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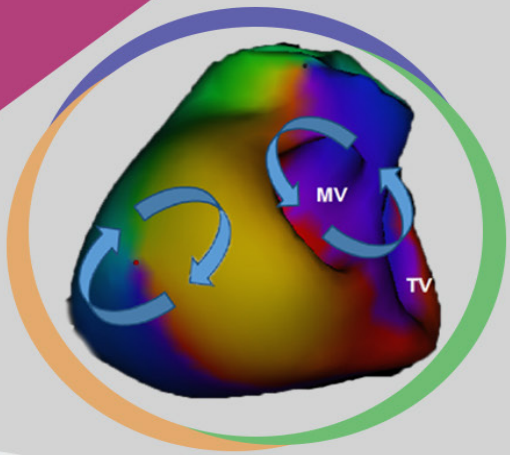

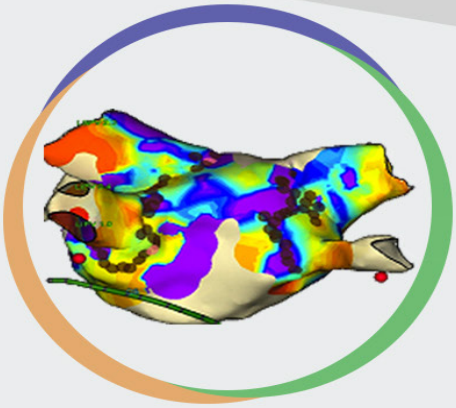

Meet the Expert Doctor

Dr. Rahul N. Doshi, M.D., F.A.C.C., F.H.R.S

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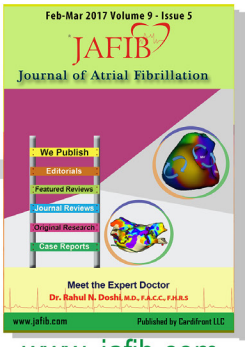

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Science at cross roads! Budget cuts, scientific antipathy and more.....

Dear Colleagues

The spirit of spring is here, at least for those of us in the northern hemisphere. The first quarter of the year here in the United States has been quite chaotic with all the sweeping changes in the politics and policies which had a significant impact on the scientific community. The scientific community stood united in their unwavering support of innovation, creativity and principles of integrity against all other distractors. The newly announced budget cuts will dramatically reduce the funding to NIH. Unfortunately, the funding from the private bodies is not encouraging either. Declining interest in the value of science that is being generated through public funding sources is a major concern. It is quite alarming to see that physician turned politicians are willing to embrace pseudoscience in order to appease a segment of political demographic. Their feverish disregard to scientific facts, questioning the global public health importance of vaccines and the real looming threat of global warming are testament to the scientific antipathy that is vivid. Whether it is the politics or the economics or scientific apathy that brought us here, there is an urgent need to reevaluate our goals and priorities on how science is going to evolve in the coming decades. This calls for greater collaboration and communication to prevent duplication and redundancy at all levels. The value of private-public partnerships is ever more important.

The International Symposium on Left Atrial Appendage (ISLAA 2017) concluded in Austin, TX during the first week of March with several amazing technologies and solid science were evaluated by experts in the field. With the Watchman device's approval by FDA, the science of LAA has come to the forefront in a big way. The systemic role left atrial appendage (LAA) in various pathophysiologic processes of the human body was reviewed. There are three major trials that are ongoing in the LAA space. The AMAZE trial is looking at the adjunctive benefits of LAA exclusion using the Lariat device to pulmonary vein isolation and cavotricuspid isthmus ablation in non-paroxysmal AF patients. The AMULET IDE study is evaluating the comparative efficacy of the SJM Amulet LAA plug against the Watchman device. There are design differences between the two and Amulet allows for the use of dual antiplatelet therapy during the first 6 weeks after device deployment. The WAVECREST IDE study compares J and J's Wavecrest device against Watchman for non-inferiority outcomes. These 3 major randomized controlled trials will redefine the LAA space in the next few years.

This issue of the journal has several important and interesting original studies published. Ranging from the impact of steroids on the outcomes of AF ablation to the changing paradigms in the use of intravenous sotalol there is wealth of new information that will keep you engaged. We once again thank all of our contributors, reviewers, editorial board members and above all you, the readers for your support of the journal. There were a few glitches in the PUBMED transition that are being addressed. Thank you for your patience.

Best wishes

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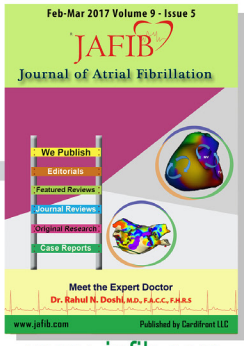

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Use Of Oral Steroid And Its Effects On Atrial Fibrillation Recurrence And Inflammatory Cytokines Post Ablation – The Steroid Af Study

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Abstract

Use of corticosteroids before and after atrial fibrillation (AF) ablation can decrease acute inflammation and reduce AF recurrence.To assess the efficacy of oral prednisone in improving the outcomes of pulmonary vein isolation with radiofrequency ablation and its effect on inflammatory cytokines, a total of 60 patients with paroxysmal AF undergoing radiofrequency ablation were randomized (1:1) to receive either 3 doses of 60 mg daily of oral prednisone or a placebo. Inflammatory cytokine levels (TNF-α, IL-1, IL6, IL-8) were measured at baseline, prior to ablation, immediately after ablation, and 24 hours post ablation. Patients underwent 30 day event monitoring at 3 months, 6 months and 12 months post procedure. Immediate post ablation levels of inflammatory cytokines were lower in the steroid group when compared to the placebo group; IL-6: 9.0 ±7 vs 15.8 ±13 p=0.031; IL-8: 10.5 ±9 vs 15.3 ±8; p=0.047 respectively. Acute PV reconnection rates during the procedure (7/23% vs 10/36%; p = 0.39), and RF ablation time (51±13 vs 56±11 min, p = 0.11) trended to be lower in the placebo group than the steroid group. There was no difference in the incidence of early recurrence of AF during the blanking period and freedom from AF off AAD at 12 months between both groups (5/17% vs 8/27%; p = 0.347 and 21/70% vs 18/60%; p=0.417 in placebo and steroid groups respectively).

CONCLUSION: Although oral corticosteroids have significant effect in lowering certain cytokines, it did not impact the clinical outcomes of AF ablation.

Introduction

Pulmonary vein isolation (PVI) is an effective treatment for symptomatic, drug refractory patients with paroxysmal atrial fibrillation (AF). Although the procedure decreases symptoms and AF burden in patients, the success rate of single procedure is only between 50%-75% [1]-[3] necessitating repeat procedures to improve the overall success rate.[4]-[9] Immediate post procedural atrial tissue inflammation can cause significant early recurrence of AF (ERAF). The long term recurrence of AF often is thought to be due to a persistent conduction gaps between the left atrium (LA) and pulmonary veins (PV).[10]-[13] The Inflammatory process associated with PVI can create significant local tissue edema resulting in transient loss of conduction in an area where permanent injury has not occurred. This can result in under ablation and subsequent reconnection of the PVs.

The anti-inflammatory effect of corticosteroids was studied extensively in cardiac surgery in the past. Corticosteroids have been shown to exert significant anti-inflammatory response as is evidenced by decreasing the levels of IL-6, IL-8, TNF, CRP, and oxygen free radicals after cardiac surgery .[10]-[13] Since the inception of our study, a few groups around the world have published data on the impact of steroids and AF ablation outcomes with significant variability. Koyama et al reported that the use of corticosteroid after AF ablation significantly decreases the immediate and late AF recurrence. However, 3 subsequent studies with different doses of IV corticosteroids found no effect in preventing early and late recurrence of AF .[3] [13]-[15] All of these studies attempted to understand the impact of only intra or post procedural steroid use. This approach may potentially suppress the immediate post ablation inflammation but may not have any impact on the intra-procedural reduction of tissue edema. We therefore attempted to study the impact of pre-treating at least 48 hours prior to the procedure to enable effective suppression of intra-procedural acute inflammatory response. This has not been addressed by any other study done so far. We aimed

Key Words

Atrial Fibrillation, Ablation, Pulmonary Vein Isolation, Interleukin, Tumor Necrosis Factor, Corticosteroid, Recurrence, Inflammatory cytokines, Prednisone.

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to systematically assess these effects through the measurement of inflammatory markers. The purpose of our study was to determine if the use of pre procedural corticosteroid can prevent early and late AF recurrence post ablation and evidence of reduction of inflammation through systemic cytokine assessment.

Methods

Study Population

We screened 105 patients of whom 60 patients with symptomatic drug refractory paroxysmal AF met inclusion and exclusion criteria and were enrolled in the study between September 2010 and November 2013. There were 30 patients in the steroid group and 30 patients in the placebo group. All patients were de novo AF ablation candidates. All patients failed at least 1 antiarrhythmic drug (AAD). AADs were discontinued 5 half-lives before the ablation procedure except for amiodarone. In those who were on AAD, it was continued for at least 8 weeks post ablation, and discontinued if no recurrence was found. The study was approved by the Institutional Review Board, and written consent was obtained from all participants. Patients were excluded due to history of corticosteroid use within 1 week of the study, use of non-steroidal anti- inflammatory drugs (NSAIDs), or colchicine within 1 week of the study,immunosuppressive disorders, chronic persistent AF, uncontrolled diabetes, or any other autoimmune disorders.

Table 1: Comparison of baseline characteristics, procedural variables and outcomes of atrial fibrillation after atrial fibrillation ablation between both the groups

Clinical characteristics	Placebo (n=30)	Corticosteroid (n=30)	p Value
Age	63 ± 8.9	63 ± 8.7	0.65
Body mass index	28.5 ± 5.2	30.5 ± 5.9	0.21
AF Duration (year)	6.9 ± 6.7	4.1 ± 4.1	0.059
LV Ejection Fraction (%)	56.2 ± 8.4	57 ± 4.7	0.70
LA Diameter (cm)	4.2 ±0.64	4.6 ±0.7	0.12
Procedure time (Minutes)	166 ± 47	174 ± 38	052
Male	22 (73)	24 (80)	0.76
Caucasian	26 (87)	26 (87)	1.0
Hypertension	12 (40)	18 (60)	0.19
Coronary Artery Disease	9 (30)	12 (40)	0.58
Valvular disease	13 (5.8)	11 (6.2)	2 (4.3)
COPD	1 (3.3)	2 (6.7)	1.0
Antiarrhythmic			
Class 1	8 (26.6)	4 (13.3)	0.33
Class 3	15 (50)	17 (56.7)	0.79
Medication			
Beta Blocker	13 (43)	12 (40)	1.0
Calcium channel blocker	7 (23)	6 (20)	1.0
Total Fluoroscopy Time (minutes)	54.8 ± 17.2	54.7 ± 16.5	0.9
Total RF tim (minutes)	51 ±13.5	56 ±10.7	0.11
Acute PV Reconnection rate	7 (23)	10 (36)	0.39
Early Recurrence (0-3 months); %	5 (17)	8 (27)	0.347
Recurrence after blanking period (3-12 months); %	9 (30)	12 (40)	0.417

Study design

This is a prospective, randomized, double-blinded study. All patients were randomized for treatment with corticosteroid (corticosteroid group), or a placebo (placebo group) 1 day prior, on the day of ablation and 1 day after the procedure with the help of the investigational pharmacy staff to blind and dispense the drug and the placebo.

Steroid Administration

In the corticosteroid group, 60 mg of oral prednisone was administered one day prior, on the day of procedure and one day after the procedure. An oral lactose pill was administered to the placebo group with the same schedule.

Adverse effect monitoring

Fasting glucose levels were performed on all patients. Glucose levels were checked before each meal and before bed in patient with diabetes mellitus (DM). Hyperglycemia was defined as fasting glucose >110 mg/dl and post prandial glucose >180 mg/dl. Patients were also monitored for signs of fluid retention and infection.

Monitoring of AF Recurrence

Patients were monitored on telemetry during hospitalization. After discharge, patients underwent 1 month event monitoring at 3 months, 6 months and at 12 months post procedure. Any episode of AF lasting more than 30 seconds was considered as recurrence. Recurrence of any atrial arrhythmias (atrial tachycardia (AT) or AF) at 3 months, 6 months, and 12 months post ablation was recorded for the assessment of endpoints.

Inflammatory Cytokines Monitoring

A blood sample (5 ml) from the antecubital vein was collected from all subjects at the time of before randomization which served as baseline sample. Blood samples were collected at the beginning and end of the ablation procedure and at 24 hour post ablation for cytokine measurement (IL1, 6, 8, and TNF α). All blood samples were centrifuged to collect serum and frozen at -70° C. Enzyme-linked immunosorbent assays (ELISA) were performed on the serum samples using kits (ELISA kit II, BD Bioscience, USA) for human-specific IL1 ρ (Cat. No: 557966), IL6 (Cat. No: 550799), IL8 (Cat. No: 550799) and TNF-α (Cat. No: 550610), according to the manufacturer's instructions.

Catheter Ablation and assessment of PVI

All patients underwent pre-procedural Cardiac CT to define the pulmonary vein anatomy and pre -procedural TEE to exclude thrombus. Three dimensional mapping of the LA was reconstructed with CARTO (Biosense Webster, Inc, Diamond Bar, CA, USA) or Velocity (SJM, Minneapolis, MN,USA) electroanatomic mapping system. PVI was performed using 3.5/4.0 mm irrigated tip catheter (Thermocool, Biosense Webster, Inc or Coolpath Flex, SJM) with a maximum temperature of 50 ° C and power output of 25-35 Watts using a roving Lasso technique at the antral level. A circular mapping catheter (Lasso, Biosense Webster, Inc) was used to confirm PVI. Bidirectional conduction block from the atrium to the PV and vice versa were confirmed. We performed induction testing using burst pacing or isoprotenolol and targeted if there were other non PV triggers only. If a patient had inducible right atrial flutter or a prior history of flutter, a cavo-tricuspid isthmus ablation was performed. No other lesions were allowed. Thirty minutes after the isolation of each PV, reconnection rates were assessed and re-ablated if necessary. Adenosine was not used for evaluation of dormant conduction. All patients had all PVs isolated at the end of the procedure.

Follow Up

Patient remained hospitalized under continuous rhythm monitoring for at least 24 hours after radiofrequency ablation (RFA) with subsequent follow up in 3 months, 6 months and 12 months. A 12-lead ECG was performed during every clinic visit with intensive

questioning regarding any arrhythmia related symptoms. Additionally patients underwent 30 day event monitors at 3, 6 and 12 months post-ablation. All patients remained on antiarrhythmic drugs for the first 2 months. In those who had symptomatic recurrences within the first 2 months, cardioversion was performed and/or AADs were changed; repeat ablation were performed if cardioversion and change in AAD did not alleviate AF symptoms.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation and categorical variables as proportions. Univariate analyses were performed using Chi-Square test (with or without Fisher's exact correction) for categorical variables and Student t-test for continuous variables. Paired tests were performed when appropriate. McNemar test was used for evaluating paired samples. Pre and post ablation inflammatory markers were compared using paired t-test. Statistical analysis was considered significant at p values ≤ 0.05. Statistical analysis was performed using SPSS version 23.0 (IBM Inc., USA). Binary logistic regression was used for multivariable analysis. All known variables impacting the recurrence of AF were entered into the multivariate model. A two sided p-value ≤0.05 was considered statistically significant.

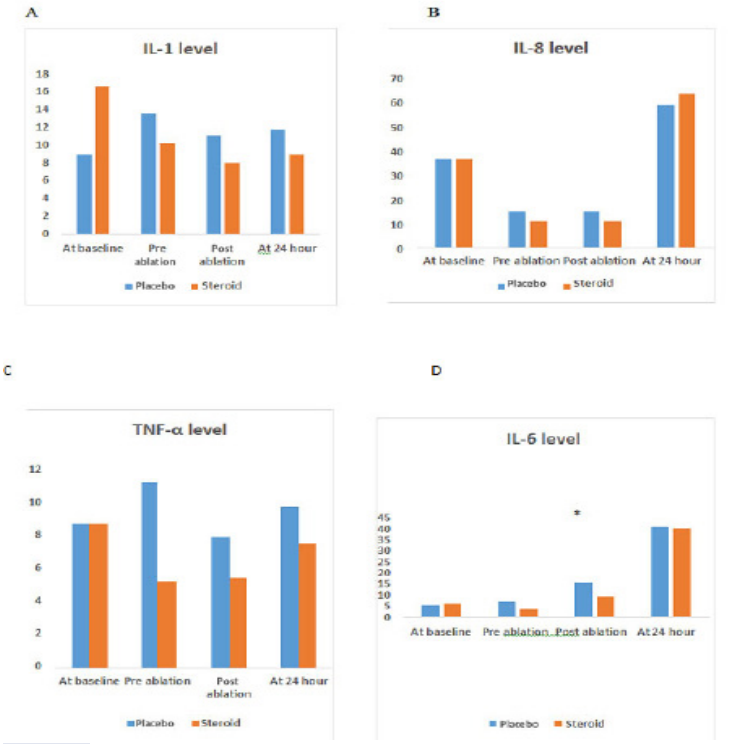

Figure 1: **Comparison of inflammatory cytokines level at 4 different time points**

Results

Study population

We screened a total of 105 patients of whom 60 patients met inclusion criteria and were subsequently randomized to receive prednisone or placebo.

Baseline and clinical Characteristics

Baseline characteristics are shown in [Table 1]. Both groups were comprised of 30 patients each. Baseline characteristics of mean age, gender, comorbidities, echocardiographic parameters, antiarrhythmic drugs and medications were not significantly different between the 2 groups.

Procedural Characteristics

Catheter ablation parameters and intra-procedural recurrences are presented in [Table 1]. PVI was successfully performed in all patients and bidirectional block was achieved in all PVs. The catheter ablation parameters were comparable between the 2 groups. Total procedure and fluoroscopic times were not different between them. Acute PV reconnection rates during the procedure (23% vs 36%; p=0.39), and RF ablation time (51 ±13 vs 56 ±11 mins, p = 0.11) were lower in the placebo group than the steroid group although not statistically significant.

Discussion

Major Findings

The main findings of our study are - 1) Oral prednisone during peri-procedural period did not impact the outcome of AF ablation. 2) The levels of inflammatory cytokines, specifically the IL-6 and IL-8 immediately post- ablation were significantly lower in the steroid group after ablation suggestive of effective suppression of systemic anti-inflammatory response by steroids.

Role of Steroid in AF Recurrence post Ablation

Previous Studies

There were no prospective clinical studies performed at the time of conception of this study. However, multiple studies were published since and have variable results. The role of steroids in preventing AF recurrence post ablation was first studied by Koyama et al in 2010 and showed decreased AF recurrence rate in the immediate (0-3 days) and during long term follow up (14 months). This study used 2mg/kg IV hydrocortisone on the day of procedure, followed by oral prednisolone (0.5 mg/kg/day) for 3 days. In addition, cavo-tricuspid isthmus ablation was done in all patients and additional ablation consisting of linear ablation of LA roof line and SVC isolation was performed if AF was induced with coronary sinus burst pacing and isoproterenol.[15] Later Won et al (2013) performed a similar study using low dose hydrocortisone (IV 100 mg) administered within 30 minutes post procedure with no difference in AF recurrence between steroid and placebo group. [13] Similarly, Andrade et al (2013) with 250 mg IV hydrocortisone immediately after transseptal puncture, Kim et al (2015) with low dose (100 mg IV hydrocortisone) and high dose (125 mg IV hydrocortisone) within 30 minutes post procedure did not show any difference in recurrence of AF. [14] Most of the clinical studies have been negative akin to our current study. This clearly points to the fact perhaps use of systemic corticosteroids and suppression of inflammation has no definitive impact on clinical outcomes in AF ablation.

Type and timing of Steroid Administration

The major difference between our study and the previous 4 studies described above was the timing of steroid administration and the type of steroid used. Prednisone has a half-life of 12-36 hours and it has 5 times more glucocorticoid potency than hydrocortisone. Based on pharmacologic properties (See [Figure 2]), we chose prednisone which is an intermediate acting steroid and administered 3 doses prior to ablation to maximize the anti-inflammatory effect and prevent tissue edema which was thought to contribute to gaps in PV isolation. The 60 mg prednisone is equivalent to 300 mg IV hydrocortisone which has half-life of 8-12 hours. Contrary to our hypothesis, this strategy did not show any efficacy in preventing AF recurrence. Our study is in agreement with 3 previous studies.

Positive effects reported by Koyama et al may be due to prolonged post procedural steroid therapy and possible suppression of regional and systemic inflammation in the setting of more aggressive ablation. [13]

Steroids and AF Recurrence

Although not statistically significant, our study found a trend towards higher recurrence rate in the steroid group. Studies have shown that acute administration of hydrocortisone can result in rapid concentration dependent cellular hyperpolarization in neural and cardiac tissue. [3,16-18] This hyperpolarization is thought to counteract RF induced membrane depolarization in the surrounding tissue requiring prolonged ablation time and higher probability of conduction gaps or acute reconnections. [19]

Table 2: Corticosteroid Comparison Chart

Drug	Equivalent dose (mg)	Glucocorticoid Potency	mineralocorticoid potency
Prednisone	5	4	0.8
Methylprednisolone (solumedrol)	4	5	0.5
prednisolone (medrol)	5	4	0.8
Hydrocortisone (solucotef)	25	1	1
Dexamethasone (decadron)	0.75	25	0
fludrocortisone (Florinef)	N/A	10	125

Drug	Plasma Half-ilfe	Biologic Half-life
Prednisone	160 min	12-36 hrs
Methylprednisolone (solumedrol)	80-180 min	12-36 hrs
prednisolone (medrol)	115-250 min	12-36 hrs
Hydrocortisone (solucotef)	80-115 min	8-12 hrs
Dexamethasone (decadron)	110-120 min	36-72 hrs
fludrocortisone (Florinef)		

Effects of Steroid on Pulmonary Reconnection Rates and Radiofrequency time

Similar to study by Andrade et al, our study shows trend towards higher RF time and PV reconnection rate. Interestinglystudy by Andrade et al shows those pre-procedural steroids are associated with higher prevalence of dormant conduction and increased RF ablation time to accomplish PV isolation.[3] In addition, two large population based case control study found an increase risk if AF during current use [20] or high dose [21] regimen of corticosteroid therapy.[22] Perhaps steroid inhibits effective scar formation from the ablation lesions. As a result of which partially injured atrial tissue has a higher propensity to recover due to the effect of the steroids and result in non-durable PV isolation.

Inflammatory Cytokines and AF Recurrence

Our study showed a significantly lower IL-6 and IL-8 post procedure in the steroid group which reflected the anti-inflammatory effect of steroid, however, they was no association between these cytokine changes and AF recurrence. There is uncertainty whether the inflammation from ablation promotes AF, or if the inflammation is caused by the arrhythmia itself or both. Previous studies have shown CRP elevation after RFA which correlated with early arrhythmia recurrence suggesting that extensive tissue damage from ablation may be pro inflammatory. [23]-[25] However, animal studies by Nascimento et al using young healthy pigs without arrhythmia that was divided in to placebo, sham ablation, and ablation with 500 mg IV methylprednisolone showed no difference in CRP level and similar histological findings in all 3 groups suggestive of extensive tissue damage due to ablation suggesting that RF energy per se was not responsible for systemic inflammation and the rise in CRP was rather related to procedural stress.[25]

Study Limitation

It is a relatively small study with all the obvious limitations. We also realize that our study was probably underpowered to detect a difference in outcomes between the groups. However, this was a randomized double blind placebo control study with relevant inflammatory markers measured at various time lines clearly establishing the linear relationship between steroid use and anti-inflammatory effects. We did not measure CRP levels as we deemed it to be too non-specific and has not been shown to be very useful in the previous studies.

Conclusion

Use of oral corticosteroids resulted in significant anti-inflammatory effect as evidenced by reduction in inflammatory cytokine levels with no impact on the clinical outcomes of AF ablation. There is a trend towards higher incidence of AF recurrence, higher PV reconnection rate, and longer RF ablation time with administration of steroids.

Conflict Of Interests

None.

Disclosures

None.

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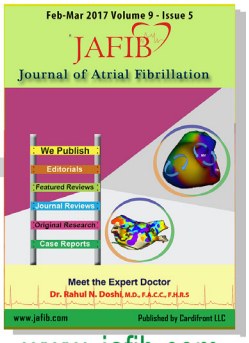

Peri-procedural Corticosteroid Use in Improving Outcomes Following Atrial Fibrillation Ablation: Back to Square One?

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Bilateral pulmonary vein (PV) isolation by catheter ablation has become an established therapy for highly symptomatic, drug refractory, paroxysmal atrial fibrillation (AF) [1, 2]. The efficacy of pulmonary vein isolation has improved over the years through refinement of procedural technique as well as improved ablation technology involving irrigated ablation, contact force sensing, and "single shot" ablation techniques such as cryo, laser, and multielectrode ablation catheters[1, 3-5]. However, durable pulmonary vein isolation has remained a significant challenge with increasing rates of pulmonary vein reconnection noted during long-term follow-up [6, 7]. Similarly, acute reconnections as well as early recurrences during the blanking period have been associated with reduced freedom from AF during follow-up[8]. With radiofrequency (RF) ablation, acute inflammation from the ablation lesions itself have been thought to have a major role in AF recurrences during the immediate peri-procedural period [9].

Several studies have noted that pro-inflammatory processes might play an important role in the initiation and maintenance of AF [10, 11]. Koyama and colleagues in 2009 showed that immediate recurrence of AF (within 3 days) after ablation was closely associated with an acute inflammatory process, as assessed by a high body temperature, elevated C-reactive protein (CRP) and signs of pericarditis. Interestingly, during the early post-ablation course (4-30 days), inflammatory markers were highest in patients with premature atrial contractions and non-sustained AF. Recurrence of AF within the first month after ablation independently predicted late AF recurrences during follow-up [9]. Multiple mechanisms, including ablation-induced local myopericarditis, local tissue edema resulting in gaps in the ablation line, and changes in action potential duration have been suggested as the link between ablation-induced inflammation and enhanced arrhythmogenecity during follow-up [9, 12].

Corticosteroids exert their anti-inflammatory effects by inhibition of the synthesis of all the known inflammatory cytokines. The findings linking ablation-related inflammation and AF recurrence, along with beneficial data on corticosteroids in preventing AF recurrence after cardiac surgery [13], led to several studies evaluating anti-inflammatory therapies in reducing recurrent AF following RF ablation. Koyama et al, in 2010, randomized 125 paroxysmal AF patients to receive placebo or corticosteroids (hydrocortisone [2 mg/kg IV] on day of PVI followed by oral prednisolone [0.5 mg/kg/day] for 3 days after the procedure). They measured body temperature and CRP levels to assess the anti-inflammatory response. The study showed that corticosteroid use decreased immediate and late recurrence of AF following PVI [14]. Another prospective study by Kim et al in 2015 showed that steroids reduced early AF recurrence post-ablation but had no impact on late recurrences [15]. In contrast, 3 nonrandomized case-control studies utilizing single dose of intravenous corticosteroids did not show any benefit in preventing early and late AF recurrence [16-18].

In this edition of the Journal, Iskander and colleagues report the results of the STEROID AF Study, a prospective, randomized, double-blind, placebo controlled trial that evaluated the efficacy of peri-procedural oral prednisone in preventing early and late AF recurrences in patients undergoing their first RF ablation (PV isolation) for symptomatic, paroxysmal AF [19]. All patients had failed at least one antiarrhythmic drug. A total of 60 patients were randomized 1:1 to oral prednisone (60 mg per day given the day before, the day of, and the day after the ablation procedure) or matching placebo. Inflammatory cytokines (IL-1, IL6, IL-8, and TNF-α) were measured at baseline as well as prior to, immediately after and 24 hours after ablation procedure. Patients were followed for one year with 30-day event monitoring at 3 months, 6 months, and 12 months. There were no significant adverse effects related to steroid use. Despite being started a day before ablation, oral prednisone did not have any beneficial effect on reducing acute PV reconnection during the procedure (36% vs. 23% in placebo group, p=0.39) and radiofrequency ablation times (56 ±11 vs. 51 ±13 min in placebo group, p=0.1). Peri-procedural prednisone did not reduce the incidence of early recurrence of AF during the blanking period (27% in steroid group vs. 17% in placebo group; p=0.347) as well as freedom from AF at 12 months of follow-up (60% vs. 70% in placebo group; p=0.417). In fact, there was a non-significant trend

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towards worse outcomes in the prednisone group. The levels of IL-6 and IL-8 were significantly lower in the steroid group post-ablation whereas no significant changes were seen in the levels of TNF-α and IL-1.

The authors concluded that peri-procedural prednisone, despite significant acute lowering of IL-6 and IL-8 immediately post-ablation, did not impact early and late AF recurrences. The STEROID-AF study differs from prior studies in the pre-procedural use of prednisone as well as serial measurements of inflammatory cytokine levels.

The strength of the STEROID AF study is its randomized, double-blind, placebo-controlled design, lending excellent validity to the results reported. Other strengths include serial measurement of specific inflammatory cytokine levels as well as three separate 30-day event monitoring during the 12 month period to assess for AF recurrence. However, in assessing the clinical implications of this study, several limitations should be considered. The sample size is small and the statistical power to assess outcomes is not reported. Therefore, as the authors rightly reported, it is likely that the study may have been underpowered to assess the outcome variables. This is especially important given the fact that there was a trend towards worse outcomes in the steroid group and further exploration of this in a larger sample would have been useful.

Given significant difference in outcomes between studies evaluating steroid use in AF ablation, the specific role of peri-procedural inflammation in affecting short and long-term outcomes post-ablation is brought into question. The STEROID AF study clearly shows that prednisone reduced cytokine levels but that did not lead to improved ablation success. Thus, the mechanisms by which steroid use affects AF ablation outcomes remain unclear. It is possible that the beneficial effects of steroids in reducing cytokine levels may be offset by inhibition of adequate scar formation following ablation, allowing recovery of PV conduction. Also important will be to assess for any differences between the type of corticosteroid used, dosing and route of delivery. Whether other ablation modalities such as cryoablation and laser ablation have similar association with inflammation as RF ablation needs further study.

Interestingly, at 24 hours after ablation, the levels of IL-6 and IL-8 show a significant increase, compared to immediate pot-ablation levels, in both placebo and steroid groups. One would suspect that there was only a transient suppression of inflammatory cytokines followed by 'rebound' to level much higher than baseline and wonder whether 3 days of oral steroids may be enough for sustained suppression of inflammation; perhaps a longer course of anti-inflammatory therapy is needed, and may explain the beneficial effects from a 3-month course colchicine when used in a similar clinical situation [20].

The STEROID-AF data is a welcome addition to the debate on the role of inflammation in the early and late recurrence of AF following RF ablation as well as the appropriate role, if any, as well as the type and dose of corticosteroids in this population. It may be fair to say that we are back to square one. We have more data now and more is needed before we can put this debate to rest in our continuing quest to improve ablation success in AF patients.

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Disclosures

continuing quest to improve ablation success in AF patients.

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Baseline Demographics, Safety, And Patient Acceptance Of An Insertable Cardiac Monitor For Atrial Fibrillation Screening: The REVEAL -AF Study

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Abstract

Given the high prevalence and risk of stroke associated with atrial fibrillation (AF), detection strategies have important public health implications. The ongoing prospective, single-arm, open-label, multicenter REVEAL AF trial is evaluating the incidence of previously undetected AF using an insertable cardiac monitor (ICM) in patients without prior AF or device implantation, but who could be at risk for AF due to their demographic characteristics, +/- non-specific but compatible symptoms. Enrollment required an elevated AF risk profile defined as $CHADS_2 \geq 3$ or $CHADS_2=2$ plus one or more of the following: coronary artery disease, renal impairment, sleep apnea or chronic obstructive pulmonary disease. Exclusions included stroke or transient ischemic attack occurring in the previous year. Of 450 subjects screened, 399 underwent a device insertion attempt, and 395 were included in the final analysis (Reveal XT: n=122; Reveal LINQ: n=273; excluded: n=4). Participants were primarily identified by demographic characteristics and the presence of nonspecific symptoms, but without prior documentation of "overt" AF. The most common symptoms were palpitations (51%), dizziness/lightheadedness/pre-syncope (36%), and shortness of breath (36%). Over 100 subjects were enrolled in each pre-defined $CHADS_2$ subgroup (2, 3 and ≥4). AF risk factors not included in the $CHADS_2$ score were well represented (prevalence≥15%). Procedure and/or device related serious adverse events were low, with the miniaturized Reveal LINQ ICM having a more favorable safety profile than the predicate Reveal XT (all: n=13 [3.3%]; LINQ: n=6 [2.2%]; XT: n=7 [5.7%]). These data demonstrate that REVEAL AF was successful in enrolling its target population, high risk patients were willing to undergo ICM monitoring for AF screening, and ICM use in this group is becoming increasingly safe with advancements in technology. A clinically meaningful incidence of device detected AF in this study will inform clinical decisions regarding ICM use for AF screening in patients at risk.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is a leading cause of morbidity and mortality. Approximately 33.5 million patients worldwide in 2010 had been diagnosed with AF and the figure is projected to double by mid-century.[1]-[5] This increasing burden of AF will likely lead to a higher incidence of stroke, systemic embolism, heart failure, and death: known sequelae of this arrhythmia.

The true burden of AF may be even higher than currently estimated. Although some patients are aware of their AF episodes, up to two-thirds of patients are asymptomatic, having so-called "silent AF."[6], [7] Importantly, silent AF carries the same risks as symptomatic AF.[8] Indeed, monitoring studies with previously implanted cardiac devices have demonstrated an association between asymptomatic AF episodes of brief duration and increased risk of stroke/systemic embolism in such patients.[9]-[13] Of concern, AF may only be diagnosed after complications like ischemic stroke have occurred.[14], [15] Given the high prevalence and risk associated with AF, there is considerable interest in: the development of screening strategies to detect AF and hopefully modify morbidity and mortality by early institution of preventive therapies, such as oral anticoagulation (OAC); to do so in patients with or without underlying electrical disorders necessitating pacemaker or defibrillator implantation; and to understand if the consequences of "silent AF" are as significant in patients without underlying device-requiring disorders as in those with them. The key issues related to AF screening, as with screening for any disease, are: 1) who to screen and 2) how to screen to optimize treatment and cost-effectiveness.

Key Words

Atrial fibrillation, screening, insertable cardiac monitor.

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To be useful and cost-effective, a screening strategy needs to balance the correct detection tool with the targeted at-risk population. Common devices used to screen for atrial fibrillation range from non-invasive devices using smartphone, hand-held, and wearable platforms employing external ECG, and/or pulse detection to provide snapshot screening, to insertable cardiac monitors (ICMs; subcutaneous ECG recorders) that provide continuous long-term monitoring for up to three years.[16]-[19] In a lower risk population, a simpler, less invasive, and cheaper test may be sufficient. In a higher risk population that is a) more likely to develop AF and b) at higher risk of morbidity/mortality secondary to the disease, a minimally invasive tool with a better detection rate yet potentially higher cost might be justified. However, the patient acceptance, safety and efficacy of such a strategy are unknown.

The REVEAL AF study (NCT01727297) is designed to evaluate the incidence of AF using an ICM device in patients with elevated risk profiles.[20] Although follow up for the primary endpoint is ongoing, enrollment is complete and all patients have undergone their baseline visit and device insertion. In this manuscript, we report selected baseline demographic data, patient acceptance of the REVEAL AF ICM monitoring strategy, and procedure and safety details of ICM insertion. During the course of the trial, a new miniaturized ICM became commercially available and was implemented in the study. As such, REVEAL AF provides a unique opportunity to characterize the safety profile of evolving ICM technology within a patient population suspected to be at high risk for AF.

Materials and Methods

The REVEAL AF trial design has been described in detail previously.[20] Briefly, REVEAL AF (NCT01727297) is an ongoing prospective, single-arm, open-label, multicenter, clinical study that enrolled patients in 58 centers in the United States and Europe between November 2012 and June 2015. Four hundred and fifty adults suspected to have or be at risk of AF (due to demographics and/or symptoms) with elevated AF risk profiles based on $CHADS_2$ score plus additional markers were enrolled in the study. Elevated risk for AF per $CHADS_2$ was defined as a score ≥ 3 or a $CHADS_2$ score = 2 with at least one of the following additional risk factors documented: coronary artery disease, renal impairment, sleep apnea, or chronic obstructive pulmonary disease. Patients were excluded if they had an ischemic stroke or a transient ischemic attack in the previous 12 months, or a history of hemorrhagic stroke. All consented patients were required to have a minimum of 24 hours of external ECG assessment (using Holter monitoring or other techniques) within the previous 90 days prior to enrollment or before device insertion. Patients were excluded from the trial if AF was diagnosed by external monitoring. Baseline demographics, medical history, blood samples for biomarker analysis (as possible predictors), echocardiogram, and a quality of life questionnaire were collected. This study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by each site's institutional Review Board or Ethics Committee and all patients provided written informed consent prior to participating in the study.

The ICM (Reveal XT or Reveal LINQ, Medtronic, plc, Dublin, Ireland) procedure occurred within 6 weeks of study enrollment and was performed in accordance with each hospital's standard insertion practice and the Medtronic Reveal ICM insertion instructions. The Medtronic REVEAL ICM insertion instructions for the Reveal XT device require a single-incision procedure with normal aseptic techniques. A small subcutaneous pocket slightly smaller than the width of the device is created, the device is inserted into the pocket with electrodes facing outward, and secured to underlying

Table 1: Baseline patient characteristics

Characteristic	All attempted insertions (N = 395)
Device inserted/attempted	
Reveal LINQ	273 (69.1%)
Reveal XT	122 (30.9%)
Demographics	0.734
Age, years	
N	395 (100.0%)
Mean ± Standard Deviation	71.6 ± 9.8
Age category	0.191
Under 65	88 (22.3%)
65 to 75	131 (33.2%)
75 and older	176 (44.6%)
Gender	
Male	207 (52.4%)
Female	188 (47.6%)
Body mass index (BMI)	
N	395 (100.0%)
Mean ± Standard Deviation	31.2 ± 6.5
$CHADS_2$ score	
1	1 (0.3%)
2	158 (40.0%)
3	131 (33.2%)
4	105 (26.6%)
Reason AF is suspected	
Symptoms	93 (23.5%)
Demographics	62 (15.7%)
Both symptoms and demographics	240 (60.8%)
Symptoms within 3 months of consent	
None	38 (9.6%)
Chest pain	80 (20.3%)
Dizziness/lightheadedness/presyncope	142 (35.9%)
Rapid heart beat	81 (20.5%)
Shortness of breath	142 (35.9%)
Edema	51 (12.9%)
Fatigue/weakness	119 (30.1%)
Palpitations	201 (50.9%)
Syncope	77 (19.5%)
Other	20 (5.1%)
Medical history	
Renal Dysfunction	64 (16.2%)
Congestive Heart Failure	81 (20.5%)
Coronary Artery Disease	234 (59.2%)
Hypertension	370 (93.7%)
COPD	76 (19.2%)
Sleep apnea	104 (26.3%)
Diabetes	249 (63.0%)
Vascular disease	
Cerebrovascular accident (stroke)	80 (20.3%)
Transient Ischemic Attack	76 (19.2%)

tissue using the suture holes on the device header. For the LINQ device, the Medtronic REVEAL ICM insertion instructions require use of conventional antiseptic and local anesthetic procedures. The skin adjacent to the incision location is pinched, and the incision tool provided with the device is used to make a less than 1 cm incision. The insertion tool preloaded with the LINQ device is then inserted and rotated 180 degrees to create a pocket approximately 8 mm under the skin. The plunger on the insertion tool is pushed to deliver the device into the pocket approximately 10mm past the incision. Details on device insertion were collected, including device location and orientation, suture placement, and R-wave diagnostic sensing. Device programing was set to maximize the device's storage of ECG recordings of AF episodes.[20] Patients are being followed for a minimum of 18 and maximum of 30 months. Procedure and device related adverse events (AEs) were adjudicated by investigators as well as an independent Clinical Events Committee (CEC) composed of non-industry employed physicians. CEC adjudication was conducted via quorum, with at least three voting members of the CEC. Procedure-related AEs were defined as an adverse event that occurs due to any procedure related to the implantation or surgical modification of the system. Device related adverse events were defined as an adverse event that occurred due to the Reveal XT or Reveal LINQ device. AEs are considered serious if an event led to death or serious deterioration in the health of a subject (as indicated by a life-threatening illness or injury, permanent impairment of a body structure or a body function, in-patient hospitalization or prolonged hospitalization, or medical or surgical intervention to prevent permanent impairment to a body structure or a body function).

Statistics

Baseline characteristics are summarized using descriptive statistics. Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as count and percentage. All analyses were completed using SAS version 9.4 (SAS Institute, Cary, NC).

EnSite NavXTM system (St. Jude Medical, St. Paul, USA) was used to construct the LA geometry and a voltage map of the antral

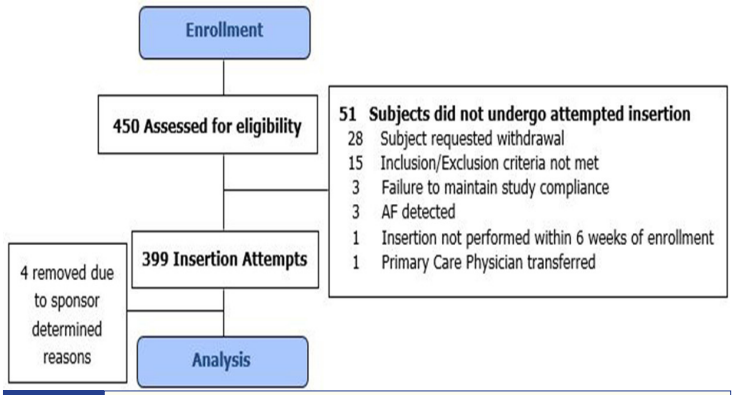

Figure 1: Subject flow diagram

Region of the 4 PVs using a segmented cardiac CT template with/out fusion of the images.

Results

Demographics

Four hundred and fifty subjects were enrolled at 58 sites. Of these, 51 did not undergo a Reveal ICM insertion attempt due to subject withdrawal (n=28), not meeting inclusion/exclusion criteria (n=15), failure to maintain study compliance (n=3), AF detected prior to device insertion (n=3), device insertion not completed within 6 weeks of enrollment (n=1), and a change in primary care physician (n=1). Consequently, 399 subjects (US: n=306, Europe: n=93) underwent an insertion attempt. Of these, four subjects at a single site were excluded for sponsor determined reasons. Thus, 395 subjects at 57 sites were included in the present analysis [Figure. 1].

P-wave Sixty nine percent (69%) of subjects received the Reveal LINQ ICM and 31% of subjects received the predicate Reveal XT ICM device(Fig. 2). Baseline demographics and medical history are presented in [Table 1]. Subjects aged 38-92 years were enrolled, with a mean age of 72 ± 10 years. Seventy eight percent of the study population was aged ≥65 years. Males accounted for 52% of the study population. At least 100 patients have been enrolled and undergone an insertion attempt in each pre-defined $CHADS_2$ subgroup (2, 3 and ≥4). Due to errors in scoring, one patient with a $CHADS_2$ score

Figure 2: Image of Reveal XT (left) and LINQ (right) devices

of 1, and one patient with a $CHADS_2$ score of 2 without additional protocol-specified AF risk factors underwent device insertion.

Most subjects were suspected to have AF based on both symptoms and demographics (61%), followed by symptoms alone (24%). The most common symptoms were palpitations (51%), dizziness, lightheadedness or pre-syncope (36%), and shortness of breath (36%). Less common symptoms included fatigue/weakness (30%), rapid heartbeat (21%), chest pain (20%), syncope (20%) and edema (13%).

Hypertension was present in 94% of subjects. Other common demographic characteristics included diabetes (63%), coronary artery disease (59%), sleep apnea (26%) and heart failure (21%). Twenty percent of patients had a previous stroke and 19% had a previous transient ischemic attack greater than 12 months prior to enrollment.

Insertion Procedure

Procedure data are presented in [Table 2]. The most common insertion location was between the 1st and 4th rib close to the sternum for both devices (Reveal XT: n=76 [62%]; LINQ: n=129 [47%]). Twenty five percent of Reveal XT (n=30) and 17% of LINQ devices (n=45) were placed between the 1st and 4th rib, but more lateral to the sternum. LINQ devices were also frequently placed inferior to the 4th rib close to the sternum (n=70 [26%]), whereas Reveal XT devices were not (n=6, 4.9%). The ICM was most frequently oriented

vertically for the Reveal XT (n=67 [55%]), and at a 45 degree angle for Reveal LINQ (n=232 [85%]). The Reveal XT device was often sutured during the insertion (n=107, [88%]), whereas few LINQ devices were sutured (n=13 [5%]). Ninety-eight percent (n=385) of ICM devices were inserted with electrodes directed outwards, as recommended by the manufacturer, and R-wave diagnostic sensing was completed on 96% of ICMs.

Safety

Procedure and device related AEs are displayed in [Table 3]. For subjects receiving the Reveal XT device, 4.1% (n=5) and 5.7% (n=7) experienced a procedure and device related AE, respectively. Procedure related AEs included impaired healing (including pruritus or erythema, n=2), insertion site infection (n=2), and insertion site pain/irritation (n=2). Device-related AEs associated with the Reveal XT ICM included insertion site infection (n=1), discomfort (n=1), and insertion site pain/irritation (n=5).

Overall, the CEC classified three (2%) procedure related AEs and six (5%) device related AEs as serious for the Reveal XT device. Serious procedure related AEs included two insertion site infections that were resolved by device explant and one case of pain around the device at the insertion site. Device related AEs classified as serious by the CEC included four cases of pain around the device at the insertion site, one case of discomfort and one case of insertion site infection. All of these events resulted in device explant.

Subjects receiving the Reveal LINQ device had a lower rate of procedure or system related adverse events, with 1.8% (n=5) experiencing a procedure related AE and 2.6% (n=7) experiencing a device related AE. Procedure related AEs included device dislocation/site erosion (n=3), impaired healing (n=1), and shock/dyspnea (n=1). The patient who experienced shock/dyspnea had a reaction to antibiotic administration prior to device insertion (see below). Device related AEs observed with Reveal LINQ included device dislocation/site erosion (n=4), impaired healing (n=1), insertion site pain/irritation (n=1) and oversensing (n=1).

