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Editorial

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World Atrial Fibrillation Awareness Day: Creating Grassroots Level Awareness to Combat a Global Scourge

Dear Colleagues

It needs no reiteration that atrial fibrillation (AF) is the most common cardiac arrhythmia in the United States (US), affecting approximately 6-7 million individuals nationally and projected to increase in prevalence to nearly 16 million patients by the year 2050. The incremental cost of AF to the US healthcare system was last estimated to be on the order of US $26 billion in the year 2005. Despite preponderance for developed countries, AF is very much a global epidemic, affecting an estimated 33.5 million individuals worldwide. Risk factors for AF include advancing age, elevated body mass index, diabetes mellitus, hypertension, chronic kidney disease, heavy alcohol consumption, the presence of cardiovascular disease (e.g. coronary and/or valvular heart disease, heart failure), and obstructive sleep apnea . Importantly, many of these risk factors are modifiable, though lack of education and, often times, awareness of the diagnosis are major barriers for patients.

Thanks to the efforts of Global AF Alliance Foundation (GAFA), World Atrial Fibrillation Awareness Day is celebrated on the second Saturday of September each year for the last several years. The second Saturday of September each year has received official proclamations by Kansas Governor Sam Brownback, as well as Arkansas governor Asa Hutchinson. GAFA is working on obtaining a national proclamation by the President of the United States. The event provides an opportunity for the AF community at-large, including patients and their families, healthcare providers, industry partners, and others to come together through a program of education and physical activity aimed at addressing this increasingly prevalent disease and its deleterious physical and emotional effects, including but not limited to stroke, heart failure, myocardial infarction, chronic kidney disease, and dementia.

GAFA a 501(c) (3) non-profit organization established by a group of volunteer physicians, nurses, patients and other health care providers (none has a paid position in the organization) aims to bring together all of these invested parties, with a mutual goal of increasing knowledge regarding AF and its sequelae, promoting awareness and early detection in an upstream approach, and providing support to patients afflicted with AF and their loved ones. GAFA, JAFIB and the Electrophysiology Section of the American College of Cardiology are working together to improve the participation of all stake holders to make this grassroots effort more effective towards better patient education and access to care. In this vein, the GAFA chapter of the Greater Kansas City Area has been instrumental in planning and organizing a series of events including yearly commemorations of World Atrial Fibrillation Awareness Day.

We congratulate several other organizations who have supported this cause. StopAFib.org, Afibbers.org, Heart Rhythm Society and AF Alliance have all done various activities in September to energize this movement. So far this effort has been in silos. We need to b ring all of these organizations together in working towards a common goal creating a world that are less burdened by AF. Over time, the reach of these World Atrial Fibrillation Awareness Day events has grown beyond Kansas City to include Tulsa, Oklahoma, Scottsdale, Arizona, and Little Rock, Arkansas, as well as international events in Hyderabad, India, Rio de Janeiro, Brazil, and Taipei, Taiwan. In conjunction with educational and outreach efforts by physician-led organizations such as the Heart Rhythm Society, the American College of Cardiology, and the American Heart Association, as well as patient advocacy and charitable groups such as the Atrial Fibrillation Association and StopAfib.org, World Atrial Fibrillation Awareness Day represents another opportunity to unite patients, healthcare providers, other advocates, and industry partners in an effort to effectively combat the ill effects of atrial fibrillation at both an individual and societal level. There are several important educational

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events in the next few weeks. The 11th Annual VT symposium (October 7th-8th, New York City) and Asia Pacific Heart Rhythm Society Annual sessions (October 13th-15th, Seoul, Korea) are going to be great opportunities to learn.

New this year, JAFIB is proud to present a new feature called Story Core where we showcase the story of a patient whose life is affected by AF and their journey to recovery and remediation. This issue features a heart transplant patient with AF. On the other hand all of the articles in this issue are very interesting and will make a worthwhile read. We once again thank all of our contributors, reviewers, editorial staff, supporters and readers who help us stay the course and provide you the best education on Atrial Fibrillation and other cardiac arrhythmias.

Fall is already here. Enjoy your pumpkin spice lattes and have a terrific Halloween.

Best wishes

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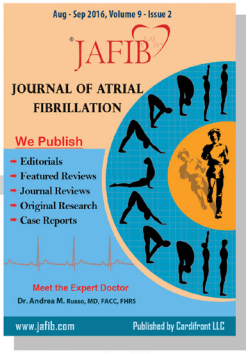

A Meta-Analysis Of Quadripolar Versus Bipolar Left Ventricular Leads On Post-Procedural Outcomes

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Abstract

Objective: We aimed to perform a meta-analysis from eligible studies to analyze the true impact of QL when compared with BL with regard to post-procedural outcomes including lead deactivation, revision or replacement.

