacute ruptures rather than acute[6]. Percutaneous closure using an AVP II device, is a well-known technique with high success rates (>95%) and is an alternative to surgical repair[7].

Conclusion

Our case offers a unique perspective into the feasibility and safety of percutaneous closure of VFWR with percutaneous closure devices such as AVP II under TEE and angiographic guidance in patients who survive VFWR (mostly a fatal condition otherwise) and are not candidates for surgical repair. The lack of randomized evidence to standardize the duration and regimen of antiplatelet therapy following placement of these devices is to be noted.

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An Itchy Lead: First Reported Case of Ventricular Pacemaker Lead Self-Extraction

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Abstract

We present a particularly rare case and the first ever report of a ventricular self-extraction in a 98-year old female. Our patient had a past medical history significant for severe Alzheimer's dementia, paroxysmal atrial fibrillation, and sick sinus syndrome who was admitted in clinically stable condition following the unwitnessed self-extraction the ventricular lead of her dual chamber pacemaker. This case highlights the potential risks and other clinical challenges of pacemaker and ICD placement in elderly patients and in patients with cognitive impairment.

Introduction

Cardiac pacemaker and implantable cardioverter-defibrillator (ICD) mechanical lead dislodgements are rare but potentiality serious complications of cardiac device implantation. Although the overall rate of dislodgement of cardiac leads is believed to be decreasing, a previous review revealed that the rate of lead dislodgement could be as high as 2.4%[1]. Most of the lead dislodgements occur within 24–48 hours of implantation, and are most commonly diagnosed through device interrogation showing intermittent undersensing, loss of capture, or post-procedure chest x-ray revealing macro or micro movements of the leads. Although perforations of the vascular structures or myocardium are considered rare, some reports suggest a higher incidence around 1% for pacemaker implantation and up to 15% subclinical perforations[2,3]. Rarely, these perforations can lead to life-threatening cardiac tamponade, especially if the right ventricle is the site of perforation[2]. The "risk factors" for pacemaker and ICD lead complications include operator experience, in that complications rates are inversely proportional to total cases by the operator and the yearly case rate[1]. However despite proficient surgical technique, lead dislodgements and other late presenting mechanical complications still occur for uncontrollable and unpredictable reasons. To further illustrate this point we are presenting a rare case of a late presenting cardiac pacemaker "lead complication," involving what we believe to be the first reported case of ventricular pacemaker lead self-extraction.

Case Report

Our patient is a 98-year old female with a past medical history significant for severe Alzheimer's dementia, paroxysmal atrial fibrillation, hypertension, stage 4 chronic kidney disease and depression. She had recently moved to a local memory care facility. Approximately 6 months prior to her presentation, she received a permanent, dual chamber DDD (Boston Scientific Altrua®) pacemaker for sick sinus syndrome and a documented episode of syncope. EKG prior to pacemaker implantation showed sinus bradycardia without evidence of high grade AV block. Implantation of the pacemaker was performed by an experienced cardiologist and was completed without any evidence of periprocedural complications.

On the date of her acute presentation, she was transferred to our facility from her memory care unit after being found with a wire sticking out of her skin near the pacemaker pocket site. The patient remained hemodynamically stable on arrival with blood pressure of 147/62 and pulse rate of 87. Due to her late stage dementia, she was unable to provide a reliable history. The memory care unit staff stated that the patient was found with blood on her clothing and with the transected lead lying on the floor. Patient was unaware of anything bothering her on her chest. Her physical exam on presentation was remarkable for an irregular heart rhythm and left anterior chest pacemaker lead broken off and protruding from chest wall near her pacemaker pocket site. The skin near the area where the transected lead was protruding was markedly thin, mildly erythematous, and without any excoriations. Chest radiograph [Figure 1] showed extraction and transection of the patient's ventricular lead and undisrupted atrial lead. EKG on admission [Figure 2] showed atrial paced, ventricular sensed rhythm. Pacemaker interrogation revealed sudden change in RV lead impedance from 490 ohms to > 2500 ohms. Temporary cessation of pacing showed underlying sinus bradycardia with a rate of less than 30 bpm. She remained 91% atrial paced following the self-extraction of the lead. The patient was placed on levofloxacin for antimicrobial coverage given the concern for infection with disruption of the subcutaneous pacemaker pocket.

Key Words

Ventricular Lead, Self-Extraction, Atrial Fibrillation

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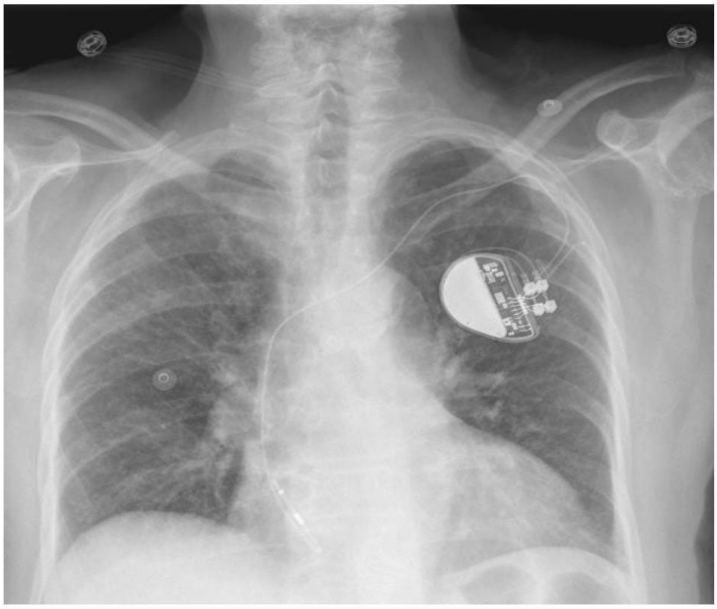