Table 2: Insertion procedure

	LINQ (N=272)	Reveal XT (N=122)	All insertions (N=394)
Device location			
Between clavicle and 1st rib (close to sternum)	2 (0.7%)	2 (1.6%)	4 (1.0%)
Between clavicle and 1st rib	0 (0.0%)	4 (3.3%)	4 (1.0%)
Between 1st and 4th rib (close to sternum)	129 (47.4%)	76 (62.3%)	205 (52.0%)
Between 1st and 4th rib	45 (16.5%)	30 (24.6%)	75 (19.0%)
Inferior to 4th rib (close to sternum)	70 (25.7%)	6 (4.9%)	76 (19.3%)
Inferior to 4th rib	19 (7.0%)	4 (3.3%)	23 (5.8%)
Other	7 (2.6%)	0 (0.0%)	7 (1.8%)
Device orientation			
Horizontal	7 (2.6%)	4 (3.3%)	11 (2.8%)
Vertical	21 (7.7%)	67 (54.9%)	88 (22.3%)
45 degrees	232 (85.3%)	42 (34.4%)	274 (69.5%)
135 degrees	10 (3.7%)	3 (2.5%)	13 (3.3%)
Other	2 (0.7%)	6 (4.9%)	8 (2.0%)
Device sutured during insertion	13 (4.8%)	107 (87.7%)	120 (30.5%)
Electrodes outward (as recommended)	263 (96.7%)	122 (100%)	385 (97.7%)
R-wave diagnostic sensing completed	259 (95.2%)	119 (97.5%)	378 (95.9%)

For Reveal LINQ, the CEC classified four (1%) procedure related AEs as serious. These included three situations in which the device migrated out of the incision pocket. In addition, one subject had an allergic reaction to antibiotic administration prior to device insertion. This subject was stabilized and transferred to the ICU, and did not receive a LINQ device. The CEC also classified five (2%) device related AEs as serious. These included four situations in which the device migrated out of the incision pocket. Additionally, one patient experienced poor device sensing. This was resolved by repositioning the device, which required an invasive procedure.

There was occasional disagreement between the CEC and investigators in terms of severity of AEs. CEC and investigator classifications are presented in Table 3. Investigators considered fewer events to be serious compared with the CEC.

Discussion

AF is Considering the frequency of AF and the severity of its clinical sequelae, there is a clear need for rigorous AF screening programs, especially for patients at higher risk. Screening strategies should balance the cost and invasiveness of a diagnostic device with a population's level of risk for AF. In a lower risk population where the consequences of missing even short AF episodes are lower, a simpler, less expensive test with a lower detection rate may be sufficient as an initial step. Such tests include blood pressure monitors with AF detection and hand-held ECG devices (including smart phones). While the benefit of these systems includes low cost and non-invasive nature, they are limited by their ability to provide only a snapshot into the overall frequency and burden of AF in an individual patient.

Wearable ECG systems and ICMs have been developed in order to facilitate continuous AF screening in higher risk populations. While wearable ECG devices have the advantage of being non-invasive, they are limited in the duration (1-4 weeks) of continuous monitoring afforded, and are susceptible to subject compliance challenges. Subcutaneous ICMs improve compliance by inhibiting removal/nonuse and provide continuous monitoring for up to three years.21 However, the minimally invasive nature of these devices warrants their use in a higher risk patient population. AF detection by pacemakers and ICDs have provided proof of concept of AF detection with an implanted device, but they have done so only in patients with concomitant electrical disorders, which may or may not be reflective of event rates and significance in a broader population of patients.

Accordingly, a number of ongoing trials employ ICMs to screen for AF in patients without a previous history of this arrhythmia, but who are at higher risk for AF and subsequent stroke if AF is present. These include REVEAL AF, PREDATE AF (NCT01851902), ASSERT II (NCT01694394), and LOOP (NCT02036450). The REVEAL AF study is specifically assessing the value of ICM monitoring in a patient population suspected to be at high risk for AF based on a modified $CHADS_2$ score. The baseline data from this study demonstrate that a) the study enrolled its target population and will be able to evaluate the efficacy of the envisioned screening strategy, b) there are patients at high risk for AF willing to undergo ICM monitoring, and c) ICMs are safe for use in this population, and are becoming safer with advancements in technology.

Subject demographics

To be clinically impactful, it is important that diagnosis be linked to clear recommendations for a meaningful change in therapy (e.g. initiation of OAC therapy for stroke prevention). In the current

Table 3: Procedure and device related adverse events

Combined results		Reveal XT (N=122)			Reveal LINQ(N=272 + 1 attempt)		
		Total	Serious per CEC	Serious per investigator	Total	Serious per CEC	Serious per investigator
Device and/or procedure related		11 (10*, 8.2%)	7 (5.7%)	2 (1.6%)	9 (3.3%)	6 (2.2%)	4 (1.5%)
Procedure related		6 (5*, 4.1%)	3 (2.5%)	1 (0.8%)	5 (1.8%)	4 (1.5%)	3 (1.1%)
Device related		7 (5.7%)	6 (4.9%)	1 (0.8%)	7 (2.6%)	5 (1.8%)	3 (1.1%)
Individual results		**Total**	**Serious per CEC**	**Serious Per Investigator**	**Total**	**Serious per CEC**	**Serious Per Investigator**
Device dislocation/ device site erosion	Device and/or procedure related	0	0	0	4 (1.5%)	4 (1.5%)	3 (1.1%)
	Procedure related	0	0	0	3 (1.1%)	3 (1.1%)	2 (0.7%)
	Device related	0	0	0	4 (1.5%)	4 (1.5%)	3 (1.1%)
Impaired healing (including pruritus or erythema)	Device and/or procedure related	2 (1.6%)	0	0	2 (0.7%)	0	0
	Procedure related	2 (1.6%)	0	0	1 (0.4%)	0	0
	Device related	0	0	0	1 (0.4%)	0	0
Insertion site infection	Device and/or procedure related	2 (1.6%)	2 (1.6%)	1 (0.8%)	0	0	0
	Procedure related	2 (1.6%)	2 (1.6%)	1 (0.8%)	0	0	0
	Device related	1 (0.8%)	1 (0.8%)	0	0	0	0
Insertion site pain / irritation	Device and/or procedure related	6 (4.9%)	4 (3.3%)	0	1 (0.4%)	0	0
	Procedure related	2 (1.6%)	1 (0.8%)	0	0	0	0
	Device related	5 (4.1%)	4 (3.3%)	0	1 (0.4%)	0	0
Oversensing	Device and/or procedure related	0	0	0	1 (0.4%)	1 (0.4%)	0
	Procedure related	0	0	0	0	0	0
	Device related	0	0	0	1 (0.4%)	1 (0.4%)	0
Shock/ dyspnea	Device and/or procedure related	0	0	0	1 (0.4%)	1 (0.4%)	1 (0.4%)
	Procedure related	0	0	0	1 (0.4%)	1 (0.4%)	1 (0.4%)
	Device related	0	0	0	0	0	0
Discomfort	Device and/or procedure related	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0
	Procedure related	0	0	0	0	0	0
	Device related	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0

In patients with SSS and AF before PM implantation, both of RAA pacing and RAS pacing decreased patients with AF. But as a whole RAA pacing increased patients with AF and RAS pacing decreased that

REVEAL AF study, a modified $CHADS_2$ scoring system was used to guide patient enrollment. The $CHADS_2$ and CHA_2DS_2-VASc scoring systems provide a framework for identifying patients that would benefit from OAC to decrease their risk of stroke due to AF. Of note, the risk factors for developing AF overlap heavily with the risk factors for stroke in the $CHADS_2$ and CHA_2DS_2-VASc systems. Consequently, a high $CHADS_2$ or CHA_2DS_2-VASc score might not only identify patients at high risk of stroke due to AF, but also those that are at high risk of developing AF. There have been a number of recent analyses that support this supposition.[22]-[27]

In REVEAL AF, subjects were required to have a $CHADS_2$ score ≥ 3 or a $CHADS_2$ score = 2 with at least one of the following additional AF risk factors documented: coronary artery disease, renal impairment, sleep apnea, or chronic obstructive pulmonary disease. Here we report that REVEAL AF was successful in enrolling patients in the originally defined target population. Each pre-defined $CHADS_2$ subgroup (2, 3 and ≥4) was well represented (>100 subjects), and a reasonable prevalence of AF risk factors used to guide enrollment for subjects with a $CHADS_2$ score of two was attained. Specifically, coronary artery disease, renal impairment, sleep apnea, and chronic obstructive pulmonary disease were all present in over 15% of the population. Of these risk factors, coronary artery disease was the most common, occurring in 59% of subjects. By achieving our target population, the REVEAL AF study will be able to determine the efficacy of the originally designed screening strategy. As such, when the follow up (minimum of 18 months to a maximum of 30 months) for the primary endpoint (AF detection) is complete in early 2017, a greater understanding will be attained of how predictive the risk factors specified above are for AF development. Importantly, these demographic characteristics reflect those reported for ischemic stroke populations in large epidemiological studies,[15], [28], [29] which further highlights the clinical importance of screening the REVEAL AF patient population for primary stroke prevention. In REVEAL AF, also planned are assessments of possible genetic and circulating biomarkers as predictors of AF and or associated adverse consequences. Moreover, if the frequency of AF detection is substantial (for example higher than 10-20%), there will be significant implications for screening of large segments of our older population as well as the need for larger phase 3 trials.

Patient acceptance

In addition to efficacy, patient acceptance is a key aspect of a successful screening paradigm. In the REVEAL AF study, we were able to meet our enrollment goal of 450 subjects. This indicates that there are patients believed to be at high risk for AF who are willing to participate in an ICM screening strategy. The higher prevalence of subjects enrolled with symptoms compared to those without may reflect greater patient acceptance in this cohort. The study did have enrollment challenges, evident by a 2.5 year enrollment period for 450 subjects across 58 centers. While this may be due in part to inclusion/exclusion requirements of the study, the 2.5 year timeframe

likely reflects some subject concern around engaging in an ICM screening strategy for AF detection. Additionally, 6% of consented subjects did not receive an ICM due to subject withdrawal. Patient acceptance will likely evolve with future clinical evidence and technological advances that increase device safety and/or reduce patient burden. This is supported by the observation that over twice as many subjects were inserted with the newer miniaturized Reveal LINQ ICM than the predicate XT device in this study, despite the LINQ ICM only being commercially available during the second half of the enrollment period.

Safety of ICM Monitoring in Patients at High Risk for AF

In order for adoption of ICM's as a method to detect AF in a high-risk population, the overall safety of the device and procedure must be demonstrated. While the safety of predicate ICM devices have been characterized in different patient populations,[30]-[36] prior investigations have not specifically evaluated safety in individuals suspected to be at high risk for AF outside the context of post-stroke cardiac monitoring. Moreover, limited data exist on the safety of the new miniaturized Reveal LINQ ICM, as this device has only been commercially available since 2014.

In REVEAL AF, we observed a low rate of serious procedure and/or device related adverse events (3%), which primarily included a low reported incidence of device dislocation/site erosion, insertion site infection, and insertion site pain/irritation. The miniaturized Reveal LINQ ICM had an improved safety profile compared with the predicate Reveal XT device. Specifically, in patients who received the Reveal XT, serious procedure related adverse events occurred in 2.5% of patients, and serious device related adverse events occurred in 4.9%. In the Reveal LINQ subgroup, procedure-related serious AEs occurred in 1.5% of patients, and serious device related AEs occurred in 1.8%. Importantly, these rates are in line, which those recently reported for the Reveal LINQ device (≤2%) in both clinical trial[37], [38] and real world settings.[37] Overall, these data add to the mounting evidence supporting the safety of ICM insertion in broad patient populations, and highlights that ICM safety is improving with advancements in technology. Importantly, if a clinically meaningful yield of AF detection is observed in REVEAL AF and other ongoing trials, these safety data will support clinical adoption of ICM-based screening programs.

Conclusions

AF remains an important cause for morbidity and mortality, particularly by increasing the risk of ischemic stroke. In higher risk populations, where therapy may be significantly altered, more intensive screening tools that provide a longer monitoring period may be employed. Data from REVEAL AF demonstrate that a portion of patients believed to be at high risk for AF are willing to undergo ICM screening, and ICM devices are safe for use in this population, and becoming safer with evolving technology. If successful, REVEAL AF and other ongoing studies may have a substantial impact on informing clinical care for patients at high risk for AF.

Conflict Of Interests

None.

Disclosures

Drs. Reiffel, Gersh, Kowey, Wachter, Halperin and Verma are consultants for, and receive modest honoraria from Medtronic. Rachelle Kaplon and Erika Pouliot are employed by and stock owners of, Medtronic.

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Evaluating the Utility of Mhealth ECG Heart Monitoring for the Detection and Management of Atrial Fibrillation in Clinical Practice

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Abstract

Little attention has focused on the integration of mobile health (mHealth) technology with self-management approaches to improve the detection and management of atrial fibrillation (AF) in clinical practice.The objective of this study was to investigate the differences between mHealth and usual care over a 6-month follow-up period among patients with a known history of atrial fibrillation. A pilot cohort from within the larger ongoing randomized trial, iPhone® Helping Evaluate Atrial fibrillation Rhythm through Technology (iHEART), was evaluated to determine differences in detection of AF and atrial flutter (AFL) recurrence rates (following treatment to restore normal rhythm) between patients undergoing daily smartphone ECG monitoring and age and gender matched control patients. SF-36v2™ QoL assessments were administered at baseline and 6 months to a subset of the patients undergoing daily ECG monitoring. Differences between groups were assessed by t-test, Fisher's exact test, and Cox proportional hazard models. Among the 23 patients with smartphone ECG monitors (16 males and 7 females, mean age 55 +/- 10), 14 (61%) had detection of recurrent AF/AFL versus 30% of controls. During the follow-up period, patients given smartphone ECG monitors were more than twice as likely to have an episode of recurrent AF/AFL detected (hazard ratio: 2.55; 95% CI: 1.06 – 6.11; p = 0.04). Among the 13 patients with baseline and 6 month QoL assessments, significant improvements were observed in the physical functioning (p = 0.009), role physical (p = 0.007), vitality (p = 0.03), and mental health domains (p = 0.02). Cardiac mHealth self-monitoring is a feasible and effective mechanism for enhancing AF/AFL detection that improves quality of life.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice and is a global epidemic with an estimated worldwide prevalence in 2010 of 20.9 million men and 12.9 million women. [1] The condition is expected to more than double over the next 35 years, [2] which further highlights the societal burden of AF and the need for innovative ways to improve its detection, treatment, and management. Individuals affected by AF may experience a variety of symptoms ranging from palpitations and fatigue to dyspnea and chest pain. [3] Many patients are asymptomatic or experience very brief episodes associated with vague symptoms such as fatigue that could be related to other co-existing conditions such as heart failure or age-related changes. The lack of consistent follow-up further highlights the challenges encountered in documenting AF. Individuals with AF that goes unrecognized and untreated are at an increased risk for stroke and overall mortality. [3] Thus, it is critical to evaluate advances in mHealth monitoring to determine how advances in technology can be utilized to improve AF detection and treatment. The affordability of smartphones has enabled mHealth technology to be integrated rapidly into day-to-day living. For example, 2 billion people, equal to approximately 28% of the global population, currently use smartphone technology. [4]Additionally, there are over 100 million active iPhones® in the United States alone[5] (https://9to5mac.com/2015/11/19/apple-100-million-active-iphones-us/), making mHealth technology a logical avenue for widespread integration into healthcare. Since most individuals report having their cell phones with them at all times, it is feasible to consider mHealth as an effective mechanism not only to transmit real-time ECG data to a healthcare provider and receive immediate feedback, but also to improve patient engagement and self-management. The purpose of this study was to determine if an FDA approved wireless electrocardiogram (ECG) monitor designed for use with smartphones (AliveCor™ ECG) could be utilized to detect and manage recurrent AF or other atrial arrhythmias better than usual medical care (without mHealth ECG monitoring). The primary outcome of this study was the detection of recurrent AF or

Key Words

MHealth, ECG, Atrial Fibrillation, QoL.

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Figure 1: AliveCor™ ECG device attaches to smartphone with one-time adhesive.

other atrial arrhythmias over a 6-month period of time, using the AliveCor™ ECG monitor as compared to usual cardiac care without mHealth daily monitoring.

Methods

Recruitment and the Informed Consent Process

This investigation was approved by the Columbia University Medical Center Institutional Review Board (IRB) prior to subject enrollment (IRB-AAAJ7801). Subjects were recruited for this pilot study from the departments of cardiac electrophysiology and cardiac ambulatory care at Columbia University Medical Center in New York, NY, USA. These individuals were identified as potential study subjects by their healthcare providers during routine care visits within these departments. The healthcare provider obtained verbal approvals from the patients before the study team approached them. If the participants agreed to be approached, the study team discussed the study with them, allowed them to read the informed consent, and answered all questions. If the patients agreed to participate, they were asked to sign the informed consent which was available in both English and Spanish (participant's preference). All participants were given a copy of their signed consent form for their personal records.

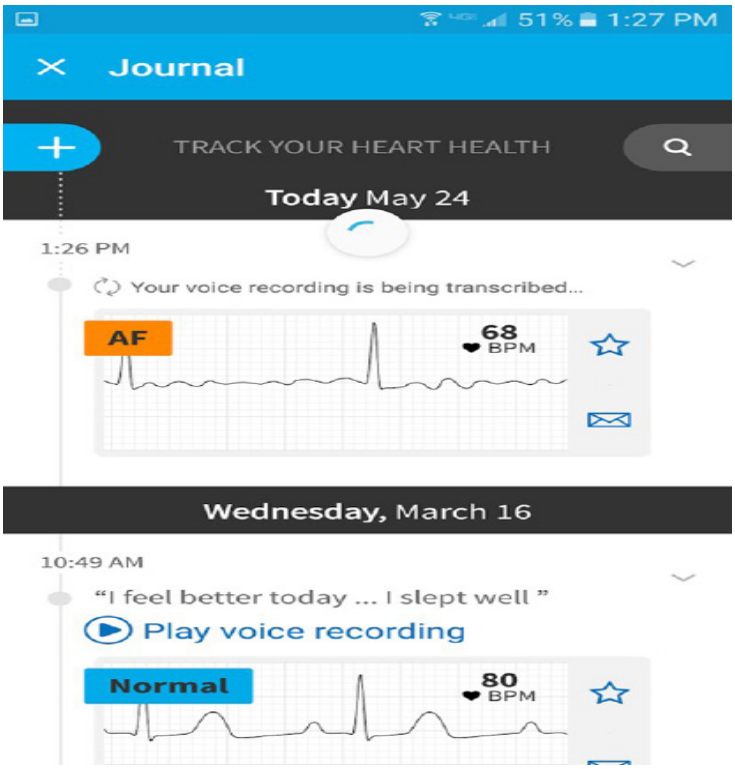

Figure 1a: AliveCor Kardia application

Study Subjects and Sample Size

Twenty-three subjects participated in the ECG monitoring pilot study. All subjects were 21 years or older, with a documented history of AF and were scheduled to undergo a cardioversion, ablation, and/or medical management aimed at maintaining a normal sinus rhythm. Patients who successfully had normal sinus rhythm restored were given a heart monitor (AliveCor™) compatible with iPhone® or Android™ (ECG monitoring group). The control group consisted of 23 age (within 5 years) and gender matched patients with a documented history of AF receiving usual cardiac medical care (no daily ECG self-monitoring) as part of their usual clinical management. In addition, baseline and 6 month SF-36v2™ Quality of Life assessments were administered to 13 patients in the ECG monitoring group in order to evaluate perceptions of their physical and mental health. These 13 patients also filled out a questionnaire at 6 months which queried their attitudes toward ECG monitoring.

Table 1: Clinical Characteristics

Variable	ECG Monitoring Group (N = 23)	Control Group (N=23)	p value
Age (mean ± SD, years)	55 ± 10	55 ± 9	—
	# (%)	# (%)	
Males	15 (71%)	15 (71%)	—
Previous Cardioversion	16 (70%)	13 (57%)	0.54
Cardiac Ablation	10 (43%)	11 (48%)	1.0
Coronary Artery Disease	3 (13%)	3 (13%)	1.0
Stroke/TIA	3 (13%)	0 (0%)	0.23
Congestive Heart Failure	6 (26%)	3 (13%)	0.46
CHA_2DS_2-VASc > 1	5 (22%)	3 (13%)	0.70
Diabetes	1 (4%)	3 (13%)	0.61
Hypertension	11 (48%)	13 (57%)	0.77
Obesity	9 (39%)	15 (65%)	0.14
History of Smoking	9 (39%)	3 (13%)	0.09
Medications			
Anticoagulants	22 (96%)	20 (87%)	0.61
Beta Blockers	15 (68%)*	19 (83%)	0.31
Antiarrhythmics	10 (43%)	11 (48%)	1.0
Diuretics	6 (26%)	4 (17%)	0.72
Calcium Channel Blockers	5 (22%)	7 (30%)	0.74
ACE/ARB	1 (4%)	4 (17%)	0.35

* 1 response missing

Device Training

After collecting baseline information, patients in the ECG monitoring group were provided with a heart monitoring device for compatible smartphones. The AliveCor™ ECG device attaches to the smartphone with a one-time adhesive (Figure 1). A member of the study team downloaded the "AliveECG" application to the patient's smartphone (Figure 1a). Subjects were then trained on how to use the heart monitor and capture an ECG. A test ECG recording and transmission was performed during baseline enrollment to ensure the quality of the ECG data being collected and that the participant was comfortable and could independently perform the ECG capture. This training session took from 15-30 minutes, depending on the

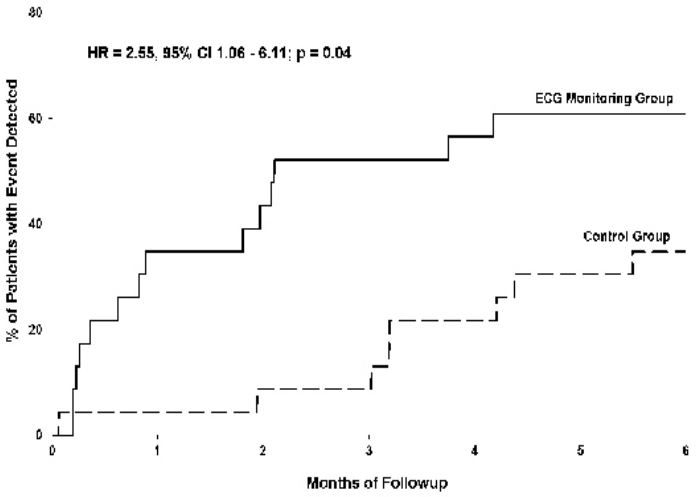

Figure 2: Kaplan-Meier Curves for AF/AFI Detection

user's familiarity with technology.

Patients in the ECG monitoring group were asked to use the wireless ECG device at least daily (and when symptomatic) to record ECG readings for a period of 6 months; transmission time took less than 5 minutes per day. All ECGs were reviewed daily for AF and other rhythm disturbances and the results were sent to the patient's primary care physician. The patient's physician/healthcare team performed the treatment and management of any recorded AF or other cardiac arrhythmias. No members of the research team were involved in direct clinical care.

Quality of Life

Quality of Life was assessed using the SF-36v$_2$™ multi-item scale that measures eight health concepts (four physical and four mental health domains) rated on a 3- to 6-point Likert scale. [6] Responses to the questionnaire were transformed into norm-based physical and mental scores.The four physical domains (physical functioning, role-physical, bodily pain, general health) and four mental health domains (vitality, social functioning, role-emotional and mental health) were determined along with the physical component summary (PCS) and mental component summary (MCS) scores. These measures were scaled to have a mean of 50 and a standard deviation of 10 in the general population.

Statistical Analyses

All demographic and clinical data with the exception of age are reported as frequencies and percentages; age is reported as mean and standard deviation. Means and standard deviations were also used to characterize the SF-36v2™ domain and summary scores in the ECG monitoring group at baseline and 6 months. Fisher's exact test were used to assess differences in clinical characteristics, medications, and AF procedures between those in the ECG monitoring group and the control group. Kaplan-Meier curves were created for AF/AFL detection rates for the ECG monitoring and control groups over the 6 month follow-up period. Differences in AF/AFL detection rates between groups were assessed using Cox proportional hazards models. Paired t-tests were used for testing differences in QoL health domains and summary scores between baseline and 6 months among patients in the ECG monitoring group. Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). A critical p-value of 0.05 was used for significance in all analyses.

Results

The demographic and clinical characteristics of the patients in the ECG monitoring and control groups are listed in Table 1. The ECG monitoring group consisted of 16 males and 7 females (mean age 55 +/- 10) with control subjects matched for age and gender. Within the ECG monitoring group, 16 (70%) had been previously treated with cardioversion while 10 (43%) had undergone cardiac ablation; these rates did not differ significantly in the control group. There were no significant differences between groups with respect to the prevalence of coronary artery disease, stroke/TIA, congestive heart failure, cardiovascular risk factors, or medication usage. Kaplan-Meier curves depicting the AF/AFL detection rates for the ECG monitoring and control groups are shown in Figure 2. Over the six month follow-up period, 14 patients in the ECG monitoring group (61%) and 7 patients in the control group (30%) had episodes of AF/AFL detected. Cox proportional hazard model analysis yielded a hazard ratio of 2.55 with a 95% confidence interval of 1.06 to 6.11, p = 0.04. Among the 13 patients in ECG monitoring group who had QoL assessments at baseline and 6 months, PCS scores increased significantly from 50.3 +/- 7.6 to 55.9 +/- 5.3 (p = 0.02) while MCS scores did not change significantly from baseline to 6 months (47.5 +/- 7.2 and 51.7 +/- 9.6, respectively). The baseline and 6 month domain scores are listed in Table 2. Figure 3 shows the change in domain scores from baseline to 6 months. Significant increases were observed for physical functioning, role physical, vitality, and mental health domain scores. At 6 months, none of the patients in the ECG monitoring group reported trouble using the device. In addition, 92% of respondents thought the device was beneficial and 58% said that they were more health conscious after participating in the study. Additionally, there was no difference in the rate of hospitalizations between the ECG monitoring group and the control group; no deaths occurred during follow-up

Table 2: Baseline and 6 Month SF-36 Quality of Life Domains

Domain	Baseline (mean + SD)	6 Months (mean + SD)
General Health	52.0 + 9.0	54.4 + 4.1
Bodily Pain	53.0 + 6.8	54.1 + 8.0
Physical Functioning	49.9 + 7.7	55.7 + 2.5
Role Physical	44.0 + 11.4	55.5 + 4.8
Vitality	45.3 + 11.2	54.3 + 8.1
Mental Health	42.6 + 7.2	50.9 + 8.5
Social Functioning	53.1 + 6.8	53.9 + 7.9
Role Emotional	52.2 + 6.2	53.7 + 7.5

Discussion

In this convenience sample of an ambulatory cardiac electrophysiology clinic population, use of mobile ECG technology resulted in higher rate of redetection of AF/AFL than monitoring through routine care in an age and gender-matched control group. Our study adds to the growing evidence regarding the use of smartphone-based ECG monitoring in other settings, [7-12] including primary care and post-cardiac surgery, and is representative of the current "real world" shift in ECG monitoring and self-management in clinical practice.

Among patients in the Alivecor™ ECG group, significant increases in quality of life scores were observed between baseline and 6 months

follow-up, spanning both physical and mental health domains. These differences are remarkable given the increased detection of AF/AFL that was noted with more intensive ECG monitoring. While speculative, it is possible that improvements in quality of life stem from the assurance of quicker treatment of arrhythmia episodes that would otherwise have gone undetected. Furthermore, mobile phone-based ECG monitoring offers greater access to investigate symptoms that may or may not be related to cardiac arrhythmia, which may reduce the patient's level of uncertainty. Our participants had the ability to transmit anytime they were symptomatic from virtually anywhere and a trained healthcare provider was able to provide them immediate feedback on their rhythm status (i.e., AF/AFL, normal sinus rhythm, or some other rhythm such as frequent APCs/VPCs that may be associated with symptoms). Many subjects reported that knowing someone was vigilantly watching their heart rhythm was reassuring.

An important facet of new mHealth ECG technology is that multiple adhesive electrodes are not required as in Holter recording and event/patch-type ECG monitors, which can be cumbersome for patients to wear and reapply for extended periods of time leading to diminished ECG monitoring compliance. In addition, the time period is limited in which data is captured for a Holter or event/patch ECG device, ranging from 24 hours to 30 days, and requires the transmission and review of stored ECG data from the patient to a central monitoring site or service for validation and analysis. [13]Although Holter monitors have historically been the standard for clinical cardiac monitoring, their lower diagnostic yield, inconvenience, and higher costs have sparked a movement towards portable and user-friendly ECG devices. [14] The AliveCor™ device, for instance, captures a medical-grade ECG in 30-seconds, from virtually anywhere and has been validated and deemed effective in multiple studies. [15-17]An instant ECG analysis is provided using FDA-approved machine learning algorithms, which alert the patient (user) of a normal ECG reading or an indication of possible AF. Patients are also able to track their ECGs and associated symptoms using the AliveCor™ device/app and can relay this information rapidly to their doctor (via print or email as a PDF file) to inform a diagnosis/treatment plan.

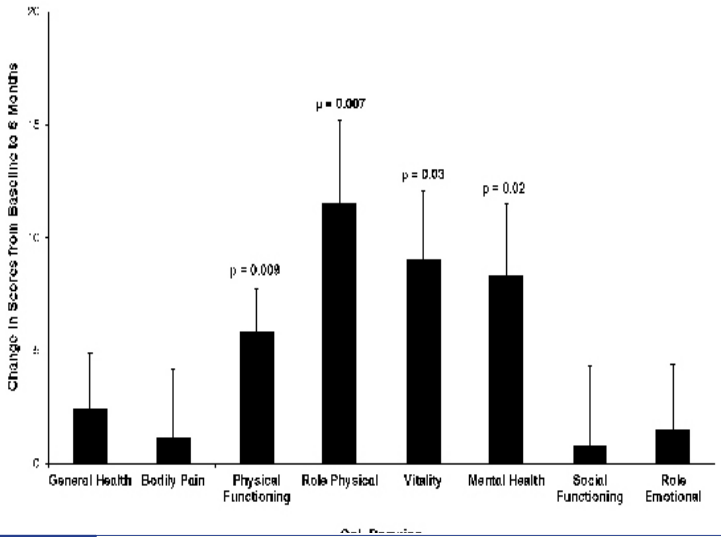

Figure 3: Change in SF-36 QoL Domain Scores

Limitations of this study include the non-randomized ECG assignment and small homogenous group of subjects. We are currently conducting a larger prospective randomized study of mobile ECG technology for AF detection among 300 patients with a history of atrial fibrillation. [18]Of note, the protocol also incorporates text messaging to the mobile ECG group in order to provide education concerning risk factors associated with AF and potential alternatives for behavior modification. This messaging may result in subjects being more engaged in their self-management and reducing their AF burden. We will also examine the impact of ECG mHealth on QoL in this larger cohort.

Conclusions

Cardiac mHealth self-monitoring with the AliveCor™ ECG is a feasible and effective mechanism for improving AF/AFL detection in the real world. Individuals with AF who engaged in self-monitoring and knew their ECGs were vigilantly being reviewed reported a better self-reported QoL.

Conflict Of Interests

None.

Disclosures

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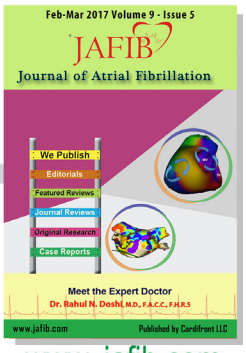

Comparison Of The Influence Of Right Atrial Septal Pacing And Appendage Pacing On An Atrial Function And Atrial Fibrillation In The Clinical Situation

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Abstract

Introduction: Atrial fibrillation is the most common cardiac arrhythmia in the United States. It has been associated with a reduction in patient quality of life and more serious complications such as stroke and heart failure. The aim of this study was to compare the efficacy of commonly performed invasive procedures in keeping patients in normal sinus rhythm.

Methods and Results: A retrospective chart review was performed on all patients who underwent primary radiofrequency catheter ablation, the complete Cox-maze, or the hybrid maze at OSF Saint Anthony Medical Center between January 2010 and December 2013 (n=140). Immediately post-procedure, arrhythmia recurrence rates did not differ between the groups ($p = 0.28$). At all follow-up points thereafter, however, differences in procedural efficacy between surgical and catheter therapy remained highly significant ($p < 0.001$). At 2 years, 20.3% of the catheter ablation patients were in normal sinus rhythm, when compared to 57.9% of hybrid maze and 72.7% the complete Cox-maze groups. A difference in major complication rates was noted ($p = 0.04$), with the complete Cox-maze having a 17.4%, the hybrid having 22.7%, and the catheter ablation group having 5.6%.

Conclusions: This study was unable to detect differences in the efficacy rates of the surgical procedures, however they were both superior to catheter ablation. Although the hybrid approach is considered minimally invasive, complication rates were similar to those of the complete Cox-maze. Catheter ablation was the safest procedure, and since evidence of reduced mortality after the use of aggressive.rhythm therapy is currently lacking, the results suggest that hybrid surgery for atrial fibrillation should be used after the failure of more conservative measures.

Introduction

As the most commonly encountered cardiac arrhythmia in the United States, atrial fibrillation is currently estimated to affect between 2 and 2.5 million people and the number suffering might rise to approximately 5.6 million by the year 2050. [1] Atrial fibrillation patients are at an increased risk of having a stroke, developing heart failure or other cardiovascular complications associated with marked reductions in quality of life. An analysis of patients in the original Framingham Study who suffered from atrial fibrillation noted that the condition is likely associated with a significant increase in patient mortality even after adjusting for other cardiac disease. [2] The condition is generally considered to be progressive in nature and involves four stages: paroxysmal, occurring in separate episodes; persistent, when it becomes constant; long standing persistent; and permanent, when the decision has been made to no longer pursue conversion to normal sinus rhythm (NSR). Currently, there are no curative options for patients with atrial fibrillation. In fact, the annual cost of treating patients in the United States is approximately $6.65 billion, which does not take into account additional costs incurred for stroke prevention, inpatient medications, comorbid conditions, or other inpatient expenditures. [3] Despite the profound impact on our society, the exact cause of this arrhythmia is still unknown. The pathophysiology of the disease however, depends on two major components: abnormal electrical triggers, thought to be cardiac ganglionic plexuses located at the pulmonary veins and left atrial junction, and an enlarged and often fibrotic left atrium, acting as a substrate for propagation of the abnormal signals. [4] Current invasive treatment strategies are based on these two notions and focus on the prevention of thromboembolism, which may lead to stroke or other cardio-embolic complications. [5] The condition can be asymptomatic, in which case, physicians may simply focus on anticoagulation and rate control. If symptoms are severe enough to warrant therapy, it is possible to utilize a number of antiarrhythmic medications in order to try and gain control of the abnormal rhythm. In addition to pharmacologic therapy, electrical cardioversion can be utilized to convert the patient back is also utilized with the aim of converting

Key Words

Atrial Fibrillation, Hybrid Maze, Cox Maze, PVI Catheter Ablation.

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the patient back to normal sinus rhythm. If that fails, patients may undergo more invasive ablation therapies. [6] It is of note that the AFFIRM trial, which is a large study that compared rate versus rhythm control in the management of atrial fibrillation patients, detected no decreases in overall mortality associated with either method compared to the other. [7] Therefore, utilization of invasive approaches for rhythm management is purely for symptomatic relief with an aim of improving quality of life. Consequently, the risks of complications should carefully be weighed against the benefits of these procedures. There are three main methods of rhythm control: medical management, catheter ablation and surgical therapy. Medical management, usually being the first-line approach, involves the use of antiarrhythmics. One of the more established invasive procedures for the treatment of recurrent symptomatic patients is radiofrequency endocardial catheter ablation, in which the pulmonary veins are electrically decoupled from the left atrium with the help of a catheter that is advanced into the left atrium usually through a vein in the groin. Epicardial ablation with left atrial appendage clipping, also known as the complete Cox-maze procedure, is the most invasive surgical approach. It is an open-heart surgery which is typically performed in conjunction with surgery to correct another heart condition like coronary artery disease or valvular disease. Studies have shown outstanding efficacy rates, but due to the invasiveness of the procedure and the potential for complications, it is not recommended for all patients. [8]–[10] Developed by Dr. James Cox in 1987, [11]–[13] the complete Cox-maze provided a basis for other currently utilized surgical procedures. The hybrid maze combines minimally invasive surgical epicardial ablation relying on a mini-thoracotomy approach and endocardial catheter ablation. The procedure can be completed in a stepwise fashion, where the patient undergoes the minimally invasive maze and then several months later, undergoes catheter ablation. Completing both stages of the procedure at one time is also possible. This therapy combines the benefit of left atrial debulking with a minimally invasive approach, which in theory would make it a preferred choice. Current data suggests that this newer hybrid procedure may be far superior in efficacy to standard endocardial catheter ablation, with studies reporting success rates greater than 90%. [14] There are three main methods of rhythm control: medical management, catheter ablation and surgical therapy. Medical management, usually being the first-line approach, involves the use of antiarrhythmics. 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The hybrid maze combines minimally invasive surgical epicardial ablation relying on a mini-thoracotomy approach and endocardial catheter ablation. The procedure can be completed in a stepwise fashion, where the patient undergoes the minimally invasive maze and then several months later, undergoes catheter ablation. Completing both stages of the procedure at one time is also possible. This therapy combines the benefit of left atrial debulking with a minimally invasive approach, which in theory would make it a preferred choice. Current data suggests that this newer hybrid procedure may be far superior in efficacy to standard endocardial catheter ablation, with studies reporting success rates greater than 90%. [14] With the utilization of newer procedures and the improvement of more established techniques, patient treatment options are expanding. Yet to our knowledge, there are currently only two studies that have compared the hybrid maze to other invasive treatment modalities, and neither has examined it in the context of primary treatment, before the failure of other invasive treatments. [15],[16] In one trial, the control was catheter ablation, however the study included only 15 patients who underwent the maze, of which less than half followed up for more than 20 months. [16]The other examined the differences in outcomes when adding a sequential catheter 'touch up' to a minimally invasive surgical ablation, essentially dicussing the plausability and potential benefits of utilizing the hybrid approach. [15] At this time, neither the 2016 European Society of Cardiology (ESC) nor the 2014 American Heart Association (AHA) guidelines provide any recommendation as to the proper utilization of this surgical technique, despite both of them mentioning that surgical ablation may still play a role in some more highly symptomatic patients. [6],[17] Because of ethical concerns

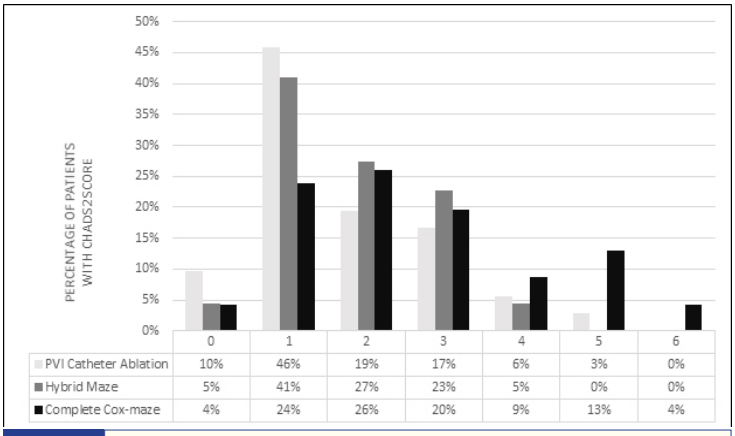


Figure 1: Percentage of Patients in each CHA_2DS_2 – VASc Score Category Stratified by Procedure

Table 1: Baseline Patient Characteristics

	PVI Catheter Ablation (n=72)	Hybrid Maze (n=22)	Complete Cox-maze (n=46)
Demographics:			
§ Age, mean (SD)	61.4 (8.5)	68.1 (10.9)	69.3 (9.0)
§ Male	68.1%	72.7%	69.6%
§ Female	31.9%	27.3%	30.4%
Comorbid Conditions:			
§ Obesity (BMI > 30)+	42 (58.3%)	18 (81.8%)	22 (47.8%)
§ Mitral Valve Disease+	12 (16.7%)	8 (36.4%)	16 (34.8%)
§ Coronary Artery Disease	24 (33.3%)	7 (31.8%)	23 (50.0%)
§ Cardiomyopathy	4 (5.6%)	1 (4.5%)	1 (2.2%)
§ Hypertension	57 (79.8%)	19 (86.4%)	40 (87.0%)
§ Diabetes Mellitus Type II	25 (34.7%)	4 (18.2%)	22 (47.8%)
§ COPD	9 (12.5%)	1 (4.5%)	9 (19.6%)
§ Sleep Apnea	25 (34.7%)	8 (36.4%)	13 (28.3%)

regarding patient safety, a randomized controlled trial examining the hybrid maze as stand-alone treatment for atrial fibrillation is currently not feasible. Therefore, the aim of this retrospective study is to compare long-term efficacy and complication rates of the hybrid maze procedure to other more commonly utilized invasive procedures—radiofrequency endocardial catheter ablation and the complete Cox-maze.

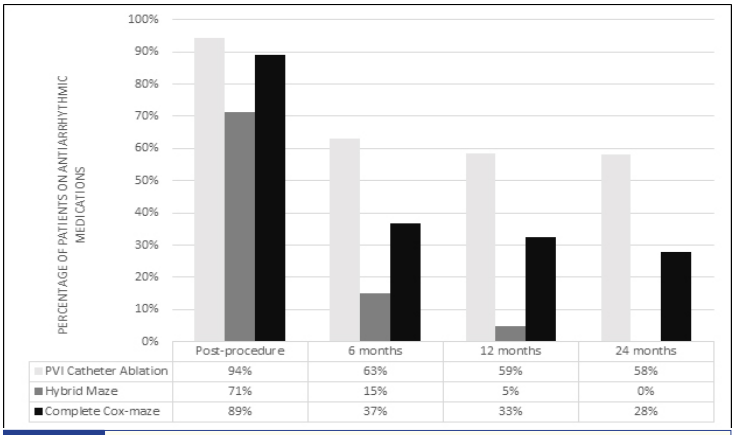


Figure 2: **Usage of Antiarrhythmic Medications Stratified by Procedure Across Time Points**

Methods

223 consecutive All patients with atrial fibrillation who have undergone radiofrequency endocardial catheter ablation, the complete Cox-maze, or the hybrid maze at OSF Saint Anthony edical Center, Rockford, IL between January 2010 and December 2013 were identified through the use of the respective CPT billing codes for each procedure – comprising 163 cases. The subjects were stratified into three groups based on the first invasive procedure they received for the treatment of their illness.

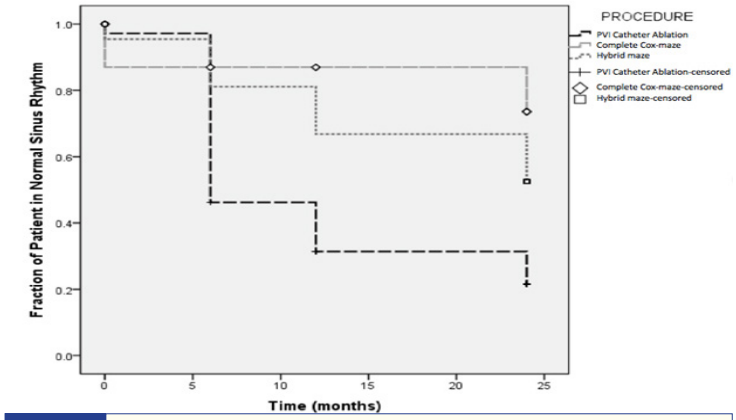


Figure 3: **Kaplan-Meier Survival Plot for All Patients in the Study**

In order to provide a fair comparison between the procedures, any patient who had received prior invasive therapy to treat their condition was excluded. This included 2 patients from the hybrid maze group, 13 patients from the PVI catheter ablation group, and 8 patients from the complete maze group. The final sample size for analysis was 140 patients. Data were extracted by two independent researchers, cross-referenced and any inconsistencies or missing values were rechecked in the electronic medical record (EMR). The patients were followed up for two years post-procedure. Data on the $CHADS_2$ score, atrial fibrillation status, anticoagulation use (including warfarin, rivaroxaban, apixaban, dabigatran, aspirin, clopidogrel, prasugrel), antiarrhythmic use (including amiodarone, flecainide, dronedarone, propafenone, sotalol, dofetilide, digoxin, procainamide, quinidine), major life-threatening complications and additional procedures were collected at four time points—immediately post-procedure prior to discharge from the hospital, 6 months, 12 months and 24 months post-procedure. A $CHADS_2$ score, which ranges from 0 to 6, where a higher number is correlated with a higher estimated risk of cerebrovascular accidents, was used as a surrogate for disease severity. $CHADS_2$ is a risk stratification schema that includes: congestive heart failure, hypertension, age (>/= 75), diabetes, and cerebrovascular accidents, including transient ischemic attacks [18]. This project was approved by the Institutional Review Boards at the University of Illinois College of Medicine at Rockford (protocol number 20150077) and OSF Saint Anthony Medical Center (protocol number #201509).

Data Analysis

The primary outcome of the study was procedural efficacy, which was defined as absence of atrial fibrillation at four time points during the 24-month follow-up. At baseline, a one-way ANOVA was used to test for differences in mean age between the different groups and a chi-square test was used for the categorical data. Due to the small sample size within the hybrid maze procedure group, a Fisher's exact test was used where appropriate. Both a chi-square analysis and a multivariate logistic regression were used to determine if there were an association between procedure used and recurrence of atrial fibrillation at different time points. All baseline variables that were significant (p-value < 0.05) were included in the final logistic regression analysis that examined procedural efficacy. When conducting the final regression analysis, the only dependent variable was procedural efficacy in keeping patients in normal sinus rhythm. The independent variables included were: age, obesity, antiarrhythmic usage, mitral valve disease, diabetes mellitus type II, and procedure utilized.