Background: Many observational and retrospective studies showed that quadripolar left ventricular leads (QL) are associated with better outcomes and fewer complications when compared with bipolar leads (BL).

Methods: We performed a comprehensive literature search through June 30, 2015 using: quadripolar, bipolar, left ventricular lead and CRT in Pubmed, Ebsco and google scholar databases.

Results: The analysis included 8 studies comparing QL and BL implantation. Post-procedural outcomes such as lead deactivation, revision or replacement were used as primary outcome and assessed with Mantel–Haenszel risk ratio (RR). Secondary outcomes included total fluoroscopy/procedure time, occurrence of phrenic nerve stimulation (PNS) and all-cause mortality on follow up. Follow-up duration for the studies ranged from 3 to 60 months. Compared with BL, the use of QL is associated with 52 % reduction (relative risk 0.48; 95% CI: 0.36-0.64, p=0.00001) in the risk of deactivation, revision or replacement of the LV lead. QL had significantly lower fluoroscopy/procedure time, PNS and all-cause mortality when compared with BL.

Conclusion: Our meta-analysis shows that QL implantation was associated with decreased risk of LV lead deactivation, revision or replacement when compared with BL.

Introduction

Cardiac resynchronization therapy (CRT) is shown to prolong survival, decrease hospitalizations and improve symptoms in patients with left ventricular ejection fraction (LVEF) of ≤35% and evidence of ventricular dysynchrony demonstrated by prolonged QRS duration on an electrocardiogram.[1-3] Despite, the effectiveness of CRT, there are several challenges associated with implantation of the left ventricular (LV) lead such as inability to cannulate the target cardiac vein, lead instability, high pacing thresholds, excessive phrenic nerve stimulation (PNS) and lead deactivation, lead revision or replacement.[4-6]

Key Words:

Cardiac Resynchronization Therapy, Quadripolar Lead, Bipolar Lead, Meta-Analysis, Congestive Heart Failure.

Disclosures:
None.

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Recently, quadripolar LV lead (QL) has been a new innovation in pacing lead technology. The QL, by using 4-electrodes offers greater flexibility and programmability in LV lead placement and CRT by offering ten possible unipolar and bipolar pacing configurations and is designed to improve ease of implantation, decrease short-term and long term complications.[7,8]

Several recent studies have demonstrated that CRT using a QL was associated with lower PNS, procedure and fluoroscopy times and fewer lead related complications including lead deactivation, lead revision or replacement.[7-18] We aimed to conduct a meta-analysis from eligible randomized controlled trials (RCTs) and observational studies comparing QL versus bipolar LV leads (BL) performance and its impact on post-procedural CRT outcomes.

Methods

Search Strategy

We searched MEDLINE, the Web of Science, EBSCO database, Cochrane Central Register of Controlled Trials, Google Scholar, scientific conference sessions and the reference lists of retrieved reports from inception to June 30, 2015 using the search terms 'cardiac resynchronization therapy'; 'quadripolar lead'; 'bipolar lead'

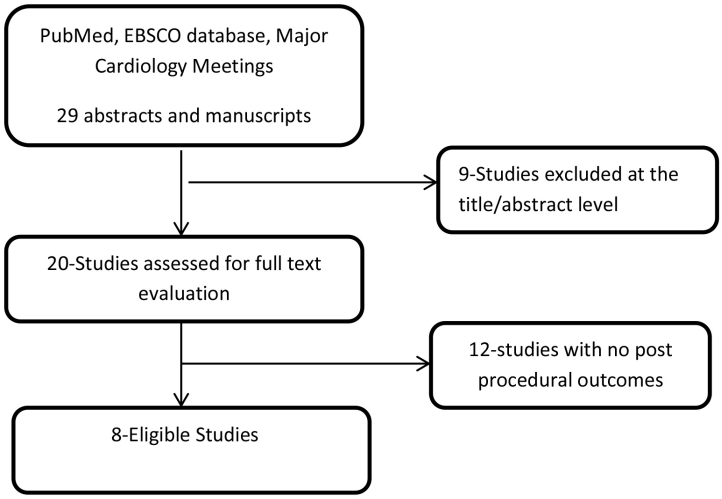

Figure 1: Flow diagram for the included studies

and 'left ventricular lead' to identify all RCT's and observational studies comparing the effects of QL with BL lead on outcomes of CRT. A hand search was also performed in major search databases to identify potentially relevant literature on QL with regard to CRT.