Figure 1: Admission chest x-ray showing transected ventricular lead and intact atrial lead

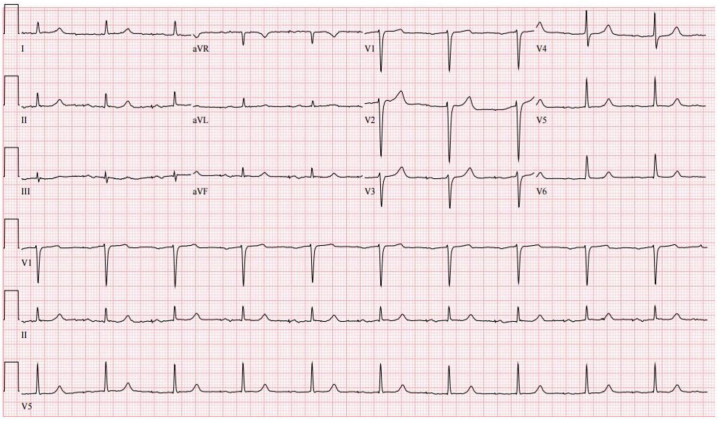

Figure 2: Admission EKG showing atrial paced rhythm after ventricular lead removal

On hospital day 2, the patient was taken to the OR for removal of the transected ventricular pacer lead and revision of a subcutaneous pocket with repositioning of the remaining atrial lead. Postoperatively, the patient recovered without incident. Her vitals remained stable throughout her hospital course and she was discharge on post-operative day 1 with her remaining atrial pacemaker in place.

Discussion

To the best of our knowledge this is the only the second report of pacemaker lead self-extraction and the first report of the self-extraction of a ventricular lead. In 2015, Yıldız et al reported a similar case of the self-extraction of atrial lead without any mechanical dislodgement of the ventricular lead[4]. Much like our patient, the authors reported no apparent symptoms, hemodynamic instability, or signs of perforation related to the dislodgement of the lead.

Our case report is remarkable in that the patient self-removed the ventricular lead without disrupting the atrial lead and later transected the ventricular without damage to the myocardium or vasculature. It is extraordinary that this event occurred while the patient remained nearly fully pacemaker dependant on the remaining atrial lead.

The findings of Yildiz et al and our case report suggest a need for further reconsideration of the risks of pacemaker and ICD placement in elderly patients, particularly those with cognitive impairment. The thin skin commonly found in patients in their eighth and ninth decade of life is likely to pose a physical obstacle to safe cardiac device placement[4]. It has been previously reported that the thickness of epidermis decreases about 6.4% per decade, most notably in female patients[5]. This suggests a need for a modification of common cardiac device implantation technique in this patient population and deep sub-fascial lead placement near the pocket site.

Our case report also suggests that there are additional risks of pacemaker implantation in patients with clinically significant cognitive impairment that need further consideration. We believe that the risks of self-extraction, unintentional pocket disruption, and mechanical lead dysfunction should be considered to be higher in this particular patient population. Closer post-procedural follow-up and caretaker/family education about these risks may be warranted, despite the rarity of this clinical phenomenon.

Advances in cardiac device technology, most notably "leadless" pacemakers, could be of increased value in patients of advanced age and/or cognitively impairment were clinically indicated. Although the patient we present here would not have been a candidate, "leadless" pacemakers are indicated in patients who need ventricular pacing support. Nanostim® leadless cardiac pacemaker (St. Jude Medical) and Micra® intracardiac transcatheter pacing system (Medtronic) are both implanted directly within the right ventricle and have been prospectively shown to be similar to traditional transvenous pacemakers in terms of function and safety[6,7].

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Complexities in the Atrial Fibrillation-Stroke Relationship: Improving Comprehension of Temporal Discordance, Magnitude Synergism, and Subclinical Atrial Fibrillation -- Three Sources of Consternation for Physicians Who Care for Patients with Atrial Fibrillation

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Abstract

That clinically-documented atrial fibrillation (AF) in association with a variety of elevated clinical/laboratory risk markers is associated with an increased risk of stroke is well known – regardless of whether the AF is paroxysmal, persistent, or permanent. Moreover, data is accumulating to suggest that the absolute rate of stroke should be expectedly higher with a greater burden of AF and greater degree of comorbid contributors. Relatedly, stroke prevention with chronic oral anticoagulation (OAC) is recommended for AF patients with appropriate risk markers by all major medical, cardiologic, and surgical guideline-writing organizations. However, at least two major clinical concerns about the above AF-stroke statements remain. First, if AF is related to stroke, why then is there not a consistent temporal relationship between a stroke and AF? Second, is there importance to and what should we do about device-detected AF (so-called subclinical AF [SCAF]) in the absence of clinically-recognized AF? This paper is designed to enhance the understanding of these issues and reduce the consternation of physicians who care for patients with AF with respect to them.