Table 2: **Number of Complications Associated with Each Procedure during the two-year timeline**

Complication	PVI Catheter Ablation (n=72)	Hybrid Maze (n=22)	Complete Cox-maze (n=46)
Major Events:			
Pneumonia	0	1	3
Acute Kidney Injury	0	0	1
Dressler's Syndrome	0	1	1
Cardioplegic Syndrome	0	0	1
Pleural Effusion	0	2	1
Acute Heart Failure	0	0	1
Stroke/Transient Ischemic Attack (TIA)	0	0	0
Pericardial Effusion/ Cardiac Tamponade	4	0	0
Procedure-related Death	0	1	1
Total number of events	4 (5.6%)	5 (22.7%)	8 (17.4%)
Minor Events:			
Pseudoaneurysm	2	0	0
Groin Hematoma/Bleed	2	0	0

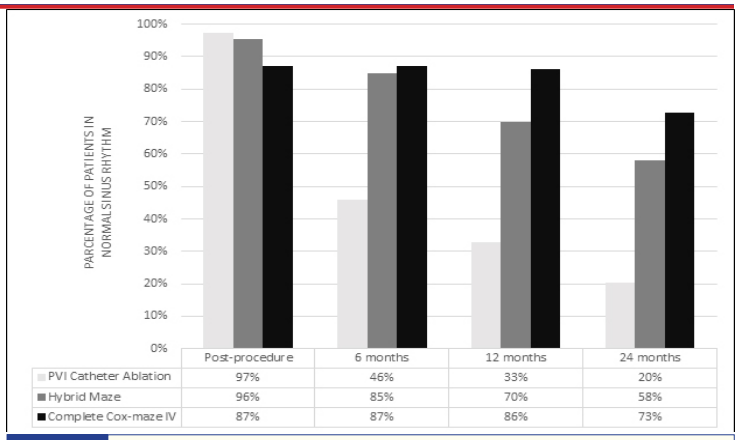
Results

Baseline demographic characteristics and co-morbid conditions stratified by procedure utilized are presented in [Table 1]. The mean age of subjects within the PVI catheter ablation group was 61.4±8.5 years, 68.1±10.9 for the hybrid maze group, and 69.3±9.0 in the

complete Cox-maze group. The majority of participants in the study were males, with 68.1% in the catheter ablation group and 72.7% and 69.6% in the hybrid and complete maze groups respectively.

Discussion

Indications of the complete Cox-maze have been thoroughly studied along with its excellent long-term efficacy. However, in patients needing primary treatment solely for atrial arrhythmia, a more minimally invasive approach is preferred. Despite a clear superiority of the hybrid maze procedure when compared to pulmonary vein catheter ablation, at this time, the most appropriate indications for the procedure is yet to be identified. The current American Heart Association and European Society of Cardiology guidelines for the treatment of atrial fibrillation lack any recommendations for hybrid surgical therapy. They both do mention, however, that a standalone surgical ablation procedure can be reasonable in a symptomatic patient that is not controlled with other less invasive approaches. The ESC states that: "Although preliminary experience with hybrid simultaneous ablation shows promise, procedural time and rates of bleeding complications are higher" [17]. Therefore, the question remains whether this procedure has a role when deciding between treatment options for patients in whom medical management has failed. Based on both the bivariate analysis and multivariate logistic regression model, it is apparent that there is a difference in atrial fibrillation recurrence at 6 months and beyond, depending on which procedure was utilized. Catheter ablation patients were much more likely to suffer from a recurrence of their atrial arrhythmia, despite the highest utilization of antiarrhythmic medication across all time points. The study was unable to demonstrate any difference between the efficacies of the hybrid maze and the complete Cox-maze, providing further evidence that the combined minimally invasive maze and catheter ablation approach might indeed be associated with favorable efficacy rates. It is important to note that the failure of this study to prove inequality between the efficacies of the hybrid maze and the complete Cox-maze does not imply equality. In a subgroup analysis of 43 patients with longstanding persistent atrial fibrillation, the results mimicked the overall cohort, with the catheter ablation procedure having an even lower efficacy when compared to the other two procedures. Despite its promising efficacy rate, the hybrid maze procedure was associated with a significant number of complications and a possible increase in mortality. Pneumonia, Dressler's syndrome, pleural effusion, and one death were observed. In the complete Cox-maze group, acute renal failure was most common, but pleural effusion, respiratory failure, aspiration pneumonia, heart failure and Dressler's syndrome were all recorded complications. It is important to note that most complications encountered with both of the surgical treatments happened during patient recovery, and not at the time of the procedure. As catheter ablation procedures do not require long term hospitalization, patients are not as susceptible to hospital-associated adverse events. The majority of catheter ablation complications did not require any significant intervention from a physician, when compared to the other two procedures, which tended to require the involvement of a team of treating physicians in order to prevent long-term consequences or death. The most commonly encountered complication in the catheter ablation group was a pericardial effusion. At this time, it is precisely because of the high complication rates associated with surgical procedures that they are utilized as a third-line treatment, only after the failure of both medical management and catheter ablation [6],[17],[21],[22]. The FAST



	Post-procedure	6 months	12 months	24 months
PVI Catheter Ablation	97%	46%	33%	20%
Hybrid Maze	96%	85%	70%	58%
Complete Cox-maze IV	87%	87%	86%	73%

Figure 4: Percentage of Patients in Normal Sinus Rhythm at each Time Point

trial, which current guidelines are mainly based on, is the largest randomized control trial comparing minimally invasive surgical ablation and catheter ablation. It was performed by Boersma et al. in two centers, one being in Spain and the other in the Netherlands. Unfortunately, this study did not evaluate the hybrid maze, therefore surgical patients were not followed-up with a catheter procedure. Also, the patients being examined had either left atrial dilitation and hypertension or a failed prior catheter abltation, suggesting a population that is inherently resistant to treatment. Despite these differences, both complication rates (5.6% vs 3.2% in the catheter ablation group and 22.7% vs 23.0% in the minimally invasive surgical group) and efficacy rates (33.0% vs 36.5% in the catheter ablation group and 70.0% vs 65.6% in the minimally invasive surgical group) at 12 months in this study were found to be similar to those of the FAST trial, suggesting that the hybrid maze may be considered a viable option in highly symptomatic patients that have failed medical therapy [21]. There are several notable limitations to this study. Due to it being a single center retrospective analysis of electronic medical records, there is an inherent reliance on the accuracy of the records. As a result of the retrospective nature of the study, there is no way to accurately measure if the patients actually experienced any improvement of their atrial fibrillation symptoms following a procedure. Instead, the success of a procedure is based on the complete lack of recurrence of the arrhythmia. Also, because of the lack of randomization, there is no way to account for effects of other variables that were not measured at baseline. Lastly, like many other studies in this field, due to the limited utilization of surgical ablation procedures, there is a limited cohort size. Thus, as mentioned previously, the study was underpowered, and its inability to identify a difference in the efficacies of the Cox-maze IV and the hybrid maze does not imply their equality. Adequately powered studies in patients with symptomatic longstanding persistent atrial fibrillation are still necessary to investigate whether the superior efficacy observed with surgical procedures might in fact outweigh the risk of procedural complications and ultimately provide some benefit in mortality.

Conclusions

This study was unable to detect any differences in efficacies of the two surgical procedures under investigation, however they were both found to be significantly superior to a pulmonary vein isolation catheter ablation in keeping patients in normal sinus rhythm. Although the hybrid approach utilized a minimally invasive method of gaining access to the left atrium, adverse event rates were similar to those of the complete Cox-maze. Catheter ablation

had a significantly lower efficacy when compared to the surgical procedures, with most arrhythmia recurrences occurring within the first 6 months post-procedure. However, it was associated with the fewest number of potentially life threatening adverse events. Since, at this time, evidence of any long-term survival advantage after the use of aggressive rhythm therapy is lacking, the results of this study suggest that stand-alone surgical treatments for atrial fibrillation should be used as a third-line approach, only after the failure of more conservative measures. It is important to note that patients with longstanding persistent atrial fibrillation may often suffer from a substantially increased burden of disease. There is a lack of data regarding the proper utilization of the hybrid maze procedure in the treatment of this population and therefore further studies with a primary focus on these patients are necessary.

Conflict of Interests

None.

Disclosures

None.

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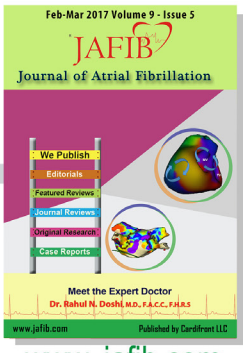

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Left Atrial Appendage Characteristics In Patients With Persistent Atrial Fibrillation Undergoing Catheter Ablation (Laapaf Study)

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Abstract

Despite technological and scientific efforts, the recurrence rate of persistent atrial fibrillation (AF) remains high. Several studies have shown that in addition to pulmonary vein (PV) isolation other non-PV triggers, particularly left atrial appendage may be the source of initiation and maintenance of AF. There are few studies showing the role of left atrial appendage (LAA) isolation in order to obtain higher success rate in persistent AF patients. We analyzed the LAA volume, volume index and shape relative to the LA in patients with persistent AF undergoing AF ablation. Fifty-nine consecutive patients with persistent AF who underwent catheter ablation were enrolled. Computerized tomography (CT) was performed in order to assess left atrial and PV anatomy including the LAA. Digital subtraction software (GE Advantage Workstation 4.3) was used to separate the LAA from the LA and calculate: LA volume (LAV), LA volume index (LAV/body surface area), LAA volume (LAAV), LAA volume index (LAA volume/LA volume), and LAA morphology [chicken wing (CW) or non-chicken wing (NCW)]. The mean age was 64.6 ± 9.8 years, 44 % male, and LA diameter 47.6 ± 7.8 mm. Median follow-up (FU) was 13 months. All patients had antral isolation of PVs and ablation of complex fractionation ± linear ablation (roof line/superior coronary sinus/mitral line). Among 59 patients with persistent AF, 26 (44 %) patients were diagnosed with AF recurrences. Mean LAV was 145.0 ± 45.9 ml, LAVI 68.9 ± 20.0 ml/m², LAAV 10.3 ± 4.0 ml, and LAAVI 7.3 ± 2.7 ml/m². LAA shape was non-chicken wing (NCW) in the majority of patients (51 %). LAA parameters were not significantly different between patients with and without AF recurrence (LAAV 11.0 ± 4.3 ml vs. 9.7 ± 3.8 ml, p=0.26; LAAVI 7.5 ± 3.0 ml/m² vs. 7.2 ± 2.5 ml/m², p=0.71; LAA shape of NCW 50 % vs 52 %, p=0.75, respectively). LAV was significantly correlated with the LAAV (r: o.47, p=0.009). The incidence of NCW LAA was significantly higher in patients with previous stroke/TIA (80 % vs. 20 %, p=0.04). The LAA anatomical characteristics (volume/volume index and the shape) were comparable in patients with/out AF recurrence post PVI. It remains to be determined if additional LAA isolation will impact outcomes in patients with persistent AF.

Introduction

Atrial Fibrillation (AF) affects approximately 2.3 million people in North America. [1] Treatment of AF is based on an understanding of the underlying mechanisms. The pulmonary vein isolation is the cornerstone of the catheter ablation of AF. [2] The success rate of catheter ablation is approximately 70% in patients with paroxysmal AF and 50-55% in patients with persistent AF. [1] Long standing persistent (LSP) atrial fibrillation (AF) is the most challenging type of AF to treat with catheter ablation.

Several studies have shown that in addition to pulmonary vein (PVs) isolation other non-PVs areas may be the source of initiation and maintenance of atrial fibrillation in patients. [3] The most common sites are: the superior vena cava, the ligament of Marshall, the coronary sinus, the crista terminalis, the left atrial posterior wall and the left atrial appendage (LAA).

Key Words

Atrial Fibrillation,Cardiac CT,Left atrial appendage,Catheter ablation.

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Embryologically, the LAA is a remnant of the primordial embryonic left atrium (LA), which explains its trabecular appearance (pectinate muscles). The LAA has an important impact on thromobogenicity of the left atrium; particularly shape of the LAA has utmost importance. [4] The LAA has also been implicated as a significant source of atrial tachycardia and AF. [5] In a study by Di Biase et al, close to 30% of AF triggers in persistent AF were found to be non-pulmonary venous (non-PV), especially LAA, in origin. [3] Successful ablation or isolation of the LAA seems to significantly impact arrhythmia control (reduce AF burden) in these patients. It has been demonstrated that LAA ligation with an epicardial approach (LARIAT device [SentreHEART, Redwood, CA], AtriClip [AtriCure, West Chester, OH], surgical ligation) typically result in both mechanical and electrical isolation because they tend to compress the tissue, resulting in ischemic necrosis of the LAA distal to the site of exclusion [6]-[9]. Most recently, Di Biase et al [10] in a randomized study demonstrated that empirical isolation of the LAA improved long-term freedom from AF in patients with LSP without increasing complications.

Recurrence rate of catheter ablation of persistent AF remains high. It is well known that LA characteristics (dimension, volume, and volume index) are predictors of AF recurrence [11] because it has

been established that persistent AF increases predisposition to LA remodeling, however the concept of LAA remodeling has not been adequately investigated. Therefore this study aimed to explore the association between the anatomical and volumetric characteristics of the LAA and AF recurrence after ablation in persistent AF patients.

Methods And Materials

Patient demographics

Consecutive patients from Aug 2014 to April 2016 with longstanding persistent AF who underwent AF ablation were enrolled retrospectively. All patients underwent transthoracic echocardiography (TTE) and cardiac computed tomography (CT) prior to catheter ablation. Longstanding persistent AF was defined according to the HRS/EHRA/ECAS 2012 Consensus Statement as an episode of AF greater than 12 months. [1] Patient demographics and medications at the time of initial ablation were obtained from medical records. Exclusion criteria were defined as follows: patients < 18 years old, paroxysmal and/or permanent AF, patients with LA/LAA thrombus, and unwillingness to participate in the study. Anti-arrhythmic medications (except amiodarone for a minimum of 4 weeks) were discontinued for five half-lives prior to the procedure, and all patients provided written informed consent. 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 standard, full transthoracic echocardiography (TTE) with a Vivid E95 machine (GE Healthcare, USA) according to ASE guidelines. [12] The LA size was assessed at admission by a transthoracic echocardiographic measurement of the short and long-axis views in the parasternal window. LA size was considered severely enlarged when LAD ≥ 50 mm. Nevertheless, TTE biplane method of disks was used to calculate LA volume. LA volume index (LAVI) was calculated by dividing LA volume by the body surface area of patients. Transesophageal echocardiography was performed to exclude any atrial thrombi 24 hours before ablation.

Cardiac computed tomography

All coronary CTA imaging was performed with a 64-MDCT scanner or 320-Toshiba (GE Healthcare, USA) using retrospective gating. ECG-based tube current modulation was used when appropriate. Contrast-enhanced image acquisition was performed during a single breathhold. Imaging parameters included a slice collimation of 64 × 0.625 mm (GE) or 320 x 0.5 mm (Toshiba), gantry rotation time of 350 milliseconds with a tube voltage of 100–120 kV and effective tube current of 550–750 mAs. Intravenous contrast (Omnipaque 350) 50cc, followed by 50cc contrast:saline solution (60:40 ratio) followed by 40cc saline chaser was administered at 5cc/s (GE scanner) or 80cc IV contrast (Omnipaque 350, GE Healthcare,) followed by 40cc saline chaser at 5cc/s.

The LAA volumes were calculated using GE Advantage Workstation 4.3. Volume rendered (VR) images of the left atrium were populated automatically by the software. The left atrial ridge was used as a consistent landmark to identify the LAA ostium. The remainder of the ostium was estimated by visual inspection using a combination of VR and multiplanar 2D images. The remainder of the left atrial volume was cropped leaving only the LAA volume (Figure). LA and LAA volumes were indexed for body surface area calculated using the Du Bois formula [13]. The morphology of the LAA was also assessed. CW was defined as LAA with an obvious bend in the proximal and middle part of the dominant lobe, or the LAA folding back on itself at some distance from the perceived LAA orifice. Non-CW (cauliflower, cactus, and wind sock) was defined as LAA without any bends. [14]

Periprocedural Anticoagulation

Patients were anticoagulated with warfarin and the procedure was performed without interruption of therapy, with an INR level between 2 and 3. Patients on any new oral anticoagulants (NOAC) were instructed to withhold the doses for 48 hours prior to the procedure. After transeptal access to the LA, intravenous unfractionated heparin was administered at 20-minute intervals to attain a target-activated clotting time of 300-350 seconds.

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

Number of patients	59
Age, years	64.6 ± 9.8
Gender, male	26
BMI, kg/m^2	32.0 ± 5.8
DM, n (%)	12 (20)
HTN, n (%)	41 (69)
CAD, n (%)	11 (19)
CVA-TIA, n (%)	10 (17)
SA, n (%)	20 (34)
CHA_2DS_2VasC	2.3 ± 1.2
AAD, n (%)	19 (32)
EF, %	53.3 ± 11.3
LAD, mm	47.6 ± 7.8
PT, min	293 ± 79
FT, min	21.3 ± 8.3
Recurrence, n (%)	26 (44)
FU, months*	13 (4 and 67)

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 drugs; EF, ejection fraction; LAD, left atrial diameter; PT, procedure time; FT, fluoroscopy time; FU, follow-up.
* median (min, max)

Electrophysiology study and Ablation

Patients were brought to the Electrophysiology lab fasting, 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 right femoral vein as appropriate for the procedure: (1) Decapolar coronary sinus catheter (IBI Inquiry, St. Jude Medical, St. Paul, MN, USA), (2) duodecapolar halo-type catheter (Supreme, St. Jude Medical, St. Paul, MN, USA) positioned in the right atrium, (3) mapping and ablation catheter (Tacticath™ Quartz, St. Jude Medical, St. Paul, MN, USA) delivered through a 9 Fr femoral sheath (St. Jude Medical, Minneapolis, MN) (4) long steerable sheath (Agilis, St. Jude Medical, Minneapolis, MN) was used in cases for better stability, or longer reach to the TV annulus, 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 certain cases. Following this, a spiral multipolar PV catheter (AFocus II, St. Jude Medical, St. Paul) and CF-sensed catheter (TactiCath Quartz, St.Jude Medical St Paul, MN) were used to perform the ablation. Before mapping, the CF enabled catheter, TactiCath™ Quartz was calibrated either outside the body, or while freely floating in the mid right atrium to set the baseline value of contact force at zero

grams. Afterwards, a 3-D reconstruction of the LA and pulmonary veins was created with the use of EnSite Velocity™ system (St. Jude Medical, St. Paul, USA)

AF ablation was performed with a standard wide area circular ablation (WACA) approach. No traditional lines were routinely performed. 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 (TactiCath Quartz, St.Jude Medical St Paul, MN). For each lesion, CF of at least 10 grams, and lesion duration of at least 40 seconds were targeted. In sites with low CF such as LA/LAA ridge, FTI > 400 gs was targeted. The PV isolation was considered complete when the circular catheters no longer recorded any PV potentials. Acute reconnection was assessed in both groups at the end of the procedure. It was defined when the LA-PV conduction spontaneously re-appeared after a waiting period of 20 minutes following the completion of the PV isolation, or when PV dormant conduction was evoked by an intravenous adenosine infusion. The patients were kept overnight, and discharged the following day.

Table 2: Cardiac CT parameters

LAV, ml	145.0 ± 45.9
LAVI, ml/mm²	68.9 ± 20.0
LAAV, ml	10.3 ± 4.0
LAAVI, ml/mm²	7.3 ± 2.7
LAA shape, NCW (%)	30 (51)

LAV, left atrial volume; LAVI, left atrial volume index, LAAV, left atrial appendage volume; LAAVI, left atrial appendage volume index, NCW, non-chicken wing

Follow up

Post ablation, all patients received anticoagulation for at least 3 months. They were maintained on anticoagulation according to the CHA_2DS_2VASc score. 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). [1]

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 was 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 its underlying distribution. The association between LAA parameters and AF recurrence was assessed using independent samples t-tests, with the Mann-Whitney U test in the event of non-normal distributions. A p -value less than 0.05 was considered significant.

Results

Fifty-nine consecutive patients with persistent AF undergoing catheter ablation for AF were included in this study. Demographics and procedure details are depicted in [Table 1]. Mean left atrial diameter (LAD) was 47.6 ± 7.8 mm. During a median follow-up of 13 months (range 4 and 67 months) after a single ablation procedure, 33 patients (56 %) maintained sinus rhythm [Table 1].

Analysis of the cardiac tomography (CT) parameters is depicted in [Table 2]. LAA shape was non-chicken wing in majority of patients (51 %).

As depicted in [Table 3], age, comorbidities, LVEF, and procedure details were comparable in patients with AF recurrence, and to those without. Patients with AF recurrences had a larger LA size than those without recurrences (50.1 ± 8.3 mm vs. 45.8 ± 6.9 mm, p=0.05) [Table 3].

CT findings of patients with and without AF recurrence are listed in [Table 4]. LA volume, LA volume index, and LAA volume tended to be higher in patients with AF recurrence, however this difference did not reach statistical significance. LAA volume index and the shape of the appendage were comparable in both groups [Table 4]. Patients with history of cerebrovascular accident (CVA)/transient ischemic attack (TIA) had significantly higher frequency of non-chicken wing LAA morphology (NCW of 80 % vs. CW of 20 %, p=0.04).

Procedural Outcome

Acute procedural success was achieved in all 59 (100 %) patients, and all patients were in sinus rhythm at the end of the procedure. AF terminated to SR or organized atrial tachycardia in 23 patients. Sinus rhythm was achieved by electrical cardioversion in the remaining patients.

Follow up

During a follow-up of 13 months (range 4 and 67 months) after a single ablation procedure, there were 26 patients (44 %) with AF recurrences. Of those 26 patients, 12 patients underwent another catheter ablation, 6 patients required electrical cardioversion, and the remaining 8 patients were followed up with antiarrhythmic treatment.

Discussion

In our cohort, although LAAV tended to be higher in patients with AF recurrence compared to those without AF recurrence, however this did not reach statistical significance. Also the other LAA parameters (LAAVI and LAA shape) were comparable between groups. The prevalence of NCW LAA was significantly higher in patients with CVA/TIA.

Despite successful and permanent PV isolation, patients may experience AF recurrences due to non-PV triggers responsible for initiation of AF [3], [15]. The most common and reported non-PV triggers are the superior vena cava, the coronary sinus, atrial septum, ligament of Marshall, and left atrial appendage. Several predictors of AF relapse after ablation procedures have been suggested, including age and comorbidities, type of AF, episode duration, electrocardiographic parameters, biomarker levels. Much attention

Table 3: Comparison of patients with and without recurrence of AF

	Recurrence (n=26)	Non-recurrence (n=33)	p value
Age, years	63.8 ± 8.7	65.2 ± 10.8	0.60
Gender,male	15	11	0.07
BMI, kg/m²	32.3 ± 5.7	31.9 ± 5.9	0.80
DM, n (%)	6 (23)	6 (18)	0.89
HTN, n (%)	20 (76)	21 (64)	0.54
CAD, n (%)	4 (15)	7 (21)	0.52
CVA-TIA, n (%)	6 (23)	4 (12)	0.48
OSA, n (%)	10 (38)	10 (30)	0.43
CHA_2DS_2VASc	2.4 ± 1.2	2.2 ± 1.2	0.73
AAD, n (%)	7 (27)	12 (21)	0.49
EF, %	53.6 ± 12.1	52.9 ± 10.8	0.87
LA, mm	50.1 ± 8.3	45.8 ± 6.9	0.05
PT, min	292.7 ± 88.6	292.9 ± 73.2	0.99
FT, min	21.0 ± 6.6	21.6 ± 9.9	0.86
FU, months	21.3 ± 17.0	16.7 ± 12.9	0.25

was paid to LA size and function as well. However the role of LAA has not been investigated thoroughly.

Recently, the LAA has been reported as an unrecognized and overlooked trigger site of AF especially in persistent AF patients [16]. Yamada and colleagues [5] demonstrated first case of atria tachycardia originating from the LAA. Di Biase and colleagues [16] have reported a series of 266 patients undergoing redo AF ablation procedures with demonstrated silent PVs in 27 % of these patients. This group of patients had a driving trigger from the LAA and that was the only site responsible for AF recurrence. After this report, many case series have shown the relevance and importance of the LAA for triggering and maintenance of AF. [5],[7],[17],[18] Hocini et al [19] reported patients with localized re-entrant arrhythmias originating within the LAA after failed standard AF ablation and supported the hypothesis of the LAA as a main trigger for the maintenance of AF.

Table 4: Comparison of cardiac CT parameters in patients with and without AF recurrence

	Recurrence (n=26)	Non-recurrence (n=33)	p value
LAV, ml	153.6 ± 54.0	139.1 ± 39.3	0.26
LAVI, ml/mm²	74.4 ± 22.4	65.2 ± 17.8	0.11
LAAV, ml	11.0 ± 4.3	9.7 ± 3.8	0.26
LAAVI, ml/mm²	7.5 ± 3.0	7.2 ± 2.5	0.71
LAA shape, NCW (%)	13 (50)	17 (52)	0.75

Epicardial mechanical and electrical exclusion of LAA has shown promising results in decreasing the burden of AF and this was more pronounced in patients with persistent AF. [9],[20]-[22] LAA exclusion using a suture or a clip causes an acute infarct of the tissue and results in a significant voltage reduction. A recent article by Han et al. [9] showed that snare closure of the LAA using the LARIAT device produces an acute reduction in LAA voltage and inhibits capture of the LA during LAA pacing. Recently, the LAALA-AF (Left Atrial Appendage Ligation and Ablation for persistent Atrial Fibrillation) registry has shown a lower AF burden by mechanical inducing electrical isolation with the LARIAT closure device. [23] Ligation of the LAA possibly can remove the reentrant and triggered arrhythmias that arise from the structure. Typically there is a 10 % to 40 % reduction in LA volume and surface area after LAA exclusion, which essentially decreases the available LA substrate for AF propagation and perpetuation. [20] Chan et al. [24] also suggested the LAA isolation may be caused by disruption of Bachman's bundle, which runs along the LA anterior wall and surrounds the LAA. BELIEF randomized study has been recently published and showed that empirical electrical isolation of the LAA improved the ablation outcome at follow up of long-standing persistent AF patients. [10]

The main criticism against LAA electrical isolation is its potential thromboembolic risk. Recent studies showed that around 50 % of patients have flow velocity within normal range after LAA isolation and with proper anticoagulation. [10],[25]

Nedios et al. reported that normal maximal LAA volume in end-systole was 6.5 ± 1.9 ml. [26] In addition MRI and CT studies showed that LAA volume is increased in persistent AF patients compared those with paroxysmal AF. [27]-[29] In our study, LAA parameters (volume and volume index) were comparable in patients with and without AF recurrence. However, mean LAAV was 10.3 ± 4.0 ml in a study cohort. Nevertheless LAAV tended to be higher in patients with AF recurrence. It has previously been demonstrated that LAA volume index (LAAVI) larger than 5.6 ml/m² indicates LAA enlargement. [30] In our study population, mean LAAVI was 7.3 ± 2.7 ml/m² indicated enlarged LAA.

In addition to the LAA volumetric measurements the shape of the LAA has also been investigated in our study. Previously, Gerede et al. [31] demonstrated that a low LAA velocity (<30 cm/s) was an independent predictor of AF recurrence after cryoballoon ablation. Kanda et al. also demonstrated that low LAA flow velocity was associated with AF recurrence after initial RF ablation of persistent AF [32]. There are 2 different LAA morphologies: CW and NCW (cauliflower, cactus, and wind sock). Patients with persistent AF have a higher prevalence of non-CW morphology LAA than did those in the paroxysmal AF group. [33] Non-CW morphology LAA patients have larger LAA size and volume. In our study, the prevalence of NCW LAA was comparable in patients with and without AF recurrence. However, the prevalence of NCW LAA was significantly higher in patients with previous stroke and/or TIA. Our results are in accordance with these previous findings showing that patients with NCW LAA morphology are more likely to develop thromboembolism than patients with CW LAA morphology. [4] The possible explanation is LAA volume is higher in patients with NCW LAA and LAA volume is negatively correlated with LAA flow velocity, suggesting that larger LAAV may lead to blood stasis. [34],[35]

Limitations

Several limitations to this study warrant mention. First, this is a single-center, retrospective study, and bias is inherent to this type of design. Hence, large-scale, prospective studies are required. Second, there is no landmark for CT measurement, which divides the LA and pulmonary veins. Third, the lack of LAA flow velocity is one of the limitations in this study. Fourth, electrical signals and activation of the LAA has not been investigated in our study. Finally, in all AF studies, conventional approaches to documenting asymptomatic recurrences are prone to underestimate the overall recurrence rate during follow up.

Conclusions

Anatomical and volumetric characteristics of the LAA were comparable in patients with AF recurrence compared to those without AF recurrence, however this result does not diminish the role of the LAA in patients with persistent AF because electrical activation of the LAA is still a matter of importance.

Conflict Of Interests

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 Atrial Fibrillation. 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.

Disclosures

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High Voltage Guided Pulmonary Vein Isolation In Paroxysmal Atrial Fibrillation

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Abstract

Ablation of the pulmonary vein (PV) antrum using an electroanatomic mapping system is standard of care for point-by-point pulmonary vein isolation (PVI). Focused ablation at critical areas is more likely to achieve intra-procedural PV isolation and decrease the likelihood for reconnection and recurrence of atrial fibrillation (AF). Therefore this prospective pilot study is to investigate the short-term outcome of a voltage-guided circumferential PV ablation (CPVA) strategy. We recruited patients with a history of paroxysmal atrial fibrillation (AF). The EnSite NavX system (St. Jude Medical, St Paul, Minnesota, USA) was employed to construct a three-dimensional geometry of the left atrium (LA) and voltage map. CPVA was performed; with radiofrequency (RF) targeting sites of highest voltage first in a sequential clockwise fashion then followed by complete the gaps in circumferential ablation. Acute and short-term outcomes were compared to a control group undergoing conventional standard CPVA using the same 3D system. Follow-up was scheduled at 3, 6 and 12 months.Mean age Thirty-four paroxysmal AF patients with a mean age of 40 years were included. Fourteen patients (8 male) underwent voltage mapping and 20 patients underwent empirical, non-voltage guided standard CPVA. A mean of 54 ± 12 points per PV antrum were recorded. Mean voltage for right and left PV antra were 1.7±0.1 mV and 1.9±0.2 mV, respectively. There was a trend towards reduced radiofrequency time (40.9±17.4 vs. 48.1±15.5 mins; p=0.22), Voltage-guided CPVA is a promising strategy in targeting critical points for PV isolation with a lower trend of AF recurrence compared with a standard CPVA in short-term period. Extended studies to confirm these findings are warranted.

Introduction

Catheter ablation is an effective therapy for patients with symptomatic, drug-refractory atrial fibrillation (AF). [1-3] The pulmonary veins (PV) play a major role in the initiation of AF [4] and pulmonary vein isolation (PVI) constitutes the cornerstone for ablative treatment of paroxysmal and persistent AF. [5]

Histological studies demonstrate that the LA (left atrium)-PV junction is composed by discrete myocardial sleeves that extend from the LA into the PV, separated by gaps of connective tissue. Automated electro-anatomic mapping of cardiac tissue has been used to identify low voltage regions, which have been shown to be a surrogate marker of potential scar tissue. [6] Therefore, areas of high voltage are likely to identify areas of viable myocardium and hence, can be used to define putative muscular connections from PV antra into the pulmonary veins themselves. Scar or adventitial tissue would therefore be represented by relatively low voltage areas in the intervening regions. [6, 7] We hypothesize that an ablation strategy targeting regions of high voltage in PV antra could improve the outcomes as this allows for focused ablation on critical areas of muscular connections. This should also translate into a lower risk of reconnection and therefore less chance of early recurrence of AF.

Key Words

Circumferential pulmonary vein isolation (CPVA), voltage-guided ablation, radiofrequency ablation and AF ablation.

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Patients and methods

Patients Characteristics

In this single-centred prospective pilot study we enrolled patients undergoing a first catheter ablation for paroxysmal AF. Inclusion criteria were as follow: (i) age > 18 years; (ii) history of AF with documentation on 12-lead ECG, Holter or event monitor; (iv) refractoriness to at least one class I and/or III antiarrhythmic drug. Exclusion criteria were: (i) previous ablation for AF; (ii) intracardiac thrombus; (iii) contraindication to oral anticoagulants and (iv) unwillingness to participate in the study. Also there were no "lone AF" patients in our study group.

Anti-arrhythmic medications (except Amiodarone for a minimum of 4 weeks) were discontinued for 5 half-lives prior to the procedure and all patients provided written informed consent.

Electrophysiology study

The procedure was conducted under conscious sedation with intravenous fentanyl and midazolam. An initial 12-lead ECG was performed to confirm sinus rhythm. Venous access was gained from the femoral veins. A deflectable decapolar catheter (Inquiry, St. Jude Medical, St. Paul, USA) advanced to the coronary sinus, a

quadriapolar catheter (St. Jude Medical, St. Paul, USA) was placed at the right ventricular apex. Transseptal access was performed using a standard technique with a BRK Brockenbrough needle and SL1 sheath (St. Jude Medical, St. Paul, USA). Following this, a spiral multipolar PV catheter (AF Focus II, St. Jude Medical, St. Paul) and an open irrigated ablation Coolflex catheter (St. Jude Medical, St. Paul, USA) were used to perform the ablation.

EnSite NavX™ system (St. Jude Medical, St. Paul, USA) was used to construct the LA geometry and a voltage map of the antral region of the 4 PVs using a segmented cardiac CT template with/out fusion of the images.

Periprocedural Anticoagulation

Table 1: Study demographics of Voltage guided and control cohorts. Data is presented as a mean ± SD. Pre LVEF = pre procedure left ventricular ejection fraction. LA= left atrium. RF time = radiofrequency ablation time. BSA = body surface area.

	Voltage-guided PVI (n=14)	Standard PVI group (n=20)	P value
Age (years)	59.8± 16	61.8 ± 11.8	0.66
Weight (Kg)	84.8 ± 17.6	89.2 ± 25.9	0.57
Height (cm)	166.8 ± 22.1	173.6 ± 9.6	0.29
BSA	2.0 ± 0.3	2.0 ± 0.3	0.93
Pre LV EF (%)	54.1 ± 9.6	55.2 ± 5.6	0.70
LA Diameter (mm)	40.2 ± 7.6	36.8 ± 4.2	0.36
LA Volume (ml^3)	66.2 ± 22	63.3 ± 13.6	0.65
Procedure Time (mins)	248.9 ± 53.7	233.9 ± 36.1	0.32
Fluoroscopy Time (mins)	33.6 ± 17.7	28.7 ± 8.9	0.36
RF Time (mins)	40.9 ± 17.4	48.1 ± 15.6	0.22
Initial Diagnosis (months)	36.8 ± 26.4	29.9 ± 25.8	0.46
Recurrence, n (%)	3/13 (23 %)	7/18 (39 %)	0.41
Acute reconnection, n (%)	3 (20)	7 (35)	
Reconnected veins			
LSPV, n	2	2	
LIPV, n	0	1	
RSPV, n	1	3	
RIPV, n	1	0	

Patient's anticoagulated with warfarin the procedure was performed without interruption therapy with an INR level between 2 and 3. Patients on direct oral anticoagulants (DOACS) were instructed to withhold the doses for 48 hours prior to the procedure. After establishing LA access, intravenous unfractionated heparin was administered at 10 to 20 minute intervals to attain a target-activated clotting time of 300-350 seconds.

Voltage mapping and anatomical identification

Bipolar voltages of both the right and left antra were recorded during continuous pacing from distal coronary sinus poles using a spiral-mapping catheter (AF Focus II, St Jude Medical, St. Paul, USA).

The voltage map was created and the readings were scaled. A voltage of 0.5 to 1.5 mV was considered to be viable normal myocardium and < 0.5 mV was considered to be scar or adventitia.[8] Voltages > 1.5 mV were regarded as high voltage regions (Fig 1). Anatomical identification of high voltage points and areas were studied against the critical points and located in main 4 quarters (superior, inferior, anterior and posterior) .

Critical points were identified as isolation or delay of PVPs.

Excluded patients

We aimed to compare 20 study patients with 20 controls. However, 6 patients from the study group were excluded from the study because -they were in AF at the time of procedure - to homogenize the voltage map techniques during pacing from the proximal coronary sinus catheter at CL of 600 ms. This was there as a consistent reference point allowing for a legitimate comparison of voltage points acquired in each antrum. If sampled in AF, oscillating and meandering rotors through the PV-LA junctions may have given an erratic activation pattern making it difficult to compare adjacent regions of varying voltages.

Ablation procedure

Radiofrequency (RF) energy was applied in the antral regions of the PVs, starting at the site of maximum voltage. Initially, we aimed high voltage areas because of fear of tissue oedema around the vein. When elimination of local electrograms was achieved, the adjacent remaining sites of maximum voltage were targeted in a sequential fashion (clockwise circumferential pattern) until isolation of the vein was achieved. If no isolation was achieved, the strategy of contiguous lesion application that is with completion of a full and complete circumferential ablation in the antrum with additional ablation guided by earliest activation on the PV spiral catheter was performed. The definition of adequate lesion was as follows: Under adequate power (30- 35 W) and irrigation with saline at a rate of 17- 25 ml/min, individual RF delivery was applied for approximately 40 seconds until the elimination of the atrial potential. In addition to that, signal resolution as Q formation or S>R was an end point to indicate successful lesion. [9] An impedance drop of 15 ohms is another confirmation of effective lesion in our study. [10] After ablation, the catheter was moved to the next site along the line. This was continued until ablation of the standard set of lesions was complete. 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 (Cool Flex 7F, St Jude Medical, St Paul, MN).

No additional linear ablation was performed in this group of patients with paroxysmal AF. Similar settings and techniques were employed in control group with standard circumferential PVI without voltage mapping. Acute reconnection was assessed in both groups at the end of the procedure and was defined if any gap (PV signals) were found after adenosine administration.

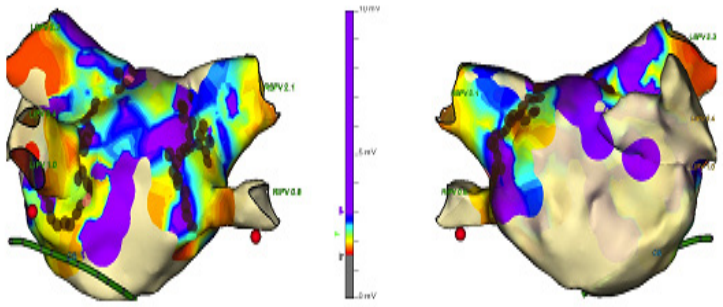

Figure 1: This depicts voltage map in left atrium and corresponding antral RF ablation (brown dots). Both of posterior and anterior views of LA are demonstrated. The voltage map was set at 0.5 – 1.5 mV. The middle column illustrates the voltages ranges between 0 mV and 10 mV, coloured region represents areas ≥ 1.5 mV.

Follow-up

Oral anticoagulation was reinitiated 8 hours post-procedure if no bleeding complications (i.e. pericardial tamponed or access site significant haematomas) were noted. All patients were kept on either a class I or class III antiarrhythmic drug with/out a beta-blocker or calcium channel blocker and an oral anticoagulant (warfarin or DOAC) for at least 3 months post procedure.

First follow-up occurred at 12 weeks post PVI and subsequent visits at 6 month and 12 months. All patient had a 24-hour holter and 12 lead ECG at follow-up. Secondary end point is recognised as AF recurrence more than 30 seconds or atrial arrhythmia documented in ECG or holter monitor. We opted to exclude 6 patients From Voltage guided ablation arm (out of 20 patients) that were in AF on the day of the procedure.

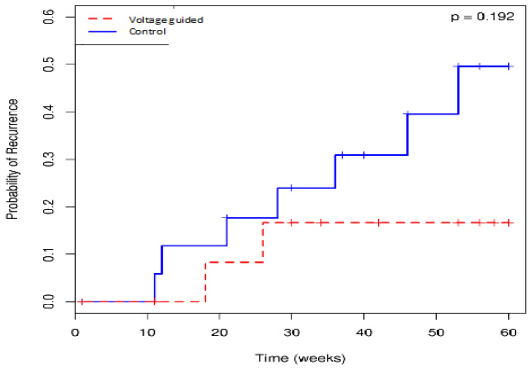

Figure 2: Free Kaplan – Meyer cumulative rate occurrence of AF recurrence over the follow up period in weeks. Lower rate is observed in voltage guided CPVA group.

Statistical analysis

Statistical analysis was performed with R version 3.2.1 (R foundation, Vienna University of Economics and Business, Austria). Data were expressed as mean ± standard deviation (SD) for continuous variables, and frequencies and percentages for categorical variables. T-tests (continuous variables) and chi-square tests (categorical variables) were used for statistical analysis. The logistic model for anatomical location of point-to-point analysis was used. Kaplan – Meyer cumulative rate occurrence of AF recurrence over the follow up period was calculated. The statistical significance results were considered if $p < 0.05$.

Results

Characteristics of patients

Baseline characteristics of patients and control group are depicted in Table 1. No differences in demographics or echocardiographic parameters were identified. Radiofrequency time, fluoroscopy time and total procedure time were not statistically different in both groups (Table 1).

Relationship of high voltage areas and critical points

Voltage point's distribution and their frequency around each antrum are illustrated in table 2. The 50th quartile points correspond with voltages at 0.86 mV. The number and percentages of the points (to total points) at 10th, 25th, 50th, 75th and 90th percentiles are also documented. Total critical points identified were 526 points where, 369 (70.2 %) critical points were identified at 75th quartile or higher. On the other hand, no critical points were recognised in low voltages areas below the 25th quartile. (Table 2)

These points were confirmed at the boundaries of the HV regions when the logistic model was applied (P = 0.06 at 1.5 mV).

Follow-up and AF recurrence

The mean follow-up data was 46.4 ± 13.7 weeks. One patient in the voltage-guided group and 2 in the control group were lost to follow-up.

Cumulative recurrence rate using Kaplan-Meier curve showed that voltage guided ablation had a trend of lower recurrence than patients in the standard ablation group; 3/13 (23 %) vs. 7/18 (39 %), respectively ([Figure 2]).

Anatomical frequency of critical points

The antrum of each PV was divided in 4 anatomical regions in a clockwise fashion: superior, inferior, anterior and posterior.

As shown in ([Figure 2]), the superior and inferior segments were more likely to harbour critically high voltage points.

Discussion

Major Findings

This prospective study presented a new approach to identify critical areas of PV and antral connections in order to achieve superior results for PV isolation. Antral high voltage guided ablation, in clockwise fashion, corresponded with critical points and revealed lower trends for AF recurrence compared to standard CPVA procedure over a follow up period of one year.

Table 2: This demonstrates the number of voltages points and their percentages at 10th, 25th, 50th, 75th and 90th quartiles. The critical points and their percentages (in comparison to the total critical points)

	Total points	Voltages at 10th Quartile (≤ 10th)	Voltages at 25th Quartile (10th to 25th)	Voltages at 50th quartile (25th to 75th)	Voltages at 75th Quartile (75th to 90th)	Voltages at 90th Quartile (≥ 90th)
Voltages values (mV)	NA	0.12	0.29	0.86	2.2	3.98
Voltage Points (N)	1479	145	361	458	369	146
Percentages of voltage points (%)	100	9.8	24.4	30.9	24.9	9.9
Number of Critical points ≥ (n, %)	526	0	0	157, (29.8%)	223, (42.4%)	146, (27.8 %)

Rationale of the technique

In our cohort, we targeted antrum ablation, which previously proved superior outcome to ostial and intra-vein ablation, and carries a better long-term prognosis. [11] However, anatomically, the earliest activation seen on the spiral catheter during atrial pacing or sinus rhythm may not necessarily correspond with the optimal ablation site in the antrum, given that the muscle sleeves entering into each vein, may follow an often unpredictable course.[12] Significant voltage variation is also recorded at various extent proximal to the PV ostium at the level of the antral region.[13] A thickened PV-LA junction wall is a predictor of late recurrence and dormant conduction and hence these regions may represent critical areas for LA/PV conduction [14] Therefore, antral ablation to achieve PV isolation is challenging. Thus far ablation is essentially done empirically in a continuous anatomic fashion to encircle each pair of PV.

Though, over the last few decades, various approaches were implemented to improve PVI outcome. Of these defragmentation of complex fractionated atrial electrograms (CAFÉ), mainly in persistent

AF, was proposed by Nademanee et al. [15] [16] However, the success of that approach comes at the price of possible iatrogenic macro-reentrant flutter [17] [18] as well as the risk of thermal esophageal injury. [19] Nevertheless, antral isolation is evidently effective to treat patients with paroxysmal AF when compared with CAFÉ defragmentation. [20] Interestingly, complex fractionations in normal atrial voltages may only represent the response of healthy atrial tissue to rapid pulmonary veins activation rather than a substrate to AF.[21]

Recovery of conduction in previously ablated muscle fascicles in the antrum is a common finding in patients with recurrent AF. [22] Circumferential ablation primarily achieves PV-left atrial block but also serves to reduce atrial ectopy decreasing the risk of AF recurrence.[23]

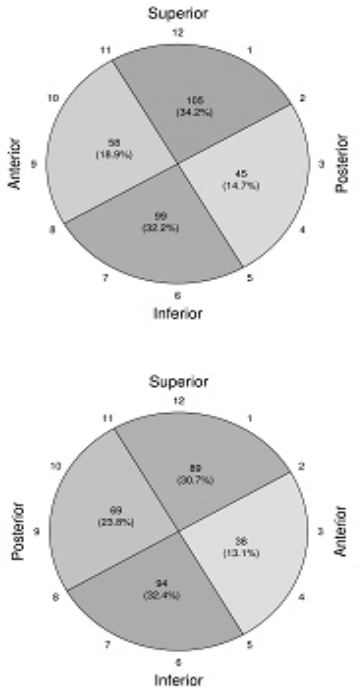

Figure 3: this diagram depicts the frequency (%) of the critical points (sites of the isolation and delay of pulmonary vein potentials) around antral regions: A) left pulmonary vein antrum, B) right pulmonary vein antrum

In our study, we proved most of the critical points (70.2 %) were located in the 75th quartile of voltage value or higher. In another word, most of the critical points were identified in higher voltage antral region and strikingly no critical points seen in voltages lower than the 25th quartile.