Study Selection

The inclusion criteria of our meta-analysis consisted of RCTs and observational studies of patients undergoing biventricular device implantation in age ≥18 years' assigned to QL or BL which reported post-procedural outcomes including lead deactivation, revision or replacement at any time during follow-up. Our literature search was limited to studies published in peer-review journals in English. We excluded studies having no reported procedural outcomes. Studies published in animal models and foreign languages were excluded. A search for unpublished literature was not performed.

Data Extraction

Two investigators independently performed a search strategy for eligible studies. All items were initially reviewed at the title and abstract level. Potential eligible manuscripts were reviewed in full text. The data was extracted using a standardized form.

Primary Outcome

The primary endpoint was post-procedural outcomes including lead deactivation, lead revision or replacement.

Secondary Outcome

Total duration of the procedure/fluoroscopy, PNS and all-cause mortality were assessed as secondary outcomes with random effect meta-analysis.

Quality Assessment

We followed the criteria established by Juni et al in the quality assessment of the included RCTs in the meta-analysis.[19]

Statistical Analysis

After the data elements were verified for accuracy, systematic and statistical analyses were conducted using Cochrane RevMan version 5.3, and results were expressed as risk ratio (RR) for dichotomous outcomes and mean difference for continuous variables with 95% confidence intervals (CIs). The difference between the QL and BL were estimated by weighted mean difference (WMD) with a two-tailed 95% CI in a DerSimonian-Laird random-effects model for heterogeneous studies. Statistic value I2 was used to quantify the degree of inconsistency. P < 0.05 was considered statistically significant. For the I2 statistic, heterogeneity was defined as low (25%–50%), moderate (50%–75%), or high (>75%). A fixed-effects model was only used if heterogeneity was low.

Results

Search Results

The original search strategy retrieved 29 clinical studies. The title and abstract were reviewed and after applying the inclusion and exclusion criteria, 20 articles were selected for further detailed assessment. After the exclusion of review articles, duplicates and studies with irrelevant outcomes, we found a total of 8 studies comparing QL and BL implantation in CRT outcomes for inclusion in the final analysis (Figure 1). Follow-up duration for the studies ranged from 3 to 60 months. The years of publication ranged from 2012 to 2015 (Table 1).

Study Characteristics

Table 1 summarizes the characteristics of included studies. The meta-analysis includes a total of 8 studies (one randomized control study, four prospective observational and three retrospective studies). Baseline characteristics, procedural details and patient's follow up were similar across all studies. A total of 5,763 patients with QL and 20,894 patients with BL were found. The median follow-up duration was 7.5 months (range 3 months to 60 months), and the median sample size was 248 patients (range 29 to 24,293 patients).

Quadripolar Leads Last Longer Than Bipolar Leads

Compared with BL, the use of QL is associated with 52 % reduction (relative risk 0.48; 95% CI: 0.36-0.64, p=0.00001) in the risk of deactivation, lead revision or replacement of the LV lead (Figure 2).

QL Leads Require Reduced Fluoroscopic Exposure And Procedure Time For Optimal Placement

Compared with BL, the use of QL reduced fluoroscopy by a mean duration of 5.21 minutes (95% CI: -7.67 to -2.75, P<0.0001) and mean procedure time by 10.33 minutes (95% CI: -16.85 to -3.81, P=0.002) (Figure 3A, 3B).

QL Leads Are Associated With Decreased Phrenic Nerve Stimulation

Compared with BL, the use of QL is associated with 76 % reduction (relative risk 0.24; 95% CI: 0.09-0.65, p=0.005) in risk of PNS due to the LV lead (Figure 4).