Introduction

That clinically-documented atrial fibrillation (AF) in association with a variety of elevated clinical/laboratory risk markers[1] is associated with an increased risk of stroke is well known -- regardless of whether the AF is paroxysmal, persistent, or permanent. Moreover, data is accumulating to suggest that the absolute rate of stroke should be expectedly higher with a greater burden of AF and greater degree of comorbid contributors[4-7]. Relatedly, stroke prevention with chronic oral anticoagulation (OAC) is recommended for AF patients with appropriate risk markers by all major medical, cardiologic, and surgical guideline-writing organizations. However, at least two major clinical concerns about the above AF-stroke statements remain. First, if AF is related to stroke, why then is there not a consistent temporal relationship between a stroke and AF? Second, is there importance to and what should we do about device-detected AF (so-called subclinical AF [SCAF]) in the absence of clinically-recognized AF?[8].

Discordance of Temporal Relationship Between AF and Stroke:

[1] If stroke in high-risk-marker-present AF patients is related to the AF, then why can such strokes be temporally unrelated to the timing of AF? In some studies, the last AF event prior to a stroke has been noted to occur >30 days before, while in others, AF is first demonstrated on continuous monitoring (initiated post stroke) one or more years post stroke. Additionally, if AF is causative of strokes in high-risk-marker patients, then why is not properly administered OAC preventative in 25% of cases or more? Is our model wrong, or have we oversimplified it? For several reasons I, among others, [9] strongly suspect the latter.

(a) AF in the absence of co-morbidities, has an incredibly low risk of stroke. So, the story cannot be AF in and of itself. Moreover, many of the high-risk-marker comorbidities, such as hypertension, diabetes, vascular disease, are themselves associated with an increased risk for stroke, independent of AF. Thus, a stroke in an AF patient may be a consequence of comorbid disorders and not directly due to AF. AF may simply be a marker of greater atrial myopathy with the latter the proximate cause of thrombus formation. Accordingly, is it ever possible to know if AF was causative of a stroke or just a marker of a thrombogenic comorbidity? When AF is present at the time of an imaging-documented embolic stroke, being causative seems likely. But, temporal discordance does not exclude AF as a factor just as an embolic event from a comorbidity in a patient who happens to be in AF does not absolutely indicate AF was the cause (see below). Thus, we should temper our statements regarding causality and our therapeutic expectations re: OAC protection. A stroke in an anticoagulated AF patient may not mean the OAC failed. Moreover,

Key Words

Atrial Fibrillation, Magnitude Synergism, Temporal Discordance, Subclinical Atrial Fibrillation

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the absence of laboratory measurement of anticoagulant activity with the non-vitamin K OACs at the time of a thromboembolic event further limits our ability to assess this relationship.

(b) AF induced strokes are ischemic, consequent to thromboembolism. However, a stroke in an AF patient can also be non-embolic, embolic but not from the left atrium (e.g., aorta, carotid, patent foramen, etc.), hemorrhagic (due to the OAC or not), or lacunar. Thus, OAC should not be expected to prevent all strokes in AF patients. Lumping together all strokes as a single outcome event in clinical trials, as is usually/often done may be a disservice re: their interpretation[10].

(c) In patients with AF and stroke-risk comorbidities, including older age, hypertension, diabetes, heart failure, and more, the left atria are not normal. Rather, there are endothelial, metabolic, anatomic, histopathologic, and contractile alterations in the atria that can be prothrombotic – including endothelial dysfunction, atrial dilation, and hypocontractility. These contributory dysfunctions can result from the comorbidities present as well as from any superimposed atrial tachycardic myopathy consequent to the AF itself and should contribute to thromboembolic risk synergistically[4-11]. Importantly, any component due to the AF may not resolve either immediately or completely upon cessation of AF (whether paroxysmal AF, cardioverted AF, or SCAF). Post-ablation and post-cardioversion imaging studies have demonstrated this clearly. Moreover, if a clot forms during a period of AF, it need not resolve or embolize synchronously with the termination of AF. Conceptually, it may even be more likely to embolize after some improvement of atrial contractile function following AF cessation. Thus, AF may contribute to causation but not be present at the time of thromboembolism. Understanding this allows us to recognize why there can be a temporal disconnect between the timing of AF and the timing of an AF-mediated stroke – though in a given patient at the time of a stroke, a causative relationship between the stroke and somewhat remote AF can never be certain.

Sub-Clinical Atrial Fibrillation – Is It Really a Dilemma?