In our approach, by identifying sites of critical connection in high voltages areas in each antrum, the operator can focus ablation in terms of adequate power delivery, impedance changes as well as diminishing signal amplitude during the ablation. This will also avoid superfluous antral lesions that may raise significant edema preventing effective RF delivery to critical regions.

Follow up results

Our technique showed a trend to a reduction in the procedure time and radiofrequency time. This can be explained by the strategy of eventually completing a circumferential ablation set os lesions in each antrum, in the voltage guided group even after the PV isolation. This was to ensure that the staggered ablation lesions sets do not become the pro arrhythmic substrate for macro-re entrant tachycardia in this pilot group.

Although we eventually accomplished a complete CPVA lesion set in each antrum, the identification and prioritized ablation of HV critical regions made it possible to deliver effective transmural lesions at these sites before any reactionary oedema due to RF was invoked. This formed the basis of our strategy.

Anatomically, wide areas of interspersed connective tissue between the myocardial muscle fibers characterize myocardial sleeves extending into the PVs; this heterogeneous composition of the PV-LA junction is also reflected in their varied refractory periods. Then presents a milieu for micro-re entry as wave fronts of activation from triggers within the PVs encounter the PV-LA interface.[4] An ablation line at this critical junction has the potential to eradicate this critical substrate for re-entry and hence reduce recurrence of AF. [7]

Collectively, this mechanistically explains the lower trends for AF recurrence - over almost a year follow up - in the voltage guided PVI group as opposed to unguided anatomical CPVA as was performed in our control cohort.

Study limitations

Some limitations can be noted in our study. First, the sample size was very small, however this pilot study was performed to investigate whether the results are promising. Therefore we think that it is reasonable to perform a larger randomized controlled study to obtain more precise and proper answers. Second, the study was not randomized and the comparison group consisted of a higher number of patients undergoing a standard approach of RF ablation. We elected to exclude those patients who presented in AF "in voltage-guided group" to ensure a constant study protocol. Both groups, however, were matched in terms of clinical characteristics and the primary operators were the same. Second, contact force technology was not used; however this applies to both groups.

Conclusion

A voltage guided CPVA strategy was useful in identifying critical points for PV isolation. Voltage-guided procedures showed lower trends in AF recurrence than anatomical CPVA in this pilot cohort. Further prospective evaluation will enhance our observation in this pilot study.

Conflict Of Interests

None.

Disclosures

None.

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Bonus vs No Bonus Cryoballoon Isolation for Paroxysmal Atrial Fibrillation Ablation

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Abstract

Aim

To evaluate the benefit of Bonus freeze using second generation cryoballoon after pulmonary vein isolation (PVI) for paroxysmal atrial fibrillation (PAF)

Methods

A bonus freeze is performed after proven pulmonary vein isolation (PVI) for cryoballoon ablation of paroxysmal atrial fibrillation (PAF) as standard. In the current study, no additional freeze (No Bonus) after PVI was compared with additional freeze (Bonus) after PVI using second generation cryoballoon.

Results

A total of 136 patients (mean age 58 ± 13 years, 76 male) were included. No Bonus and Bonus groups had 56 and 80 patients, respectively. Follow-up electrocardiography and Holter monitoring were performed at 1, 3, 6, 12 months, and biannually thereafter. The PVI rate was similar after the initial ablation (82% in No Bonus group, 80% in Bonus group, p>0.05) and, at the end of the procedure (99% in No Bonus group and 99% in Bonus group, p>0.05). The median procedure and fluoroscopy times in No Bonus group were 67 (60-74) minutes and 13 (10-15) minutes, which were significantly shorter than the median durations, 85 (76-90) minutes and 17 (15-21) minutes in Bonus group, respectively (all p<0.001). Phrenic nerve palsy was observed less frequently in No Bonus group compared to Bonus group (1 patient (2%) vs. 5 patients (6%), respectively) without statistically significant difference. During a median follow-up of 13 (11-15) months, the rates of patients free from AF were 82% in No Bonus group and 84% in Bonus group, respectively (p>0.05).

Conclusions

The rate of sinus rhythm at 18 months was similar in patients with PAF who received bonus cryoablation vs patients who did not receive bonus cryoablation.

Introduction

Cryoablation is an effective and reliable therapy in achieving pulmonary vein isolation (PVI) in the treatment of paroxysmal atrial fibrillation (PAF).[1]-[4] Conventionally, 240 seconds freeze duration and then a bonus freeze is applied for successful electrical isolation of the pulmonary veins (PVs). The novel second-generation cryoballoon (CB-Adv) (CB, Arctic Front Advance, Medtronic, Inc., Minneapolis, USA) facilitates PVI by technical improvements compared to its predecessor.[5], [6] Therefore, a strategy that limits the number of freezing cycles might still achieve durable PVI with CB-Adv. There is limited data on the early and late outcomes of cryoablation without bonus freeze applications. The current study sought to assess the acute procedural success, early and 18 months clinical outcomes after PVI, as well as procedural parameters using the novel CB-Adv in patients undergoing a single 240 seconds application per vein compared to the standard bonus freeze application.

Key Words

Atrial Fibrillation,Bonus,Cryoablation,Recurrence

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Methods

Study design

This study was a non-randomized single center trial. All data including clinical, laboratory and procedural were retrospectively examined and prospectively analyzed. The study protocol was approved by the institutional review board. All participants enrolled provided written informed consent.

Study population

The study population consisted of 136 consecutive patients with drug-resistant symptomatic PAF who underwent PVI using the CB-Adv. All inclusion and exclusion criteria for eligible patients were detailed in Supplement 1. Informed consent to the ablation procedure was also obtained from all patients. A transesophageal echocardiogram was performed to exclude the presence of thrombi in the LA and LA appendage before the procedure. Patients were assigned to No Bonus and Bonus groups if they underwent PVI with no additional cryoballoon ablation or additional ablation after PVI, respectively. After ablation, patients entered a standard 3-month blanking period in which recurrent atrial tachyarrhythmia were recorded and also

included in the analyses after the 3-month blanking period.

Ablation procedure

Continuation of oral anticoagulants was permitted until the day of procedure. The procedure was performed under conscious sedation using midazolam, fentanyl and propofol. Femoral venous and arterial accesses were gained from the right and left femoral veins and left femoral artery. A 6F quadripolar or decapolar catheter was introduced via the left femoral vein and positioned in the coronary sinus (CS) for atrial pacing and intracardiac rhythm monitorization. During right-sided PVI, this diagnostic catheter was positioned within the superior vena cava (VCS) for phrenic nerve stimulation. Transseptal access to the left atrium was gained with brockenbrough transseptal needle and 8F transseptal sheath under fluoroscopic guidance. This was exchanged over a guidewire for a 15F steerable sheath (Flex Cath, Medtronic, Inc., Minneapolis, USA). A full dose heparin was administered just before or after transseptal puncture according to operator preference and, additional boluses were given to maintain an activated clotting time between 300-350 seconds during the procedure. Also transseptal sheath was continuously flushed with heparinized saline. Selective PV angiographies were performed via multipurpose catheter using standard views. Real-time PV recordings were obtained with a circular mapping catheter (Achieve, Medtronic, Inc., Minneapolis, USA) during cryoablation. A 28 mm CB advanced to the PV ostium and occlusion assessed by distal contrast media injection through the central lumen of the inflated CB. If optimal vein occlusion was achieved, single cryotherapy was applied for 240 seconds with confirmation of entrance and exit block for each vein 20 minutes after the last application. For the first group, all procedures were performed with a single 240 seconds application for each vein. If PVI was not achieved with a single freeze cycle, an additional freeze application was delivered until electrical isolation was demonstrated. If electrical isolation could be verified after the first freeze, no additional bonus freeze was applied. In the second group, after successful PVI, an additional freeze cycle was applied. In the presence of a common ostium, the ablation was applied as separate branches. Various maneuvers including pull down, hockey stick, C or reverse C were used to improve the occlusion and temperature drop. No additional ablation lesion except cavo-tricuspid isthmus linear ablation for typical atrial flutter during the procedure was permitted. During ablation of the right-sided PVs, pacing catheter in the CS was advanced in the VCS for continuous phrenic nerve pacing at 1500 ms cycle length and 20 mA output in order to avoid phrenic nerve palsy (PNP). Freezing was immediately discontinued if weakening or loss of diaphragmatic movement was noted during tactile sense. Transthoracic echocardiography was performed after the procedure to exclude pericardial effusion. Oral anticoagulation with warfarin or novel oral anticoagulants were started in the same evening of ablation and continued for at least 3 months or longer according to the CHA_2DS_2-VASc score. Antiarrhythmic drugs at the discretion of the investigator were allowed during the 3-month blanking period but were discontinued at the end of the blanking period. In the case of recurrence, antiarrhythmic treatment was reordered and a redo procedure was suggested if symptoms persisted.

Table 1: Baseline demographic, clinical and laboratory characteristics

	No Bonus Group (n=56)	Bonus Group (n=80)	P value
Age (years)	58 (48-67)	62 (49-68)	0.299
Male, n (%)	32 (57)	44 (55)	0.862
Male, n (%)	32 (57)	44 (55)	0.862
Hypertension, n (%)	25 (45)	35 (44)	1.000
Diabetes mellitus, n (%)	7 (13)	8 (10)	0.782
Hyperlipidemia, n (%)	14 (25)	19 (24)	1.000
Smoking, n (%)	21 (27)	20 (21)	0.539
Coronary artery disease, n (%)	7 (13)	9 (11)	1.000
CHA_2DS_2-VASc score	1.1 ± 1.3 / 1.0 (0-2.0)	1.1 ± 1.2 / 1.0 (0-2.0)	1.000
AF duration (months)	36 (24-48)	42 (24-60)	0.167
Hemoglobin (gr/dl)	14 (12-15)	14 (13-16)	0.090
Creatinine (mg/dl)	0.9 (0.7-1.0)	0.9 (0.7-1.0)	0.837
Left ventricular EF (%)	57 (54-66)	56 (54-66)	0.599
Left atrial diameter (mm)	38 (36-42)	39 (36-42)	0.312
Antiarrhythmic drug			
Propafenone, n (%)	44 (79)	65 (81)	0.828
Amiodarone, n (%)	9 (16)	12 (15)	1.000
Sotalol, n (%)	3 (5)	3 (4)	0.690

AF, atrial fibrillation; EF, ejection fraction
For continuous variables, the data were presented as median (25th and 75th interquartile ranges).
CHA2DS2-VASc score was also presented as mean ± SD.

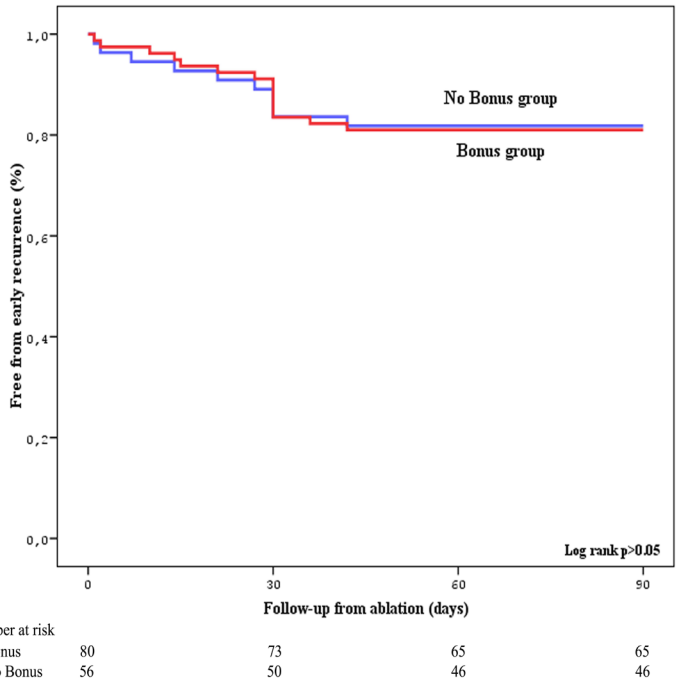

Figure 1: Kaplan-Meier curves of the freedom from any ATs recurrence in the blanking period.

Follow-up

All patients underwent continuous ECG monitoring during hospital stay. After discharge from the hospital, all patients were scheduled for follow-up visits at 1, 3, 6, 12 months, and biannually thereafter. Baseline ECG and 24-hour Holter recordings were obtained at each follow-up visit, and also during symptom driven admission. All documented atrial tachyarrhythmia (ATs) episodes of >30 seconds beyond the blanking period by ECG or Holter monitoring were considered as a recurrence. All recordings were blindly analyzed

and reviewed by experienced electrophysiologists. Time to first recurrence of symptomatic or asymptomatic AF, atrial flutter, or atrial tachycardia lasting >30 seconds documented by ECG or Holter monitoring was the primary efficacy outcome. Serious adverse events related to the procedure were also recorded.

Statistical analysis

The primary objective of this study was to demonstrate the efficacy of no bonus application during cryoballoon PVI compared to bonus application. Continuous variables were compared using the T test or Mann-Whitney test for independent samples and categorical variables were compared using the X2 or Fisher's tests as appropriate. Continuous variables were expressed as mean ± SD and median values with interquartile ranges. Data were presented as frequencies and percentages for categorical variables. Cox regression analysis was performed and presented as hazard ratios (HRs) with 95% confidence intervals. Event rates were plotted over time using Kaplan-Meier method. In addition to primary analysis, patients who suffered from a recurrence within the 3-month blanking period were recorded as having had the primary event at the beginning of the follow-up period. All analyses were performed using SPSS 17.0. A P value of ≤0.05 was considered significant.

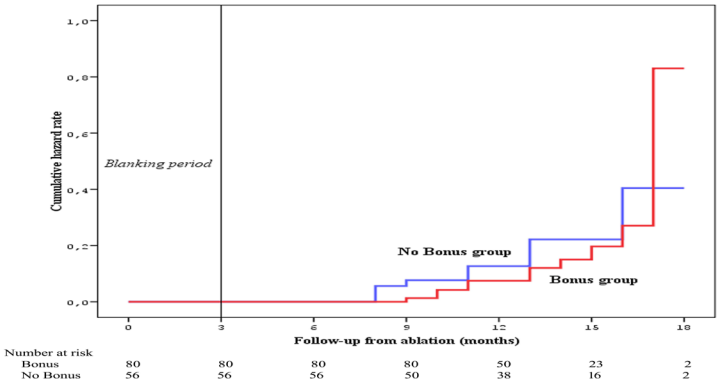

Figure 2: Kaplan-Meier curves of time to first recurrence of any ATs after the blinking period.

Results

Baseline characteristics

In total, 136 consecutive patients (mean age 58 ± 13 years, 76 male [56%]) were included in the study. No Bonus group consisted of 56 patients who did not have additional cryoablation whereas Bonus group was comprised of 80 patients who did have additional ablation. [Table 1] gives baseline demographic and clinical characteristics of the study population. No differences were found in regard to demographic, laboratory and echocardiographic findings.

Procedural characteristics

In 136 patients, a total of 529 PVs including 17 left common PVs, 1 right common PV and 3 right accessory PVs were detected. In total, 523 of 529 (99%) PVs were successfully isolated. After initial freeze application, PVI was observed in 104 of 119 (87%) left superior PVs, 100 of 119 (84%) left inferior PVs, 115 of 135 (85%) right superior PVs, 97 of 135 (72%) right inferior PVs, 8 of 17 (47%) left common PVs, 3 of 3 (100%) right accessory PVs, with no isolation of 1 right common PV.

In No Bonus group, 290 cryoablations were performed on 217 PVs (1.34 ablation per PV). The PVI rate after the initial ablation was 82%. In Bonus group, 722 cryoablations were performed on 312 PVs (2.31 ablation per PV). After the first application, PVI was achieved in 80% of PVs. No differences could be observed regarding first application isolation rate (p>0.05). Study population in the current study underwent cryoballoon isolation performed by senior operators and also arrhythmia fellows. Therefore, the PVI rate after the first application was rather low. The procedure and fluoroscopy times in No Bonus group were significantly shorter compared to procedure and fluoroscopy times in Bonus group. Cavo-tricuspid isthmus ablation was performed in 7% of the population ([Table 2]).

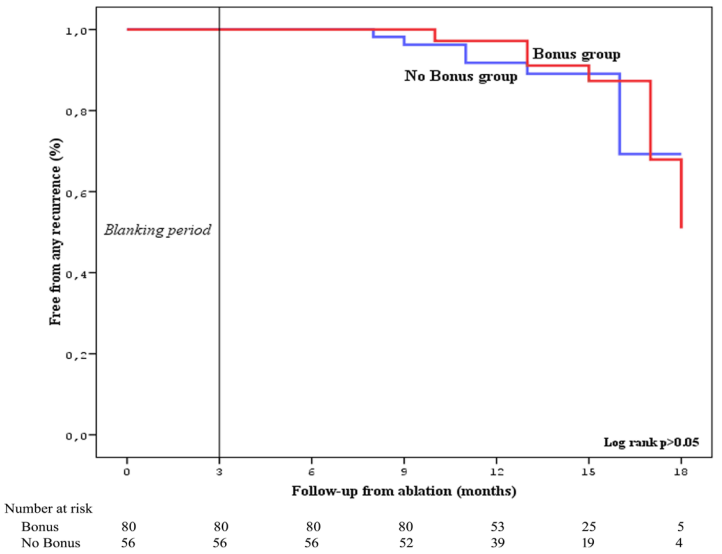

Figure 3: Kaplan-Meier curves of the freedom from any ATs recurrence after a redo procedure.

Complications

The most frequent complication observed was PNP during PVI. The occurrence of PNP was observed less frequently in No Bonus group compared to Bonus group, without statistically significant difference. All PNPs were resolved during follow-up. Four patients, all in Bonus group, showed resolution before discharge. One patient in Bonus group and 1 patient in No Bonus group showed PNP recovery at 1 and 6 months after ablation respectively. One patient developed femoral pseudoaneurysm without surgical intervention and one patient had pericardial tamponade requiring pericardiocentesis in Bonus group during the catheter manipulation. No other procedure-related complications were noted ([Table 2]).

Efficacy outcomes

The median time to the first early recurrence was 27 (12-30) days. There was no significant difference between Bonus and No Bonus groups, 30 (14-30) days vs 24 (6-30) days, p>0.05, respectively. The freedom from early recurrence was 82% in No Bonus group compared to 81% in Bonus group ([Figure 1]).

The mean follow-up duration after the 3-month blanking period in No Bonus group was 12 ± 3 months and 13 ± 3 months in Bonus group (p>0.05). During follow-up, recurrence of any ATs occurred in 10 patients (18%) in No Bonus group compared with 13 patients (16%) in Bonus group (HR, 0.72; 95%CI, 0.31-1.67; p = 0.440; [Figure 2]).

With including recurrences in the blanking period, recurrence of any ATs occurred in 15 patients (27%) in No Bonus group compared with 25 patients (31%) in Bonus group (HR, 0.96; 95%CI, 0.50-1.84; p = 0.898).

Table 2: Procedural parameters and adverse events

	No Bonus Group (n=56)	Bonus Group (n=80)	P value
Anatomic characteristics			
Voltage Points (N)	1479	145	146
Percentages of voltage points (%)	100	9.8	9.9
Number of Critical points ≥ (n, %)	526	0	146, (27.8 %)
PV number per patient*	4 (3-5) / 4 (4-4)	4 (3-5) / 4 (4-4)	0.709
Anomalous PV, n (%)	9 (16)	12 (15)	1.000
Total number of PVs	217	312	
Procedural characteristics			
Total number of cryoballoon	290	722	
The number of cryoballoon per PV	1.3 (1-1.5)	2 (2-2.5)	<0.001
Acute procedural success, n (%)	215/217 (99)	308/312 (99)	1.000
Nadir temperature (°C)			
LSPV	48 (46-51)	49 (45-52)	0.573
LIPV	46 (44-49)	46 (44-49)	0.301
RSPV	48 (46-50)	47 (45-49)	0.224
RIPV	44 (43-47)	45 (43-48)	0.105
LCPV	50 (49-52)	48 (47-52)	0.225
RCPV¶	47	-	-
RAPV¶	46	46 and 44	-
Time to isolation (seconds)			
LSPV	38 (32-49)	38 (32-52)	0.931
LIPV	40 (33-51)	40 (33-53)	0.903
RSPV	37 (30-48)	36 (29-49)	0.914
RIPV	41 (34-56)	41 (34-54)	0.964
LCPV	64 (50-73)	44 (38-54)	0.107
RCPV	No recording	-	-
RAPV☐	28	No recordings	-
Real-time PVI, n (%)			
LSPV	35 (71)	49 (70)	0.866
LIPV	34 (69)	48 (69)	0.925
RSPV	38 (69)	56 (70)	0.910
RIPV	36 (66)	54 (68)	0.804
LCPV	4 (57)	7 (70)	0.644
RCPV	No recording	-	-
RAPV	1(2)	No recordings	-
Procedure duration (minutes)	67 (60-74)	85 (76-90)	<0.001
Fluoroscopy duration (minutes)	13 (10-15)	17 (15-21)	<0.001
CTI ablation, n (%)	5 (9)	5 (6)	0.740
Complications			
Phrenic nerve palsy, n (%)	1 (2)	5 (6)	0.400
Pericardial effusion requiring			
pericardiocentesis, n (%)	0	1 (1)	1.000
Access site complication, n (%)	0	1 (1)	1.000
Death, n	0	0	-
Systemic embolism, n	0	0	-

CTI, cavo-tricuspid isthmus; LCPV, left common PV; LIPV, left inferior PV; LSPV, left superior PV; PV, pulmonary vein; RAPV, right accessory PV; RCPV, right common PV; RIPV, right inferior PV; RSPV, right superior PV
For continuous variables, the data were presented as median (25th and 75th interquartile ranges).
*First numbers are single mean value with lower and upper values.
¶Exact temperatures for each patient.

Exact time to isolation.

A redo procedure was performed in 5 patients in No Bonus group, and 6 patients in Bonus group. A cavo-tricuspid isthmus dependent atrial flutter was present in one patient in No Bonus group. Radiofrequency ablation of the isthmus with demonstration of bidirectional block was performed. All remaining redo procedures were also cryoballoon isolation using the CB-Adv with previously described no bonus technique. The median reconnected vein number was 1 (1-2) in No Bonus group compared to 1 (1-1) in Bonus group (p>0.05). In No Bonus group, 3 of 6 (50%) reconnected PVs were right inferior PV, 1 was right superior PV, 1 was left inferior PV, and 1 was left common PV. In Bonus group, 4 of 7 (57%) reconnected PVs were right inferior PV, 1 was right superior PV, 1 was left superior PV, and 1 was left common PV. The mean time to redo procedure was 8 ± 3 months with no difference between the two groups (p>0.05). After the second procedure, the mean follow-up time was 4 ± 1 months with no difference between the two groups (p>0.05). After the redo procedure, 88% of patients in No Bonus group and 89% of patients in Bonus group were free from any recurrent ATs ([Figure 3]).

Discussion

The main findings of our study were as follows:
(1) The rate of sinus rhythm during 18-month follow-up period in patients who received no additional cryoablation was high and similar to patients who received a bonus freeze after proven isolation.
(2) The most common complication was PNP and, it occurred more frequently with routine use of a bonus freeze application.
(3) Mean fluoroscopy and procedural times were significantly lower with no bonus freeze application.

Previous single-center studies applying different numbers of freezing cycles on the use of the second generation CB demonstrated different results.[7]-[9] In earlier studies on applying one or two additional freeze applications following proven PVI, PNP was observed more frequently during the second bonus freeze.[10], [11] Accordingly, the reduction of the freeze cycle times may contribute to the avoidance of potential serious complications.

The novel second-generation CB redesigned to improve procedural outcomes significantly. The number of injection ports has been doubled, from 4 to 8 and these have been positioned more distally. These changes result in a large cooling area lying between the equator and the tip with a consequent more homogeneous zone of freezing on the balloon surface compared to the previous version.[8], [9], [11], [12] In a conventional ablation procedure using a second generation CB, repeat freeze cycle is deployed on the PV once successful isolation has been demonstrated. However, in the current study, the rate of sinus rhythm at 18 months was similar in patients who received additional cryoablation vs those who did not. Considering the findings from the present study, the routine use of an insurance freeze application may not be essential.

Our results are consistent with a recent study by Wisner at al.[13] The authors have concluded that with implementing a 'no bonus' freeze protocol, 82% of patients treated with the second generation CB remained free from ATs during a follow-up period of 1 year, similar to our results. The mean procedure duration was 113 minutes and the average fluoroscopy time was 19 minutes. It was, however, a study

conducted without a comparison group. Therefore, they underlined that the procedure duration and fluoroscopy time were lower than previously reported from their laboratory utilizing a single-bonus freeze cycle per PV by 16 minutes and 5 minutes, respectively while procedural success rates were similar in both groups. In Wisner's observation, PNP developed 2% of patients during the second freeze-cycle, which was lower than earlier studies.[9], [11], [13] In the current study, PNP was observed less frequently with no bonus freeze protocol. However, there was no statistically significant difference. Presumably, the sample size was relatively small and larger studies may demonstrate a statistical significance.

The rationale to utilize no additional freeze cycle after proven PVI is based on recent observations reporting a single application success rate ranging from 84% to 90%.[14], [15] Similarly in our study, we demonstrated an overall 81% isolation rate during the initial 240 seconds freeze cycle.

Recently, Ciconte at al. have demonstrated encouraging 1-year follow-up results applying single 3-minute freeze cycle. In their observation, a single 3-minute strategy showed equal efficacy compared to the conventional 4-minute plus bonus freeze approach at 1-year follow-up, providing shorter procedure and fluoroscopy times.[16] Our results extending beyond 1 year have also demonstrated that PVI without bonus freeze was highly effective with and without redo procedure as 88% and 82% in sinus rhythm, respectively.

Study limitations

This study also has limitations. First, this was a single center retrospective trial enrolling a relatively limited number of patients. Follow-up was limited to ECG and 24-hour Holter recordings without using extended methods such as longer Holter recordings, external loop recorders and implantable devices, might have resulted in underestimation of asymptomatic cases and potentially affecting the primary outcome. In addition, we had no data regarding PV stenosis and esophageal temperature during the procedure. Future multicenter and randomized studies with long-term follow-up are necessary to confirm our findings.

Conclusion

A single 240 seconds application per vein using the second generation CB strategy seems to show equal efficacy compared to the conventional 240 seconds plus bonus freeze approach in 18-month follow-up. Furthermore, this shortened CB ablation protocol significantly reduced procedure time with lower fluoroscopy exposure. Whilst the optimal ablation duration has to be defined, it becomes more evident that further cryoenergy applications if isolation is already proven during the first freeze, may not be necessary. Further randomized studies are needed to confirm these promising results.

Conflict Of Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Disclosures

None.

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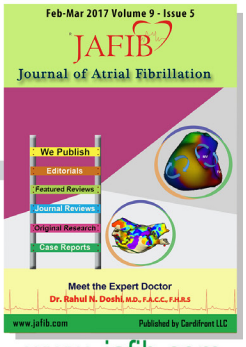

Reconnection Rate and Long-Term Outcome with Adenosine Provocation During Cryoballoon Ablation for Pulmonary Vein Isolation

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Abstract

Background

Adenosine can unmask dormant conduction during pulmonary vein isolation (PVI) for atrial fibrillation (AF). Studies of adenosine use in radiofrequency PVI show high reconnection rates and conflicting results for long-term success, however there is limited data with cryoballoon ablation (CBA).

Methods

A prospectively maintained database of patients undergoing first CBA at a single institution was analyzed. Adenosine use was at the discretion of the primary operator. Additional freezes were delivered for reconnected veins until dormant conduction was eliminated. The primary endpoint, time to AF recurrence defined as any episode < 30 seconds after a 3-month blanking period, was assessed by Kaplan-Meier analysis.

Results

From 2011 to 2015, 406 patients underwent CBA, 361 of whom had > 3 months follow-up. The mean age was 61.7 years, 69% were male, and the prevalence of paroxysmal AF was 79% with no significant difference between those that did and did not receive adenosine (77% vs 86%, respectively, p = 0.23). Adenosine testing was performed in 78 patients (21.6%) with a mean dose of 10.6 mg/vein. Of the 306 veins evaluated, 17 (6%) demonstrated dormant conduction. Over a median 14.4 months follow-up, there was no significant difference in freedom from AF with adenosine use (p= 0.86).

Conclusions

Dormant conduction with adenosine is uncommon following CBA and its use does not improve long-term success rates.

Introduction

Pulmonary vein isolation (PVI) is the primary method of catheter ablation for atrial fibrillation (AF), however its long term efficacy is limited, in part, by electrical reconnection of the veins to the left atrium. Dormant conduction has been shown to be a predictor of late reconnection and recurrence of AF[1]. If discovered at the time of ablation, additional lesions can be delivered to the implicated vein to achieve complete isolation. Adenosine has previously been demonstrated to reveal dormant conduction by activating adenosine-sensitive potassium channels leading to hyperpolarization of the resting membrane potential [2]. Large trials of adenosine usage with radiofrequency ablation (RFA) have shown conflicting results with regards to long term benefit on recurrence of AF [3], [4]. Unlike radiofrequency ablation, cryoballoon ablation (CBA) provides a circumferential lesion which theoretically can result in a more complete isolation of the pulmonary veins, however overall effectiveness is similar between radiofrequency and CBA [5]. As reconnection rates in general are lower with CBA than RFA, the utility of adenosine in this setting is unclear [3], [4], [6], [7].

Key Words

Atrial fibrillation, Cryoballoon ablation, Adenosine, Pulmonary vein isolation abbreviations, Atrial fibrillation (Af), Pulmonary vein Isolation (Pvi), Cryoballoon ablation (Cba), Radiofrequency ablation (Rfa), Intracardiac echocardiography (Ice).

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Materials and methods

Data Source

A prospectively maintained database of patients undergoing first CBA at Northwestern Memorial Hospital was analyzed. Patients were included who underwent CBA between 2011 and 2015. Both patients with paroxysmal and persistent AF were included. This study was approved by the institutional review board at Northwestern University.

Ablation Procedure

A decapolar catheter was advanced through a left femoral venous

sheath and positioned in the coronary sinus. An intracardiac echocardiography (ICE) catheter (AcuNav, Biosense Webster, Diamond Bar, California) was then advanced through a left femoral sheath into the right atrium. Baseline ICE imaging was done to survey left atrial and pulmonary vein (PV) anatomy and evaluate for thrombus. Transseptal catheterization was performed from the right femoral vein using a transseptal sheath (SL1, St. Jude Medical, St. Paul, Minnesota or Preface, Biosense Webster) with fluoroscopy and ICE for guidance. Intravenous heparin was administered with goal activated clotting time < 270 seconds (i-STAT 1, Abbott Point of Care, Princeton, New Jersey). A comprehensive EP study was performed in patients with a history of suspected supraventricular tachycardia. In some cases, chamber reconstruction of the left atrium was performed using a mapping system (NavX, St. Jude Medical). The transseptal sheath was exchanged for a larger steerable, 15F outer diameter sheath (Flexcath, Medtronic, Minneapolis, Minnesota) to accommodate the cryoballoon (CB) (Arctic Front or Arctic Front Advance, Medtronic) and circular mapping catheter (Achieve, Medtronic). The circular mapping catheter was advanced through the CB catheter into the pulmonary veins. Ablation was performed with the CB catheter. The choice of 23mm vs. 28mm CB was based on pre-procedural computed tomography or magnetic resonance imaging. Prior to each ablation, a pulmonary venogram was performed to assess balloon occlusion of the PV ostium. In cases where pre-procedure imaging was not performed, pulmonary venography was utilized to guide selection of CB size. A minimum of two cryoablations were made per PV, with each ablation lasting 3-4 minutes. During isolation of the right-sided PVs, a catheter was positioned in the superior vena cava to perform high-output pacing to monitor for phrenic nerve injury. Monitoring of compound motor action potential amplitude was added to the protocol early in the CBA experience [8]. Acute PVI was defined as entrance block [9], [10]. If PVI could not be achieved with the CB, focal ablation was performed using a conventional cryocatheter (Cryocath, Medtronic) or radiofrequency catheter to achieve PVI. Following PVI, reconnection was assessed after a mandatory 30-minute waiting period. The decision to use adenosine during the procedure was at the discretion of the primary operator. Adenosine was administered 30 minutes after attempted PV isolation starting in increments of 6 mg and increasing until transient complete heart block was achieved. Additional freezes and/or RF lesions were delivered for reconnected vein until dormant conduction was eliminated.

Table 1: Baseline Characteristics

Variable	No Adenosine	Standard PVI group (n=20)	P value
Age (years)	61.3 ± 10.4	62.9 ± 8.4	0.20
Female, No. (%)	94 (33%)	18 (23%)	0.09
Diabetes, No. (%)	28 (10%)	7 (9%)	0.83
Hypertension, No. (%)	116 (41%)	37 (48%)	0.27
Structural Heart Disease, No. (%)	44 (16%)	6 (8%)	0.07
CHADS2 score, No. (%)			0.37
. 0	141 (50%)	37 (47%)	
. 1	98 (35%)	30 (38%)	
. 2	36 (13%)	7 (9%)	
. 3	7 (2%)	3 (4%)	
. 4	0 (0%)	1 (1%)	
. 5	1 (0%)	0 (0%)	
AF Duration (Years)	5.8 ± 5.9	4.8 ± 3.8	0.14
Antiarrhythmic Drug Use	1.0 ± 0.7	0.9 ±0.7	0.30
Left Ventricular Ejection Fraction	56.2 ± 10.7	59.2 ± 5.5	0.08
Left Atrial Diameter (cm)	3.8 ± 0.7	3.9 ± 0.6	0.60
Redo, No. (%)	56 (20%)	16 (21%)	0.90
Device, No. (%)	30 (11%)	7 (9%)	0.67
Baseline Rhythm, No. (%)			0.45
. AF	86 (30%)	22 (28%)	
. Atypical Atrial Flutter	2 (1%)	0 (0%)	
. Other	1 (0%)	1 (1%)	
. Sinus	187 (66%)	55 (71%)	
. Typical Atrial Flutter	7 (2%)	0 (0%)	

Post-Procedure Care and Follow-up

Oral anticoagulation was resumed within 6-24 hours of the procedure per the patient's prior regimen of warfarin or other oral anticoagulant. In the case of warfarin, unfractionated heparin was administered by intravenous infusion starting 6 hours following removal of sheath unless the procedure was performed with a therapeutic INR. This regimen was transitioned to subcutaneous low molecular weight heparin the following morning to continue until therapeutic international normalized ratio was achieved. The first 3 months following the procedure were considered a blanking period during which time arrhythmic events were not classified as treatment failures. All antiarrhythmic medications were stopped after the blanking period. Rhythm follow-up included, at minimum, a 3-week AF monitor at 3 months post-procedure, and 24 to 48-hour Holter monitors thereafter at 6-month intervals up to two years, or downloads from implanted devices when available. Additional

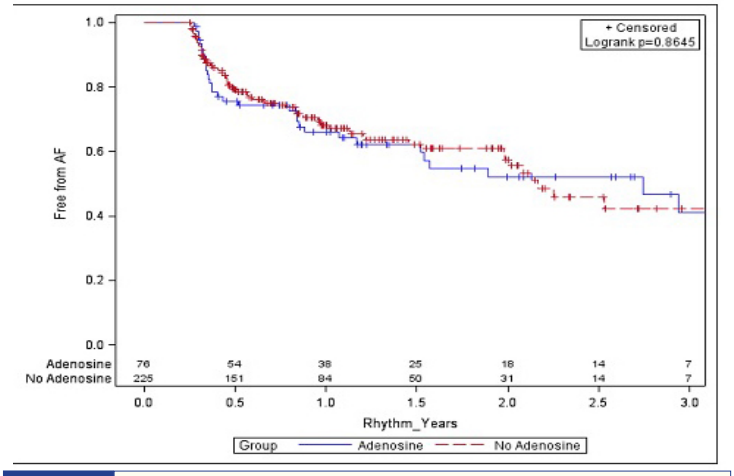


Figure 1: Distribution of reconnection of pulmonary veins with adenosine

Right Superior Pulmonary Vein (RSPV)
Left Superior Pulmonary Vein (LSPV)
Right Inferior Pulmonary Vein (RIPV)
Left Inferior Pulmonary Vein (LIPV)
Left Common Pulmonary Vein (LCPV)

monitoring was performed in response to patient symptoms. Surface ECGs were obtained at each clinic visit.

Statistical Analysis

The primary endpoint, time to AF recurrence without the need for antiarrhythmic drugs, was defined as any episode >30 seconds after a 3-month blanking period and was assessed by Kaplan-Meier analysis. These designations are consistent with the HRS/EHRA/ECAS definition of recurrent AF.[9] Continuous variables were summarized by mean and standard deviation. Categorical variables were summarized by frequencies and proportions.

Results

From 2011 to 2015, 406 patients underwent CBA, 361 of whom had greater than 3 months follow-up. The mean age was 61.7±10.0 years and 69% were male. There was no significant difference in duration of AF, prior use of anti-arrhythmic drugs, or CHADS2 score between those that did and did not receive adenosine ([Table 1]). In the adenosine group, 14% had persistent AF, compared with 23% in the no-adenosine group; the remainder were classified as paroxysmal AF except for one patient in the no-adenosine group with long-standing persistent AF. In the adenosine group, 31% of ablations were done with the first generation cryoballoon, compared with 13% of the no-adenosine group (p < 0.001). Fifteen percent of the ablations in the adenosine group were performed with the 23mm cryoballoon, compared with 10% of the no-adenosine group (p = 0.21).

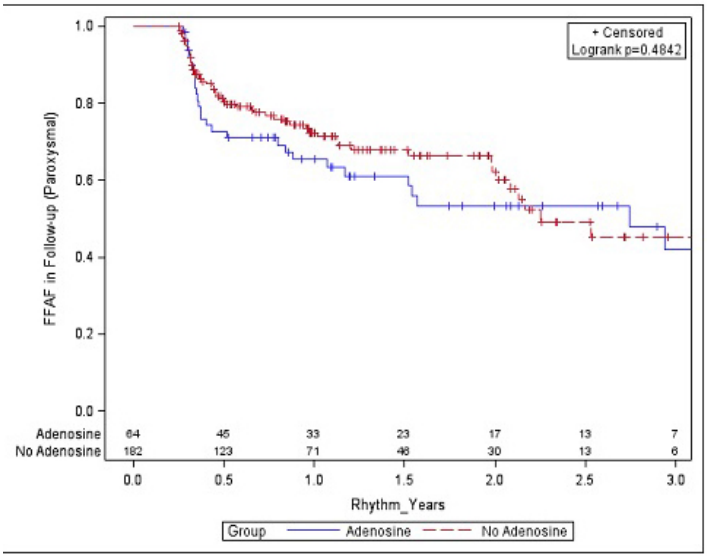


Figure 2: Freedom from AF by adenosine group; there was no significant difference in freedom from AF by adenosine group overall or by type of AF

Panel A: Overall
Panel B: Paroxysmal AF
Panel C: Persistent AF
Adenosine group – blue solid line
No – adenosine group – red dashed line

Adenosine testing was performed in 78 patients (21.6%) with a mean dose of 10.6 mg/vein. Of the 306 veins evaluated, 17 (6%) demonstrated dormant conduction with adenosine. Reconnection of pulmonary veins is summarized in [Figure 1]. The most commonly reconnected vein was the left inferior (6 occurrences), then right superior (4 occurrences), followed by left common (with 3). Left superior and right inferior were the least common veins to reconnect.

There was no significant difference between the mean dose of adenosine that resulted in dormant conduction (11.2 ± 3.1) and the mean dose that did not lead to reconnection (10.5 ± 3.7), p = 0.50. There were 8 veins (2.6%) that spontaneously reconnected during the 30-minute waiting period prior to the administration of adenosine. A common left pulmonary vein was present in 19% and 20% of the no-adenosine and adenosine groups, respectively. One patient had a third right pulmonary vein and received 2 CBA lesions to that vein. Over a median follow-up period of 14.4 months, there was no significant difference in freedom from AF between those that did and did not receive adenosine (p = 0.86) ([Figure 2]). Results were similar when stratified by paroxysmal and persistent AF ([Figure 3]). There was no significant difference in freedom from AF in 1st generation compared to 2nd generation cryoballoon (p = 0.91). Nine patients (2%) experienced complications, (7/283 in no-adenosine group and 2/78 in adenosine group, p = 0.96) with the most common complications being phrenic nerve injury (including transient injury) and bleeding events ([Table 2]). RFA was also used, primarily for additional lesion sets, in 8 patients (10%) in the adenosine group and 43 patients (15%) of the no-adenosine group (p = 0.65).

Discussion

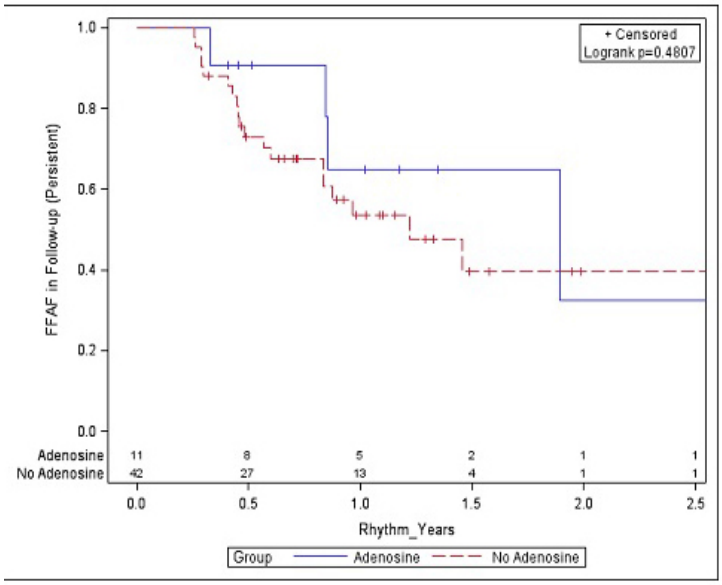
In this study of 361 patients who underwent CBA, adenosine usage during CBA for AF did not improve freedom from AF. Notably, of those patients who received adenosine, the rate of reconnection was quite low at 6% of veins that were tested. This is similar to the rate noted by Ciconte et al. who found that just 4% of veins demonstrated reconnection after CBA [6].

Table 2: Procedural Complications

	No adenosine (N = 283)	Adenosine (N = 78)	P-value
Procedural Complications, No. (%)	7 (2%)	2 (3%)	0.96
Bleeding, No. (%)	1 (0%)	1 (1%)	0.33
Perforation, No. (%)	0 (0%)	1 (1%)	0.06
Stroke, No. (%)	0 (0%)	0 (0%)	.
Pneumothorax, No. (%)	0 (0%)	0 (0%)	.
Phrenic nerve injury, No. (%)	3 (1%)	0 (0%)	0.36
Death, No. (%)	0 (0%)	0 (0%)	.
Other complication, No. (%)	4 (1%)	0 (0%)	0.29

Reconnection rates are higher in RFA with three large studies finding rates of 21% (ADVICE), 27% (UNDER-ATP) and 34% [3], [4], [7]. With far fewer veins reconnecting with adenosine during CBA, the lack of difference in recurrence of AF over time is not surprising. With improvement in rates of complete isolation of the pulmonary veins, the additional effect of adenosine is considerably lessened. As a result, we found that routine use of adenosine in CBA does not improve long-term outcomes in AF. Results from the randomized trials of adenosine with RFA have been mixed. Interestingly, Ghanbari et al. noted that although adenosine did reveal dormant conduction, this difference did not translate to improvement in long-term outcomes. It is speculated that adenosine identifies acute pulmonary vein reconnection but is not predictive of long term reconnection [7].

In contrast to our findings, a study by Kumar et al. involving 90 patients (45 of whom received adenosine) and a study by Van Belle et al. of 99 patients (34 receiving adenosine) did find an improvement



in clinical success rates for AF with CBA, despite similarly low rates of vein reconnection [11], [12]. A second study also by Kumar et al. investigated this question as well in 40 patients using CBA but did not find any difference in long-term success with 337 ± 92 days of follow-up [13]. The differing results obtained in the present study are likely due to the larger sample size. Additionally, the present study includes the longest follow-up to date of any CBA study with adenosine. Differences in effectiveness of adenosine in previously published studies may in part be due to variation in incorporation of a waiting period after ablation prior to giving adenosine or pursuing further ablation. Incorporation of a thirty minute waiting period after CBA has previously been shown to increase the incidence of dormant conduction in a study by Compier et al [14].

Although the decision to use adenosine was at the discretion of the primary operator, the majority of adenosine cases were performed by a single operator who routinely used adenosine in all cases. The dose of adenosine used was not significantly different for the veins that reconnected and those that did not; in each case, this dose was based on the minimum amount necessary to achieve AV block, a strategy supported by a study by Kapa et al [15].

Table 3: Additional lesion sets

Type of lesion set, No. (%)	No-adenosine (N=41)*	Adenosine (N=5)*
Cavotricuspid linear lesion	32 (78)	4 (80)
Ablation at fractionated electrogram sites in left atrium	6 (14)	1 (20)
Left atrial linear roof line	6 (14)	0
Left atrial linear mitral isthmus line	6 (14)	0
Other left atrial linear lesion	3 (7)	0
Isolation of superior vena cava	3 (7)	0
Ablation of autonomic ganglion plexus	1 (2)	0
Ablation at fractionated electrogram sites in right atrium	1 (2)	0

*Because some patient had multiple lesion sets performed, categories may add up to more than 100

The most common veins to demonstrate dormant conduction with adenosine were the LIPV and RSPV in our study. In comparison, UNDER-ATP reported that LSPV and RSPV were the most common to reconnect with RFA [3].

Limitations of this study include the lack of a randomized study design. Additionally, rhythm evaluation at follow-up was determined by routine ECGs and event monitors at 3-month intervals or if symptoms necessitated additional evaluations, however it is possible that asymptomatic recurrence of AF in between evaluations was not detected. The AchieveTM catheter was used to detect PV potentials in all cases; though this catheter may detect more farfield signals than the typical lasso used in RF, the sensitivity of the AchieveTM for detecting dormant potentials has not yet been determined [16].