Placement Of QL Leads Improves Survival

Compared with BL, the use of QL is associated with 44 %

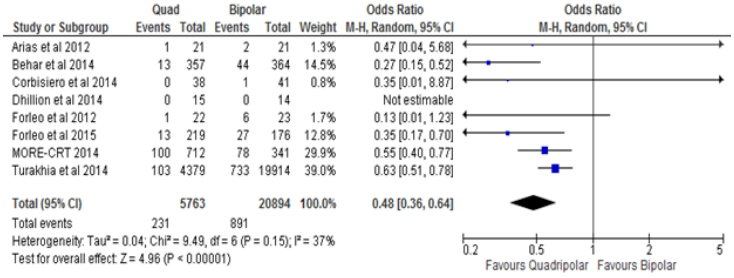

Figure 2: Forest plot showing relative risk (RR) of lead deactivation, revision or replacement with quadripolar lead (QL) and bipolar lead (BL) at follow-up. The use of QL results in a 52% reduction (relative risk 0.48; 95% confidence interval [CI]: 0.36-0.64, p=0.00001) when compared with BL. M-H: Mentel-Haenszel

Table 1:

Study ID	Type of Study	Age Mean±SD	Sample Size	Longest follow up	Risk difference between QL versus BL (95% CI)
Arias et al 2012	Prospective Observational	65.6 ± 9.9	42	9 months	-0.05 [-0.20, 0.11]
Forleo et al 2012	Retrospective	68.3±10.7	45	6 months	-0.23 [-0.43, -0.03]
Corbisiero et al 2014	Retrospective	No data	79	3 months	-0.02 [-0.09, 0.04]
Dhillion et al 2014	Retrospective	71±8	29	6 months	0.00 [-0.12, 0.12]
MORE-CRT 2014	Prospective randomized	68±10	1,068	6 month	-0.03 [-0.06, 0.01]
Turakhia et al 2014	Prospective Observational	69.8±11.3	24,293	12 months	-0.01 [-0.02, -0.01]
Forleo et al 2015	Prospective Observational	70.3±9.2	418	39 months	-0.05 [-0.10, -0.01]
Behar et al 2015	Prospective Observational	68.4 ± 0.55	721	60 months	-0.08 [-0.12, -0.05]

reduction (relative risk 0.56; 95% CI: 0.38-0.81, p=0.002) in the risk of all-cause mortality at follow up (Figure 5).

Discussion

Major Findings

The principal finding of this meta-analysis of RCTs and observational studies is that QL had lower post-procedural complications including lead deactivation, lead revision or replacement when compared with BL. To our knowledge, this is so far the first comprehensive meta-analysis comparing post procedural CRT lead outcome of QL and BL.

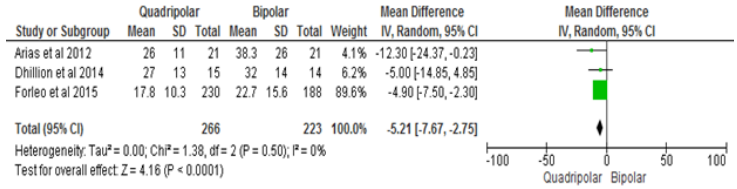

Figure 3A: **Reduction in fluoroscopy duration. Forest plot showing unadjusted difference in mean (95% confidence interval [CI]) fluoroscopy duration with quadripolar lead (QL) and bipolar lead (BL). QL results a reduction in mean fluoroscopy duration of 5.21 minutes (95% CI: -7.67 to -2.75, P<0.0001) when compared with BL. IV: inverse variance**

Impact On Lead Longevity

The current meta-analysis confirms the findings of several recent studies showing that QL are more durable. The most plausible explanation for the decreased need for lead revision or lead replacement with QL is the flexibility in programming in the presence of multiple poles.

Impact On The Procedure Duration

The current meta-analysis results are consistent with the findings of prior studies demonstrating superiority of QL when compared with BL.[12,13,20] Our meta-analysis including 26,657 patients demonstrated that QL was associated with a 52% reduction in post procedural complications in a median follow up of 7.5 months when

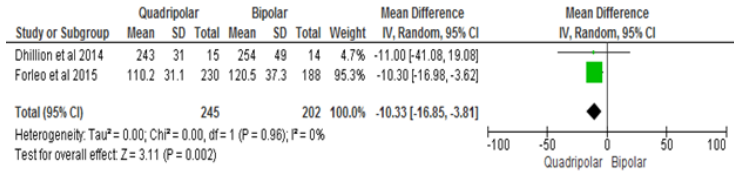

Figure 3B: **Reduction in procedure duration. Forest plot showing unadjusted difference in mean (95% confidence interval [CI]) procedure duration with quadripolar lead (QL) and bipolar lead (BL). QL results a reduction in mean procedure duration of 10.33 minutes (95% CI: -16.85 to -3.81, P=0.002) when compared with BL. IV: inverse variance**

compared with BL placement. Our data supports and extends the current notion that optimal lead implantation using QL is easier than BL. A significantly lower fluoroscopy and procedure time was noted with QL when compared with BL with a mean difference -5.21 minutes and -10.33 minutes respectively. The lower rate of lead revision and total procedure/fluoroscopy time in the QL versus BL was most likely due to ease of implantation from the programming flexibility due to multiple pacing vectors the lead has offered. The alternative pacing vectors with the QL can also overcome other commonly encountered challenges commonly seen with BL such as PNS, higher pacing thresholds and micro-dislodgement of the LV lead without the need for another surgical procedure. Furthermore, QL are reported to have lower impedance and use lower energy to capture the left ventricle that promotes longevity of the device and lowers the need for replacement.[11,12]