[2] SCAF is of growing interest with respect to the above issues. Is SCAF of relevance and if so, when? It is only recently that SCAF has become a concern. A Medline search on the term "subclinical atrial fibrillation" produced no entries between 1990 and 2009 but 49 (including letters) between 2010 and the present, with 34 of the latter between 2016 and now. Notably, the importance of SCAF as a factor in thromboembolic risk originally grew out of observations made in patients implanted with pacemakers or defibrillators (P/ICD) but has been expanded by the recent trials utilizing insertable cardiac monitors in patients without known AF but identified as being at AF risk by demographic, echocardiographic, and/or laboratory risk markers. The P/ICD trials, using a variety of AF durations to define SCAF, clearly revealed an epidemiological link to increased stroke risk[1,8]. Some have suggested that the risk is greater the longer the duration of AF (a contributor to overall AF burden). My own belief (with clinical trial support) is that there cannot be an absolute threshold for SCAF duration and embolic risk; rather, the risk must be dependent upon the AF burden and the number and magnitude of the comorbidities present[4-7]. The greater the atrial pathophysiology created by the synergism of AF and underlying disease, the greater the risk. Hence the concept of magnitude synergism should be applied to understanding SCAF and considered when designing future clinical trials and interpreting their results[1,4]. It is not enough to just note the presence of SCAF and its longest duration; rather, a quantitative description of the setting in which it occurs is also a necessity (quantitative and qualitative comorbidity) and an assessment of AF burden should also be considered[4,7]. The recent KP-RHYTHM study [3] demonstrated that AF burden, not just the presence of AF, is important in quantitating the risk for stroke. In the KP-RHYTHM study: "the highest tertile of atrial fibrillation burden was associated with a more than 3-fold higher adjusted rate of thromboembolism….compared with the combined lower 2 tertiles…" Importantly, currently ongoing anticoagulation trials in device-detected SCAF patients [12,13] will add a great deal regarding the importance and treatment of SCAF.

Certainly, there is much more to debate about AF, stroke, clinical trials of such, and therapies. But given the discussion in recent times about the above two issues in particular, a better understanding of them can only improve upon our forward direction.

Disclosures

In the past 36 months, Dr. Reiffel has served as Principal Investigator of the REVEAL-AF trial, sponsored by Medtronic; as a member of the steering committee of the ORBIT AF trials and of CABANA; as a consultant to Janssen, Portola, Sanofi, Acesion, InCardia Therapeutics; on the speaker's bureau for Janssen; and as a member of the AF SCREEN program.

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Clinical Relevance of the Spectral Tissue Doppler E/e' Ratio in the Management of Patients with Atrial Fibrillation: A Comprehensive Review of the Literature

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Abstract

Atrial fibrillation is the most common cardiac rhythm disorder observed in clinical practice. It carries high morbidity and mortality rates, primarily related to heart failure, stroke and death. Validation of noninvasive markers in the diagnosis of heart failure with preserved ejection fraction and risk stratification is relevant in this clinical setting. The spectral tissue Dopplerderived E/e' ratio is a simple and reproducible index, which has been validated in noninvasive assessment of left ventricular diastolic pressures, regardless of rhythm. Septal E/e' >11 is a good predictor of invasively determined left ventricular diastolic pressure >15 mmHg in patients with atrial fibrillation. Several studies have validated the clinical relevance of abnormal values for E/e' at rest and during exercise in the diagnosis and risk stratification of heart failure with preserved ejection fraction in patients with atrial fibrillation. Increased E/e' value is associated with adverse outcome (death, left atrial appendage thrombus, stroke and heart failure) in patients with atrial fibrillation and predicts arrhythmia recurrence after cardioversion and catheter ablation. In conclusion, E/e' by spectral tissue Doppler is clinically relevant in the clinical management of any patients with atrial fibrillation referred for transthoracic Doppler echocardiography.

Introduction

Atrial fibrillation (AF) is the most common cardiac rhythm disorder observed in clinical practice. Despite advances in its diagnosis and therapeutic management, this condition remains one of the most common causes of cardiovascular morbidity and mortality, primarily related to stroke, heart failure and death[1]. This condition affects about 3% of the population over 20 years of age. Its prevalence is increasing, which is linked to a better detection of silent AF, the ageing of the population and an increase in diseases leading to its occurrence[1]. Experts recommendations issued in 2016 have highlighted the importance of cardiac imaging in the management of patients with AF[2]. Therefore, validation of simple, noninvasive parameters that can help diagnose concurrent heart failure, particularly with preserved ejection fraction, and predict outcome as well as arrhythmia recurrence, is of paramount importance in clinical setting.

Since the landmark studies by Nagueh et al.,[3] the clinical relevance of the spectral tissue Doppler E/e' ratio by transthoracic Doppler echocardiography has been definitely established. In particular, E/e' provides relevant information in noninvasive assessment of left ventricular diastolic pressures and function, diagnosis and prognosis in outpatients, heart failure irrespective of ejection fraction, ischemic heart disease, hypertrophic cardiomyopathy, arterial hypertension and more broadly critically ill patients[4-24]. E/e' would therefore be to left ventricular diastolic function what ejection fraction is to systolic function in clinical practice[8,15]. Evidence has emerged that E/e' is also useful in patients with AF. The purpose of the present review is therefore to assess the diagnostic and prognostic relevance of the E/e' ratio in patients with AF.