Conclusion

Dormant conduction with adenosine is uncommon during CBA compared to RFA and use of adenosine does not improve freedom from AF.

Conflict Of Interest

None.

Disclosures

Kaplan – none; Dandamudi – none; Bohn – none; Verma – none; Tomson – none; Arora – none; Chicos – none; Goldberger – none; Kim – none; Knight – speaker's bureau, compensation for services, research grants from Medtronic; Lin – none; Passman – speaker's bureau, compensation for services, research grants from Medtronic

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Pacemaker implantation In Elderly Patients: Safety of Various Regimens of Anticoagulant Therapy

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Abstract

To study incidence of hemorrhagic complications after pacemaker implantation in elderly patients receiving antithrombotic therapy with warfarin or uninterrupted dabigatran.126 patients aged 83 [82-85] years who receive continuous antithrombotic therapy after pacemaker implantation, were enrolled in the study. Adverse event data were collected during hospitalization and further 12 weeks.95 subjects (75.4%) received warfarin therapy and 31 subjects (24.6%) received dabigatran. All patients in dabigatran group received 220 mg/day skipping the last dose before a surgery and resumed the drug intake in 36-48 hours after it. Patients of warfarin group underwent surgery if INR was NMT 3; they didn't stop taking the drug for the duration of operation.No statistically significant differences of hematoma incidence were detected in dabigatran (incidence is 0.065, 95%CI (-0.02–0.15)) and warfarin (incidence is 0.05, 95%CI (0.006–0.01)) groups, p(Fisher)= 0.55. Three cases of nonfatal gastrointestinal bleeding (warfarin group) and 1 similar event in dabigatran group were detected during a follow-up (12 [6; 20] weeks): RR= 0.98 (warfarin group), p(Fisher)=0.68. No statistically significant difference of age, sex composition, history of IHD and diabetes was detected between groups by comparison of individual characteristics of patients whose surgeries were complicated/non-complicated by hematoma formation. Upon that, hematoma formation rate was significantly higher in patients with adjunctive pacemaker muscular fixation: 71.4% vs 31.9% (patients without hematomas), p(Fisher)= 0.045.Incidence of hematoma formation after pacemaker implantation in patients > 75 years receiving warfarin or dabigatran, is the same as in general population of patients treated with anticoagulants. Adjunctive pacemaker muscular fixation is a significant risk factor of hematoma formation.

Introduction

Permanent pacemaker implantation is the most common procedure of cardiovascular surgery. In the setting of increase in life expectancy and implementation of ambitious medical care programs, there is a growth of both total number of pacemaker implantations (for example, according to Mond et al. [2], 590 procedures per 1 million of population are performed in Australia and results of other studies are the same – [3]) and number of procedures in elderly patients: 70-80% of pacemaker implantations in patients > 65 years [4] and to 32% in patients > 80 years in several populations . [5], [6], [7] In spite of reports about relative safety of such interventions in elderly patients [8], many specialists consider this group as one with increased risk of periprocedural complications in routine clinical practice. The latter is particularly true concerning patients receiving continuous antithrombotic therapy. This number increases during last few years because elderly age is not only a risk factor of atrial fibrillation but an independent predictor of thromboembolic events .[9]

Pacemaker pocket hematoma is one of the most common postsurgical complications whose incidence is 0.6-2.0% according to most of sources. [10], [11], [12], [13], [14] At the same time, according to the one of recent reports related to pacemaker implantation in New South Wales,[14] total incidence of complications is 11.9%. Lead dislodgement and postsurgical hematomas are the bulk of it. At that, there are only several available studies particularly evaluating clinical factors causing pacemaker pocket hematomas in elderly patients. [9], [15], [16]

Due to this fact, the objective of this study is to investigate incidence and possible predictors of pocket hematoma formation after pacemaker implantation in elderly patients receiving antithrombotic therapy with warfarin or uninterrupted dabigatran.

Materials and methods

Patients > 75 years receiving continuous antithrombotic therapy (CHA_2DS_2-VASc score >2) were enrolled in the prospective non-randomized study. They have undergone primary pacemaker implantation in Saratov Regional Cardiology Health Center since January, 2013 till February, 2015. Patients, who had undergone immediate pacemaker implantations, and ones with prior elective interventions were included in this study. Indications for pacemaker implantation: II and III grades of AV-block associated with symptoms, sick sinus syndrome (SSS), atrial fibrillation associated with bradycardia (average heart rate < 40 beats in minute according to 24-hour monitoring). Exclusion criteria: previously implanted device required reimplantation without lead replacement, cardioverter

Key Words

Pacemaker, Complications, Hematomas, Dabigatran, Warfarin.

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defibrillator causing major intervention, as well as high risk of bleeding (HAS-BLED score >3) resulting in contraindications for elective antithrombotic therapy of atrial fibrillation. Adverse event data were collected during hospitalization and further follow-up period (12 weeks).

All pacemakers were implanted by cardiac surgeons who carried out not less than 100 similar procedures in angiographic operating rooms last year. The type of pacemaker to be implanted was selected according to bradyarrhythmia type, patient's age, physical status and comorbidity. Local or general anesthesia was selected in virtue of operating surgeon's preference. All patients received preventive antibiotic therapy before a surgery and in 2 days after it. V. cephalica was commonly used for venous access. In case of technical difficulties, subclavian vein puncture was carried out. Correct positioning of implanted leads after implantation was confirmed by intracardial cardiograms (endograms), pacing threshold analysis and radiographs of thoracic organs. Cardiac pacing conditions were reported in dismissal and a follow-up was prescribed in 4-6 weeks after it. Besides, additive phone contacts were performed.

Table 1: Antithrombotic therapy type-based characteristics of patient subgroups

Characteristic	Warfarin group, n= 95	Dabigatran group, n= 31	p
Age (years)	83 [82; 85]	83 [81; 85]	0.063 (U)
Men	40	8	0.55 (c^2)
CHA_2DS_2-VASc	4 [3; 5]	4 [4; 4]	0.57 (U)
HAS-BLED	2 [2; 3]	2 [2; 3]	0.3 (U)
INR before implantation	2.7 [2.2; 3.2]	2.8 [2.0; 3.6]	0.8 (U)
Implantation duration (min)	77 [65; 85]	84 [70; 90]	0.057 (U)
Access via v. subclavia	76 (80%)	26 (84%)	0.6 (z)
Average number of leads per patient	1.2	1.1	0.8 (U)
Antiplatelet therapy	19	5	0.63 (c^2 Pearson)

Incidence of pocket hematoma formation within 6 weeks after pacemaker implantation was evaluated as a primary endpoint. Hematoma was diagnosed due to opinion of the surgeon (who had implanted a device) confirmed by ultrasonographic data. During further analysis hematomas were divided depending on need for drainage. Type of received anticoagulant and antithrombotic therapy, as well as their potential interaction with hematoma development were considered. According to international practice, [13], [14] other postsurgical complications were evaluated as secondary endpoints, such as: cardiac stimulant system infections, lead dislodgement, pneumothorax, myocardial rupture, life-threatening arrhythmias (resuscitation is required) and death.

Data are presented as frequency (categorical variables), medians and interquartile range (quantitative variables). Differences of proportions were analyzed using either chi-square test or Fisher exact test. Continuous quantitative variables were analyzed with Mann-Whitney test. Statistic analyse were carried out in Statistica 10 (StatSoft, Inc, 2011) application software package. In order to review statistical hypotheses, critical significance level was set to 0.05%. Diagram was formed using MedCalc 12.5.0.0 (MedCalc Software bvba, 2013).

Results

During the specified period pacemaker implantations were performed in 126 patients (48 men and 78 women) > 75 years receiving elective antithrombotic therapy due to permanent or persistent atrial fibrillation. Data of follow-up or phone contacts with patients (or their relatives) were received for all enrolled subjects. At the time of surgery average age of patients was 83 [82; 85] years; the maximum age in observed cohort was 93 years. The most common indication for pacemaker implantation was high grade AV-block (68 cases, 54.0%), atrial fibrillation with slow ventricular rate (29 cases, 23.0%) and SSS (29 cases, 23.0%) were rather rare ones. Cardiac pacing was performed in DDD(R) and VVI(R) modes in 21 (16.7%) and 105 (83.3%) cases, respectively. Forty six percent of surgeries were immediate or urgent (in case of syncopal conditions).

Ninety five (75.4%) of total number of enrolled subjects received elective anticoagulant warfarin therapy and 31 patients (24.6%) used dabigatran. Subgroup data had no significant differences of basic characteristics ([Table 1]). Duration of antithrombotic therapy course was 14 days at least before a surgery in all patients.

All patients of dabigatran group received 220 mg/day skipping the last dose before a surgery (withdrawal interval was 12 hours). After a surgery interval before the first dabigatran intake was defined at operating surgeon's discretion (36-48 hours). In order to confirm INR value < 3, morning presurgical and postsurgical INR monitoring was performed in patients received antithrombotic warfarin therapy. In case of greater values, surgery may be delayed in the setting of short-term warfarin withdrawal until target INR value is obtained. Wafrarin intake wasn't stopped for the duration of surgery. Patients took usual drug dose of the drug after the implantation.

No serious hemorrhagic (such as profuse bleeding, hemothorax, hemopericardium, gastrointestinal bleeding) or thromboembolic (ishemic stroke, deep venous thrombosis of lower limbs, pulmonary artery thromboembolia) complications were detected during initial hospitalization.

Subcutaneous hematomas developed in 2 patients of dabigatran group (incidence is 0.065, 95%CI (-0.02–0.15)) and 5 patients treated with warfarin (incidence is 0.05, 95%CI (0.006–0.01)). Differences of incidence between two groups were not statistically significant – p(Fisher)= 0.55. Moreover, the only one patient (warfarin group) had a hematoma with a need for drainage. Hematoma formation was associated with target INR level defined before a surgery in all patients received warfarin. In all cases of hematoma formation this complication developed within 12-24 hours after a surgery. It was primary, i.e. it was not a result of lead positioning correction or local infectious process required antibiotic therapy. In case of developed hematomas, reinitiation of antithrombotic therapy was delayed for 1-3 days till confirmation of dimensional stability according to repeated ultrasonic examination. No complications caused by hematoma formation were detected in future (including contamination, lead dislocation or capture failure, pneumothorax and thrombembolia). In the single case required drainage repeated hematoma formation was not detected.

During follow-up (12 [6; 20] weeks) 3 cases of nonfatal gastrointestinal bleeding (warfarin group) and 1 similar event in dabigatran group were recorded; RR= 0.98 (warfarin group), p(Fisher)= 0.68 (see [Figure 1]).

No fatal cases related to hemorrhagic or thromboembolic events

were detected during follow-up period. Two (warfarin group) and 1 (dabigatran group) fatal cases occurred as a result of IHD. There were no statistically significant differences of lethality rate between two groups (p(Fisher)= 0.72).

No statistically significant difference of age, sex composition, history of IHD and diabetes was detected between groups by comparison of individual characteristics of patients whose surgeries were complicated/non-complicated by hematoma formation. Upon that, hematoma formation rate was significantly higher in patients with adjunctive pacemaker muscular fixation: 71.4% vs 31.9% (patients without hematomas), p(Fisher)= 0.045, see [Table 2].

Discussion

Pacemaker implantation is a common life-saving procedure which is, however, associated with defined risk of postsurgical complications.

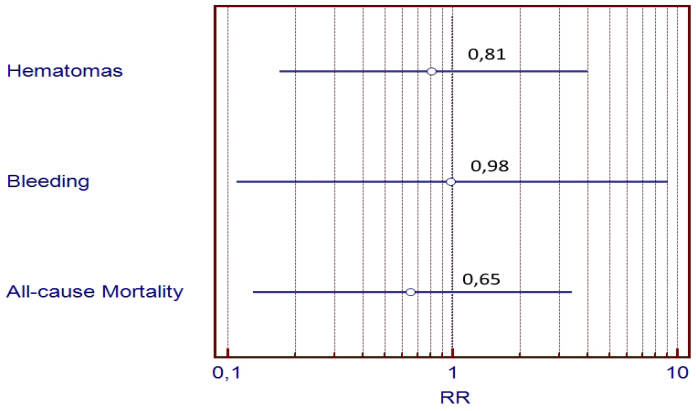

Figure 1: Relative risk of basic events for warfarin and dabigatran groups

One of stages of the surgery is a pacemaker pocket formation, when surrounding tissues are prepared without ligation. It may cause poor hemostasis [17]. As a result, formed hematoma is uncomfortable for a patient increasing risk of contamination and lengthening postsurgical hospital period.

Actually, about 1 million of pacemakers are annually implanted worldwide and this number even grows every year. In 2011 a total 32 317 antiarrythmic devices were implanted in the Russian Federation but number of implantations annually increases by 8-10% [1] at average. In spite of lead dislodgement, pocket hematoma formation (including ones required operative exploration) is one of the most common complications after pacemaker implantation. However, confident quantitative evaluation of this complication incidence is difficult in Russian population because individual statistic recording related to the procedure complications is required in the Russian Federation. Due to this fact, we selected information from documents (a report of Australian interventional arrhythmological center activities) including record of corresponding complications in population in order to perform a comparative study. In 2005 a total 11 850 pacemakers were implanted in Australia [2]. Reported data related to prevalence rate of pacemaker implantation complications showed 11.9% (total incidence), 2.6 % of which was hematoma formation [18]. This pattern is comparable to major international register data (total incidence of complications is 4.5 - 10.1%, 0.6-1.9% of which is hematoma rate [10], [11], [12], [13]). According to our data, incidence of pacemaker pocket hematomas is 5.0-6.5% in patient subgroups receiving various antithrombotic therapy which is significantly consistent with reported information.

Potential causes of slightly higher incidence of hematoma formation in our study cohort may be related to enrolling of elderly patients receiving anticoagulant therapy and immediate or urgent performance of essential part of implantations. Thus, according to Link et al. [19], incidence of complications after two-chamber pacemaker implantation in patients > 65 years was 6.1%, 4.4% of which required reintervention. As follows from this work [16], incidence of hematomas in elderly patients was 4.9% with any antithrombotic therapy during perisurgical period as a main risk factor of this complication. However, a material constraint of this study [16] is a fact that 41% of patients received warfarin before a surgery were transferred into temporary anticoagulant therapy (so-called "bridging therapy"). It can be an independent risk factor of postsurgical complications related to blood-clotting disorders [20], [21], [22]. Thus, Chow et al. [16] mentioned that postsurgical hematomas formed in patients received anticoagulants only in cases of temporary anticoagulant therapy (21 vs 0); as a whole, hematomas formed in 65.6% of 32 patients who have administered excitatory amino acid. Besides that, according to Chow et al. [16], influence of anticoagulant therapy on hematoma formation depends on degree of intervention urgency; immediate procedures duplicate this risk. Although authors withheld representation of this observation, we can suggest that urgent intervention complicates adequate control in case of prescribing of temporary "short-term" anticoagulant during presurgical period. Such a theory is indirectly confirmed by the fact that no statistically significant influence of intervention urgency on hematoma development risk was obtained in the frame of our study (without included regimen of temporary anticoagulant therapy).

Table 2: Possible predictors of hematoma formation

	Patients with hematomas, n=7	Patients without hematomas,n=119	p(Fisher)
Urgent intervention	4 (57.1%)	44 (36.9%)	0.248
Elective intervention	3 (42.9%)	75 (63.1%)	
Number of DDD(R) devices	3 (42.9%)	18 (15.1%)	0.09
Number of VVI(R)	4 (57.1%)	101 (84.9%)	
devices			
Pacemaker muscular fixation	5 (71.4%)	38 (31.9%)	0.045

The fact of additional interest is that antiplatelet therapy (used in 19.8% subjects of our study) was not a predictor of hematoma formation. It is a promising factor for patients with coronary blood flow disorders (including ones with implanted coronary stents). In this case withdrawal of antiplatelet drugs may be associated with increased risk of coronary thrombosis.

Table 3: Hematoma formation predictors - odd ratio; significance point according to multivariant model

	OR	95% CI	p
Urgent intervention	2.1	0.46-10.1	0.26
DDD(R) device	3.7	0.8-18.0	0.11
Pacemaker muscular fixation	4.4	0.82-23.8	0.007

According to reported data [19], [23], [24], higher incidence of pneumothorax is observed due to pacemaker implantation in elderly patients vs. younger ones along with similar incidence of other complications. Additional risk factors of this complications were

female sex, lower body weight, lower Karnofsky score and higher Carlson score [24], [25], [26]. Karnofsky Performance Scale displays degree of patient's activity naturally decreasing with age. Furthermore, low body weight and kyphosis (which are common in elderly patients) can cause higher incidence of this complication.

Hypertension does not significantly influence the incidence of complications after device implantation because interventions are carried out via venous access.

Armaganijan et al. [25] highlighted relatively higher incidence of early complications (such as lead dislodgement, capture failure, myocardial rupture, infection) along with similar incidence of late ones (lead integrity violation) in elderly patients. However, according to later large study [26], absolute number of complications were rather small (even in patients > 80 years). Comorbidity was a predictor but not patient's age.

Limitations

Present study was not randomized and has a relatively small sample size, which can lead to absence of difference in study endpoints due to lack of statistical power. Furthermore, the small number of events precluded us to perform multivariate analysis to identify independent predictors of hematoma formation. However, our data is consistent with other studies which did not demonstrate the increased hematoma frequency after device implantation in senior patients receiving uninterrupted dabigatran [27].

Conclusions

This study demonstrated relatively small total incidence of complications and incidence of hematoma formation after pacemaker implantation in patients older than 75 years receiving elective anticoagulant therapy (continuous warfarin or dabigatran intake). Adjunctive pacemaker muscular fixation was found to be a risk factor of hematoma formation.

Conflict Of Interests

Conflict of interest holds in abeyance; additional sources of funding were not used in this study.

Disclosures

None.

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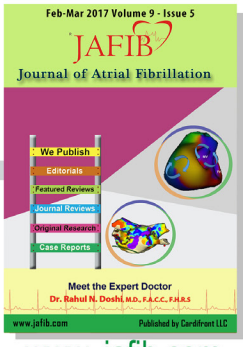

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Comparison Of Initial LA Patterns As The Road To Successful Endocardial Box Lesion Ablation

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Abstract

Atrial fibrillation (AF) is the most common arrhythmia in the population. Still there is no unity in understanding of mechanisms and their influence on catheter ablation results. In our study we tried to evaluate accurate initial quantitative indicators of electromechanical remodeling that can border patients from expected good to expected poor results of catheter ablation. We performed electroanatomical mapping and ablation procedures in 94 patient (45 female) in 2012 with 3-year follow-up period. The target points were left atria surface area, complex fragmentation atrial electrograms (CFAE) duration and surface area. We investigated primary procedure efficacy and initial preoperative patterns of patients in sinus rhythm after 3-year follow-up. Patients with paroxysmal AF had about 3-4 such areas with the median duration of fragmentation 84,5 msec and area 10,4 cm^2. In persistent AF were 5-6 zones, duration of 149 msec and area 22,95 cm^2. In long standing (LS) persistent AF 6-9 zones with duration up to 200 msec and area close to 30 cm^2. General efficacy of radiofrequency ablation (RFA) in paroxysmal group was 58,8%, in persistent 33,3% and in LS persistent 12,9% according to Kaplan-Meyer curve with p=0,001. Retrospectively we found that every index in AF recurrence group was 1,5-2 times higher than its equivalent in sinus group. LA surface area was 131,8 cm^2 vs 103,7 cm^2 respectively. Median CFAE duration in AF patients was 157 msec and 87,5 msec in sinus patients. The principal index of CFAE square area was 2,5 times bigger (24,6 cm^2 vs 10,3 cm^2 relatively). We concluded that parameters of mechanical (LA volume and surface area) and electrical (CFAE duration and surface area) remodeling have to be defining in tactics and prognosis of catheter ablation in different types of AF. In order to achieve higher efficacy we advise to use stepwise tactic.

Introduction

Atrial fibrillation (AF) still appears to be the most challenging form of cardiac arrhythmias. There are different strategies for treating this cardiac disorder i.e. from drugs and defibrillation to intervention and open-heart surgery [1]. We will have drastically differing results, especially when comparing surgery and catheter ablation.

Several authors describe efficacy of different types of RFA in various groups of patients. Mean percentage of people in sinus rhythm range from 15% to 88% after primary or secondary procedure [2]. But still in practical guidelines we can see only recommendations for treating AF according to it forms [3].

That's why despite the great variety of published articles no one can provide clear recommendations and values of heart indexes, which are extremely substantial to gain success in interventional treaments of AF. In this article we tried to evaluate accurate initial quantitative indicators of electromechanical remodeling that can border patients from expected good to expected poor results of catheter ablation.

Material and Methods

Study population

The ablation procedures were performed in 2012 with a subsequent 3 years follow-up. The overall population consisted of 94 patients (49 male and 45 female) with different forms of AF: 34 paroxysmal, 30 persistent and 30 long standing (LS) persistent. Among them 41 patients had a moderate functional mitral regurgitation, 22 patients had not significant ischemic heart disease and NYHA class less than 2. All patients had documented AF on ECG and Holter. Previously they were treated with beta-blockers and amiodarone as the main antiarrhythmic therapy (AAT) and with warfarin as the anticoagulation drug. All AAT was canceled before RFA procedure at different times: a week in case of b-blockers and not less then 40 days in case of amiodarone. We used bridge anticoagulation therapy within two days before and after the procedure.

Design

This is a prospective cohort study. The main goals were definition of degree of electromechanical remodeling and efficacy and recurrence risk after RFA. Primary endpoints were recurrence of AF, stroke, different cardiac events (myocardial infarction, surgical operation and others) and death. Secondary endpoint was the end of 3-year follow-up. Patients were divided into 3 subgroups according to the form of AF. All of them underwent three types of RFA: lone pulmonary veins isolation (PVI), PVI with additional CFAE applications and endocardial modification of epicardial "box lesion" set. An electroanatomical mapping with CFAE evaluation was performed in all cases before ablation. Retrospective analysis of initial pattern was performed after reaching the endpoints, either primary or secondary. Patients were divided in two groups according to presenting sinus rhythm in the end of primary study. The basic aims were identification of primary structural and electrical parameters of the heart, which can influence on reverse atrial modeling and design of therapeutic algorithm on this cohort of patients.

Key Words

Endocardial ,Ablation,Atrial Fibrillation

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Diagnostics

Patients from the study underwent Echo and Cardiac computer tomography (CT) routinely before the procedure. Echo was performed with the HP SONOS 5500 (Hewlett Packard Company, Palo Alto, CA, USA) and GE Vivid S5 (GE Healthcare, General Electric, Fairfield, CT, USA) devices. 2D systolic and diastolic parameters of the heart were measured by the Teichholz method. M- and B-modes were used to evaluate conditions of valves, local kinetics and contractility of myocardia and overall hemodynamic. CT was performed on Philips Brilliance CT (Koninklijke Philips N.V., Amsterdam, Netherlands) device. It included pinpoint contrasty scans of left atria (LA) with pulmonary veins (PV) and appendage (LAA) in three dimensions with calculated volumes.

Table 1: Baseline characteristics of all groups of patients

Parameter	Paroxysmal group	Persistent group	LS persistent group	P
Age, y	51.91±11.49	55.83±7.87	56,1±11,66	0.217
Gender (m/f)	15/19	20/10	14/16	-
AF duration, month	11.57±4.13	22.67±8.84	39.98±12.44	0.001
LVED, cm2	5.17±0.56	5.36±0.59	5.2±0.45	0.341
EDV, ml	128.09±30.5	140.9±35.6	135.4±32.2	0.314
LV EF, %	64.3±7.75	61.5±9.17	59.9±8.1	0.12
LA diameter, cm	4.07±0.66	4.6±0.8	5.08±0.75	0.001
LA LD, cm	6±0.7	6.9±1.2	7.4±1	0.002
LA AP, cm	3.8±0.6	4.8±0.9	5.2±1	0.001
LA TD, cm	6.11±0.9	7.3±0.9	7.07±0.9	0.003
LA vol, ml	96.9±23.6	153.9±72.05	173.7±66.05	0.001
LA area, cm^2	99.11±18.7	164.05±46.4	191.6±43.8	0.001
CFAE duration, msec	84.5 (78;89)	149 (112;159)	176.5 (163;196)	0.001
CFAE zones, n	3 (3;4)	6 (5;6)	8 (6;9)	0.001
CFAE surface area, cm^2	10.4 (8.7;11.9)	22.95 (19,3;24,8)	27.85 (25.9;29.9)	0.001

Intraoperative mapping

Intraoperative stage consisted of electrophysiological (EP) study, electroanatomical mapping procedure and RFA. EP findings were investigated with the help of GE CardioLab XT recording System. Mapping procedure was performed with SJM EnSite NavX (SJM EnSite Velocity, St. Jude Medical Inc., Little Canada, MN, USA). AF paroxysm was induced by the rapid atrial pacing, if patient was in sinus rhythm at the beginning of operation. This stage consisted of several steps: lead-up, CFAE mapping, fusion with CT images, post processing of endograms and CFAE calculation in cm2. After this we compared LA surface area, which have been received with the help of Knud Thomsen formula of the surface area of an ellipsoid (S≈2π[(apbp+apcp+bpcp)/3]1/p, when p » 1.6075), to total CFAE square area. All these steps were necessary to evaluate the degree of atrial remodeling.

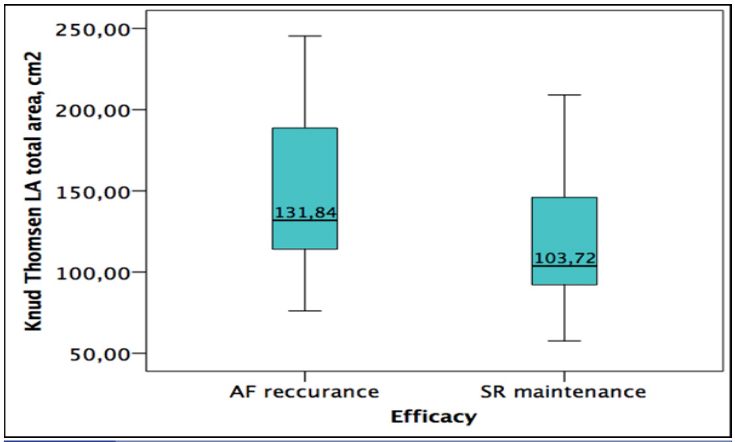

Figure 1: Median LA surface area in patients with and without sinus rhythm in 3-year follow-up

Radiofrequency ablation

Lone antral PVI was performed with open-irrigated catheters BW Celsius Thermocool (Biosense Webster, Johnson and Johnson, New Brunswick, NJ, USA) and circular diagnostic duodecapolar catheters BW Lasso. In the second type additional to PVI radiofrequency applications was performed in the areas of CFAE. The third type – endocardial "box lesion" set – consisted of antral PVI, roof line, posterior line and mitral line. After this applications CFAE areas were also ablated if they were not included in posterior box. RFA was admitted as successful if AF stopped during the procedure. Patients with AF after RFA were defibrillated.

Follow-up

Patients were discharged from the hospital on the 3d day after procedure. All of them received amiodarone for at least 6 months and warfarin for anticoagulation with target INR of 2-3. Late follow-up lasted for three years. Patients were examined after 3, 6, 12 months after ablation and then every year. AF paroxysm on ECG or Holter with duration more than 30 seconds was considered as AF recurrence.

Statistical analysis

Statistical analysis was performed with SPSS Statistics v.21 (SPSS Inc., IBM Corp. Armonk, NY, USA), statistical significance was accepted as p<0,05. Quantitative parameters that were close to the normal distribution were evaluated with median and standard deviation by the Tukey criterion. Other parameters were compared with an independent Kruskal-Wallis test for equality of medians with the help of Kendal coefficient. Regression analysis was performed with Cox test with co-variants and had an exponential graphical design. All survival curves were build with Kaplan-Meyer on the basis of evaluation of the median survival with criteria Breslow and Taron-Weyer to determine the significance of differences.

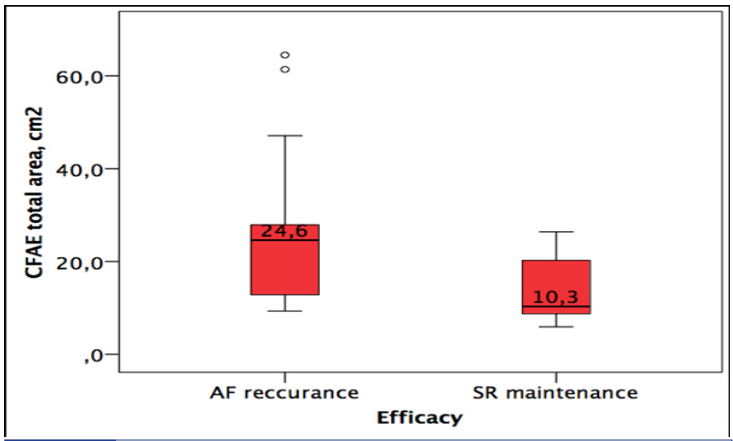

Figure 2: Median CFAE area in patients with and without sinus rhythm in 3-year follow-up

Results

The baseline characteristics of the three investigated groups are

presented in [Table 1]. There were some significant differences between the groups. First of all we are talking about LA dimensions. They varied with the deterioration of the form of AF. We noticed the enlargement of LA chamber from 96.9±23.6 ml in paroxysmal AF to 173.7±66.05 ml in LS persistent AF (p=0,001). This was rightly to LA surface area (99.11±18.7 cm^2 in paroxysmal AF to 191.6±43.8 cm^2 in LS persistent AF). Since patients with PV abnormalities were not included in the study, PV diameters didn't show meaningful diversity. For example, right and left superior PV were not much than 2.2 cm in every group. On the other hand, main parameters of LV were not significantly different (LV EF about 60-65% in all groups, p=0.12).

Prospective study

We distinguished 3 electromechanical indexes (CFAE duration, number of zones and square area) that could help us to estimate the degree of remodeling. Patients with paroxysmal AF had about 3-4 such areas with the median duration of fragmentation 84.5 msec and area 10.4 cm^2. It occupies meanly 10.5% to compare it with the total LA surface area. The same values in persistent AF were 5-6 zones, duration of 149 msec and area 22.95 cm^2, generally 13.98% of LA. In LS persistent AF 6-9 zones with duration up to 200 msec and area close to 30 cm^2, nearly 19% of LA surface.

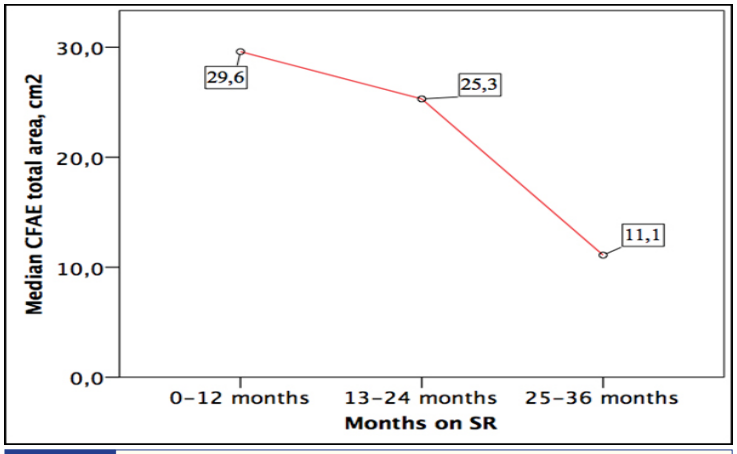

Figure 3: Relation between median CFAE total area in patients with sinus rhythm after 1, 2 and 3 years of follow-up

General efficacy of RFA was 35.8% (OR 0.3111, p 0.1644-0.5865). This value in paroxysmal group was 58.8%, in persistent 33.3% and in LS persistent 12.9% according to Kaplan-Meyer curve with p=0.001. Recurrence risk amounted 0.53, 1.09 and 2.01 in different forms of AF respectively (p=0.001). The most promising result was gained in the group of patients with paroxysmal AF, who underwent epicardial "box lesion" ablation. It was 81.8% after 3 years. The worst results were in persistent and LS persistent groups after PVI: there were no patients in sinus rhythm in 3-year follow-up with OR 0.0005, p=0.5005-0.0959 in both groups. On the whole, efficacy of different ablation techniques arised to 15.6% (OR 0.0347, p 0.0072-0.1548) in PVI 35.5% (OR 0.3030, p 0.0932-0.9643) with addition of CFAE areas and 56.3% (OR 1.6535, p 0.5502-5.0148) in "box lesion" group.

Retrospective analysis

Retrospective comparison of initial parameters showed no differences in LV parameters in patients with sinus rhythm or AF recurrence ([Table 2]). Nevertheless, all LA parameters, except diameter of right inferior PV, were extremely different. For example median LA volume in sinus rhythm patients was 102.5 ml while 25%-quartile of LA volume in another group was 114 ml. In general, all LA patterns of the sinus rhythm patients were less or equal 25%-quartile of the same patterns in patients with AF after 3-year follow-up.

Quantitative analysis of electromechanical and EP findings showed even more disappointing results. Every index in AF recurrence group was 1.5-2 times higher than its equivalent in sinus group. LA volume and surface measured by Knud Thomsen formula were 154,9ml vs 94.5ml and 131.8cm^2 vs 103.7cm^2 respectively ([Figure 1]). Median CFAE duration in AF patients was 157 msec, which is also 2 times higher (87.5msec in sinus patients). And the principal index of CFAE square area was 2.5 times bigger (24.6cm^2 vs 10.3cm^2 relatively – [Figure 2]). If we also will look at this indexes in view of every year efficacy, we will observe, that patients with less CFAE area were more likely on sinus rhythm in the end of the study ([Figure 3]).

Table 2: Initial cardiac measurements in patients with sinus rhythm and AF recurrence

Parameters	Groups	p	Median	Quartile	
				25	75
LVES, cm	AF recurrence	0,738	3,4	3,1	3,8
	SR maintenance		3,4	3,1	3,85
LVED, cm	AF recurrence	0,893	5,3	4,9	5,5
	SR maintenance		5,3	4,8	5,7
ESV, ml	AF recurrence	0,405	47,5	37,25	62,75
	SR maintenance		51	40	66
EDV, ml	AF recurrence	0,499	133,5	111,5	148,25
	SR maintenance		134	114	162
SV, ml	AF recurrence	0,457	79	68	91
	SR maintenance		82	70,5	102,75
LVEF, %	AF recurrence	0,912	62	56	66
	SR maintenance		61	56	67,5
dLA, cm	AF recurrence	0,001	4,875	4,2	5,5
	SR maintenance		4,2	3,7	4,6
LA LD, cm	AF recurrence	0,01	7	6,25	7,925
	SR maintenance		6,3	5,7	6,6
LA AP, cm	AF recurrence	0,007	4,8	4,075	5,6
	SR maintenance		4,1	3,6	4,6
LA TD, cm	AF recurrence	0,012	7,2	6,5	7,75
	SR maintenance		6,5	5,6	6,9
LA vol, ml	AF recurrence	0,0001	140	114	183,5
	SR maintenance		102,5	84,63	126,5
LA index, abs	AF recurrence	0,13	71,4	57,205	101,61
	SR maintenance		52,5	43,64	83
RSPV, cm	AF recurrence	0,013	2	1,8	2,3
	SR maintenance		1,75	1,575	2,05
RIPV, cm	AF recurrence	0,67	1,7	1,5	1,9
	SR maintenance		1,65	1,375	1,9
LSPV, cm	AF recurrence	0,04	2	1,825	2,275
	SR maintenance		1,85	1,575	2,05
LIPV,cm	AF recurrence	0,03	1,8	1,6	1,9
	SR maintenance		1,55	1,5	1,8

Discussion

We found some interesting features during our investigation, which were not observed yet in different randomized trials. First of all, we don't see systolic dysfunction even in the cases with mitral regurgitation without organic valve pathology. Anamnestic data have shown that patients suffer from moderate heart failure symptoms only on paroxysms of AF. Furthermore, they notice decrease of symptoms during the transition to persistent forms. It can be proved by EchoCG data of LV indexes, especially LV EF, that wasn't lower than 55% in all groups of patient. Contrariwise, diastolic dysfunction still is presented according to symptoms and physical analysis. We can assume that only presence of proven organic pathology of mitral valve (rheumatic disease, bacterial endocarditis, ischemic pupillary muscles dysfunction) will lead to severity of systolic heart failure in AF patient population. Recent article by Prabhu et al. can partly confirm our statement. They have shown that in patients without structural cardiomyopathy catheter ablation had resulted in improvement in symptoms and LE EF compared to patients with heart disease [4]. Close to the same results were in meta-analysis of efficacy and safety of catheter ablation vs. rate control tactics by Zhang et al [5].

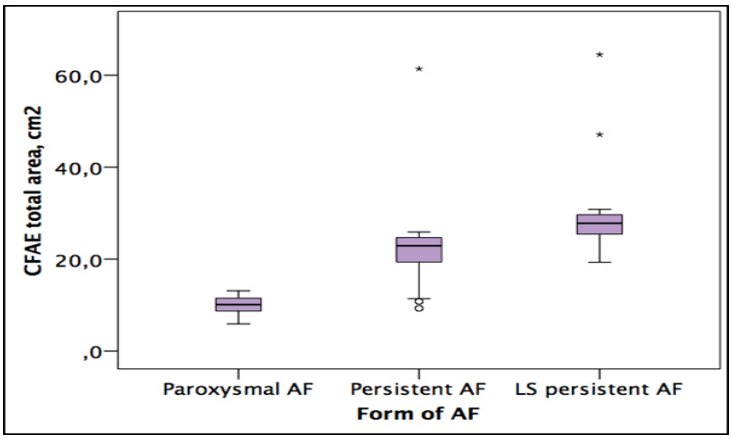

Figure 4: Median CFAE surface area in patients with different form of AF

The second thing is that there are significant differences between paroxysmal and non-paroxysmal patients, while inside the last one group they are not so expressed. It concerns all heart index values from LA volume to PV size. For example, the main parameters of our study – LA and CFAE surface areas – are twice higher in non-paroxysmal forms ([Figure 4],[Figure 5]). On the other hand, difference in persistent and LS persistent patients was not so explicit. Thus we can claim that the decisive moment of electroanatomical remodeling of atria is the transition from paroxysmal to persistent, not from persistent to LS persistent and permanent. In that case is very important to analyze and compare anamnestic data with instrumental diagnostics. [6],[7] But lack of such studies or its one-sided view leads to disclosure of one risk factor or pathologic mechanism that is responsible to one type or subtype of arrhythmia, but not for the whole process . [8] Indirectly it was verified in meta-analysis by Piccini et al, where differences among persistent and LS persistent AF were only in clinical and physiological levels, but not in diagnostically findings. [9] Hunter et al gave another interesting opinion 2010. In the CFAE AF Trial they identified that alone CFAE areas were not define the substrate of arrhythmia by themselves, but were only the expression of speed and homogeneity of AF waves, and them had changed to upwards after catheter ablation.[10]

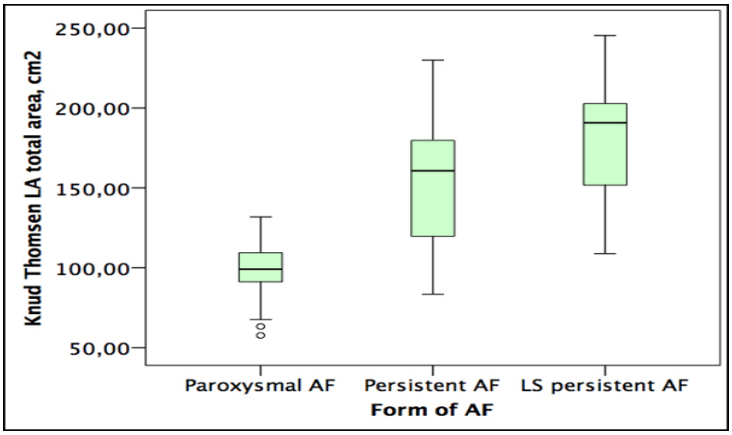

Figure 5: Median LA surface area in patients with different form of AF

Nevertheless it will be the great mistake to underestimate the role of secondary interventional procedures in maintenance of sinus rhythm in late follow-up. In our study we leaned on significance of primary catheter ablation guided by electroanatomical patterns. This is the cause of such moderate results. And it was intentionally done to separate our methods from only anatomically guided procedures. In the latter case efficacy is rather promising, and we admit the necessity of secondary ablation, as it was mentioned by Bhargava et al. in 2009 [11]. However some studies also recommend to rely on electroanatomical indexes even in the secondary procedures. [12]

Study limitations and perspectives

The study population was rather small (94 patients) and heterogeneous. We plan to enlarge it and perform the closer investigation in every type of AF patients with structural heart diseases. Also we have some doubts in validity of Holter as the main diagnostic procedure to evaluate sinus rhythm after ablation.

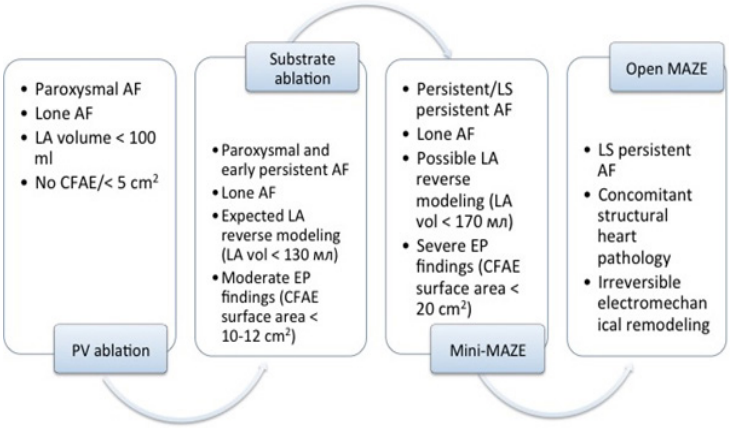

Figure 6: Stepwise approach to gain success in AF patient interventional and surgical treatment

Conclusion

Parameters of mechanical (LA volume and surface area) and electrical (CFAE duration and surface area) remodeling have to be defining in tactics and prognosis of catheter ablation in different types of AF. We recommend to apply RFA procedure in patients with LA volume less than 120ml and LA surface area less than 10-12 cm^2. At the same time electrical patterns should be the following: CFAE duration up to 150msec with surface area less than 15cm^2. In order to achieve higher efficacy we advise to use stepwise tactic

([Figure 6]).

Conflict Of Interests

None.

Disclosures

None.

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Rescue leadless pacemaker implantation in a pacemaker-dependent patient with congenital heart disease and no alternative routes for pacing

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Abstract

Congenital heart disease patients are considered a unique group of patients regarding their high risk of conduction abnormalities , whether de novo or surgically induced , and the challenges in both implantation and management of device related complications. We present a case of a pacemaker-dependent patient with congenital heart disease who experienced complications of both previous epicardial and transvenous pacing which rendered her a non-suitable candidate of both routes.

Introduction

Patients with congenital heart disease and symptomatic bradyarrhythmias requiring pacemaker implantation are among the most challenging clinical cases, owing to complex anatomy, frequently limited vascular access, higher risk of pacemaker related complications and risk of life-long pacemaker dependency.

Case Report

We report a case of a forty-seven years old lady with a history of congenital heart disease (Dextrocardia, situs inversus, double outlet right ventricle and ventricular septal defect). When she was 7 years old, a corrective surgical intervention was complicated by complete A-V block which necessitated the implantation of transvenous endocardial single chamber pacemaker. After the second replacement of the pacemaker generator in 1991, the patient had experienced pacemaker lead malfunction (progressive increase of pacing impedance and threshold) .Multidetector computed tomography (MDCT) revealed complete occlusion of the superior vena cava and innominate veins with extensive venous collaterals ([Figure 1]). The decision was taken to abandon the transvenous lead and implant an epicardial one (Medtronic Legend II) with the battery placed in the right upper abdominal quadrant ([Figure 2]).

Key Words

Congenital heart disease, Transvenous pacing, Epicardial pacing system, Leadless pacemaker.

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Over the following 10 years, elective generator replacement was done twice due to battery depletion. In 2014 , the patient presented with recurrent dizzy spells. Pacemaker interrogation revealed markedly elevated pacing threshold (4 V at 1.0 msec PW) with near End-Of-Life (EOL) . In the light of none available vascular access for regular transvenous pacing added to the failure of the epicardial pacing system , we decided to implant a leadless pacemaker (Medtronic Micra TM).

After getting a left femoral vein access and passing dilators of increasing size over a stiff wire, the Micra sheath was advanced to the junction of inferior vena cava (IVC) and right atrium. The device mounted on a steerable catheter was then advanced and manipulated to the right ventricular apical septal area. After confirming good contact with attaining the goose neck shape of the catheter and contrast material injection, the device was deployed and tine stability was confirmed by gentle pulling of the tether ([Figure 3]). Interrogation of the device revealed R wave amplitude of 8 mV and capture threshold of 1.0 V at 0.4 msec PW. The post-procedural course was uneventful with confirmed pacemaker position by chest X-ray ([Figure 4]) and good pacemaker parameters the day after the procedure.