Impact Of QL Leads On The PNS

While implanting a CRT, it is of paramount importance to locate a suitable coronary sinus vein or tributary which is associated with low PNS and pacing thresholds. Prior studies have reported post-implantation PNS rates with bipolar leads ranged from 7.4-14% and were more commonly associated with the LV lead location.[21-24] PNS was more commonly seen with the LV lead in the mid-apical, posterior and lateral sites and less common with the LV lead in the anterior or basal site. Our meta-analysis demonstrates that compared with BL, the use of QL is associated with 76 % reduction in PNS. The QL has low PNS as it offers LV pacing from any of the four electrodes as cathode, and RV coil and LV electrodes as anode when compared with BL that offer LV pacing from the ring or the tip as cathode with various anode options. Furthermore, PNS can be posture-dependent and is usually detected post-implantation rather than during implantation. Post-procedural lead re-intervention including CRT termination due to PNS with BL was reported to be 2-13%.[21-25] A QL due to its multiple electrodes and pacing options

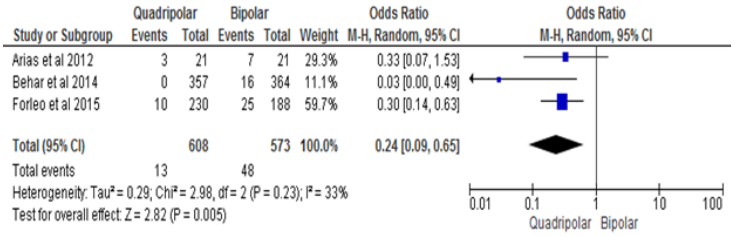

Figure 4: **Forest plot showing relative risk (RR) of phrenic nerve stimulation (PNS) with quadripolar lead (QL) and bipolar lead (BL) at follow-up. The use of QL results in a 76 % reduction (relative risk 0.24; 95% CI: 0.09-0.65, p=0.005) of PNS when compared with BL. M-H: Mentel-Haenszel**

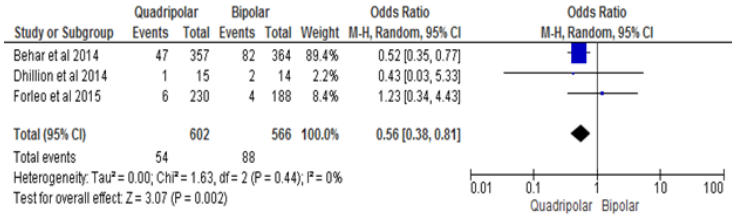

Figure 5: **Forest plot showing relative risk (RR) of all-cause mortality with quadripolar lead (QL) and bipolar lead (BL) at follow-up. The use of QL results in a 44 % reduction (relative risk 0.56; 95% CI: 0.38-0.81, p=0.002) in all-cause mortality when compared with BL. M-H: Mentel-Haenszel**

overcomes the necessity for re-intervention by physically moving the LV lead to another location or CRT termination.

Improved Survival With QL

Our meta-analysis also demonstrates that compared with BL, the use of QL is associated with 44 % reduction in risk of all-cause mortality. These finding can be attributed to the ease of implantation and identification of optimal pacing site with QL which could have resulted in reverse myocardial remodeling and hemodynamic benefit when compared with BL. Implantation of LV lead at the site of a myocardial scar in patients with ischemic cardiomyopathy and presence of atrial arrhythmias has been associated with non-CRT responders.[6,26,27] QL with their multiple programming and pacing vectors can avoid such areas of myocardial scar improving outcomes in patients when compared with BL.

Strengths Of The Current Meta-Analysis

The potential strengths of this meta-analysis are that it is large and includes 26,657 patients. There was no heterogeneity or publication bias among individual studies as noted from our analysis. There is no previous meta-analysis comparing the effectiveness of QL when compared with BL with respect to post procedural complications. The current meta-analysis is the first attempt to explore the beneficial effects of QL over BL in regards to post procedural complications.