Key Words

Atrial Fibrillation, Tissue Doppler Imaging, Heart Failure, Stroke, Prognosis

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Relevance of E/e' in Noninvasive Assessment of Left Ventricular Diastolic Pressures in Patients with AF

The accuracy of E/e' in measuring left ventricular filling pressures is based on the fact that the mitral E velocity is primarily related to left atrial pressure and left ventricular relaxation in order of decreasing significance, and that the e' velocity by spectral tissue Doppler at the mitral annulus reflects left ventricular relaxation in patients with structural heart disease. The relation between these two velocities theoretically allows to overcome the influence of diastolic function and partially reflect left atrial pressure[7,22]. E/e' has been correlated to invasively determined left ventricular diastolic pressures and function in patients, irrespective of left ventricular ejection fraction[3,6-8,14,15,23]. E/e' is not accurate in assessing left ventricular diastolic pressures in healthy individuals and in patients with organic mitral valve disease and left ventricular wall motion abnormalities related to myocardial infarction, left bundle branch block, paced rhythm or coronary bypass[7]. Nevertheless, some studies have reported fair correlations between E/e' and invasively determined left ventricular diastolic

pressures[25,26].

One should keep in mind that accurately measuring invasive left ventricular filling pressures can be challenging in practice, which has been recently highlighted by fair correlations and wide scatter between pulmonary capillary wedge pressure and left ventricular end-diastolic pressure[27,28]. Last, this correlation, although statistically significant, allows only a semi-quantitative assessment of invasive left ventricular diastolic pressures. Several studies have specifically evaluated the reliability of E/e' in assessing left ventricular diastolic pressures in patients with AF. In the landmark study by Sohn et al. that included 27 consecutive patients with AF, in whom tissue Doppler velocities and invasive recordings were simultaneously assessed, e' measured at the septal side of mitral annulus was significantly and inversely correlated with tau (r = -0.51, p <0.01), and septal E/e' was strongly correlated with invasive left ventricular diastolic pressure (r = 0.79, p <0.001)[29]. E/e' >11 had a sensitivity and specificity of 75 and 93%, respectively, in the prediction of invasive left ventricular diastolic pressure >15 mmHg. Currently, large evidence is that E/e' is significantly correlated with invasive left ventricular filling pressures in patients with AF (r = 0.404 to 0.765, p <0.05)[30-34]. Best results were obtained by measuring E and e' simultaneously[31,32]. However, this technology is not available on most current ultrasound machines, and several consecutive cycles must be recorded and averaged for E and e'.

Relevance of E/e' in the diagnosis and prognosis of heart failure with preserved ejection fraction in patients with AF

Nearly half of patients with heart failure have preserved ejection fraction. The diagnosis is difficult in this setting and requires comprehensive assessment of left ventricular diastolic function by transthoracic Doppler echocardiography and/or catheterism. E/e' is clinically relevant in the diagnosis and risk stratification of heart failure with preserved ejection fraction, regardless of clinical presentation[7,8,15,20,21,35,36]. AF is a common comorbid condition in patients with heart failure and preserved ejection fraction[37]. Several studies have established the diagnostic relevance in this setting. A first work evaluated the value of E/e' in the diagnosis of heart failure with preserved ejection fraction in patients with AF with acute dyspnea[38]. Forty-one consecutive patients with left ventricular ejection fraction >50% were included, and septal E/e' >13 had a sensitivity and specificity of 82 and 89%, respectively, in the diagnosis of acute heart failure. Another study has confirmed these results in 73 patients with NYHA functional class I to IV[39]. Septal E/e' >11.7 had a sensitivity and specificity of 87 and 93%, respectively, in the diagnosis of heart failure with preserved ejection fraction (area under the ROC curve of 0.96) by using Framingham criteria as diagnostic reference. E/e' is inversely and independently correlated with functional capacity in patients with AF, confirming that an abnormal value for E/e' at rest and/or exercise strengthens the diagnosis of heart failure with preserved ejection fraction in patients with isolated exertional dyspnea and reduced exercise capacity[40-43]. In the study by Lee et al. that included 73 patients with AF, septal E/e' was an independent predictor of functional capacity (p = 0.03), after adjusting for age (p = 0.006) and heart rate (p = 0.03)[40]. In another work that included 50 patients with AF and preserved ejection fraction, the E/e' ratio (septal, lateral and average) was inversely correlated with the six-minute walk test and the quality of life questionnaire[41]. In another study that included 94 patients with AF and preserved ejection fraction, multivariate analysis revealed that a resting lateral E/e' ratio >9 was independently associated with a decrease in peak VO2 (p <0.001), after adjusting for age (p = 0.006) and female sex (p = 0.001)[42]. In a second study by the same team that evaluated 145 patients with AF, preserved ejection fraction and lateral E/e' ratio <9 at rest, lateral E/e' >9 at exercise was independently associated with a decrease in peak VO2 (p = 0.001), after adjusting for age (p = 0.001) and female sex (p = 0.001)[43]. All these findings are consistent with those observed in patients in sinus rhythm[7,36].