Discussion

Congenital heart disease (CHD) patients account for a small proportion of the patients requiring a pacemaker or defibrillator implantation. It was found that the overall long-term pacing- related complication rate in CHD was close to 40 %, compared with 5 % (or 0.5 % per year) in non-CHD. [1] Epicardial pacing system was associated with a higher lead failure rate as observed in our case. Endocardial pacing was found to be more durable but with multiple inherent risks as thromboembolic complications , reported to be more

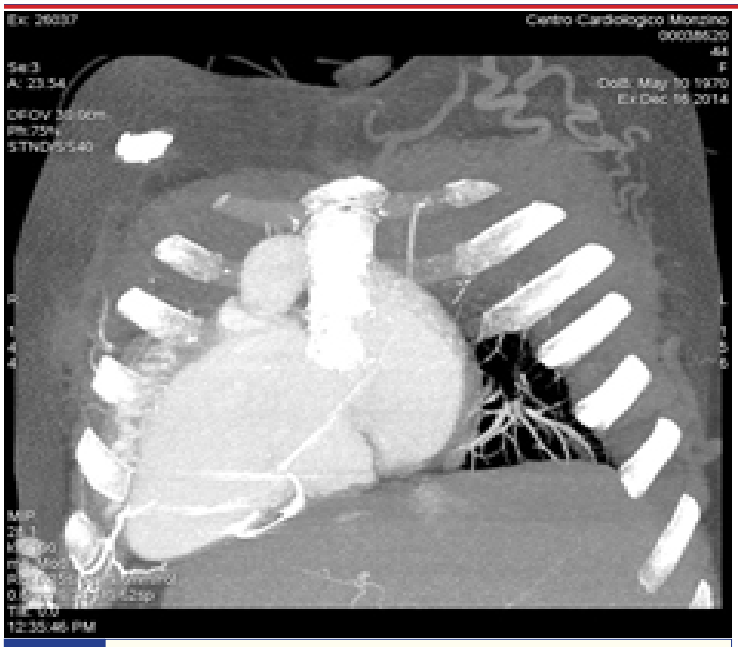

Figure 1: MDCT chest reveals extensive collateral formation (arrow) form the venous occlusion.

than 2 folds in patients with intracardiac shunts and transvenous endocardial leads [2], and the risk of venous occlusion ranging from

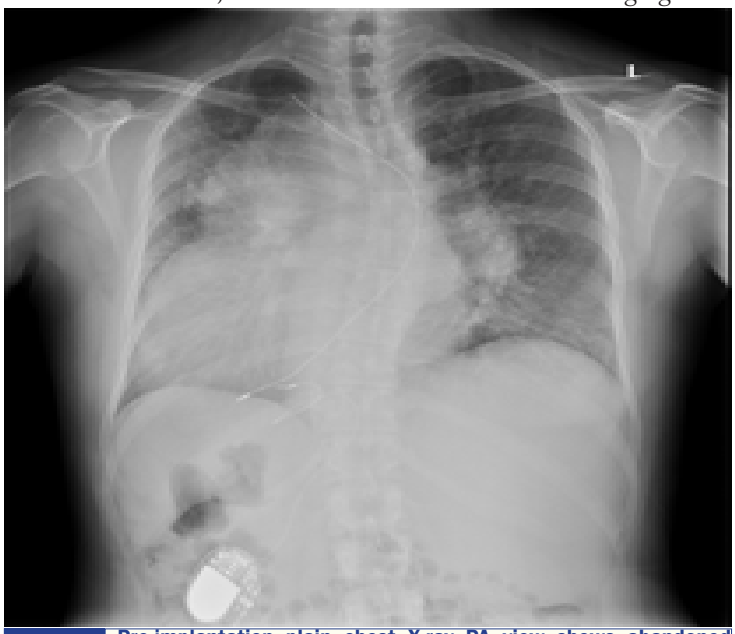

Figure 2: Pre-implantation plain chest X-ray PA view shows abandoned transvenous lead (asterisk) , the failed epicardial lead (arrow head) and pacemaker generator implanted in the right hypochondrium (arrow)

5-10% in long term follow-up studies. The case described in our report is challenging considering both the pacemaker-dependency in addition to absent any other remaining route for pacing lead implantation.

The non-surgical implantation of a small and self-contained single chamber leadless pacemaker mounted on a catheter and advanced through the femoral venous access was proved to be safe and effective by two recent published trials on the two commercially available leadless pacemaker systems. [3],[4] In our case, considering the bilateral venous access block and the failed epicardial pacing system, leadless pacemaker remained to be the only choice for the patient.

Conclusion

Leadless pacemaker implantation may be a reasonable strategy

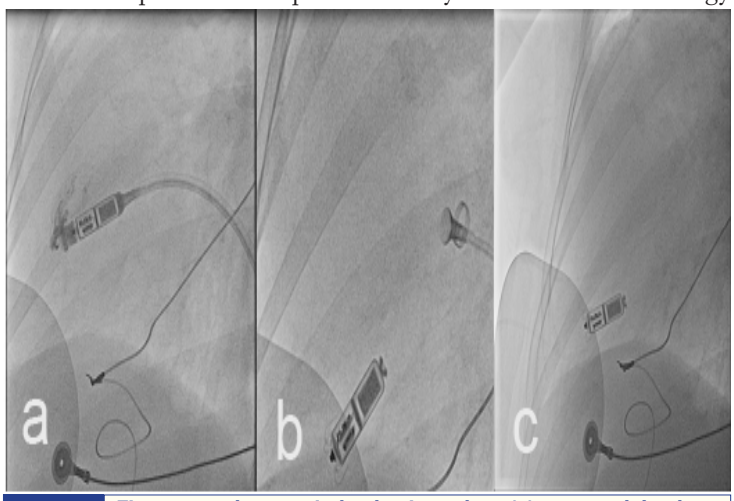

Figure 3: Fluoroscopy images during implantation : (a) contrast injection to confirm the device contact with the ventricular wall, (b) gentle pull back of the catheter to confirm device stability, and (c)Final device position in the apical RV septum.

in patients with congenital heart disease and limited approaches for pacing. Some developments such as dual chamber and

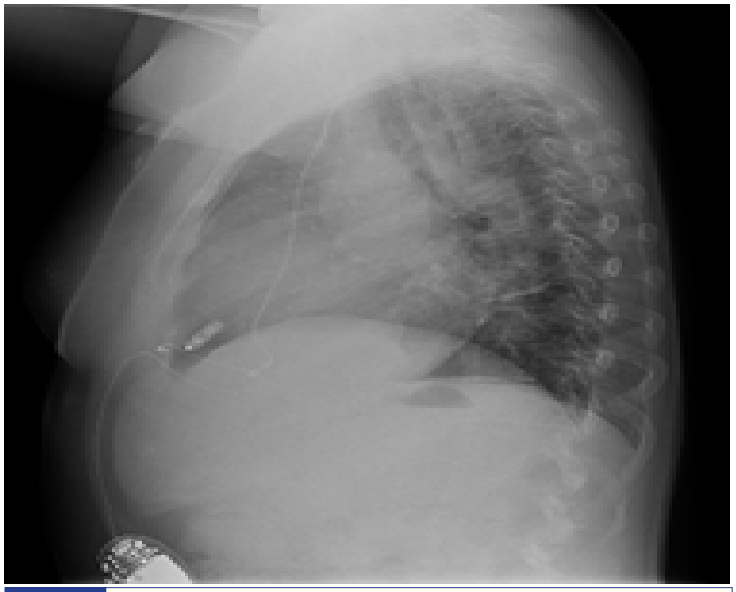

Figure 4: Post-implantation lateral CXR shows the final position of Micra leadless pacemaker (arrow) in the apical RV septum

resynchronization leadless pacing systems as well as long term assessment of this modality in this unique patient population may be needed before being used on a large-scale.

Conflict Of Interests

None.

Disclosures

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Valproic acid as a cause of transient atrio-ventricular conduction block episodes

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Abstract

Herein we share, to our knowledge for the first time, a a case of valproic acid use complicated by symptomatic atrio-ventricular conduction block episodes on Holter monitoring. Symptomatic atrio-ventricular block episodes should be considered as an unusual side effect of valproic acid despite normal blood therapeutic level. Before consideration of pacemaker implantation in such cases, valproic acid usage should be investigated, and dose reduction should be attempted.

Case Report

A 19-year old female patient was referred to the Cardiology Department for implantation of pacemaker with the diagnosis of symptomatic recurrent transient atrio-ventricular conduction block. The patient had a history of epileptic seizures which was treated and controlled with valproic acid. Over the last two years, the patient experienced multiple episodes of near syncopes with most of them occurring in the six months before admission. During her evaluation of of presyncope, multiple transient atrio-ventricular block episodes lasting between 20-26 s were discovered on 24 hour Holter rythm monitoring performed in in an outside facility. Her Holter monitoring was repeated seven times and each test revealed revealed similar findings. Her history revealed that most episodes happened in resting position. The patient was referred to our clinic for further work up and recommendation of pacemaker implantation. At the admission, her physical examination was unremarkable. Her ECG and echocardiography were within normal limits. Exercise test revealed adequate chronotropic competence. The patient underwent 48 hour Holter monitoring. We discovered multiple episodes of atrio-ventricular conduction blocks lasting 28 s on Holter monitoring [Figure]. Before consideration of pacemaker implantation we decided to .to reduce the dose of valproic acid from 500 mg t.i.d to 500 mg b.i.d. After four weeks patient was called to hospital for control. Valproic acid serum level was 49.5 ug/mL. The patient was asypmtomatic except one attack of self limited seizure.

The 48 hour Holter monitoring revealed complete disappearence of previous atrio-ventricular block episodes. We decided that atrio-ventricular blocks was stemming from valproic acid at the doses of 500 mg t.i.d despite normal blood therapeutic level (71.7ug/mL). We considered changing the anti epileptic drug and pacemaker implantation was canceled.

Key Words

Vaproic acid, Atrio-ventricular block, Drug.

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Discussion

Our case indicates that the electrocardiographic atrio-ventricular conduction blocks as an unusual side effect of valproic acid should be kept in mind. In such a case, unless there is a compelling reason, the dose of valproic acid should be reduced or changed to another anti epileptic drug to avoid unnecessary pacemaker implantation.

It should be noted that drug induced bradyarrythmia should be differentiated from peri ictal or seizure related bradyarrhythmias [1]. Seizure-related bradyarrhythmias including sinus bradycardia, atrio-ventricular conduction blocks and asystole have been reported rarely in case series studies and sudden unexpected death in epilepsy accounts for 8–17% of the deaths in patients with epilepsy [2].

Although the most frequent cardiac arrhythmia seen during epileptic seizures is sinus tachycardia that occurs in most seizure episodes and is usually of no consequence, autonomic alterations during seizures potentially can result in cardiac dysfunction." Then begin next sentence as "Some postulated mechanisms for this phenomenon, which may also be associated with sudden cardiac death, are heart rate variability, ictal bradycardia, atrio-ventricular block, and asystole. that have been postulated to be some of the underlying mechanisms for sudden unexpected death including heart rate variability, ictal bradycardia, atrio-ventricular block and asystole. Peri ictal atrio-ventricular conduction block has been rarely reported [2].

The differentiation of epileptiform seizure-induced cardiac arrhythmias from drug associated atrio-ventricular conduction block is paramount. It is thought that seizure activity predominantly in the left temporal lobe potentially can activate parasympathetic function and results in bradyarrhythmias [3]. In order to differentiate drug induced bradyarrhythmias from seizure related bradyarrhythmias the most important point is simultaneous Holter monitoring and video electroencephalogram documentation of bradyarrhythmia during an ictal discharge which usually starts 10–30 s after the seizure initiation

and apparently after the seizure discharges become bilateral [3]. It should be known that the all undesirable cardiac effects of epilepsy can best be avoided by complete seizure control with administration of appropriate anticonvulsant drugs whereas drug induced bradyarrhythmias necessitate drug cessation or modification of given

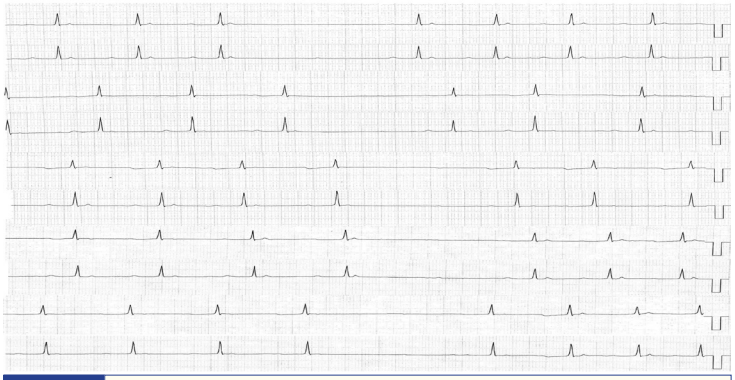

Figure 1: Holter monitoring strips revealing atrio-ventricular conduction block are shown

doses. However, it should be kept in mind that antiepileptic drug therapy may also potentially alter autonomic function or produce proarrhythmogenic effects as in our case.

On several occasions, our case was extensively investigated at an outside hospital for near syncope and atrio-venricular block attacks on Holter monitoring and the cause of the atrio-venricular block remained unexplained, despite investigations. Finally pacemaker insertion was recommended. In hindsight, it was apparent that she was suffering from side effects of valproic acid. This case report reminds us to review our patients' medications meticulously when they present with symptoms that are difficult to explain. We suggest that patients in whom atrio-ventricular block is shown on Holter monitoring valproic acid usage should be checked as illustrated by our case in order to lessen the misdiagnosis, as well as avoid unnecessary pacemaker implantation.

Conclusions

Healthcare providers must be alert to the possibility of side effects of valproic acid when patients suffer from atrio-ventricular block recurrently with symptoms that are difficult to explain.

Conflict Of Interests

None.

Disclosures

None.

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Time To Revisit The Time In The Therapeutic Range

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Abstract

In recent clinical trials, the \"quality\" of warfarin management has been characterized by the time in therapeutic range (TTR) – with the therapeutic range being an INR between 2.0 and 3.0. In many reviews of recent clinical trials, differences in the TTR have been used comparatively to critique and contrast the trials. However, TTR is a more complex measurement than is commonly appreciated, and many factors that underlie the TTR calculation, which can differ from trial to trial, have not been adequately addressed. This manuscript attempts to explain these issues so as to help the reader understand the factors that contribute to TTR and to understand the limitations of TTR so as to better understand anticoagulation trial results. It also addresses the issue of INRs below or above the therapeutic range, that can differ among trials, that are not provided simply by presenting a TTR value, but that can in a substantial way affect the bleeding risk and embolism-prevention likelihood of anticoagulation in a trial.

Introduction

Warfarin is a drug we love to hate. Despite the fact that we are extremely familiar with it (as it has been available to clinicians for over 60 years) and recognize that, when used properly, it is highly effective for reducing stroke and systemic embolism (SSE) [1] in at-risk patients with atrial fibrillation (AF) and/or mechanical heart valves as well as for treating and preventing venous thromboembolism (VTE), it is difficult to use. Patients and physicians alike find reasons to avoid it – too many doses to choose from, too many dietary interactions, too many drug and herbal interactions (both pharmacokinetic and pharmcodynamic), the risk of bleeding, and the need to monitor it closely because of these concerns. With respect to the latter, monitoring has taken the form of measuring the prothrombin time (PT), and reporting it as an international normalized ratio (INR) so that the results are consistently understandable regardless of the specific laboratory methodology. The target INR that appears to most effectively balance the risk of SSE or VTE versus the risk of bleeding is a range between 2.0 and 3.0 [2],[3] [except for a slightly higher range with mechanical valves and a slightly lower range in some Asian populations].

Rarely, however, does the INR remain stable in a given patient across time. More typically it varies, sometimes dramatically, in association with: dietary fluctuations; changes in the pharmacy-dispensed formulation; initiation, discontinuation, or change in dose of one or more concomitant medications, supplements, or over-the counter agents; changes in bowel flora or bowel function due to intercurrent or chronic diseases or the effect of drugs (such as antibiotics, NSAIDS, etc.[4]); and more [Table 1]. Thus, as a means of assessing the stability of warfarin anticoagulation (often used synonymously with the adequacy of anticoagulation), the Time in the Therapeutic Range (TTR)[5] has become a common reportable measure in clinical trials. TTR is presumed to represent the percent of time the INR remains in the target range across time.

While "on the surface"TTR should be an easily understandable and easily calculated number, this turns out not to be as straightforward as it may seem. Shouldn't the TTR simply be the number of INR values in the target range (numerator) over the total number of INR values measured (denominator)? At first glance, that might seem to be the case. Notably, this approach has been useful in assessing individual patients and has been the one most often used by practitioners [6] but it falls short when applied across patients in clinical trials [7] for multiple reasons: (1) How should one account for values measured in the first week or two before the warfarin effect is stabilized and the INR has had an opportunity to reach the target range? (2) How should one account for differences in frequency of INR measurements, such as daily or weekly versus monthly (and the non-measured fluctuations that might occur between measurements)? (3) How should one handle INR results during planned temporary discontinuations of warfarin, as, for example, due to surgery? (4) How should one assess the TTR as reported across clinical trials if the issues raised above are not handled identically from trial to trial or across geographical regions or types of practices within a single trial? A second approach that has been tried in clinical trials to deal in part with some of the above concerns is the cross-section-of-files method, where the INRs of all patients in a trial are sampled at a given point in time. [7] However, this approach also fails to successfully deal with all of the above issues. Patients will be missed if all subjects in a trial do not have an INR check in the same time frame/at the same frequency. And, variation due to changes in dose or diet will only be detected by chance. Accordingly, a third method was proposed by Rosendaal

Key Words
Therapeutic Range, TTR, Time in the Therapeutic Range.

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and colleagues. [8] It uses linear interpolation to assign an INR to each day in which an INR was not actually measured, based upon the prior and next actually measured INRs (see more below). Then the total number of measured or assigned INRs in the 2.0-3.0 range over the total number of combined measured and assigned INRs is used to determine the mean TTR. However, while this method is now the most common approach used in recent clinical trials, it, too, has major limitations.

Consider: is it possible to meaningfully compare the TTRs across the following examples?

(1)In trial A, a phase 2 study of a new oral anticoagulant versus warfarin, a 2-month run-in phase is followed by a 10-month maintenance phase. Warfarin is begun and INRs are checked per protocol on day 1, 3, 7, 11,14, 28, and then every 4 weeks. The INR exceeds 2.0 for the first time on day 14. Should the INR values on days 1, 3, 7, and 11 be included in the calculation of the TTR? If one uses the method of Rosendaal et al [8] they would be. Such was the case in the ROCKET-AF and ARISTOTLE trials [9],[10] of rivaroxaban vs warfarin and apixaban vs warfarin in patients with AF. However, this was not the case in the RE-LY trial [11] of dabigatran vs warfarin in AF patients, in which values in the first week were not used (a modified Rosendaal method).

(2)In trial B, which is identical to trial A in all respects, 20% of the patients required temporary discontinuation of anticoagulation during the trial because of surgery or an interventional procedure. Should any INRs obtained during the discontinuation periods be used in the TTR calculations for the trial? They will certainly be lower than in those patients in whom no interruption occurred, and will reduce the mean TTR reported for the trial. This has not commonly been discussed in clinical trial reports (though such days have been excluded in modified Rosendaal calculations).

(3)In trial C, which is identical to trial A except that the frequency of INR checks is left to the individual physician managing each patient. How should one compare the TTR in trial A, where values are checked only monthly to those in trial C, in which there is an average of 2.7 checks/month? If all of the monthly checks in trial A were in range the TTR would be 100%; however, if all the q4 week checks in trial C were in range but several of those checked during the month were not (and led to a change in warfarin dose), the TTR would be lower, despite the same values at the same 4-weekly checks. The Rosendaal approach to different frequency of INR checks, as per the above, uses linear interpolation of values for days between checks, such that an assumed value can be assigned to each day between actual checks. However, this cannot reflect the reality of the PT values when a low result leads to an increase in warfarin dose (and an increase in the PT in an average of 3 days) or a decrease in warfarin dose (and a decrease in PT in 3 days). In a representative patient in whom an INR of 1.5 leads to an increase in warfarin dose the day the low value is reported with a resultant rise in INR to 2.4 in 4 days, 2.6 at 2 weeks, and stability the rest of the month, the actual TTR would be higher in this patient than it would have been simply using the Rosendaal method and interpolating values from 1.5 to 2.6 four weeks. Interpolation will not increase the INR from 1.5 to 2.4 in 4 days, but rather, interpolated values would reach 2.4 in over 3 weeks and would be under 2.0 for almost 2 weeks.

(4)Trials D and E are both multinational studies of a new oral anticoagulant versus warfarin. Participating centers in trial D include: 40% U.S. and Canada, 30% western Europe, 15% eastern Europe, 10% Asian, and 5% south American. Participating centers in trial E include: 10% U.S. and Canada, 35% western Europe, 25% eastern Europe, 25% Asian, and 5% south American. In ROCKET-AF, INR rechecks averaged 8 days in North America if the INR was <1.5 and 14 days for an INR 1.5-1.9; however, it was 30 days in non-U.S., non-Western Europe centers. [12], [13] In ROCKET-AF, the mean TTR was 36% in India and 75% in Sweden. [11] If the same geographical differences in recheck frequency (often reflecting access to care, local traditions, source of payment for care, and more) occurred in trials D and E as occurred in ROCKET-AF, then could we truly compare the mean TTR values in trial D to those in trial E?

(5)In trial F, all patients receive all of their care from the physicians in the trial centers. In trial G, patients receive care from their trial physicians as well as from their individual primary care physicians. In the latter case, dietary changes and prescriptions for non-trial drugs are handled by the primary care physicians – often without the trial physician knowing until the patient's next study visit. Some of the primary care physicians rechecked INRs on their own when a dietary or drug change was made (some via an anticoagulation clinic, some not). Trial G has significant potential for alterations in the PTs between trial visits (and at the next trial INR measurement) whereas this is much less likely in trial F. So, again, how could one meaningfully compare the mean TTR between trials F and G?

The above examples illustrate some of the complexities in the assessment and use of TTR values to make comparative judgements about the quality of warfarin treatment across centers, populations, or trials. These complexities seem to me to have been under-considered by some critics when trials of the new direct oral anticoagulants have been reviewed and compared, one against the other, and even in the FDA approved wording in the package inserts of these new agents. Going forward, I believe we should attempt to "use a level playing field" when utilizing the concept of TTR in trial assessment.

Finally, we also need to consider two important numbers that the TTR does not tell us. That is, the percent of INRs that are below 2.0 (low) and above 3.0 (high). Each of two trials could have a mean TTR of 68%, but in one, 30% of INRs are low and 2% are high, while the opposite is true in the other. In the former, the concern would be an increased risk of thromboembolism while in the latter, the concern would be an increased risk of bleeding. Might such account for differences in NOAC vs warfarin bleeding rates among the recent pivotal trials? We cannot know since such information has not been uniformly provided. Accordingly, a more meaningful although more complex measure might be TTR-F, M%, N, R, X%/X%, where F=average time between INR checks, M=mean of all INRs, N=number of INR measurements, R = range of INR values, and X%/X% = the percent of INRs 2.0/3.0. This approach would provide not only the mean TTR but information regarding important variables that affected its calculation plus important information regarding risks that the TTR does not detail. However, this suggestion has not yet been tested clinically. If significant differences exist among these numbers across trials, despite similar TTRs, they could be important in understanding and comparing the reported efficacy and bleeding rates in the trials, such as those of the recent pivotal NOAC versus warfarin trials in atrial fibrillation.

Thus, in sum: assessing and understanding TTR is a complex issue. Simple numerical averaging in a given patient is simple to calculate, but this approach is not truly suitable to clinical trials or even to inter-patient comparisons, though it can be of importance in the

Table 1: Some factors that can affect the INR and that relate to the interpretation of TTR

A.Common factors that can affect the INR:
Dietary fluctuations;
Changes in the pharmacy-dispensed formulation;
Initiation, discontinuation, or change in dose of one or more concomitant medications, supplements, or over-the counter agents;
Changes in bowel flora or bowel function due to intercurrent or chronic diseases or the effect of drugs (such as antibiotics, NSAIDS, etc.);
Patient's compliance with medication and dietary instructions, and monitoring.
B.Important factors that can affect the TTR:
Method used for TTR calculation;
Frequency of INR rechecks;
Geography and local traditions regarding INR recheck frequency;
Handling of periods of temporary discontinuation of anticoagulation;
Access to care and payment for care;
Totality of care-givers involved in a patient's care, and their location and data-sharing and timing of data-sharing.
C.Clinically important values that the TTR does not provide:
The percent of time that the INR is below 2.0 (risk for thromboembolism) and that it is above 3.0 (risk for bleeding).

management of individual patients. The cross-section-of-files method has been used in some older clinical trials, but fails to adequately account for the variations in INR that occur in given patients with changes in dose, drugs, diet, frequency of INR checks, and more. It is the least frequently used approach. [6] The Rosendaal approach (or modifications of it) has been used in the most recent large clinical trials. However, it requires a computerized data set and algorithm to calculate; it is not adequately flexible to account for real changes in INR that occur between actual INR measurements if factors that can alter the INR have occurred or if the frequency of INR rechecks varies significantly among patients or centers, and more. Accordingly, even it is imperfect (and when tested against the other two methods discussed above, it has given lower values [7]). Therefore, while TTRs will undoubtedly continue to be used in assessing vitamin K antagonist therapy, being better than any alternative way to quantitatively and qualitatively assess the adequacy of the regimen being used, its limitations and biases will need to be kept in mind when the values obtained are used in patient management or trial design, interpretation, and comparison.

Conflict Of Interests

None.

Disclosures

Dr. Reiffel has been an investigator in, a consultant for, and/or served on a speaker's bureau for: Boehringer Ingelheim, BMS, Daiichi Sankyo, Janssen, Pfizer, Portola pharmaceutical companies.

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Prevention Of Cardiac Implantable Electronic Device Infections: Update And Evaluation Of The Potential Role For Capsulectomy Or The Antibiotic Pouch

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Abstract

Cardiac implantable electronic device (CIED) infections can have devastating implications for patient morbidity and mortality. Over the past decade, the infection rate has risen out of proportion to implant rates, and has prompted the development of innovative solutions designed to reduce infections. The first section of this review provides a summary of the contemporary knowledge regarding the incidence, prevalence, microbiology, and risk factors for cardiac implantable electronic device infections. The second section addresses prevention with an emphasis on the potential role of novel procedural approaches, such as capsulectomy and the antibacterial envelope, in reducing CIED infection.

Introduction

Cardiac electronic implantable device (CIED) infections are devastating, contribute to morbidity and mortality, and are potentially disfiguring for patients. [1] The focus of this document is first to review contemporary information describing incidence, prevalence and microbiology of CIED infections, and then to describe the role of novel therapeutic options developed to reduce this type of complication.

Incidence, Prevalence, and Microbiology

Ia. Definition

CIED infections encompass a spectrum of possible local and/or systemic findings. [2],[3] The clinical presentation can range from the common indolent infection to the rare presentation of acute sepsis syndrome. [3],[4]

One paradigm for categorizing these infections is based on the involved device or anatomic structures. For example, a pocket infection is generally characterized by findings localized to the soft tissue and may or may not have associated bacteremia. In contrast, endocarditis includes the presence of bacteremia with the involvement of vascular or cardiac tissue demonstrated with imaging such as transthoracic or transesophageal echocardiography. Imaging demonstrates lesions or masses on native tissue or associated with endocardial leads. However, abnormalities on imaging in the absence of bacteremia or signs of infection are not diagnostic of CIED infection. The spectrum of CIED infection also includes hematogenous seeding of endovascular leads from remote sources of infection, such as osteomyelitis.

CIED infections can also be described using the Center for Disease Control's (CDC) definition of surgical site infections. [5] The criteria for superficial incisional, deep incisional, and organ/tissue infection are shown in [Table 1]. As most CIED procedures involve the continued presence of an implanted device, the time course for the development of such an infection is out to one year after the procedure. Although a positive wound culture is not always present in situations where the device has eroded through the skin, it is important to note that these are, by expert consensus, considered infected systems. [4] [Figure 1] is an example of an erosion. In cases of erosion, negative cultures may be due, in part, to the prior use of empiric antibiotics for localized swelling or redness

1b. Incidence and Prevalence

The incidence of CIED infection for initial implants has been determined from prospective randomized trials of pre-incisional intravenous antibiotics. One of the first randomized trials of intravenous antibiotics, reported in 1981, randomized patients who were scheduled to have a transvenous pacemaker implanted, to both intravenous flucloxacillin and intramuscular benzylpenicillin or to no antibiotics.[6] Two hundred and thirty four patients received antibiotics and one hundred and ninety-seven did not. Infection rates were 0.8% for the antibiotic treated group and 3.6% in the group who did not receive antibiotics. A similar infection rate was seen in the more contemporary randomized trial of cefazolin reported in 2009.[7] In that prospective randomized trial, the overall incidence of infection was 2% with a rate of 0.6% in the cefazolin arm and 3.2% in in the placebo treated group. The incidence of infection after generator replacement has also been prospectively determined. The REPLACE Registry, a prospective multicenter registry that enrolled

Key Words

Cardiac implantable electronic device, Infection, Capsulectomy, Antibacterial envelope.

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and followed 1744 patients after pacemaker or ICD generator replacement, revision, or upgrade, described an infection rate of 1.3%. [8]

The prevalence of CIED infection varies among published series, by duration of the follow-up period, and by CIED type. For example, in a sample of single, dual and cardiac resynchronization defibrillators from the American College of Cardiology Foundation National Cardiovascular Disease Registry (NCDR) and matched Medicare claims data, the prevalence of an infection was 1.7 % over a three year period. [9] The infection rate in single chamber devices was 1.4%, in dual chamber devices 1.5%, and in CRT devices 2.0%; (P<0.001). This analysis also demonstrated that the infection rate for generator replacement procedures was greater than initial implants, 1.9% vs 1.6% respectively, (P < 0.0001).[9]

Table 1: Center for Disease Control Definitions of Surgical Site Infections (SSI)[5]

Superficial Incisional SSI: Limited to skin or subcutaneous tissue
Onset within 30d of procedure or operation
Presence of at least one of the following:
Purulent drainage from the incision
Organism identified from aseptically obtained fluid or tissue (+ gram stain or culture)
At least one clinical sign of infection such as pain, tenderness, swelling, redness, warmth
Diagnosis of superficial incisional SSI by surgeon or attending physician
Deep Incisional SSI: Involves deep tissue layers such as muscle or fascia
Onset within 30d of procedure or operation if no implant left in place with infection related to procedure or operation
Onset within 365d of procedure if implant left in place with infection related to procedure or operation
Presence of at least one of the following
Purulent drainage from deep in the incision
Spontaneous dehiscence
At least one clinical sign of infection such as temperature > 38 pain, tenderness, swelling, redness, warmth
Abscess or evidence of infection seen on direct examination or imaging
Diagnosis of deep infection by surgeon or attending physician
Organ/Space SSI: involves organ or space manipulated during operation or procedure exclusive of incision
Onset within 30d of procedure or operation if no implant left in place with infection related to procedure or operation
Onset within 365d of procedure if implant left in place with infection related to procedure or operation
Presence of at least one of the following:
Purulent drainage from a drain placed into the organ or space
Organism identified from aseptically obtained fluid or tissue culture (+ gram stain or culture) from organ/space
Abscess or evidence of infection seen on direct examination or imaging
Diagnosis of organ/space infection by surgeon or attending physician 1.6% respectively,(P<0.0001).[9]

1d. Microbiology

Causative organisms for CIED infections can result from migration from the pre-axillary flora or from hematogenous seeding. The role of the pre-axillary flora as a potential reservoir of microorganisms is found in an elegant analysis from Da Costa and colleagues.[10] Three bacteriologic specimens were taken from each patient: first from the skin prior to skin antisepsis, second, from the pocket at the time of formation; , and third, from the pocket at the time of generator insertion. Patients were followed for the development of an infection. Skin antisepsis in this series was with both a 10% and subsequent 7.5% solution of povidone iodine. Overall, preoperative

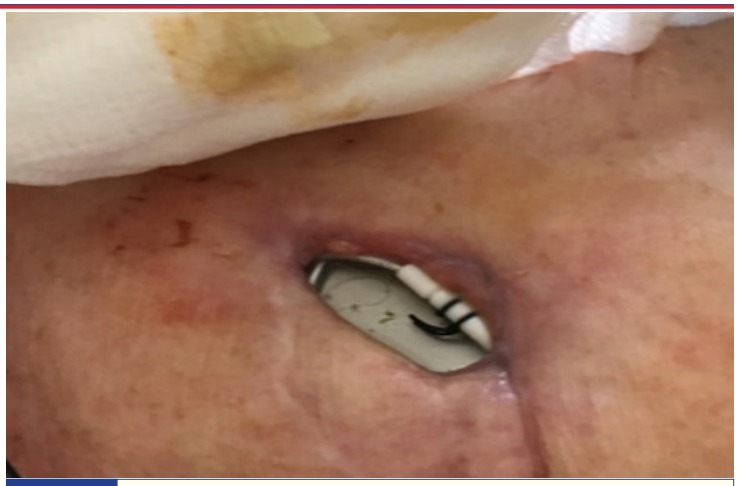

Figure 1: Pacemaker pocket with erosion.Generator and lead with suture sleeve vistible. Notice the lack of surrounding erythema

skin cultures were positive in 88.3% of samples; in 48% of samples obtained from the pocket prior to generator insertion and in 37% of samples obtained again prior to skin closing. The rate of clinical infection in these patients, who, incidentally, were not treated with pre-incisional intravenous antibiotics, was 4.5%. In 60% of the patients who developed a clinical infection, the organism cultured at the time of the procedure was present in the screening cultures. The dominant organisms in the positive cultures were of staphylococcal species, followed by enterococci and streptococcus viridans.

A recent retrospective series of CIED infections from one tertiary referral center, similarly reported a preponderance of staphylococcal infections. [11] Coagulase negative staphylococci identified in 18.8% of the cultures, methicillin-sensitive staphylococci aureus in 15.8%, methicillin resistant staphylococci in 15.0%, and methicillin resistant coagulase negative staphylococci in 18.8%. The remaining organisms cultured were atypical organisms such as vancomycin resistant enterococcus, or gram negative organisms. Cultures negative for an identifiable organism were seen in 13.2% of the cases. [11]

1e. Risk Factors for infection

Patient factors

This identification of risk factors and the strength of association with infection is dependent upon the factors collected and the infection rate. Risk factors for the development of CIED infection can be characterized as patient factors or procedural factors. Recognized patient risk factors include the presence of a fever within twenty-four hours of the implant procedure, chronic kidney disease, diabetes mellitus, steroid use, prior valve surgery, chronic lung disease, cerebrovascular disease, and development of a clinically significant hematoma. [7],[8],[12]-[14] A specific analysis of ICD infections from the NCDR in over 200,000 patients identified prior valve surgery, cerebrovascular disease, chronic lung disease, and renal replacement therapy with hemodialysis as independent risk factors for infection. [9]

Procedural Factors

Procedural factors that have been associated with infection include the presence of a temporary wire, need for re-intervention, use of drains, or multiple procedures. [9], [14],[15]

Prevention

Antibiotics: Intravenous, intra-procedural, post-procedural, skin antisepsis

In addition to proper surgical technique, intravenous pre-incisional

antibiotics is fundamental for prevention of CIED infection is pre-incision intravenous antibiotics. Prior to 1994, the data supporting the use of intravenous antibiotics was variable.[6], [16] In 1994, Drs. Mounsey and colleagues reported one of the first prospective randomized trials that demonstrated a benefit of pre-incision antibiotics. In this trial, four hundred and thirty-one patients were randomized to administration of flucloxacillin or clindamycin, or no antibiotic, administered pre-operatively and continued for forty-eight hours post procedure. The infection rate was 0% in the patients treated with antibiotics and 4% (p= 0.003) in the patients randomized to no antibiotic treatment.[15] In 2009, the landmark de Oliveria prospective double-blind placebo-controlled trial of pre-incisional antibiotics before implantable cardioverter defibrillator or pacemaker procedures was published. This trial planned to randomize 1000 patients with follow-up out to six months. The definition of infection included superficial infection of the pocket with the presence of purulence and no systemic manifestations, pocket infection with positive microbiological culture findings, and systemic infections. The infection rate was 0.63% in the antibiotic treated arm and 3.28% in the placebo arm (p=0.016). The trial was halted after 649 patients due to a significant difference in infection rate favoring the antibiotic treated arm. In 2010, the American Heart Association published a Scientific Statement "Update on Cardiovascular Implantable Electronic Device Infections and Their Management" and recommended that a parenteral administered antibiotic be given 1 hour before the procedure. [4]

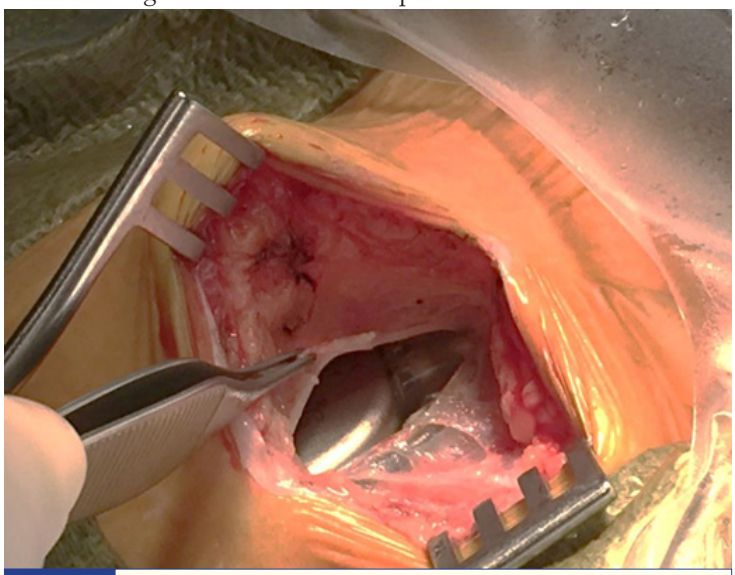

Figure 2A: Intra-operative view demonstrating the capsule The Adson's forceps are grabbing the superior surface of the fibrotic capsule

Less well evaluated is the role of intra-procedural antibiotic irrigation and post-procedural parenteral or oral antibiotics. The use of wound irrigation in contaminated wounds stems from battlefield medicine experience. Despite anecdotal experience with this practice, the effect of intra-procedural wound irrigation for prevention of CIED infection has not been specifically evaluated to date. [16] Similarly, post-operative antibiotics have been included in prior trials of parenteral antibiotics, but the effect of post-procedural antibiotic administration on the subsequent infection rate was not evaluated, possibly due to the low absolute number of infections. [15] In the prospectively designed REPLACE trial which included a pre-specified infection analysis, a higher infection rate was seen

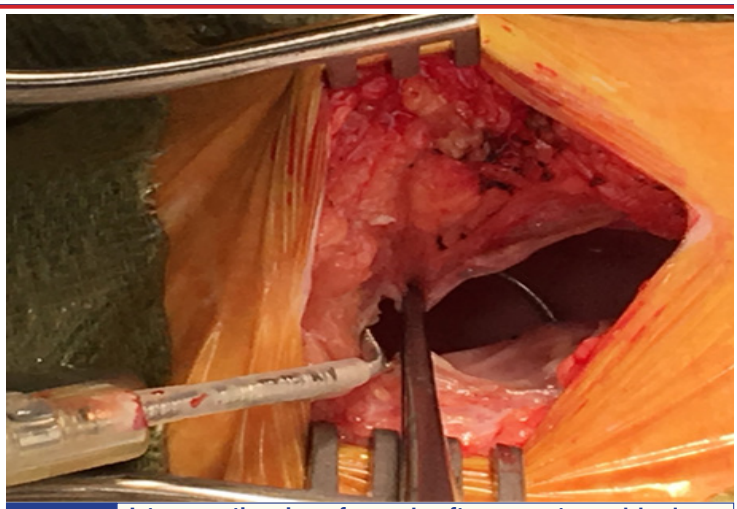

Figure 2B: Intra-operative view of capsule after generator and lead were removed.The blue arrow head identifies the surface of the fibrotic capsule.

in patients treated with post-operative antibiotics. However, in this registry, the use of any or no post-operative antibiotics was left to the individual investigator, thus limiting any specific conclusions.[8]

The on-going PADIT Trial will prospectively evaluate the practice of post-operative antibiotic administration to reduce CIED infection. This investigative strategy involves an investigative center based cluster crossover design to evaluate the role of incremental antibiotics before during and after the CIED procedure. Each implanting center will be randomized to pre-incision cefazolin (or vancomycin in penicillin allergic patients) alone, or with intra-operative bacitracin 50,000 U in normal saline wound irrigation and a two day post-operative course of oral cephalexin, or clindamycin in penicillin allergic patients. Patients eligible for inclusion are those who present for generator replacement, revision or upgrade procedures or cardiac resynchronization procedures. [17]

Skin antisepsis is another recognized tool in reducing surgical site infections. Two current formulations are available in contemporary practice, povidone iodine, and chlorhexidine gluconate. Povidone-iodine is a complex of bactericidal iodine and a synthetic polymer.[18] Chlorhexidine gluconate is both bactericidal via lysis of cell membranes, and is also bacteriostatic. To date, there have been no randomized prospective evaluations of these two agents in CIED procedures. A randomized trial performed in adult patients undergoing clean contaminated surgery in the gastrointestinal, urologic abdominal surgery, and non-abdominal surgery, demonstrated an overall surgical site infection rate of 9.5% in patients treated with chlorhexidine alcohol and 16.1% in the povidone-iodine treated patients (p= 0.004). [19] The type of skin antisepsis was also prospectively collected in the REPLACE Registry. In that pre-specified infection analysis, all patients received pre-procedural antibiotics. Centers with infection rates greater than 5%, were sites more likely to use povidone iodine as a skin antiseptic where chlorhexidine gluconate use was more prevalent at low infection rate sites. However, a subsequent single center retrospective analysis from the Cleveland Clinic of 2,792 CIED patients, demonstrated an identical infection rate of 1.1% at one year irrespective of skin antisepsis with povidone iodine or chlorhexidine gluconate. [20]

Procedural approaches to preventing CIED infections

Optimizing patients' clinical status prior to device placement is good clinical practice; a prolonged procedure during acute

decompensated heart failure is unlikely to improve compromised cardiac or pulmonary status. Yet, eliminating medical comorbidities is unrealistic, so targeting procedural factors may be an alternative approach in attempts to reduce infection. Changes in battery chemistry to improve longevity, algorithms to reduce ventricular pacing, and evoked response algorithms to allow lower pacing output voltages are a few approaches that may indirectly reduce infection by reducing the number of procedures patients face over their lifetime.

Hematomas

The development of a hematoma after CIED implant has been associated with increased length of hospital stay, increased hospitalization costs, and greater in-hospital mortality.[21] Importantly, hematoma development has been intermittently identified as a risk factor for the development of a CIED infection in multiple trials. The development of a post-operative hematoma was identified as a risk factor for infection in the REPLACE Registry.[8] The recently published BRUISE CONTROL INFECTION study demonstrated an infection rate of 11% in patients who developed a clinically significant hematoma, compared to an infection rate of 1.5% in patients who did not develop a hematoma, corresponding to a greater than seven fold risk of infection if a hematoma develops.[13]

Strategies to reduce hematomas are recommended in the AHA guidelines, such as meticulous electrocautery to control local bleeding, use of pressure dressings, and evacuating the device pocket if impending dehiscence.[4] Due in part to the BRUISE CONTROL Trial, minimizing the use of heparin products in the peri-procedural period is now standard of care.[22]

The use of topical hemostatic agents is common in surgical practice.[23] Limited data in pacemaker and ICD patients is available. Interestingly, one prospective trial of a topical hemostatic agent after CIED implant was terminated early due to the increased risk of infection, and it did not reduce the incidence of pocket hematoma.[24] Conversely, a smaller retrospective series utilizing oxidized regenerated cellulose resulted in no hematomas nor infections.[25]

Capsulectomy

Wound healing requires a multi-step series of biological processes that ultimately result in the restoration of tissue integrity. The phases of wound healing begin with inflammation, re-epithelialization, keratinocyte proliferation, matrix metalloprotinease deposition, angiogenesis, and ultimately wound contraction and closure.[26]

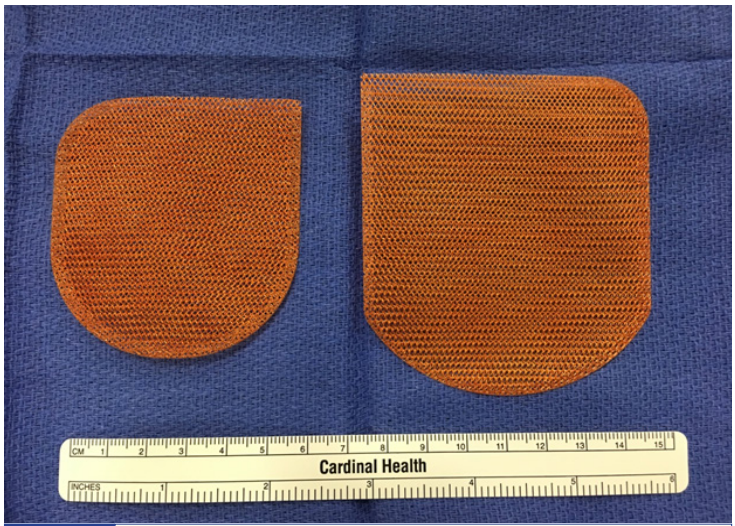

Figure 3: Tyrex TM resorbable antibiotic envelopes.

Furthermore, the body's ultimate response to a retained foreign object is a complex multi-phase inflammatory response that involves expression of transforming growth factor-B, and finally results in fibrosis. This end result is recognized as a capsule as shown in [Figure 2A] and [Figure 2B]. This fibrotic avascular capsule has been implicated as a potential source of infection due to the presence of bacterial colonization.[27] Based on this, one potential approach to reduce infection is to consider excision of this fibrous capsule at the time of generator replacement. This concept was recently evaluated in the prospective randomized single-center MAKE IT CLEAN trial.[28] Eligible patients were those who were to undergo device replacement, upgrade, or lead extraction. The randomization was between pocket revision or no pocket revision. Pocket revision was defined as complete capsule excision which included removal of the floor and roof of the capsule, and included removal of all fibrous tissue surrounding the leads and lead anchoring sleeves. All patients received pre-incisional antibiotics within one hour of the procedure. Skin antisepsis was chlorhexidine, and all pockets were irrigated with the same antibiotic that was administered prior to the incision. The use of topical hemostatic agents and the strategy for peri-procedural management of anticoagulants was at the discretion of the implanting physician. The primary endpoint was the presence of a deep pocket infection. The secondary endpoints included the presence of a superficial pocket infection, hematoma, prolonged serosanguinous drainage for greater than three days, or mortality within the one year following the procedure. Two hundred and fifty-eight patients were randomized with one hundred and thirty-one to the pocket revision group and one hundred and twenty-seven to the no revision group. Eleven patients crossed over to the other groups due to specific operative findings. Not unexpectedly, these findings included: i) a thin anterior capsule seen in frail patients that precluded pocket revision; or ii) the presence of significant adherent tissue that required removal to enable lead revision. Procedure types were similarly distributed between the pocket revision and no revision groups, and there was no statistically significant difference in procedure duration. At the one year follow-up, no deep-space infections were seen in either group, which persisted at a mean follow-up of 33± 76 months. The superficial infection rate was not statistically different between the two groups (1.5% in pocket revision group, 4.7% in non- revision group, P= 0.13). Similarly, mortality was no different with three deaths in the pocket revision group and one death in the no-revision group (P=0.3). Serosanguinous discharge for greater than three days was more common by a factor of ten in the no revision group (7% versus 0.7% in the pocket revision group, P= 0.004). The hematoma rate in the pocket revision group, 6.1%, was markedly greater than the 0.8% observed in the no-revision group (p=0.03), and two patients who had the pocket revision required a second procedure for hematoma evacuation. No patient who developed a hematoma in either group was "bridged" with heparin or enoxaparin. Thus, routine pocket revision with capsulectomy is not recommended as a preventative strategy to reduce CIED infection, and increases the risk of pocket hematomas.[28] It is important to clarify, however, that in the presence of an existing deep pocket infection, debridement of all infected tissue is imperative for complete eradication.