Study Limitations

The study has some potential limitations.

1.Most of the studies performed on QL have been from prospective registries. Only one study was a RCT. We cannot exclude the existence of potential unmeasured confounding factors in the included studies.

2.There were more patients in the BL (N=20,894) than compared to the QL (N=5,763) which can lead to some discrepancy in interpretation of results and the sample size may be not large enough to draw firm conclusions.

3.The type of lead implanted in the studies was at the discretion of the invasive cardiac electrophysiologist that could result in a selection bias.

4.Median follow- up in our study was limited to 7.5 months, so we cannot exclude the possibility of lead complications arising over a longer follow-up period.

5.Our meta-analysis does not include data regarding number of patients with ischemic cardiomyopathy and atrial arrhythmias in each individual group as it may impact CRT response and mortality.

6.We are unable to perform additional analysis due to limited number of studies and unpublished data.

Conclusions

Overall, this meta-analysis confirms and extends the findings of most clinical trials by demonstrating that QL have lower post procedural complications including lead deactivation, revision or replacement than BL in patients referred for CRT implantation. This meta-analysis encourages the use of QL and also highlights the need for large-scale multicenter trials to further validate the effectives of this LV lead technology.

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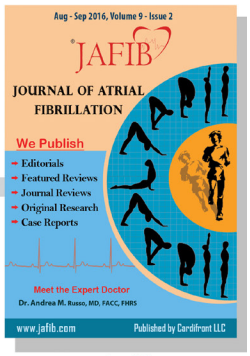

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Which Factors Influence Resident Physicians to Prescribe NOACs to Patients with Non-Valvular Atrial Fibrillation?

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Abstract

The Canadian Cardiovascular Society and the European Society of Cardiology recommend the use of non-vitamin K antagonists (NOAC) in preference to warfarin for stroke prevention in most patients with non-valvular atrial fibrillation (AF). The aim of this study was to identify factors that predict selection of a NOAC by resident physicians when faced with patients with non-valvular AF. A web-based survey was distributed to residents across Canada to learn the attitudes and behaviours regarding stroke, bleeding risk and choices of therapy in different clinical scenarios involving the same patient and one additional co-morbidity. There were a total of 1014 respondents. In an uncomplicated patient with a new diagnosis of AF, self-reported comfort level was the strongest positive predictor for selecting a NOAC (odds ratio (OR) 2.51; 95% confident interval (CI) 1.79-3.54). Residents' desire for the availability of a reversal agent was a negative predictor (OR 0.55; 95%CI 0.39-0.77). In a patient with a prior gastrointestinal bleed, each additional year of training was associated with a choosing a NOAC (OR 1.3; 95%CI 1.1-1.5). In the same patient, the desire for the availability of a reversal agent was a negative predictor of selecting a NOAC (OR 0.42; 95%CI 0.32-0.56). The most consistent predictor for prescribing a NOAC in all clinical scenarios was self-reported comfort level. Fear of adverse events, cost of agents and dosing convenience were not significant predictors. This study found that resident physicians' adherence to guideline-preferred management of AF with regards to stroke prevention is strongly associated with self-reported comfort level, training year and the desire for the presence of a reversal agent.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with an increased risk of stroke.[1] In 2010, the global burden of patients with AF was 33.5 million, of which 20.9 million were men and 12.6 million women.[2] These numbers are expected to rise due to aging population and longer life expectancies. Stroke prevention using oral anticoagulants (OAC) remains the cornerstone of AF management.

The Canadian Cardiovascular Society's (CCS) Atrial Fibrillation guidelines recommend oral anticoagulation for all AF patients ≥65 years of age or who have any one of the traditional CHADS2 risk factors of stroke or transient ischemic attack, hypertension, congestive heart failure, or diabetes mellitus. When an OAC is indicated, it is recommended to use non-vitamin K antagonists (NOAC) including dabigatran, rivaroxaban, apixaban and edoxaban (when approved in Canada) in preference to warfarin.[3] The use of NOACs in preference to warfarin in non-valvular AF is consistent with the European Society of Cardiology's AF guidelines.[4] The American College of Cardiology/American Heart Association AF guidelines do not give preference to NOACs over warfarin however do recommend to use a NOAC in patients with labile international normalized ratio (INR).[5]

Resident physicians frequently diagnose new AF or manage patients with known AF diagnosis. We have previously shown that resident physicians', from different specialties and training years, choices for anticoagulation may not be congruent with guidelines due to presence of a knowledge gap and personal preferences.[6-8] Not much is known about what the factors are that influence their decisions when choosing an anticoagulant agent. The aim of this study was to identify factors that predict selection of a NOAC by resident physicians when faced with patients with non-valvular AF.