Last, E/e' offers useful prognostic information in patients with AF and heart failure with preserved ejection fraction. In one study that specifically included 148 patients with these 2 conditions, septal E/e' >15 was a good predictor of cardiovascular death, recurrence of heart failure and stroke, with a sensitivity and specificity of 50% and 78%, respectively (area under the ROC curve of 0.65, p <0.01)[44].

Relevance of E/e' in risk stratification in patients with AF

E/e' used as a noninvasive surrogate for left ventricular diastolic pressures provides important prognostic information in multiple populations of patients in sinus rhythm[4-6,9,10,12,13,16,17,19-21,24]. AF is linked to outcome, and several studies have specifically addressed the clinical relevance of E/e' in risk stratification in this clinical setting.

Three studies first reported the relevance of E/e' in predicting death in patients with AF. In the landmark study by Okura et al., 230 patients with AF were followed, and septal E/e' >15 was an independent predictor of mortality (p = 0.03), after adjusting for age (p =0.02)[45]. In another recent work that included 488 patients with AF and preserved ejection fraction, septal E/e' >15 was independently associated with mortality (p <0.01), after adjusting for hemoglobin (p <0.001)[46]. In a prospective, multicenter study that observed 971 patients with AF, average E/e' >13 was an independent predictor of death (p = 0.03)[47].

This noninvasive index is also a potent risk marker of left atrial appendage thrombus in patients with AF[48-50]. In a first study that evaluated 376 consecutive patients with AF, septal E/e' >13 was a predictor of left atrial appendage thrombus in multivariate analysis (p =0.02), after adjusting for left ventricular ejection fraction (p = 0.005) and left atrial size (p =0.04)[48]. In another recent study that included 563 consecutive patients with AF, septal E/e' >12 and lateral E/e' >9.4 predicted left atrial appendage thrombus in multivariate analysis (p<0.01), with a sensitivity in thrombus detection close to 100% for a specificity between 38 and 55%[50]. In the landmark study of Lee et al. that evaluated 330 patients with AF and preserved ejection fraction, septal E/e' was an independent predictor of stroke in multivariate analysis (p <0.01), with arterial hypertension (p <0.01)[51]. In another study that observed 1098 consecutive patients with paroxysmal AF, septal E/e' >15 was a powerful, independent predictor of stroke (p = 0.03)[52]. Last, in a recent observational study that included 171 neurologically asymptomatic patients with AF, septal E/e' >12.4 was independently associated with silent cerebral infarction at MRI (p = 0.001), after adjusting for age (p = 0.025)[53]. The clinical relevance of E/e' has also been reported in the prediction of cardiovascular events in patients with AF. In the observational study by Su et al, 196 patients

with AF were followed for 17 months[54]. Average E/e' independently predicted death and hospitalization for heart failure (p=0.002), after adjusting for a history of chronic heart failure (<0.001), left ventricular mass index (p=0.001) and mitral L wave (p=0.016). In another study that observed 190 patients with AF, increased average E/e' was related to death and hospitalization for heart failure in univariate analysis (p<0.001)[55]. In another observational study that prospectively followed 196 consecutive patients with AF for about 17 months, an abnormal value for average E/e' was associated with sudden death, stroke and hospitalization for heart failure (p =0.001), after adjusting for chronic heart failure (p = 0.002) and the myocardial performance index (p = 0.004)[56]. Similar results have been reported in another observational study that followed 252 consecutive patients with AF for 21 months[57]. Average E/e' >8 was a powerful predictor of the composite end-point of cardiovascular death, progression of heart failure and stroke (p <0.001), after adjusting for left atrial volume and left atrial deformation by twodimensional speckle tracking echocardiography. Last, there is convincing evidence that E/e' predicts left atrial appendage thrombus, neurological events and, more generally, cardiovascular events beyond the CHA_2DS_2-VASC score[47,49,53,57,58].

Relevance of E/e' in Predicting Recurrence of AF after Catheter Ablation or Cardioversion

The relevance of invasive left atrial pressure recording in predicting recurrence of AF after catheter ablation has recently been reported by invasive means in patients referred for catheter ablation, which may be in part related to its contribution to left atrial stretch and remodeling[59,60]. In one study that included 170 patients referred for ablation procedure, invasive left atrial pressure was a powerful predictor of recurrence of arrhythmia in multivariate analysis (p = 0.006), after adjusting for left atrial volume (p = 0.007)[60]. Noninvasive assessment of left ventricular diastolic pressures may therefore be useful in predicting recurrence of arrhythmia in daily practice. Several studies have addressed the relevance of E/e' in the prediction of arrhythmia recurrence after catheter ablation and electrical cardioversion. In the study by Li et al., 103 consecutive patients were included[61]. E/e' measured during AF and after sinus rhythm restoration was a powerful predictor of recurrence of AF after ablation in multivariate analysis (p <0.001). Septal E/e' >11.2 measured before ablation had a sensitivity and specificity of 81 and 82%, respectively, in the prediction of recurrence of arrhythmia. These results were confirmed in 198 patients with paroxysmal AF[62]. Average E/e' >13 was the sole Doppler echocardiographic parameter associated with recurrence of arrhythmia. Okamatsu et al. evaluated the usefulness of E/e' in 22 patients with AF and hypertrophic cardiomyopathy[63]. Septal E/e' >15 independently predicted recurrence of arrhythmia after catheter ablation (p = 0.03). Last, the most recent study that included 215 consecutive patients with AF referred for catheter ablation has offered confirmatory findings. Average E/e' >14 was a powerful, independent predictor of arrhythmia recurrence after multiple ablation procedures (p=0.02), after adjusting for age, sex, lowvoltage-area existence and left atrial diameter[64].