Pocket-based interventions

Pocket based interventions as a technique to reduce infections have been a source of interest for a number of years. One such intervention is the prophylactic use of a removable drain such as red rubber

catheters, Penrose, or other small catheters. In a retrospective series of 288 patients from a single center in which drains were used in half of the population, the nine patients who developed an infection all had prophylactic drains placed during their procedures.[29] More recently, an envelope or pouch of porcine small intestinal submucosa extracellular matrix, the CorMatrix® CanGaroo™ Cardiovascular Device Pocket, has been available for use in cardiac surgical procedures.[30], [31] Its proposed use in CIED procedures is for pocket stabilization and reinforcement. There are no data to date on its impact on CIED infections. Similarly, antibiotic impregnated suture is available, with no clinical trials in CIED infections. Topical dressings that include silver have likewise not been systematically evaluated in CIED procedures, and are generally reserved for situations of delayed wound healing due to elevated microbial burden. [32]

As discussed in section IIa above, intravenous antibiotic administration prior to skin incision is crucial in preventing CIED infection. Topical antisepsis and pocket irrigation are short term measures; the contact time with the wound is relatively short. More prolonged local delivery of antibiotics to the pocket is one of the contemporary approaches to reducing CIED infection. The antibacterial envelope is one such approach, and is comprised of a polypropylene mesh with a bio-absorbable polymer embedded with minocycline and rifampin. Rifampin inhibits bacterial RNA synthesis by binding to the beta subunit of DNA polymerase. Minocycline, a tetracycline derivative, inhibits bacterial protein synthesis. Both agents are active against staphylococci. This envelope is designed to release the antibiotics over seven days. The current version is a mesh that is fully resorbable at 9 weeks, with no systemic absorption.

This antibacterial envelope has been evaluated in multiple retrospective cohort series. One of the first series described 642 patients undergoing pacemaker, ICD or CRT procedures who were implanted with the original non-resorbable, antibacterial pouch. [33] Three major infections developed; all three patients had three or greater risk factors for infection. A subsequent case control series of 260 patients and 639 controls from Vanderbilt University demonstrated an infection rate of 0.4% in the patients who received an antibacterial envelope versus a 3.0% infection rate in the controls (P=0.044).[34] Propensity matching was done in a 209 patient subset with similar results, 0.5% infection rate in the envelope treated patients and 4.3% in the controls, P=0.035.[34] A subsequent propensity based single center evaluation also demonstrated a significant reduction in the likelihood of infection at 6 months with use of the envelope, 1.1% versus 3.6% in matched controls, P= 0.048). [35] The on-going WRAP IT Trial, [NCT #02277990] a multicenter prospective randomized trial, is evaluating the resorbable antibacterial envelope in dual low power or high power generator replacements and initial cardiac resynchronization device implants in up to 7,764 subjects from 225 world-wide sites. For this trial, CIED infection is defined as 1) superficial cellulitis in the region of the CIED pocket with wound dehiscence, erosion, or purulent drainage, 2) deep infection as defined by the surgical site infection definitions discussed earlier, 3) persistent bacteremia, or 4) endocarditis. The primary endpoint is the major infection rate at 12 months, with secondary endpoints of procedure-related, and system related complication rates, as well as infection rates over the entire follow-up period.

Conclusion

The prevalence and incidence of CIED infection remain significant. Pre-incisional antibiotics are critical, as is careful attention to hemostasis to avoid hematomas. Interventions that target the pocket or capsule have demonstrated mixed results to date. Capsulectomy has been shown to increase the hematoma rate without any impact on the infection rate. Prophylactic use of pocket drains demonstrated no reduction in infection. A novel combination of rifampin and minocycline imbedded into a biopolymer-based resorbable mesh is being prospectively evaluated in an on-going clinical trial.

Conflict Of Interests

None.

Disclosures

Dr. Gleva reports modest research and speaking honoraria from BIOTRONIK, Boston Scientific, Medtronic, Kestra Medical, and St. Jude Medical. Dr. Poole reports honoraria from Biotronik, Boston Scientific, Medtronic, St. Jude Medical; advisory board participation for Boston Scientific, Kestra Medical; research grants from Physio Control, Boston Scientific; and equity in Cameron Health.

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Percutaneous left atrial appendage closure: is there a role in valvular atrial fibrillation

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Abstract

Atrial fibrillation, a chronic and highly morbid cardiovascular condition which affects over 33 million people worldwide, can be broadly categorized as valvular vs non-valvular in etiology. However, definitions of valvular atrial fibrillation have varied widely in the literature, and there is no clear consensus definition to date. Historically, patients with atrial fibrillation in the setting of rheumatic mitral valve disease have constituted a particularly high risk group for cardioembolic stroke, and for this reason many contemporary trials of pharmaceutical and device therapies for atrial fibrillation have systematically excluded patients with valvular heart disease. Therefore, vitamin K antagonism remains the favored approach to mitigate stroke risk in valvular atrial fibrillation, and the optimal strategy to treat atrial fibrillation patients with valvular heart disease who cannot tolerate oral anticoagulation therapy is unknown. Recent trials have demonstrated an important role for percutaneous left atrial appendage occlusion devices in patients with non-valvular atrial fibrillation, but the role of these devices in patients with valvular atrial fibrillation is uncertain. Given the worldwide burden of valvular atrial fibrillation, future trials intended to clarify the role of percutaneous left atrial appendage closure devices in valvular atrial fibrillation should provide important insight for the care of millions of patients.

Introduction

Atrial fibrillation (AF), which affects over 33 million people worldwide,[1] is a chronic illness predominantly impacting older adults and is associated with high rates of morbidity. AF is commonly associated with structural heart disease, and the term "valvular AF" has been used to describe a heterogenous group of patients with both AF and valvular heart disease. Among patients with AF, 30% have some form of valvular heart disease detectable by echocardiography.[2] Some prior studies have considered valvular AF to include only those patients with rheumatic mitral stenosis (MS) and mechanical heart valves while others have included patients with mitral bioprosthetic heart valves, mitral valve repair, and/or other moderate or severe valvular disease including aortic valve diseases.[3] In the developing world where rheumatic heart disease remains a highly morbid condition, most cases of AF are attributable to rheumatic heart disease and would be considered valvular AF.[4]

Stroke is a feared complication with an annual risk of about 5% in patients with AF who are not treated with anticoagulation,[5],[6] and the selection of rhythm vs rate control strategy does not mitigate the risk of stroke in the long-term.[7] With increasing comorbidities, the risk of stroke may also be substantially higher in a given patient.[8]

Therefore, oral anticoagulation (OAC) therapy to reduce the risk of left atrial (LA) thrombus and consequent stroke has been a cornerstone of AF therapy. However, many patients with AF are elderly with multiple bleeding risk factors, and long-term OAC poses a clinical dilemma. In practice, 2 out of 5 patients with AF do not receive OAC despite the risk of stroke, which reflects the complexity of prescribing OAC in older adults.[9] In fact, many of the risk factors that contribute to a high stroke risk as demonstrated by the CHA2DS2-VASc score also influence the bleeding rate with OAC as exhibited by the HAS-BLED score.[8],[10]

Recently, percutaneous left atrial appendage (LAA) closure has gained attention as a strategy non-inferior to OAC in reducing stroke risk of AF patients.[6],[11] However, due to a perceived higher risk of thromboembolic events in patients with valvular AF, most contemporary pharmaceutical and device trials for stroke reduction therapy in AF have excluded patients with valvular AF.[6],[11]-[14] Therefore, little is known about the optimal treatment of patients with valvular AF, and the role of LAA closure in patients with valvular AF is uncertain. OAC with vitamin K antagonism is the strategy recommended in the American and European AF guidelines to mitigate stroke risk in valvular AF,[2],[15] reflecting the lack of evidence for novel treatments in these patients.[16] In this review we discuss the role of the LAA in valvular AF related stroke and implications for percutaneous LAA closure in patients with valvular AF.

Epidemiology and classification

AF is one of the most common chronic cardiovascular conditions affecting nearly 1 in 10 United States medicare beneficiaries > 65 years old and accounting for nearly 500,000 hospital admissions and 100,000 deaths in the United States annually.15 The incidence of AF doubles with each advancing decade of life, and the number of patients affected with AF is estimated to reach nearly 16 million

Key Words

Atrial fibrillation,Valvular heart disease,Left atrial appendage closure,Watchman

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cases in the United States by 2020 as the population ages.[6],[17] Over half of all patients with AF suffer from concomitant heart failure, ischemic heart disease, and/or hypertension.[15] However, in the developing world rheumatic heart disease is by far the most common cause of AF, far outpacing coronary artery disease, hypertension, or other cardiomyopathies.[4]

Even in the developed world, AF is commonly associated with valvular heart disease and can be broadly categorized as valvular vs non-valvular AF. The term valvular AF is not well defined, and various definitions have been employed both in major society guidelines and prior clinical trials ([Table 1]).[3],[5] For example, the most recent American AF guidelines include prior mitral valve repair in the group of patients with valvular AF while the most recent European AF guidelines do not consider prior mitral valve repair as a criteria for valvular AF.[2],[15] Such discrepancies have resulted in considerable confusion among practicing clinicians. In a survey of internists and cardiologists, 1 in 3 considered isolated aortic valve disease to constitute valvular AF,[18] whereas neither the American nor European guidelines would consider such patients as having valvular AF. It is widely accepted that patients with rheumatic MS and prior mechanical heart valves should be included amongst those with valvular AF, and many authors also include those with mitral bioprosthetic valves and mitral valve repair (although the risk of stroke varies considerably between these groups).[3],[5]

Table 1: Definitions of valvular atrial fibrillation in clinical trials and practice guidelines

Author	Year	Study Design	Valvular AF Definition
Holmes et al.[6]	2009	PROTECT AF trial: RCT of percutaneous LAA closure vs warfarin to prevent stroke in nonvalvular AF	Not defined
Connolly et al.[12]	2009	RE-LY trial: RCT of dabigatran vs warfarin to prevent stroke in nonvalvular AF	Severe heart valve disorder
Patel et al.[14]	2011	ROCKET AF trial: RCT of rivaroxaban vs warfarin to prevent stroke in nonvalvular AF	Hemodynamically significant MS or prosthetic heart valve
Granger et al.[13]	2011	ARISTOTLE trial: RCT of apixaban vs warfarin to prevent stroke in nonvalvular AF	Moderate or severe MS or prosthetic heart valve
Connolly et al.[57]	2011	AVERROES trial: RCT of apixaban vs aspirin to prevent stroke in nonvalvular AF	Valvular disease requiring surgery
Giugliano et al.[58]	2013	ENGAGE AF-TIMI 48 trial: RCT of edoxaban vs warfari prevent stroke in nonvalvular AF	Moderate or severe MS or mechanical heart valve
January et al.[15]	2014	AHA/ACC/HRS guidelines for the treatment of AF	Rheumatic MS, mechanical or bioprosthetic heart valve, MVR
Holmes et al.[11]	2014	PREVAIL trial: RCT of percutaneous LAA closure vs warfarin to prevent stroke in nonvalvular AF	Significant MS or mechanical heart valve
Kirchhof et al.[2]	2016	ESC/EACTS guidelines for the management of AF	Rheumatic valvular disease or mechanical heart valve

ACC = American College of Cardiology. AF = atrial fibrillation. AHA = American Heart Association. EACTS = European Association for Cardiothoracic Surgery. ESC = European Society of Cardiology. HRS = Heart Rhythm Society. LAA = left atrial appendage. MS = mitral stenosis. MVr = mitral valve repair. RCT = randomized controlled trial.

Risk of stroke and role of the left atrial appendage in valvular atrial fibrillation

Historical data from the Framingham heart study illustrated that AF is associated with a 5-fold increased risk of stroke. Among octogenarians in that study, AF was the only independent cardiovascular risk factor for stroke with the risk of stroke attributable to AF equaling 23.5% in that age group.[19] It has long been understood that most strokes related to AF result from cardioembolism due to LA thrombus.[20] The primary importance of differentiating valvular vs non-valvular etiology of AF pertains to prognostication about the risk of future stroke. The Framingham heart study data demonstrated a 17-fold increased risk of stroke in patients with AF and rheumatic heart disease compared to a 5-fold increased risk of stroke in patients with AF without rheumatic heart disease in reference to patients without AF.[21] In patients with rheumatic MS, low cardiac output with reduced transmitral flow has been implicated as a potential mechanism for increased rate of thrombus formation.[5],[22] In a study of 1544 patients with severe MS by Mahmood and colleagues, LA thrombus was identified by transesophageal echocardiogram (TEE) in 55.7% (161/289) of patients with AF and 10.2% (128/1255) of patients without AF.[23] The finding that 1 in 10 patients in the non-AF group had LA thrombus further supports the concept that rheumatic mitral valve disease may contribute to LA thrombus formation regardless of the underlying cardiac rhythm. Moreover, multiple studies have suggested that increasing severity of mitral regurgitation in the setting of both rheumatic and non-rheumatic mitral valve disease may be a protective factor for stroke, which also supports the concept that reduced transmitral flow may be related to thrombus formation. [24]-[26]

Patients with valvular AF have been long considered a particularly high-risk subset for stroke due to higher likelihood of LA thrombus[27] in the setting of low transmitral flow, mechanical heart valves, and the risk of LA thrombus that occurs in the atrium itself. In the aforementioned study by Mahmood et al., among 1544 patients with severe MS, LA thrombus was identified in 14.5% of patients regardless of the underlying cardiac rhythm, and 10.3% of patients with an LA thrombus also had LA cavity thrombus outside of the LAA.[23] In a systematic review by Blackshear and colleagues, only 57.0% of patients with rheumatic AF and documented LA thrombus had LA thrombus located in the LAA compared with 90.5% of patients with nonrheumatic AF who had their LA thrombus isolated to the LAA.[28] These data highlight the potentially different mechanisms of LA thrombus formation in patients with valvular and non-valvular AF and the increased risk for LA cavity thrombus in valvular AF ([Table 2]).

Surgical left atrial appendage closure in valvular atrial fibrillation

Over the past 2 decades closure of the LAA has gained considerable attention as a strategy to mitigate the risk of AF-related stroke based on data supporting the LAA as the primary source of thrombus in AF-related stroke.[29]-[32] Surgical LAA closure can be accomplished by a variety of techniques, but the technical success of surgical LAA closure is highly variable, ranging from 17-93%.[1],[33] In a meta-analysis of surgical LAA closure, the operation was associated with a 54% reduction in the odds of 30-day stroke, [34] supporting the notion that LAA closure in patients with valvular AF may warrant further study. Very few studies have evaluated the

benefit of surgical LAA closure solely in patients with underlying valvular heart disease, and the results have been mixed ([Table 3]). A large multicenter randomized controlled trial of surgical LAA closure is currently underway to better elucidate this issue.[35] Currently, both the American and European AF guidelines give a class IIb recommendation to consider LAA closure in patients with AF undergoing cardiac surgery, and there is no specific distinction between valvular and non-valvular operations.[2],[15]

Table 2: Location of LA thrombus in patients with valvular heart disease with or without AF

Author	Year	Study Population	Study Design	Prevalence of LA thrombus	Location of LA thrombus
Aschenberg et al.[59]	1986	21 patients with mitral stenosis. AF present in 85.7% (n=18).	Single center series	28.6% (n=6)	100% (n=6) isolated to LAA
Hwang et al.[60]	1993	147 patients with rheumatic MS.	Single center series	20.4% (n=30) 93% of (n=28) with LA thrombus had chronic AF	36.7% (n=11) isolated to LAC, 46.7% (n=14) isolated to LAA, 16.7% (n=5) in both LAC and LAA
Blackshear et al.[28]	1996	3504 patients with rheumatic AF and 1,288 patients with nonrheumatic AF.	Systematic review of 23 studies	Rheumatic AF: 12.7% (n=446) Nonrheumatic AF: 17.2% (n=222)	Rheumatic AF: 57.0% (n=254) involving LAA Nonrheumatic AF: 90.5% (n=201) involving LAA
Kaymaz et al.[61]	2001	474 patients with rheumatic mitral valve disease. AF present in 56.3% (n=267).	Single center series	22.1% (n=105)	14.3% (n=15) isolated to LAC, 61.0% (n=64) isolated to LAA, 24.8% (n=26) in both LAC and LAA
Sriman-narayana et al.[27]	2003	490 patients with rheumatic MS and AF	Single center series	33.2% (n=163)	46.0% (n=75) involving LAC, 54.0% (n=88) isolated to LAA
Parashar et al.[62]	2016	1330 patients with AF and isolated moderate or severe AS.	Single center series	3.6% (n=48)	100% (n=48) isolated to LAA

AF = atrial fibrillation. AS = aortic stenosis. LA = left atrium. LAC = left atrial cavity. LAA = left atrial appendage. MS = mitral stenosis.

Percutaneous catheter based devices for left atrial appendage closure

The WaveCrest LAA occluder device is a nitinol frame with PTFE covering which is also available in Europe and has a very high rate of successful deployment >95%, but also has not been evaluated in patients with valvular AF.[1] In contradistinction to the Amplatzer and WaveCrest devices, which are deployed endocardially, the Lariat device is a combined endocardial and epicardial device that consists of a percutaneously delivered suture to ligate the LAA. Widespread adoption of the Lariat has been limited by concerns about technical challenges and procedural safety with complete LAA closure achieved in only 86% and major bleeding in 9% in 1 series.[41] The Lariat device has not been tested in patients with valvular AF, and robust clinical trial data for the device is lacking.

The Watchman LAA occlusion device, which gained approval from the United States Food and Drug Administration (FDA) in 2015, is the favored percutaneous device for percutaneous LAA closure in the United States.[42]-[50] The device is a nitinol occlusion cage with PTFE covering that is delivered endocardially to the LAA via transseptal approach through a 14-french delivery sheath. In the PROTECT AF trial, 707 patients with non-valvular AF were randomized 2:1 to the Watchman device or OAC with dose-adjusted warfarin therapy and studied in regards to the primary composite endpoint of stroke, cardiovascular death, or systemic embolism.6 The device was successfully implanted in 88% of cases, and the primary endpoint occurred in 3.0 per 100 patient years in the Watchman group and 4.9 per 100 patient years in the warfarin group (relative risk 0.62, 95% confidence interval 0.35 – 1.25). Based on these results the Watchman was considered to be non-inferior to OAC with warfarin, and by 5-years Watchman placement proved superior to OAC for the primary efficacy endpoint (relative risk 0.61, 95% CI 0.38 – 0.97).[51] The rate of the primary safety endpoint (composite of major bleeding, pericardial effusion, device embolization) was initially higher in the Watchman group (7.4 per 100 patient years vs 4.4 per 100 patient years, relative risk 1.69, 95% confidence interval 1.10 – 3.19). However, by 5-year follow-up the difference was no longer significant (relative risk 1.21, 95% CI 0.78 – 1.94), mainly due to a significantly higher rate of hemorrhagic stroke in the warfarin group (3.3 vs 0.4%, p = 0.005).

In light of the unfavorable safety signal initially detected in the PROTECT AF trial, the PREVAIL study was designed to further clarify these concerns. Importantly, 39% of implants were performed by new operators. Overall, 407 patients were randomized 2:1 to the Watchman device or warfarin therapy and studied in regards to

Table 3: Studies of surgical left atrial appendage closure in valvular heart disease

Author	Year	Study Design	Population	Proportion with AF	Findings
Lee et al.[63]	2014	Propensity matched observational series	238 patients (119 with and 119 without LAA resection) undergoing mitral valve surgery and maze.	100% (n=238)	No difference in stroke-free survival at mean follow-up of 3.1 +/- 2.8 years.
Nagpal et al.[64]	2009	RCT	43 patients (22 with and 21 without LAA resection) undergoing mitral valve surgery.	18.6% (n=8)	No difference in rate of post-operative cerebrovascular events.
Garcia-Fernandez et al.[55]	2003	Single center series	205 patients (58 with and 157 without LAA ligation) undergoing mitral valve replacement.	Not specified	Absence of LAA ligation was independently associated with subsequent embolic events (OR 6.7, 95% CI 1.5 – 31.0, P=0.02)
Zapolanski et al.[65]	2013	Single center series	1777 patients (808 with and 969 without LAA ligation) undergoing bypass and/or valvular surgery. Valvular surgery performed in 50.8% (n=903).	14.9% (n=262)	No difference in rates of stroke or TIA.

AF = atrial fibrillation. LAA = left atrial appendage. RCT = randomized controlled trial. TIA = transient ischemic attack.

the primary composite endpoint of stroke, systemic embolism, and cardiovascular or unexplained death.[11] At 18 months, the rate of the primary endpoint was similar between the Watchman and warfarin groups (0.064 vs 0.063, relative risk 1.07, 95% confidence interval 0.57 – 1.89) but did not achieve the prespecified cutoff for non-inferiority. However, for the secondary composite endpoint (stroke or systemic embolism >7 days after randomization), the Watchman device did meet the prespecified criteria for non-inferiority compared to warfarin. Moreover, the rate of 7-day procedural complications was 4.5% in the PREVAIL study compared to 8.7% in the PROTECT AF study. A subsequent meta-analysis of 2406 patients including both trials and their respective registries demonstrated that use of the Watchman was associated with significantly fewer hemorrhagic strokes, cardiovascular or unexplained deaths, and non-procedural bleeding episodes compared to warfarin. [46] However, the Watchman group did have a significantly higher risk of ischemic stroke (1.6% vs 0.9%, hazard ratio 1.95, P=0.05) at mean follow-up of 2.7 years. Taken together, these data have supported a role for the Watchman in patients with nonvalvular AF in whom long-term OAC is not suitable.

A role for percutaneous left atrial appendage closure in valvular atrial fibrillation?

Valvular AF patients were systematically excluded from both the PROTECT AF and PREVAIL trials, and so the role of the Watchman device in these patients is unknown. The use of the Watchman in patients with valvular AF is limited to case reports, [52-54] and to our knowledge no large registry or clinical trial to date has evaluated the use of the Watchman or any other LAA closure device in valvular AF. As aforementioned, patients with rheumatic AF are more likely to have LA thrombus outside of the LAA alone compared to patients with nonvalvular AF. For this reason, LAA closure with the Watchman (or other percutaneous device) may seem to offer inadequate stroke risk reduction in patients with valvular AF. However, the aforementioned study by Garcia-Fernandez et al., demonstrated that lack of LAA ligation was an independent risk factor for future embolic events among patients with predominantly valvular AF treated with cardiac surgery, [55] and contemporary American and European AF guidelines support the use of surgical LAA closure at the time of cardiac surgery in all patients with AF regardless of the presence or absence of underlying valvular heart disease. [2,15] Moreover, a post hoc analysis of the PROTECT AF trial and continued access registry demonstrated that the net clinical benefit of the Watchman device was greatest in patients with the highest risk for thromboembolic stroke as assessed by the CHADS2 score. [56] Given that patients with valvular AF represent a group at particularly high risk for thromboembolic stroke, these data support the need for future research into the role of LAA closure in valvular AF patients. Importantly, the role of LAA closure in patients with valvular AF who cannot tolerate OAC remains unknown and ripe for investigation given the worldwide burden of rheumatic heart disease. Additionally, much of the literature on LAA closure devices has focused on LAA closure in place of long-term OAC. However, there may be a complimentary role of LAA closure in addition to long-term OAC to reduce residual stroke risk in patients with AF and high risk of stroke. OAC does not completely eliminate the risk of stroke, and in patients with valvular AF and high risk of stroke it may be reasonable to test a strategy of combined LAA closure and OAC to improve outcomes.

Conclusions and future directions

AF is a common and highly morbid condition that impacts older adults worldwide. Stroke is a devastating complication of AF, and strategies to reduce the risk of AF related stroke include OAC or LAA closure. Patients with valvular AF, which is a heterogenous group without unified definition, have been largely excluded from major pharmaceutical and device trials in this field. Therefore, the optimal strategy to mitigate stroke risk in patients with valvular AF is unknown. OAC with vitamin K antagonism is the favored strategy for stroke risk reduction in patients with valvular AF, despite recent evidence that novel OAC medicines may be superior to warfarin for stroke risk reduction in nonvalvular AF and recent device trials demonstrating a role for LAA closure in patients who cannot take long-term OAC. There is clinical equipoise about the role of percutaneous LAA closure in patients with valvular AF. LAA closure, either as monotherapy in those who cannot tolerate long-term OAC or as combination therapy in those who can tolerate long-term OAC but have high risk for stroke, may improve outcomes in valvular AF. Future studies are needed to address these potential applications. Given the worldwide burden of rheumatic heart disease and valvular AF, clarity on the role of novel percutaneous LAA closure devices in valvular AF should provide important insight for the care of millions of patients.

Conflict Of Interests

None.

Disclosures

None.

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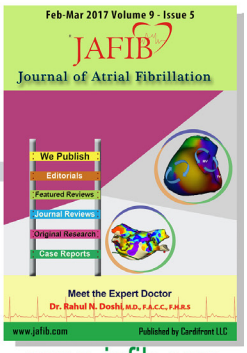

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Defibrillation Testing During Icd Implantation – Should We Or Should We Not?

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Abstract

The implantable cardioverter defibrillator (ICD) is an established therapy for improving mortality for primary and secondary prevention of sudden cardiac death. Whether to perform defibrillation threshold testing (DFT) either intraoperatively or post-operatively remains a controversial issue. The DFT is defined as the minimum energy required at which two shocks can successfully terminate ventricular fibrillation and dates from the era of surgically implanted devices with epicardial patches. Typically, a safety margin of at least 10J is employed for device programming, though some trial data suggest that a margin of 5J could be just as effective. Various methods have been utilized to perform DFT testing, and no particular method has been shown to be superior to another (Figure 1). Previously, guideline recommendations addressed the indications for ICD implantation but did not comment on DFT testing. Recent consensus statements now provide some guidance as to when it is appropriate to perform or not perform DFT testing in light of new trial data. This review will address some of the risk factors for having a higher DFT, impact of DFT testing on patient outcomes, and some of the risks and contraindications of DFT testing.

Introduction

The implantable cardioverter defibrillator (ICD) is an established therapy for improving mortality for primary and secondary prevention of sudden cardiac death. Whether to perform defibrillation threshold testing (DFT) either intraoperatively or post-operatively remains a controversial issue.[1]-[6] The DFT is defined as the minimum energy required at which two shocks can successfully terminate ventricular fibrillation and dates from the era of surgically implanted devices with epicardial patches.[7] Typically, a safety margin of at least 10J is employed for device programming, though some trial data suggest that a margin of 5J could be just as effective.[8] Various methods have been utilized to perform DFT testing, and no particular method has been shown to be superior to another [Figure 1]. Previously, guideline recommendations addressed the indications for ICD implantation but did not comment on DFT testing.[9] Recent consensus statements now provide some guidance as to when it is appropriate to perform or not perform DFT testing in light of new trial data.[10] This review will address some of the risk factors for having a higher DFT, impact of DFT testing on patient outcomes, and some of the risks and contraindications of DFT testing.

Risk factors for higher defibrillation threshold and troubleshooting high thresholds

Certain patients may be more likely to have a higher DFT, which comes primarily from observational study data. Higher risk patients include those with non-ischemic cardiomyopathy, younger patients, lower ejection fraction, longer QRS interval, undergoing generator change or replacement, or taking amiodarone.[11]-[12] It should be noted, however, that no single variable is a strong clinical predictor of high DFT.[1] A history of ventricular arrhythmias does not seem to predict risk for high DFT based on current data.[10]

Various techniques can be employed in order to achieve an adequate safety margin. In the INTRINSIC RV study of 1530 ICD patients, there were 59 patients who did not initially meet the 10J safety margin. An adequate 10J safety margin was achieved in all patients by reversing polarity in 56% of patients or repositioning the RV lead in 32%. Adding a subcutaneous array or repeating testing at a later date were other strategies utilized in 2% of patients each.[13] Repeating testing at a later date may allow for better optimization of heart failure medical therapy and performing device revision if needed. In a series published by Vischer, et al. there were nine patients who initially did not meet the 10J safety margin. An acceptable DFT was achieved by changing polarity, modifying the SVC coil to either "on" or "off", revising the "pocket" or repositioning the generator, adding a subcutaneous array, changing to a higher energy device, or adding a coronary sinus coil.[14] A series by Cesario, et al. also reported successful implantation of azygous vein coils in order to achieve adequate safety margins.[15] In a study by Guenther, et al., of 783 patients who underwent ICD implantation, eleven patients had failure of DFT testing. In two patients, there was sensing failure requiring lead modification. In three patients, reversing polarity was sufficient to achieve acceptable thresholds. The remaining six required either subcutaneous array or lead revision. Additionally, in this study, there was no difference in DFT efficacy based on single versus dual coil or based on different manufacturers.[3]

Impact of DFT testing on patient outcomes

The impact of DFT testing on patient outcomes is still

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Table 1: Summary of defibrillation testing yield in published observational studies with over 500 subjects. Adapted from Russo, et al.[6]

Study	Year	N	Implant criteria	No. of patients not meeting implant criteria	High DFT (% Implants)
Russo et al12	2005	1139	10J safety margin	71	6.2%
Blatt et al32	2008	717	30J (max 2 inductions)	0	0% (2.2% with <10J safety margin
Day et al13	2008	1530	10J safety margin	59	3.9%
Healey et al33	2010	1268	10J safety margin	44	3.5%
Sauer et al34	2011	853	10J safety margin (follow-up test)	38	2.4%
Keyser et al35	2013	718	<21J	28	3.9%
Lin et al11	2013	2138	10J safety margin	48	2.2%

controversial. As devices and techniques improve, the yield of DFT testing (requiring intervention or inability to achieve <10J margin) has progressively decreased. Recent observational studies suggest the yield of DFT testing is approaching 3%.[3] (Table 1)

Furthermore, the impact of DFT testing on outcomes has been unclear. In an observational cohort of 835 patients by Pires, et al., overall long-term survival was significantly better in the group that did not undergo DFT testing.[16] In another cohort of 256 patients by Michowitz, et al., there was no difference in overall survival between patients who were tested and those who were not tested.[17] Data from the SCD-HeFT trial suggests that any ICD shocks, whether appropriate or inappropriate, are associated with increased mortality.[18] However, meta-analysis data suggests that while appropriate shocks portend poorer outcomes, inappropriate shocks are not associated with increased mortality.[19] Whether DFT testing shocks themselves are associated with poorer outcomes is unknown.

Recently, two large clinical trials, the NORDIC and the SIMPLE trials, have attempted to address the question as to whether or not DFT testing affects patient outcomes.[20, 21] The NORDIC trial was a randomized, non-inferiority study of 1077 patients undergoing ICD implantation. All subjects had ICD shocks programmed to 40J regardless of DFT testing results and were followed for one year. The majority (65%) of patients had ischemic cardiomyopathy, and a minority (11%) were on Amiodarone. There was no difference in the primary end-point of first shock efficacy between the two groups.

There was a significant difference in intraoperative hypotension, which occurred more frequently in the DFT testing group than in those without DFT testing. Notably, patients undergoing right-sided implants or sub-cutaneous ICDs were excluded from the trial. The SIMPLE trial was another randomized, non-inferiority study of 2500 patients that compared DFT testing to no DFT testing, with all subjects having ICD shocks programmed to 31J. Subjects were followed for an average of one year. The primary outcome was a composite of failed appropriate shock or arrhythmic death. The no DFT testing group was found to be non-inferior to the DFT testing group with regards to the primary outcome. (Figure 2) Again, the majority of patients had established coronary artery disease (65%) and a minority was taking Amiodarone (15%). Also, subcutaneous devices and right-sided implants were excluded.

Areas of uncertainty and special patient populations

These recent trial data show that standard ICD programming without DFT testing is non-inferior to DFT testing at the time of device implantation. However, data are still lacking regarding DFT testing outside of the time of initial implant. There is no data to support annual DFT testing in high risk patients, though historically, this was common practice. Some argue for repeat DFT testing with certain changes in clinical condition such as when changing antiarrhythmic therapy (e.g. – initiation of amiodarone) or if concerned about a lead status; however, current guidelines do not address this, and routine follow-up testing is of low yield.[10,22] Additionally, whether to perform DFT testing at the time of generator change remains unclear, though in limited data, reported DFT failures seem to occur at rates similar to initial device implantation.[4, 14]

Table 2: Summary of HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal ICD programming and testing. Class I indicates a strong recommendation, benefit greatly exceeding risk. Class IIa is a somewhat weaker recommendation, benefit probably exceeding risk. Class III is a recommendation against treatment. Level of evidence A indicates highest level of evidence from more than 1 high-quality randomized clinical trial. Level of evidence B indicates moderate-quality evidence from either RCTs with meta-analysis (B-R) or non-randomized clinical trials with meta-analysis (B-NR). Level of evidence C indicates randomized or non-randomized observational or registry studies with limited data (C-LD).[10]

Intraprocedural DFT testing recommendations	Class of recommendation	Level of evidence
Defibrillation efficacy testing is recommended in patients undergoing a subcutaneous ICD implantation	I	C-LD
It is reasonable to omit defibrillation efficacy testing in patients undergoing initial left pectoral transvenous ICD implantation procedures where appropriate sensing, pacing, and impedance values are obtained with fluoroscopically well-positioned RV leads	IIa	B-R
Defibrillation efficacy testing is reasonable in patients undergoing right pectoral transvenous ICD implantation or ICD pulse generator changes	IIa	B-NR

Congenital heart disease patients also pose particular challenges with regard to implantation of ICDs owing to variable anatomy. Data are minimal for this patient population. In a multicenter study of 443 congenital heart disease patients by Berul, et al., the reported rate of high or inadequate DFT was similar to that reported in the general patient population at 2%.[23] However, this experience can be quite variable. A study by Stephenson, et al. described [22] congenital heart disease patients who underwent ICD implantation who could not receive a transvenous coil or epicardial patch. Four patients had a high DFT, representing 16% of the studied population.[24] Additionally, follow-up DFT testing in this patient group may be of higher yield, particularly as these patients grow and generally are more active than the elderly adult population.[25]

Risks and contraindications of DFT testing

Although rare, there are risks associated with DFT testing. Studies suggest that life-threatening complications occur at a rate of 0.17-0.4% and the mortality rate is 0.016-0.07%. Life-threatening complications generally result from the induction of ventricular fibrillation and include events such as stroke, pulmonary embolism, or prolonged resuscitation.[26, 27] Kolb, et al. performed a risk-benefit

analysis by using estimates of mortality reduction of 7-8% with an ICD and DFT testing yield of 2.5%. Under these assumptions, the mortality prevention rate by DFT testing is less than 0.2%, which would imply that the number needed to undergo DFT testing in order to save one life is 500.[28] Depending on the estimated risk of life-threatening complications (0.17% versus 0.4%), DFT testing may provide either a favorable or unfavorable risk. While DFT testing does not come with additional cost, per se, since there appears to be equipoise in terms of risk and benefit based on current literature, DFT testing seems to be cost neutral.

Absolute contraindications to DFT testing include intracardiac

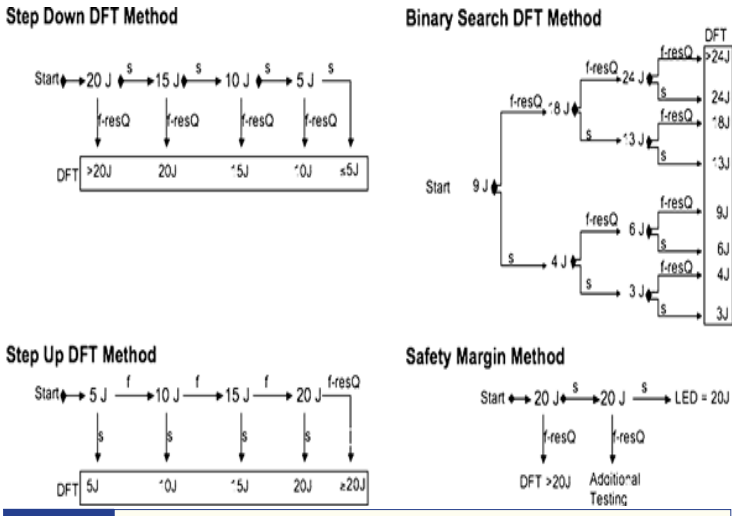

Figure 1: **Various methods to determine DFT at time of ICD implant. "s" indicates defibrillation success. "f-resQ" indicates failure followed by rescue shock. "LED" indicates lowest energy tested that defibrillates. Adapted from Swerdlow, et al.[1]**

thrombus, atrial fibrillation without anticoagulation, severe aortic stenosis, acute coronary syndrome and hemodynamic instability requiring inotropic support. Relative contraindications include severe unrevascularized coronary artery disease, recent coronary artery stent placement, recent stroke or transient ischemic attack, and hemodynamic instability not requiring inotropic support.[1, 10]

Conclusions

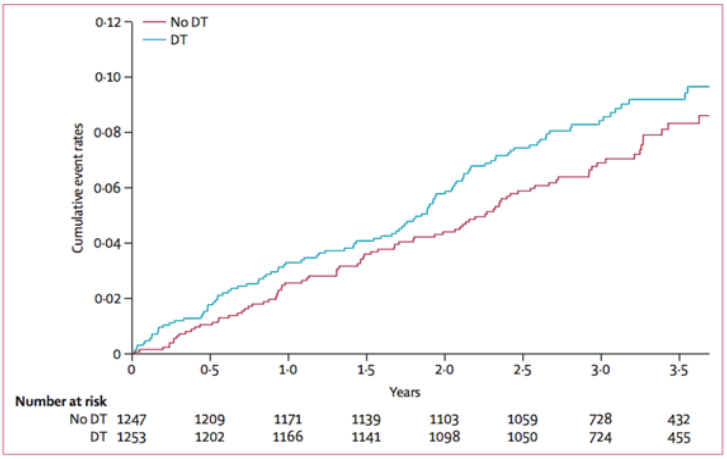

Figure 2: **Kaplan-Meier curve of time to cumulative event of either failed appropriate shock or arrhythmic death from the SIMPLE Trial.21 DT = defibrillation testing. The 'no-defibrillation testing' group was non-inferior to the testing group.**

In the large trials that established the benefit of ICD implantation, DFT testing was performed routinely per research protocols.[29, 30] Currently, FDA approved labels for usage of ICDs include information on performing DFT testing at the time of device implantation, which is at the discretion of the implanting physician.[31] However, as devices have improved, the yield of such testing has declined, and we now have randomized trial data on patient outcomes with regards to DFT testing. These data would suggest that there is no clinical benefit to performing routine DFT testing, and significant adverse events, though rare, can occur. Thus, it would seem prudent to perform DFT testing in only select individuals in whom there is a high expected yield, such as in those undergoing right-sided implants, subcutaneous device implantation, or in patients with multiple risk factors for a high DFT such as younger patients with non-ischemic cardiomyopathy on amiodarone, or in patients with complex anatomy such as those with congenital heart disease.

Conflict Of Interests

None.

Disclosures

None.

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Intravenous Sotalol - Reintroducing A Forgotten Agent To The Electrophysiology Therapeutic Arsenal

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Abstract

Sotalol is a racemic mixture possessing beta-blocker and class III anti arrhythmic properties. Approved by US food and drug administration (FDA) since 2009 based on its bioequivalence with oral sotalol, clinicians are less familiar with the potential uses of the intravenous form despite its re-launch in United States in 2015. Available literature suggests that intravenous sotalol in recommended doses can be safely administered in adult and pediatric population achieving rapid reliable therapeutic plasma concentration and without additional proarrhythmic effects when compared to its oral form as well as other antiarrhythmic medications. Intravenous sotalol may have potential uses as an alternative agent for highly symptomatic atrial fibrillation post cardiac surgery as well as in life threatening ventricular arrhythmias. As with its oral form, judicious use with close attention to QTc and renal function is warranted. Further studies are needed to better understand the safety, efficacy and different dosing regimens of parenteral sotalol in adults and children.

Introduction

Sotalol is a racemic mixture that has beta blockade (conferred by the l enantiomer) and potassium channel blockade (conferred by the d enantiomer) properties. Recognized initially for its anti-anginal and anti-hypertensive properties as a non-cardioselective beta-blocker, sotalol became known for its anti-arrhythmic effects in the 1980s. While oral sotalol is commonly utilized to maintain sinus rhythm in patients with Atrial Fibrillation (AF), Atrial Flutter (AFL) and to suppress life threatening ventricular arrhythmias (VA), its intravenous formulation is less commonly used. The US Food and Drug Administration (FDA) approved intravenous sotalol originally in 2009 based on its bioequivalence to oral sotalol; however, the drug was not available in the USA until it was re-launched in 2015. The intravenous formulation has potential as an additional rapid onset medication to treat both supraventricular and ventricular arrhythmias particularly in an emergency setting. [1]

Electrophysiology and Mechanism of Action

The Class II electrophysiological effects of sotalol are manifested as an increase in sinus cycle length, decreased AV nodal conduction and increased refractoriness. Sotalol also exhibits class III antiarrhythmic effects through Ikr blockade resulting in prolongation of atrial and ventricular monophasic action potentials, and effective refractory periods in atria, ventricle, and accessory pathways.

The beta-blocker effect of oral sotalol is non-cardioselective, half maximal at 80mg/day dose and maximal at a dose of 320-640 mg/day. Compared to some other beta-blockers= sotalol does not have a partial agonist or membrane stabilizing activity. While studies have suggested that sotalol manifests its anti-arrhythmic and QT prolonging properties only with doses in excess of 160 mg, Somberg et al noted significant QT prolongation after administration of a single low dose of sotalol. [2]

Effect of sotalol therapy has been studied in both acute onset and persistent AF. Infusion at a dose of 1.5 mg/kg decreased the energy requirement for transvenous as well as transthoracic cardioversion to restore sinus rhythm. In a study of 18 patients with persistent AF, Lai et al reported a mean decrease in transthoracic cardioversion energy of 50 J. Sotalol infusion significantly increased the mean A-A (atrial local electrogram) intervals during AF in the patients needing lower energy for cardioversion. [4] Another study found the effect to be more evident in acute AF patients using transvenous atrial defibrillation as opposed to chronic AF. [5] Slowing of atrial rate and increase in R-R interval was observed in both studies.

D-sotalol has also been shown to lower defibrillation energy (DFT) for ventricular fibrillation up to 32 ± 27% with a statistically significant increase in ventricular effective refractory period and decrease in the incidence of hemodynamically significant and sustained ventricular arrhythmias. [6],[7] This effect was studied in comparison to amiodarone in the OPTIC trial where 94 patients were randomized to receive amiodarone, beta-blockers and/or sotalol therapy. While a 1.29 J statistically significant rise in DFT was observed in the amiodarone arm when compared to a slight decrease in DFT with beta-blockers and sotalol group, the overall effect was deemed clinically insignificant. [8]

Key Words

Intravenous sotalol, Sotalol hydrochloride, Refractory ventricular arrhythmia, Atrial fibrillation, Post operative atrial arrhythmia,QT prolongation.

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Hemodynamic Effects of intravenous Sotalol in Humans

Intravenous sotalol causes a significant decrease in heart rate and cardiac output with little or no effect on mean stroke volume, right atrial and pulmonary capillary wedge pressure. These effects, evident within the first 10-15 minutes of the infusion, are seen in both healthy subjects and in patients with heart disease, at rest, with exercise and even at low doses. Thumala et al reported a significant decrease in HR, cardiac index and LV dp/dt at rest in patients with structural heart disease but with an increase in LVEDP and systemic vascular resistance. [9],[10]

Pharmacology, Safety & Dosing

Sotalol hydrochloride injection is FDA approved in the United States for life-threatening ventricular arrhythmias and maintenance of sinus rhythm in highly symptomatic, refractory AF or AFL. The principles applicable to oral sotalol in terms of safety are valid for intravenous sotalol administration as well. Per FDA labeling, intravenous sotalol is to be administered as a diluted infusion slowly over 5 hours.

Pharmacokinetics of Intravenous Sotalol

The bioavailability of oral sotalol is around 93% with peak plasma concentrations observed in 2.5-4 hours. It is not bound to plasma proteins and is excreted unchanged by the kidneys with an elimination half-life of 12-16 hours. In comparison, intravenous sotalol reaches therapeutic levels within minutes and the corresponding dose is slightly less than oral dose ([Table 1]).