Key Words:
Atrial Fibrillation, Resident Physicians, Predictors, Warfarin, NOAC, Guideline Adherence.

Disclosures:
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Methods

Survey

We invited 1844 residents from 44 programs across 11 Canadian academic centers from internal medicine, family medicine, emergency medicine and adult cardiology to participate. A web-based survey consisting of 16 multiple choice questions was distributed using SurveyMonkey (Palo Alto, CA). The survey had different clinical scenarios involving the same patient: 76-year-old male with CHADS2 score of 3, and a medical history of congestive heart failure and hypertension. One additional characteristic was added to each subsequent scenario:

1) A history of gastrointestinal bleed 1-year prior during acetylsalicylic acid (ASA) treatment.

2) Stable stage 3 chronic kidney disease (eGFR 30-59 ml/min/1.73 m^2).

3) Low risk intracranial hemorrhage 1-year prior and 4) a labile INR during warfarin treatment.

Predictor Variables

We looked at residents' training year from PGY 1 though to PGY6 as a continuous variable. The number of prescriptions of OAC (either independently or with the help of an attending physician) in the preceding three months was coded as a 3-level variable of 0-5, 6-10 and greater than 11. Residents were also asked to rank from 1 (least important) to 5 (most important) characteristics related to anticoagulation such as availability of a reversal agent, fear of adverse events, cost to patient, personal familiarity with the agents and convenience of dosing to patients. These were subsequently coded as 0 (combining the three lower ratings of importance) and 1 (combining the two higher ratings) for inclusion in multivariable modelling. Comfort level was a self-reported measure with options of very comfortable, somewhat comfortable, neither, somewhat uncomfortable, very uncomfortable. To make it comparable to the characteristics of anticoagulation, this was also coded as 0 (the three lower ratings of comfort) and 1 (the two higher ratings) for the multivariable modeling.

Outcome Variables

The response options in the survey for the clinical scenarios were: no anticoagulation, ASA, warfarin, dabigatran, rivaroxaban, apixaban, and do not know. Scenario 5 omitted ASA as an option. Respondents were permitted to select multiple potential options based on their likings in each scenario. In this manner, there was no preference given to a specific therapy. The outcome variable was the selection of any one or more of the NOACs which was coded as 1=Yes and any other combination was coded 0=No for multivariable logistic modelling.

Statistical Analysis

Data were collected within the SurveyMonkey Web site, exported in an Excel (Microsoft, Redmond, WA) format, and imported into IBM SPSS (version 22.0 for Windows, Armonk, NY) for statistical analysis. Following a descriptive analysis, a multivariate logistic regression was used to identify the demographics and values associated with selection of a guideline-preferred agent (i.e. NOAC). Since the number of variables to include in a model was not large, and the sample size was sufficiently robust, all potential covariates were entered into model rather than selecting them on the basis of a preliminary univariate analysis. This would allow us to see the respective contributions of each covariate while controlling for the others.

Results

There were 33 programs that participated, constituting a total of 1014 respondents. This included 570 internal medicine, 247 family medicine, 137 emergency medicine, and 60 adult cardiology residents. The level of training ranged from PGY1 to PGY6. The response rate was 55% and the margin of error was 2.7% at a 95% confidence level (CI). For further demographic details of the participants and a full description of the survey and clinical scenarios referenced, see our previous publication and supplementary materials.[6]

For a patient with a new diagnosis of AF, self-reported comfort level was the strongest positive predictor of choosing a NOAC (odds ratio (OR) 2.51; 95% CI 1.79-3.54), followed by training level (OR 1.51; 95%CI 1.31-1.83) and familiarity with the agents (OR 1.51; 95%CI 1.03-2.17) (see Figure 1). Residents that ranked the desire for availability of a reversal agent highly were less likely to choose a NOAC (OR 0.55; 95%CI 0.39-0.77). In a patient with a history of a low risk gastrointestinal bleed while on ASA; both self-reported comfort level (OR 1.4; 95%CI 1.01-1.91) and each additional year of training level were associated with selecting a NOAC (OR 1.31; 95%CI 1.12-1.53). In the same scenario, residents that ranked the desire for availability of a reversal agent highly were less likely to choose a NOAC (OR 0.42; 95%CI 0.32-0.56).