In one study by Caputo et al., lateral E/e' was independently associated with recurrence of AF in 51 patients referred for electrical cardioversion (p = 0.0078), after adjusting for left atrial volume (p = 0.04)[65]. Confirmatory results were observed in patients with or without left atrial dilatation. In one study that included 127 patients with left atrial dilatation, septal E/e' >11 predicted recurrence of AF after cardioversion (p = 0.001) in multivariate analysis, after adjusting for duration of arrhythmia before cardioversion (p = 0.04) and systolic pulmonary arterial pressure (p = 0.001)[66]. In another study that included 66 patients with AF and left atrial diameter <50 mm, septal E/e' was independently associated with recurrence of arrhythmia after cardioversion (p = 0.017), after adjusting for left atrial volume (p = 0.04)[67].

Conclusion

E/e'is a user-friendly and reliable Doppler index in semi-quantitative assessment of left ventricular diastolic pressures in patients with AF. However, at this time, several consecutive cycles must be recorded and averaged in the absence of simultaneous measurement of E and e' velocities to overcome potential influence of cycle irregularity on E and e' values. Evidence of an abnormal value for E/e' at rest and during exercise strengthens the diagnosis of heart failure with preserved ejection fraction and provides prognostic information on outcome and arrhythmia recurrence. In light of these findings, the measure of E/e' should be an integral part of the evaluation of any patient with AF referred for comprehensive transthoracic Doppler echocardiography. It should be kept in mind that the adoption of a higher threshold value for the E/e' ratio improves the positive predictive value of disease or event but, at the same time, impairs the negative predictive value. In addition, Measuring e' velocity by color tissue Doppler imaging might be an alternative in this setting despite paucity of data on the diagnostic and prognostic relevance of this method and the constant overestimation of spectral E/e' by color E/e'[68-72]. Accordingly, further experimental and clinical studies are mandatory to delineate the potential contribution of each method to measure E/e' according to all the aspects of cardiovascular diseases.

Conflicts of Interest

None

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Avicenna and Tremor of the Heart

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Physicians have been mesmerized by a beating heart and its relationship to the peripheral pulse since the ancient times. Although William Harvey in 1628 was credited as the first to describe "fibrillation of the auricles," chaotic irregularity of the pulse was acknowledged by some as early as in the antiquity. In fact, a close examination of history may reveal a description of cardiac arrhythmias long before the era of modern medicine.

Dhanvantari, the ancient Indian physician, concluded in the fifth century B.C. that assessment of the arterial pulse is an integral part of physical examination. In Ayurveda (knowledge of life), Dhanvantari was the first to provide a methodology for pulse examination and pioneered the modern-day approach of using the wrist to take the patient's pulse[1]. Years later, Claudius Galen described the relationship between peripheral pulse and the beating heart. Galen wrote, "the arterial pulse is an inherent property of the blood vessel. It is a vital power that springs from the heart and is transmitted through the coats of the arteries".

In the early medieval period, Avicenna, a Persian scholar became well-known for his comprehensive medical text, the Canon of Medicine. Like his predecessors, Avicenna had a fascination with the pulse. He used Galen and Dhanvantari's teachings to categorize the pulse according to its different features, but he also delivered a general understanding of cardiac arrhythmias based on the characteristics of the pulse. In fact, if dive into Avicenna's medical texts, we can find the first narrative of the most common arrhythmia, atrial fibrillation.

In the Canon of Medicine, Avicenna describes two kinds of irregular pulses: regularly, irregular and irregularly, irregular. Interestingly, he was the first to believe that an "irregular pulse" was the result of "the fluttering in the heart." Avicenna recognized the relationship between an irregular pulse, fibrillation of the heart, and a rapid heart rate. He wrote: "the irregularity increases until cardiac tremor comes on, and a thrilling pulse result." He compared the rhythm of an irregular pulse to the flight of the gazelle and continued, "if the irregularity is orderly, it betokens lesser constitutional injuries; if disorderly, it shows that there are more serious constitutional defects to deal with." It is in his narrative of the irregular pulse that we recognize, without excessive strain on the imagination, the first description of atrial fibrillation.

Avicenna's captivation with the "fluttering of the heart" did not halt with a simple description of the irregular pulse as he also elucidated associated symptoms and factors. He described palpitations as the main symptom of an irregular pulse, stating that palpitation occur secondary to the unnatural movement of the heart, resulting in disharmony in the temperament of this organ[2]. He further denoted that palpitations are associated with an increase in the heart rate, and when palpitations intensify, they bring about fainting[3]. As we know today, tachycardia, palpitations and lightheadedness are considered as some of the cardinal signs and symptoms of atrial fibrillation.