Table 1: Dose Conversion between Oral and Intravenous Sotalol

Oral Sotalol	Intravenous Sotalol
80 mg	75 mg (5 mL)
120 mg	112.5 mg (7.5 mL)
160 mg	150 mg (10 mL)

The maximum concentration (Cmax) of 75mg of intravenous sotalol is similar to an orally administered dose of 80mg when infused over 5 hours. The recommended infusion rate is based on evidence showing a large overshoot of maximum serum concentration with rapid administration and high risk of QT prolongation. [11]

Pharmacodynamic Effects of intravenous Sotalol

The beta-blocker effect is similar in both oral and intravenous sotalol and can be evaluated by decrease in HR and change in RR interval on EKG. The effect is most evident within the first half hour of drug administration, peaks at 1 hour and reaches a plateau thereafter. Further increase in RR interval may be counter acted by a reflex sympathetic activation in response to a fall in BP. The changes in RR interval are highly dose dependent and are evident at lower than anti-arrhythmic doses. [11]

In a bioequivalence study comparing oral and intravenous sotalol in 15 healthy volunteers, a strong correlation was found between serum sotalol concentration and QT prolongation with risk of Torsade de pointes (TdP) increasing when QTc exceeded 500 msec. QTc prolongation with intravenous administration occurs within 0.5 hours of infusion, reaches a maximum value at 2 hours, and shows a linear correlation with sotalol blood level. [11], [12]

Gender Differences in Response to Sotalol Therapy

Females are more likely to have drug induced excessive QTc prolongation and have a 2-3 times higher risk of developing TdP with intravenous sotalol as compared to males. The disparity in cardiac repolarization has been studied in females aged 18-45 years by Somberg et al. The mechanisms underlying this gender disparity is not completely understood but the fact that pre-pubertal males and females have no difference in QTc intervals points to some role for gonadal steroids. Therefore, close QTc monitoring is essential in females during intravenous sotalol use. [15]

Sotalol Therapy during Pregnancy and Lactation

Sotalol is classified as a category B drug with available human safety data. It does cross the placental barrier but in animal studies there was no increased incidence of congenital anomalies. [1] O'Hare et al studied 6 healthy pregnant female volunteers between 32-36 weeks of gestation and up to 6 weeks post partum receiving 100 mg intravenous and 400 mg oral sotalol. The study showed altered pharmacokinetics of sotalol in antenatal patients with similar oral bioavailability, rapid plasma clearance (6.6 hours versus 9.3 hours in post natal period) and no change in volume of distribution. [13] Although data is inconclusive there is still suggestion that sotalol can be potentially teratogenic and hence, is not often the first choice in pregnant females. Close fetal monitoring is necessary when used. It is readily secreted in breast milk and infant may ingest as much as 20% of the maternal dose. Breast-feeding decision while on therapy should be made taking into account the importance of the drug to the mother and monitoring the baby for signs of toxicity. [1],[14]

Safety Profile, Proarrhythmic Effects & Adverse Reactions

Intravenous sotalol should be initiated in a monitored clinical setting with available resuscitation equipment. QT intervals, serum potassium and magnesium need to be checked periodically. Creatinine clearance should be calculated to establish dosing interval. It is generally recommended not to initiate sotalol therapy with baseline QTc more than 450 msec (Use JT >330 msec for QRS duration > 100 msec).

Contraindications to therapy include severe sinus bradycardia, sick sinus syndrome, second or third degree AV block unless functional pacemaker in place, congenital long QT syndrome, cardiogenic shock, uncontrolled heart failure, creatinine clearance <40 ml/min, serum potassium <4 meq/L, bronchospastic conditions or known hypersensitivity to sotalol. [16]

Proarrhythmia from oral sotalol is seen in 2-4% of patients. The estimated risk is similar or lower with intravenous sotalol. Interestingly, a meta-analysis of 962 patients, with the majority having underlying heart disease, showed the risk of TdP with intravenous sotalol to be <1%. Tissue accumulation has been postulated as a possible explanation for TdP with chronic oral therapy, which is not seen with short-term intravenous use. Alternative explanations for this low incidence of TdP in this study include administration during tachycardia in the acute setting and resultant shortened QT, possible reverse use-dependence, and heterogeneity in dosing and infusion duration. [17]

Hypotension is the most commonly reported side effect after intravenous sotalol, particularly when given in the early post-cardiac surgery setting. It is also of clinical significance in patients with VT with or without concomitant use of lidocaine. The incidence is lower in comparison to amiodarone and similar in groups randomized to lidocaine or sotalol. [1], [17], [20] Bradycardia, AV block and heart failure are also reported, especially in patients with low ejection fraction. Non-cardiac adverse effects from intravenous sotalol include non-specific gastrointestinal or neurological (headache, dizziness, malaise) complaints but the incidence is significantly lower than amiodarone. Non-allergic bronchospasm from beta-blocker properties of sotalol

are reported in 1.8-2.4% cases. [1], [20]

FDA Approved Clinical Indications for Intravenous Sotalol

The current FDA approved indications for intravenous sotalol are:
As a substitution for oral formulation in patients. It can be particularly useful in the post-operative and critically ill patient group when reduced intestinal permeability and gastrointestinal absorption is insufficient to reach effective serum concentrations.
To prolong time in sinus rhythm and prevent atrial fibrillation/atrial flutter recurrence in highly symptomatic patients.
For the treatment of life threatening ventricular arrhythmia provided they are not associated with QT prolongation and TdP.
For the treatment of supraventricular and ventricular arrhythmia in pediatric population. [16]

IV Sotalol: Is there a potential role for another intravenous antiarrhythmic agent in 2016? ([Table 2])

Post-Cardiac Surgery Atrial Arrhythmias

Atrial arrhythmias are common following cardiac surgery. These arrhythmias not only increase patient morbidity but also present a therapeutic challenge in terms of rate and rhythm control. Beta-blockers are first line therapy (class IA recommendation) followed by amiodarone (class IIA) and sotalol (class IIB) in perioperative period. [18] Randomized controlled trials have shown sotalol to be more effective than placebo in treating post-operative supraventricular tachycardia. Two clinical trials have shown a non-significant difference between sotalol and amiodarone in preventing post-operative AF. Sotalol was more effective than beta-blockers in reducing the incidence of AF in cardiac surgery patients. The combination of magnesium and sotalol had an augmented significant reduction in postoperative AF. [19], [20]

Table 2: Potential Clinical Applications of Intravenous Sotalol

Clinical Applications of Intravenous Sotalol
Treatment of AF in post cardiac surgery patients (conversion rates similar to intravenous amiodarone with shorter loading time for Class III effects and shorter elimination half life upon withdrawal)
Prevention of early recurrence of atrial fibrillation post cardioversion and maintenance of SR
Potential use for reducing hospital time for sotalol initiation but further studies are needed
Life threatening ventricular tachycardia as an alternative agent to intravenous amiodarone or procainamide
Post congenital heart surgery in pediatric population
Pediatric supraventricular and ventricular tachycardia

Intravenous sotalol may indeed prove to be useful for rate and rhythm control of atrial arrhythmias in post-cardiac surgery patients without contraindication to beta-blockers. The exact time for initiation of therapy remains a concern although it has shown similar efficacy before and after surgery. Hemodynamically significant hypotension and difficulty in maintaining sinus rhythm due to interaction with anesthesia (beta-blocker properties) are major issues when loaded before surgery. Given its advantage over amiodarone in terms of short duration of action as well as short loading time to achieve steady state, intravenous sotalol may prove to be a reliable alternative agent. [19]

Available data supports the cost-effectiveness of using intravenous sotalol, showing reduction in hospital stay by 0.5 days. Further studies are needed to provide definitive information in terms of benefit gained. [19]

Restoration and Maintenance of Sinus Rhythm in Atrial Fibrillation and Atrial Flutter

Sotalol has similar efficacy compared to class IA and IC anti-arrhythmics as well as amiodarone in conversion from AF to normal sinus rhythm. [20], [21] Thomas et al showed poor overall reversion rate in patients randomized to receive sotalol, amiodarone or digoxin but overall superior ventricular rate control (less than 100 beats per minute) with sotalol and amiodarone at 6 and 12 hours in comparison to digoxin. In the same study, patients receiving amiodarone infusion were more likely to have adverse reactions including hypotension. No additional benefit and increased risk of adverse effects were observed with higher doses of class III agents. [22] in another study of 120 patients with new onset AF randomized to digoxin, sotalol or amiodarone, a definite benefit was observed with amiodarone and sotalol in terms of reduction in time to reversion to normal sinus rhythm and ventricular rate control with minimal side effects. [23]

Analyzing pooled data from randomized studies, Somberg et al. reported similar conversion rates to NSR using either amiodarone or sotalol in new onset AF with the lowest success rates in persistent AF. Although patients on amiodarone reported more adverse reactions, those treated with sotalol had higher risk of AF recurrence. [20]

Table 3: Recommendations for Use of Intravenous Class III Anti Arrhythmic Drugs in ACLS Guidelines

	IV Sotalol	IV Amiodarone	IV Ibutilide
Dosing	1.0-1.5 mg/kg over 5-30 minutes	1000 mg over first 24 hours: Initial Load: 150 mg in 100 mL infused over 10 min; followed by 1mg/min for 6 hours; followed by 0.5 mg/min thereafter	Patients weighing ≥60 kg: 1 mg over 10 minutes. Patient weighing <60 kg: 0.1 mL/kg (0.01 mg/kg) over 10 minutes. A second 10-min infusion may be administered if arrhythmia does not terminate after first infusion.
Indications	Refractory VT/VF	Refractory VT/VF	QT prolongation and Torsades de pointes
Major Warnings	QT prolongation and Torsades de Pointes	Boxed Warning for hypotension; bradycardia and AV block; hepatic injury, Pulmonary toxicity.	0.625

Only intravenous Ibutilide (given as 1-2 mg doses over 10 minutes) has been shown to be more effective than intravenous sotalol in converting AF/AFL to NSR. Similar conversion rate was observed for Dofetilide for AFL. The risk of sustained TdP with Ibutilide was around 2% when higher doses were used. [24]

In-Hospital Initiation of Sotalol for Atrial Fibrillation

Intravenous sotalol, offers significant flexibility in dosing compared to oral sotalol. It reaches therapeutic levels quicker and offers easier dose titration based on QTc and clinical response. These properties could be potentially useful in hospital initiation of sotalol and to facilitate transition to oral sotalol.

Further studies are needed and are being planned to look at dosing and duration for intravenous sotalol administered as a loading dose to initiate oral sotalol therapy in adult patients with AF.

Intravenous sotalol in prevention of early recurrence of atrial fibrillation after cardioversion

Early recurrence of atrial fibrillation (ERAF) is known to occur in 13-36% of the patients after electrical cardioversion. Repeat cardioversion without pharmacologic support is successful only in 10% of these patients. Atrial premature beats with shorter coupling interval and greater prematurity as well as sinus node suppression and bradycardia (long-short sequence) induced dispersion of

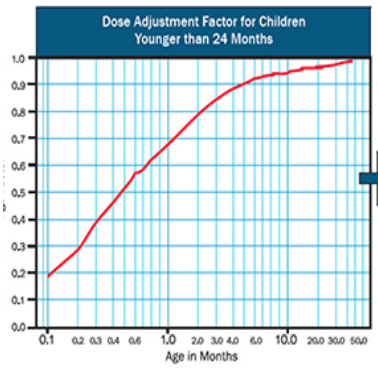
refractoriness in atrial myocardium are postulated mechanisms. With the exception of profoundly bradycardiac patients, intravenous sotalol has been shown to suppress ERAF in up to 80% of patients. Sotalol confers benefits in these cases with its beta-blocking as well as anti-arrhythmic properties. [25]

Ventricular Arrhythmias

Intravenous sotalol is approved for life threatening ventricular arrhythmias with the initial dose being 75mg infused over 5 hours once or twice daily depending on renal clearance. Doses maybe titrated to therapeutic effect while monitoring hemodynamic parameters and QTc interval. Intravenous Sotalol rapidly increased ventricular effective refractory period and acutely terminated sustained VT in 69% as opposed to 18% given Lidocaine. It has been shown to be similar to Nifekalant and Dofetilide in suppressing inducible VT. While the SWORD trial with d-sotalol (no beta blocker effect) showed increased mortality in acute myocardial infarction, later studies suggest that racemic sotalol is effective and safe in ischemic cardiomyopathy and can be used in post infraction patients without added risk. [16], [26], [27]

Although amiodarone and sodium channel blockers remain the drugs of choice for treating VT, the availability of intravenous sotalol may provide an effective substitute particularly in young patients with structurally normal hearts. Studies have shown that the risk of TdP may be comparatively lower with intravenous dosing provided it is injected slowly and in the absence of significant renal dysfunction, hypomagnesemia or hypokalemia.

The acute advantage gained by terminating VA can be transitioned over to sustained response with continued oral therapy. In a prospective multicenter trial, Sotalol significantly reduced VT/VF seen in patients with implantable cardioverter defibrillators but the rate of discontinuation of the medication because of side effects remained high (35%). [28]



Dose Adjustment Factor for Children Younger than 24 Months	
Age	Factor (Percentage of Adult Dose)
3 days	20%
1 week	30%
2 weeks	55%
1 month	70%
2 months	80%
3 months	85%
4 to 6 months	90%
7 to 20 months	95%
24 months or older	100%

Figure 1: **Recommended Dose Adjustment for Intravenous Sotalol in Pediatric Patients**

Utility in Arrhythmia therapy for Children

Sotalol is not the preferred first line of treatment in pediatric population due to lack of supporting evidence and safety concerns. It is however, used as a second line agent for incessant and refractory supraventricular and ventricular tachycardia in neonates, infants and children. High dose sotalol therapy (150 mg/m^2) was shown to be safe and efficacious in achieving partial or complete suppression of SVT (including atrial tachycardia, AV reentrant tachycardia and junctional ectopic tachycardia) in 90% of the patients between ages of 7 to 728 days. No proarrhythmic effect or significant QTc prolongation requiring alteration of therapy was observed. [28]

Similar results have been reported with intravenous sotalol with success rate of arrhythmia termination ranging from 60-70%. QT prolongation requiring treatment alteration, TdP, bradycardia, and AV block occurred only at very high doses (210 mg/m^2). Intravenous sotalol may therefore be acceptable for use in children with resistant tachycardias, when initiated in hospital setting with doses normalized to body surface area ([Figure 1]). [1], [16]

Conclusion

Intravenous sotalol may provide a new therapeutic option to US physicians for effective treatment of supraventricular and ventricular arrhythmias in the pediatric and adult population particularly those with preserved ejection fraction and renal function. Moreover, by delivering a dose-dependent serum concentration independent of absorption and bioavailability, intravenous sotalol shortens time to reach therapeutically effective levels and could allow seamless transition to oral sotalol. As with its oral form, judicious use with close attention to QTc and renal function is warranted and further studies are needed to better understand the safety, efficacy and different dosing regimens for intravenous sotalol in adults and children.

Conflict Of Interests

None.

Disclosure

SAB-No relevant disclosures.

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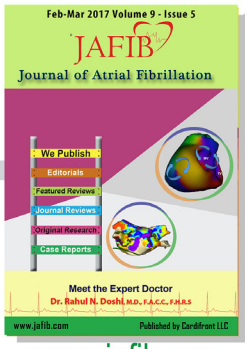

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The Novel Oral Anticoagulants And Atrial Fibrillation: Challenges And Considerations

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Abstract

The nonvitamin K antagonist oral anticoagulants (NOACs) dabigatran, rivaroxaban, apixaban, and edoxaban are used for the reduction of the risk of stroke or systemic embolism (SEE) in patients with nonvalvular atrial fibrillation (NVAF). The purpose of this review is to highlight the safety and efficacy results of the pivotal NOAC clinical trials for use in NVAF, discuss some of the unique management challenges in the use of NOACs in special populations, summarize data on emerging and novel indications, and address potential future directions. A literature search was conducted and to identify relevant clinical trials and studies regarding the use of NOACs for the prevention of stroke or SEE in patients with atrial fibrillation. Relative to warfarin, NOACs are as effective or superior in the prevention of stroke or SEE, and are associated with similar or lower rates of major bleeding and significantly decreased rates of intracranial bleeding, but may be associated with a slightly increased risk of gastrointestinal bleeding in patients with AF. The NOACs are not indicated for use and have not been widely tested in AF patients with other cardiovascular conditions. Additional ongoing and planned clinical trials will provide additional information regarding the use of NOACs in these patients. In situations requiring rapid reversal of anticoagulation, the availability of specific antidotes will improve safety and facilitate NOAC use. Use of NOACs in clinical practice requires consideration of patient characteristics as well as potentially required procedures.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting 12% of patients between ages 75 to 84. [1] It is associated with a 5-fold increased risk of stroke, a 3-fold increased risk of heart failure, and a 2-fold increase in risk of mortality, contributing to >99,000 deaths per year . [1] Anticoagulation with vitamin K antagonists (VKAs), specifically warfarin, was the standard of care for prevention of stroke and systemic embolic events (SEE) in patients with AF for more than 60 years. However, numerous limitations of warfarin, such as a need for constant monitoring of therapeutic level, food-drug and drug-drug interactions, and person-to-person metabolic variability, have posed challenges in maintenance of appropriate anticoagulant effects, leading to the development of nonvitamin K antagonist oral anticoagulants (NOACs).

Four NOACs are approved by the US Food and Drug Administration (FDA) for stroke prevention in nonvalvular atrial fibrillation (NVAF). [2]-[5] The 2014 American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) guidelines recommend anticoagulation with an oral anticoagulant based on risk using the CHA_2DS_2-VASc score, with a single point counted for congestive heart failure (C), hypertension (H), diabetes (D), the presence of vascular disease (V), age 65 to 74 (A), and female sex ("sex category" Sc), and 2 points counted for (A) age >75 and (S) prior stroke/thromboembolism. [1] The AHA/ACC/HRS guidelines recommend either oral anticoagulation with warfarin to an international normalized ratio (INR) 2 to 3 or use of the NOACs approved at the time of writing: dabigatran, rivaroxaban, or apixaban. [1] Edoxaban was approved by the FDA for stroke prevention in patients with NVAF the following year. [5]

Despite these treatment guideline recommendations, oral anticoagulation may still be under-prescribed and adherence in eligible patients with AF is poor, [6]-[8] presenting a potential barrier to effective stroke prevention in AF. Patients with AF who maintain sub-therapeutic INRs have twice the risk of stroke relative to those with INRs from 2 to 3.[9] Overall, adherence to therapy is the most important factor in decreasing patient risk of stroke or SEE.

This review highlights the safety and efficacy results of pivotal trials for NOACs in patients with NVAF, discusses some of the unique management challenges in the use of NOACs in special populations, summarizes data on emerging and novel indications, and addresses potential future directions.

Pivotal Trial Results

Four large, pivotal phase 3 trials led to the approval of NOACs for stroke and SEE prevention in patients with NVAF ([Figure 1]). [10]-[13] In these trials, NOACs were associated with similar or lower rates of major bleeding and significantly decreased rates of intracranial hemorrhage (ICH) compared with warfarin by approximately 50% ([Figure 2])). [10]-[13]

Key Words:

Atrial fibrillation, nonvitamin K oral anticoagulant, stroke, systemic embolism

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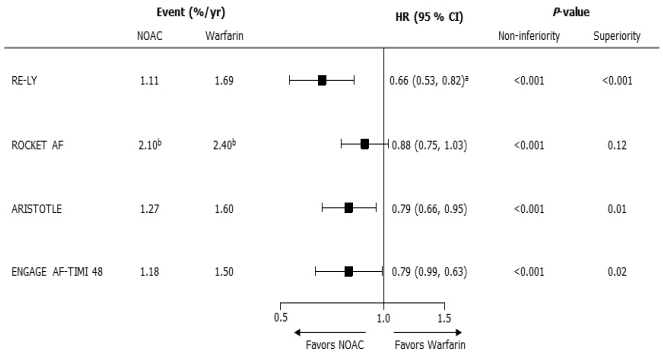

Figure 1: Forest plot of the hazard ratios (95% CI) for the risk of stroke or systemic embolism with dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, apixaban 5 mg twice daily, and edoxaban 60 mg once daily compared with warfarin is based on the results of the pivotal clinical trials. aData presents as relative risk. bReports as number/100 patient-years. c97.5% CI, dDoes not meet primary superiority endpoint. ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CI, confidence interval; ENGAGE AF-TIMI 48, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48; NOAC, nonvitamin K antagonist oral anticoagulant; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation

In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, dabigatran 150 mg was superior to warfarin in preventing stroke and SEE, and did not differ significantly from warfarin in rates of major bleeding. [10] Similarly, based on the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial, rivaroxaban was noninferior to warfarin in prevention of stroke and SEE, and did not significantly differ from warfarin in rates of major bleeding . [11] In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, apixaban was superior to warfarin in prevention of stroke and SEE prevention and had lower rates of major bleeding relative to warfarin. [12] Lastly, the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial, higher-dose regimen edoxaban (60/30 mg) was noninferior to warfarin with regards to stroke and SEE prevention and bleeding with dose-dependent lower rates of life-threatening and major bleeding .[13]

Overall, the above trials showed that, relative to warfarin, NOACs were noninferior or superior in preventing stroke/SEE in patients with NVAF. Rates of ICH were decreased with NOACs relative to warfarin .[10]-[13] Furthermore, while gastrointestinal (GI) bleeding rates for dabigatran, [10] rivaroxaban, [11] and edoxaban [13] were increased relative to warfarin, GI bleeding rates were lower in patients taking apixaban relative to warfarin (Figure 2). [12]

However, it should be noted that exclusions for GI bleeding differed between trials; patients with symptomatic or endoscopically documented gastroduodenal ulcer in the previous 30 days were

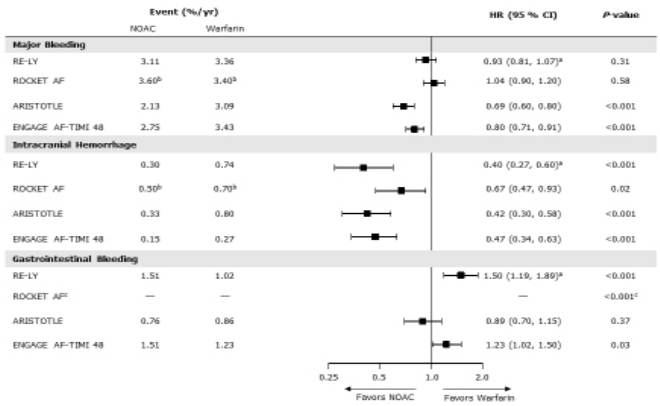

Figure 2: Forest plot of the hazard ratios (95% CI) for the risk of major or CRNM bleeding, ICH, and GI bleeding with dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, apixaban 5 mg twice daily, and edoxaban 60 mg compared with warfarin is based on the results of the pivotal clinical trials. aData presents as relative risk. bReports as number/100 patient-years. cMajor bleeding from a GI site occurs in 3.2% of the rivaroxaban group vs 2.2% of the warfarin group. CI, confidence interval; CRNM, clinically relevant nonmajor; ENGAGE AF-TIMI 48, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48; GI, gastrointestinal; ICH, intracranial hemorrhage; NOAC, nonvitamin K antagonist oral anticoagulant; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation

excluded from RE-LY, patients with GI bleeds within 6 months of randomization were excluded from ROCKET-AF, exclusions for GI bleeding were not defined for ARISTOTLE, and patients with GI bleeds within the past year were excluded from ENGAGE AF-TIMI 48 [10]-[13].

Renal Function

Factors influencing NOAC dosing include renal function, age, body weight, and drug interactions ([Table 1]). Renal impairment may increase bleeding in patients with NVAF. Overall, the rates of renal excretion between NOACs vary considerably (ie, renal clearance for an absorbed dose of dabigatran is 80%, edoxaban is approximately 50%, rivaroxaban is 36%, and apixaban is 27%) [2]-[5]. Assessment of renal function prior to beginning treatment regimens with NOACs,

Table 1: NOAC dosing for NVAF patients– general and special populations

Standard Approved Doses	Dabigatran 150 mg twice daily	Rivaroxaban 20 mg once daily with evening meal	Apixaban 5 mg twice daily	Edoxaban[a] 60 mg once daily
Dose adjustments				
Renal function	Reduce dose to 75 mg BID if CrCl 15–30 mL/min Avoid use for CrCl <30 mL and concomitant P-gp inhibitor No recommendations if CrCl ≤15 mL/min or on dialysis	No dose adjustment for CrCl >50 mL/min Reduce dose to 15 mg once daily with the evening meal for CrCl 15–50 mL/min Avoid if CrCl <30 mL/min	Serum creatinine ≥1.5 mg/dL and body weight ≤60 kg or age ≥80 years: reduce dose to 2.5 mg BID	Reduce dose to 30 mg once daily if CrCl is 15–50 mL/min CrCl <15 mL/min: not recommended CrCl >95: not indicated
Elderly	No dose adjustment	No dose adjustment	Age ≥80 years and body weight ≤60 kg or serum creatinine ≥1.5 mg/dL: reduce dose to 2.5 mg BID	No dose adjustment
Low body weight	No dose adjustment	No dose adjustment	Body weight ≤60 kg and age ≥80 years or serum creatinine ≥1.5 mg/dL: reduce dose to 2.5 mg BID	No dose adjustment
Hepatic impairment	Moderate hepatic impairment (Child-Pugh B): no dosing adjustment	Avoid use in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment, or any hepatic disease associated with coagulopathy	No dose reduction for mild hepatic impairment (Child-Pugh A) Moderate hepatic impairment (Child-Pugh B): no dosing recommendations provided Severe hepatic impairment (Child-Pugh C): not recommended	Mild hepatic impairment (Child-Pugh A): no dose reduction required Moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment: not recommended
Dual P-gp/ CYP3A4 inhibitors	Reduce 75 mg BID dose for patients with moderate renal impairment (CrCl 30–50 mL/min) with ketoconazole, dronedarone No dose adjustment required for clarithromycin, amiodarone, quinidine, verapamil, ticagrelor	Avoid use with P-gp and strong CYP3A4 inhibitors ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir, conivaptan	A 50% dose reduction is recommended for patients receiving a dose >2.5 mg BID when coadministered with strong dual inhibitors of CYP3A4 and P-gp (ketoconazole, itraconazole, ritonavir, or clarithromycin); avoid use of these drugs when dosage is 2.5 mg, BID	No dose adjustment
Dual P-gp/ CYP3A4 inducers	Avoid coadministration with rifampin	Avoid strong dual inducers of P-gp and CYP3A4 carbamazepine, phenytoin, rifampin, St. John's wort	Avoid strong dual inducers of P-gp and CYP3A4 carbamazepine, phenytoin, rifampin, St. John's wort	Avoid concomitant use of rifampin

aDo not use edoxaban in patients with CrCl >95 mL/min in the US.
BID, twice daily; CrCl, creatinine clearance; CYP3A4, cytochrome P450 3A4; NOAC, nonvitamin K antagonist oral anticoagulant; NVAF, nonvalvular atrial fibrillation; P-gp, p-glycoprotein.

and periodically thereafter, is recommended [1]-[3]. It should be noted that patients with end-stage renal disease (ESRD) (creatinine clearance [CrCl] <15 mL/min), were excluded from all the pivotal efficacy trials [2]-[5]. The appropriate NOAC dosing in patients with ESRD on dialysis is not fully elucidated.

For dabigatran, exposure is 1.5 to 3.2 times higher in patients with mild to moderate renal impairment (CrCl of 30–<80 mL/min) compared with patients with a normal CrCl (≥80 mL/min) [2]. Dabigatran should be adjusted to a dose of 75 mg twice daily for patients with severe renal impairment (CrCl of 15–30 mL/min) and for patients with moderate renal impairment (CrCl of 30–50 mL/min) who are also taking dronedarone or systemic ketoconazoles [2]. The recommendation of a 75-mg, twice-daily dose for patients with renal impairment is based on pharmacokinetic modeling analyses in subjects with renal impairment [2]; in an open-label, single-center study, mean steady-state drug exposure was similar to predicted exposure [14].

Patients with NVAF and a CrCl >50 mL/min should receive rivaroxaban 20 mg once daily with the evening meal; for patients with CrCl of 15 to 50 mL/min, rivaroxaban should be administered as a once-daily 15-mg dose with the evening meal [3]. In a subanalysis of patients with moderate renal impairment (CrCl of 30–49 mL/min) from the ROCKET AF trial, there were no significant differences in stroke or SEE, major bleeding, or ICH between rivaroxaban 15 mg and warfarin [15]. However, in a further analysis of the ROCKET AF trial, rivaroxaban was associated with lower rates of stroke or SEE vs warfarin with a similar risk of bleeding in patients with worsening renal function (≥20% decrease from screening CrCl) [16]. Emerging data may support the efficacy and safety of a 10 mg rivaroxaban dose in ESRD patients [17]; however, within a population of patients receiving dialysis, rates of hemorrhagic death were greater relative to warfarin for both rivaroxaban 20 mg (rate ratio 1.71; 95% confidence interval [CI] 0.94–3.12) and dabigatran (rate ratio 1.78; 95% CI 1.18–2.68). [18]

Apixaban dosing recommendations are based on pharmacokinetic and pharmacodynamics data in patients with ESRD maintained on dialysis [19], [20]. Patients with ESRD maintained on intermittent dialysis should receive apixaban at the usually prescribed dose [4]. In the US, a reduced dose of apixaban (2.5 mg twice daily) is recommended for patients meeting 2 of the following criteria: serum creatinine level ≥1.5 mg/dL, age ≥80 years, or body weight ≤60 kg [4].

In the US, edoxaban is not approved for use in patients with a CrCl >95 mL/min [5]. For patients with a CrCl of 15 to 50 mL/min, edoxaban should be prescribed at a reduced dose of 30 mg [5]. In a prespecified subgroup analysis (CrCl 30–50 mL/min vs >50 mL/min) of the ENGAGE-TIMI AF 48 trial, the efficacy, safety, and net clinical benefit of higher-dose edoxaban (60/30 mg) did not differ from warfarin by renal function .[21] In patients with CrCl >95 mL/min, exploratory analyses identified a statistically insignificant trend toward lower relative efficacy for the prevention of thromboembolic events with edoxaban vs warfarin . [21] Based on these data, additional studies to determine the optimal dosing of NOACS for patients at the higher range of creatinine clearance and for patients on hemodialysis may be warranted.

Age and Body Weight

Although oral anticoagulants reduce the risk of ischemic stroke in patients with NVAF, there is an increased risk of bleeding, particularly

Table 2: Select ongoing clinical trials

Study	Trial Name	NOAC Treatment Arm	Phase	ClinicalTrials.gov Identifier
Cardioversion/ ablation	—	Dabigatran	4	NCT01976507
	ABRIDGE-J[58]	Dabigatran	4	—
	RE-CIRCUIT[59]	Dabigatran	4	NCT02348723
	—	Dabigatran	3	NCT02313584
	OCEAN	Rivaroxaban	4	NCT02168829
	EMANATE	Apixaban	4	NCT02100228
	AXAFA	Apixaban	4	NCT02227550
	ENSURE-AF[60]	Edoxaban	3	NCT02072434
PCI	OAC-ALONE	Any NOAC	4	NCT01962545
	REDUAL-PCI	Dabigatran	3	NCT02164864
	PIONEER AF-PCI[55]	Rivaroxaban	3	NCT01830543
	—	Rivaroxaban	4	NCT02334254
	SAFE-A	Apixaban	4	—
CAD/PAD	—	Dabigatran	4	NCT02389582
	AFIRE	Rivaroxaban	4	NCT02642419
	COMPASS	Rivaroxaban	3	NCT01776424
	VOYAGER PAD	Rivaroxaban	3	NCT02334254
	EDOX-APT	Edoxaban	4	NCT02567461
Nondisabling cerebrovascular events (TIA/minor stroke)	TRACE[57]	Rivaroxaban	2 and 3	NCT01923818
	ADANCE[56]	Apixaban	2 and 3	NCT01924325
	—	Edoxaban	2 and 3	NCT02221102
Device-detected subclinical AF	ARTESiA	Apixaban	4	NCT01938248
	NOAH CAD/PAD	Edoxaban	3	NCT02618577
Type 2 diabetes	MicroVasc-DIVA	Rivaroxaban	3	NCT02164578

in the elderly, associated with their use. However, dose reductions for age or body weight are only recommended for patients receiving apixaban who meet 2 of the following criteria: >80 years, body weight <60 kg, serum creatinine ≥1.5 mg/dL.

In a subgroup analysis of ENGAGE AF-TIMI 48, thromboembolic and bleeding risk both increased with age, with more pronounced risk—especially for major bleeding—in patients with age ≥75 years [22]. However, regardless of age, edoxaban was associated with a similar reduction in the risk of stroke or SEE and a lower risk of major bleeding vs warfarin [22]. Therefore, due to the higher bleeding risk in the elderly relative to younger patients, the primary net clinical benefit (stroke/SEE/major bleeding/death) of edoxaban vs warfarin was improved in older patients [22]. Similarly, in a subgroup analysis of the AVERROES (Apixaban Versus ASA to Prevent Stroke in AF Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trial, apixaban was more effective than aspirin for preventing strokes or SEE in patients ≥85 years with no significant treatment-by-age interaction for bleeding [23].

Emerging and novel indications

Valvular Heart Disease

Although NOACs are not approved for patients with AF and valvular heart disease, several clinical trials and subgroup analyses of phase 3 trials have been performed to assess the efficacy and safety of NOACs in AF patients with valvular disease. Patients with mild mitral stenosis were not excluded from either the edoxaban or apixaban phase 3 clinical trials. [12], [13] In a subgroup analysis of ARISTOTLE, there were no differences between apixaban and warfarin in preventing stroke or SEE, reducing death, or causing bleeding in patients with or without valvular heart disease [25].

Dabigatran is the only NOAC investigated in clinical trials in patients with mechanical heart valves. The phase 2 dose-validation study RE-ALIGN (Randomized Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement) was terminated early due to excess thromboembolic and bleeding events in patients randomized to dabigatran. [26] In RE-ALIGN, 5% of patients on dabigatran and no patients on warfarin experienced a stroke [26]. Major bleeding occurred in 4% of dabigatran patients and 2% of warfarin patients; bleeding of any type occurred in 27% of dabigatran patients and 12% of warfarin patients. [26]

Few clinical studies have assessed the efficacy and safety of patients with AF and bioprosthetic valves. However, in a small, retrospective, single-center cohort study of AF patients with bioprosthetic valves who were prescribed NOACs, approximately 100 days after bioprosthetic valve implantation 8.2% (6/73) of patients reported a minor bleeding event and 6.9% (5/73) reported a major bleeding event with no ischemic strokes . [27]

Peripheral Arterial Disease

In a subgroup analysis of the ENGAGE AF-TIMI 48 trial, regardless of the presence or absence of peripheral arterial disease (PAD), higher-dose edoxaban (60/30 mg once daily) had similar efficacy and safety relative to warfarin [28]. Similarly, in a subgroup analysis of the ROCKET AF trial, rivaroxaban had a similar efficacy compared with warfarin in patients with and without PAD [28]. However, patients with PAD had a higher risk of bleeding with rivaroxaban vs warfarin compared with patients without PAD (P=.037). [28]

Diabetes is a risk factor for PAD and PAD-associated mortality; individuals with comorbid diabetes and PAD are at approximately twice the risk of death compared with patients with PAD alone [29]. Consistent with this, in a subgroup analysis of the RE-LY study, the incidence of peripheral vascular disease was higher in diabetic patients as compared with non-diabetic patients [30]. In addition, the numerical reduction in stroke or SEE associated with dabigatran relative to warfarin was greater in diabetic patients compared with nondiabetic patients (dabigatran 150 mg twice daily: 0.89% per year vs 0.51% per year). [30]

Myocardial Infarction

Following reanalysis of the by request of the US Food and Drug Administration, rates of myocardial infarction (MI) did not differ significantly between dabigatran and warfarin [10], [31], [32], although initial analyses showed increased risk of MI was associated with dabigatran use. Some studies suggest dabigatran may be associated with an increased risk for MI, but the data are mixed. [10], [31]-[34] In the initial analysis of the RE-LY trial, dabigatran 150 mg twice daily was associated with increased rates of MI vs warfarin (0.74% vs 0.53% per year, respectively; relative risk =1.38; [95% CI 1.00–1.91]; P=.048). [10] Following re-evaluation of the database for possible event underreporting, these rates were subsequently revised to 0.81% vs 0.64% per year, respectively (relative risk = 1.27; 95% CI 0.94–1.71; P=.12). [31] It should be noted that in RE-LY, patients who had ≥1 MI were older and had more coronary risk factors compared with those who did not experience an MI event. [32] In the ENGAGE AF-TIMI 48 and the ROCKET AF trials, there were no differences in safety between edoxaban and warfarin or between rivaroxaban and warfarin in patients with prior MI. [11], [13] There have been no subgroup analyses for apixaban and MI.

Cardioversion

Overall, the incidence of stroke in patients with NVAF who

undergo cardioversion tends to be greater within the first 30 days postprocedure relative to the period ranging from 30 days to 3 years. [35] Data for the use of NOACs following cardioversion are limited; however, several post hoc analyses of the phase 3 NVAF trials and 2 phase 3b trials were conducted.

In RE-LY, rates of stroke and major bleeding associated with dabigatran vs warfarin within 30 days of cardioversion were comparable. [36] Similarly, in an analysis of ROCKET AF, the long-term stroke rates, rates of survival following cardioversion, or ablation associated with rivaroxaban did not differ compared to warfarin .[37] In ARISTOTLE, major cardiovascular events following cardioversion were similar between patients receiving apixaban and warfarin. [38] Thromboembolic and major bleeding events within 30 days of cardioversion were infrequent and similar between edoxaban and warfarin treatments in the ENGAGE AF-TIMI 48 trial [39]. Consistent with these results, in a meta-analysis of 4 randomized controlled trials for NOACs, NOACs were at least as effective and safe as VKA for NVAF patients undergoing cardioversion procedures. [40]

The first randomized trial of a NOAC in patients with NVAF undergoing elective cardioversion was X-VeRT (eXplore the efficacy and safety of once-daily oral riVaroxaban for the prevention of caRdiovascular events in patients with nonvalvular aTrial fibrillation scheduled for cardioversion). [41] In X-VeRT, patients were randomized to receive rivaroxaban (20 mg/15 mg for CrCl 30–49 mL/min) or VKA therapy for 1 to 5 days or for 3 to 8 weeks prior to cardioversion, respectively . [41] In patients with delayed cardioversion, adequate VKA treatment required an INR in the range of 2.0 to 3.0 for at least 3 consecutive weeks prior to cardioversion [41]. Compared with VKA therapy, rivaroxaban was associated with similar rates of stroke or other cardiovascular events and bleeding, but a significantly shorter time to cardioversion. [41]

A second trial, edoxaban vs enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF), enrolled 2,199 patients to receive edoxaban (60 mg/30 mg for CrCl 15–50 mL/min, bodyweight ≤60 kg or concomitant use of P-gp inhibitors) or enoxaparin/warfarin. [42] Rates of major bleeding and thromboembolism were similar between patients treated with edoxaban and those treated with enoxaparin-warfarin, regardless of the use of conventional or transesophageal echocardiography, previous use of anticoagulation, edoxaban dose, or region [42]. In the overall population, the composite endpoint of stroke, SEE, MI, cardiovascular mortality, and major bleeding occurred in 5 patients treated with edoxaban and 11 patients treated with enoxaparin-warfarin (odds ratio 0.46, 95% CI 0.12–1.43). [42] The difference between treatment groups was primarily driven by lower cardiovascular mortality in the edoxaban group (0.1%) vs the enoxaparin-warfarin group (0.5%). [42]

Similarly, in a cohort study comparing the efficacy and safety of dabigatran vs warfarin in NVAF patients undergoing cardioversion, dabigatran was associated with a similar risk of adverse events and NVAF readmission vs warfarin, but a shorter time to cardioversion. [43] In a real-world clinical setting, rates of cerebrovascular accidents or transient ischemic attacks (warfarin: 0.97% vs NOAC 1.62%, P=.162) and bleeding events (warfarin: 1.02% vs NOAC: 0.5%, P=.247) were low in patients with NVAF undergoing direct current cardioversion who were prescribed periprocedural anticoagulants. [44] Together, these studies indicate that NOACs may be a safe and effective alternative to warfarin in patients undergoing elective electrical cardioversion.

Chronic Obstructive Pulmonary Disease

Comorbid chronic obstructive pulmonary disease (COPD) is associated with poor outcomes among patients with cardiovascular disease. [45] However, the efficacy and safety of NOACs among patients with NVAF and COPD is not well studied. In a subanalysis of the ARISTOTLE trial, comorbid COPD was associated with an elevated risk of all-cause mortality (adjusted HR 1.60; 95% CI 1.36–1.88]; P<.001). [46] In this same analysis, the reported benefits of apixaban vs warfarin in reducing the risk of stroke or SEE, bleeding, and all-cause mortality were independent of COPD status .[46]

Reversal Agents

Despite the lower risk of bleeding relative to warfarin associated with NOACs, the lack of reversal agents for NOACs remains a major concern. Reversal agents could be of use in certain situations following the administration of NOACs including life-threatening bleeding, bleeding into a critical organ or closed space, prolonged bleeding, NOAC overdose or delayed clearance, emergency surgery, or urgent interventions associated with high bleeding risks. [47] Several reversal agents have recently received approval or are in clinical development.

Idarucizumab

Idarucizumab, a human antibody fragment, is the first approved NOAC antidote indicated for the reversal of dabigatran when bleeding cannot be controlled. [48] Idarucizumab binds free and thrombin-bound dabigatran with high affinity, thereby neutralizing its activity .[49] In a phase 3 clinical trial, idarucizumab nearly fully neutralized the anticoagulant effect of dabigatran in patients who experienced serious bleeding or required an urgent procedure [49]. Several other reversal agents are in development for NOACs..

Andexanet Alfa

In phase 2 and 3 clinical trials, andexanet alfa (PRT064445, Portola Pharmaceuticals, Inc., South San Francisco, CA), a recombinant catalytically inactive FXa decoy molecule, rapidly reversed the effect of rivaroxaban and apixaban .[47], [50] Similar results were reported for edoxaban reversal in a phase 2 clinical trial .[51] Andexanet alfa is currently under regulatory review as a universal antidote for factor Xa inhibitors. [52]

Ciraparantag

Ciraparantag (PER977) (Perosphere, Inc., Danbury, CT), a synthetic small molecule that binds all 4 NOACs via hydrogen bonds, is in early-phase trials for the reversal of NOACs. In a phase 1 study in healthy volunteers receiving edoxaban, ciraparantag dose-dependently shortened whole blood clotting time and restored normal clot architecture . [47]

Prothrombin Concentrate Complexes

Prothrombin concentrate complexes (PCCs), pooled plasma products containing concentrations of 3 factors (II, IX, and X) or 4 factors (II, VII, IX, and X) and vitamin K-dependent proteins, are under clinical investigation for the reversal of NOAC anticoagulation. The studies with PCCs have had variable results; if administration is necessary, careful consideration must be given to the increased risk of thromboembolism associated with administration of these products. [53], [54]

Future Directions

[Table 2] shows a partial listing of planned or ongoing clinical

trials assessing the efficacy and safety of NOACs for emerging indications including percutaneous coronary intervention (PCI), and nondisabling stoke. These additional clinical trials will hopefully provide further information regarding the use of NOACs in these and other indications.

Percutaneous Coronary Intervention

NOACs are not indicated for antithrombotic management of patients with NVAF undergoing PCI with stenting. However, there are several ongoing clinical trials assessing the use of NOACs in these patients. The PIONEER AF-PCI (Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; clinicaltrials.gov NCT01830543) is an exploratory, open-label, randomized trial assessing the safety of 2 rivaroxaban dual-antiplatelet treatment regimens to a triple antiplatelet treatment regimen including VKA in NVAF patients who have undergone PCI with stent placement (bare metal or drug-eluting stent) [55]. The primary endpoint is a composite of the rate of major bleeding, bleeding requiring medical attention, and minor bleeding at 12 months. [55] Similarly, REDUAL-PCI (Randomized Evaluation of Dual Therapy with Dabigatran vs Triple Therapy Strategy with Warfarin in Patients with NVAF that have undergone PCI with Stenting; clinicaltrials.gov NCT02164864) is assessing the safety of 2 dabigatran dual-antiplatelet treatment regimens compared with a triple antiplatelet treatment regimen including VKA in patients with NVAF and ischemic heart disease who have undergone stent placement (bare metal or drug-eluting stents). The primary outcome is the time to first major or clinically relevant nonmajor bleeding event.

Non-Disabling Stroke

No clinical trials assessing the efficacy and safety of NOACs for preventing transient ischemic attack (TIA) and acute minor ischemic stroke have completed; 3 randomized trials are ongoing. ADANCE (Apixaban Versus Dual-antiplatelet Therapy [Clopidogrel and Aspirin] in Acute Non-disabling Cerebrovascular Events;clinicaltrials.gov NCT01924325) is a randomized, double-blind clinical trial comparing a regimen of apixaban or clopidogrel with aspirin followed by clopidogrel in patients with acute TIA or minor ischemic stroke. [56] Similarly, TRACE (The Treatment of Rivaroxaban versus Aspirin in Non-disabling Cerebrovascular Events; clinicaltrials.gov NCT01923818) is a randomized, double-blind clinical trial comparing rivaroxaban with aspirin in patients with acute TIA or minor stroke . [57] There is one planned randomized, double-blind clinical trial (clinicaltrials.gov NCT02221102) comparing edoxaban with aspirin alone in patients with acute TIA or minor stroke. In all 3 planned clinical trials the primary efficacy endpoint is the percentage of patients with new stroke (ischemic or hemorrhage).

Conclusions

In patients with NVAF, NOACs are at least noninferior to warfarin in preventing stroke or SEE and are associated with a decreased risk of ICH compared with warfarin. These agents may however be associated with a slightly increased risk of GI bleeding relative to warfarin. In general, NOACs may offer a significant advantage over warfarin for most patients, and unlike warfarin, do not require frequent laboratory monitoring. It is important to note that the available NOACs vary in dosing regimens and require dose adjustments in patients with compromised renal function based on specific criteria for each individual agent. Therefore, when considering the appropriate dose and adequate use of these agents, several important factors should be considered, especially in patients with renal impairment or cardiovascular conditions other than NVAF. Overall, the appropriate use of NOACs requires following guidelines and prescribing instructions.

NOACs are not indicated for use and have not been widely tested in AF patients with other cardiovascular conditions. Subgroup analyses of the phase 3 trial data, small clinical trials, and observational studies provide some insights into this area. Additional ongoing and planned clinical trials will provide additional information regarding the use of NOACs in these patients. In situations requiring rapid reversal of anticoagulation, such as life-threatening bleeding, NOAC overdose, and emergency surgery, the availability of specific antidotes will improve safety and facilitate the use of NOACs.

Conflict Of Interests

Dr. Plitt has no disclosures. Dr. Bansilal has received institutional research grant support from AstraZeneca and consulting fees from AstraZeneca and Janssen.

Disclosures

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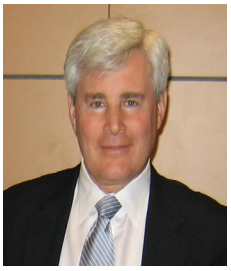

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