Based on our understanding of atrial fibrillation today, we recognize that this arrhythmia can be triggered or exacerbated by a multitude of factors including sepsis, stress, alcohol, dehydration, and volume overload. Once more, if we closely explore Avicenna's description of this arrhythmia, we are able to find some of these associated factors. For instance, he commented on the effect of alcohol consumption on the pulse, "wine has a notable effect on the pulse, in that if taken plentifully, being attenuated in nature; it gives rise to an irregular pulse." He further speculated that an irregular pulse and palpitations occur as a consequence of infections, "when abscess formation comes on, the pulse also becomes irregular." In the Cannon, he describes a patient in whom "the pulse becomes frequent, short, variable in fullness and strength, not vehement, and occasionally irregular, especially after an outburst of violent emotion." By analyzing Avicenna's account of this patient, might we conjuncture that he was describing a patient with paroxysmal atrial fibrillation?

One more illustration of how Avicenna may have recognized atrial fibrillation many centuries ago may be drawn from his treatment for an irregular pulse. In his Treatise on Cardiac Drugs, he mentions an herbal remedy named 'zarnab' (Taxus baccata L.) which he used for treatment of patients with an irregular pulse. He stated that, "zarnab sets the heart at ease" especially when the patient is suffering from palpitations. The findings of contemporary research have shown that Taxus produces negative chronotropic and atrioventricular blocking effects due to its calcium channel blocking activities suggesting that Avicenna may have pursued a "rate control strategy" for these patients.

Although Avicenna may have been the first to describe atrial fibrillation with the help of teachings from his predecessors including Galen and Dhanvantari, this historical perspective would be incomplete without recognizing the contributions of modern-era physicians. Many centuries after Avicenna, William Harvey was the

first to provide the precise description of the closed circulation of humans. Harvey also directly observed fibrillation of the atria in open chest animals and his meticulous observations established that the heart beat was initiated in the atria. In the mid-eighteenth century, Jean Baptist de Sénac expanded on Harvey's observations and made the connection between a "rebellious palpitation" to the stenosis of the mitral valve[4]. James Mackenzie provided the first in-depth explanation of atrial fibrillation's pathophysiology and demonstrated the loss of the 'a' wave during "pulsus irregularis perpetuus"[5]. The first human electrocardiogram (ECG) depicting atrial fibrillation was published by Willem Einthoven in 1903[5] enabling Sir Thomas Lewis to study electrophysiologic characteristics of this rhythm[6]. Subsequently, the foremost discoveries related to the pathophysiology and clinical features of atrial fibrillation in the 20th century developed on account of works done by Karel Wenckebach, Gordon Moe, and Maurits Allessie. Noticeably, contributions made by many physicians over the centuries have yielded a wealth of information and extraordinary growth in our understanding of atrial fibrillation and as a result many novel approaches for diagnosis and treatment of this arrhythmia have developed.

Today, we live in an era of rapid scientific advances in medicine and information drawn from ancient observations may not significantly alter our current perceptions. Yet, having a historical perspective and appreciation of the work of those before us will affords a better understanding of contemporary issues and a clearer vision as we look to the future. As Hippocrates once said: "Medicine has always existed since the beginning of time. The road has been revealed to us, and many good things have been discovered along the way. The rest remain to be discovered if one based on what is already known is capable enough to ask for more".

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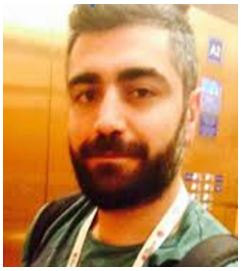

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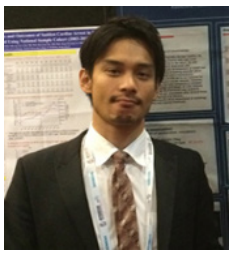

Dr. Kyoichiro Yazaki, MD

Affiliation: Ogikubo Hospital, Department of Cardiology,Cardiovascular Center, Tokyo, Japan.
Clinical research of electrophysiology, catheter ablation, and Device therapy are of my interests

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. Andres Enriquez, MD

Dr. Enriquez received his medical degree from the Universidad de Concepcion, in Chile. He specialized in Internal Medicine, Cardiology and Cardiac Electrophysiology at Pontificia Universidad Catolica de Chile in Santiago.

Between 2013 and 2015 he moved to Canada to continue his electrophysiology training at Queen's University, Kingston, Ontario.

He currently resides in Philadelphia with her wife Karen and is a second-year fellow in the Advanced Clinical Electrophysiology program at the Hospital of the University of Pennsylvania, under the mentorship of Dr. Francis Marchlinski.

Dr. Enriquez interests include electrocardiology, clinical electorphysiology catheter ablation and cardiac devices.

Dr. Ryan Dean White. MD

Dr. Ryan Dean White, MD, medical degree from the University of Missouri and currently training in internal medicine at Indiana University School of Medicine in Indianapolis, Indiana.