Scenario 3 involved a patient with a history of intracranial hemorrhage 1-year prior deemed low risk to re-bleed by a

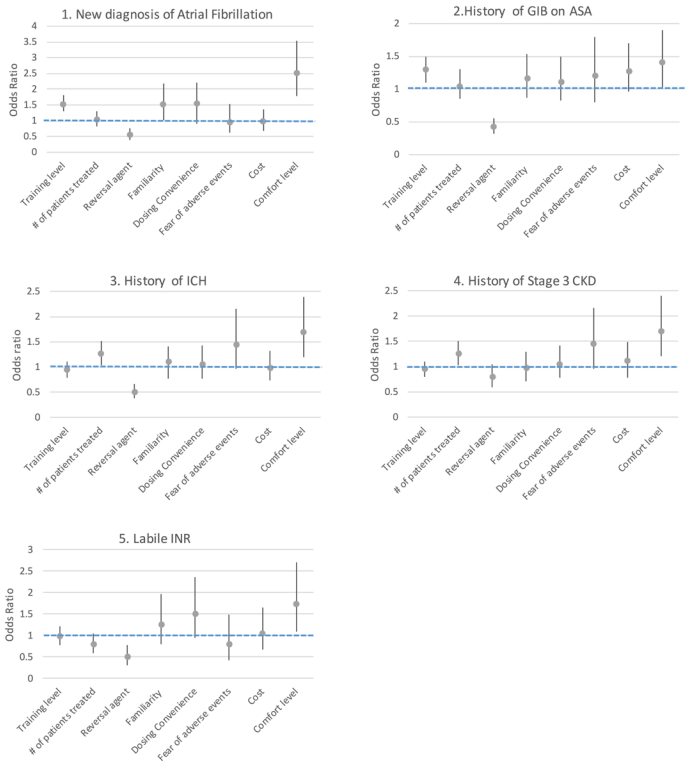

Figure 1: **Predictors of prescribing a NOAC in different clinical scenarios. Scenario 1 had a 76-year-old male with CHADS2 of 3 (history of congestive heart failure and hypertension) and new diagnosis of atrial fibrillation (AF). Each additional scenario, included same patient with one other co-morbidity. Scenario 2 added a history of low risk gastrointestinal bleed(GIB) while on ASA. Scenario 3 added a history of low risk intracranial hemorrhage (ICH). Scenario 4 added stable stage 3 CKD (eGFR 30-59 ml/min/1.73m2). Scenario 5 added a patient on warfarin with labile INRs**

neurosurgical specialist. In this scenario, comfort level (OR 1.69; 95%CI 1.19-2.39) and number of patients treated over a 3-month period (OR 1.25; 95%CI 1.03-1.51) were associated with choosing a NOAC. Furthermore, residents that ranked the desire for availability of a reversal agent highly were less likely to choose a NOAC (OR 0.50; 95%CI 0.38-0.67). For a patient with stable stage 3 chronic kidney disease, comfort level (OR 1.69; 95%CI 1.21-2.44) and the number of prescriptions over a 3-month period (OR 1.24; 95%CI 1.03-1.48) were associated with selecting a NOAC. In a patient on warfarin with labile INRs, self-reported comfort level was the only positive predictor associated with picking NOACs (OR 1.71; 95%CI 1.08-2.74). The desire for availability of a reversal agent was a strong negative predictor (OR 0.48; 95%CI 0.31-0.77).

Discussion

Our study looked at factors that resident physicians value when deciding on oral anticoagulation for their patients with atrial fibrillation. We found that self-reported comfort level with anticoagulation is the most consistent predictor in choosing a guideline preferred OAC across all training years, residency types and clinical scenarios. This study is, to the best of our knowledge, the first of its kind to explore this contemporary topic.

Although resident physicians frequently provide care to patients with AF either independently or with the help of attending physicians, the factors influencing their decisions maybe different. A prior study found that attending physicians are less likely to prescribe anticoagulants if any of their patients have experienced serious bleeding. Interestingly, the same physician survey also found that physicians were more likely to feel 'responsible' for a stroke occurring while not on OAC than a hemorrhage occurring while on OAC.[9] In our study, the fear of adverse events was not a significant predictor of choice of agent in any of the clinical scenarios. This could be due to residents' inexperience of seeing bleeding complications in their patients resulting from a lack of continuity of care during residency training. It can also be due to accumulation of knowledge playing a role in changing attending physician values and preferences over time. Our findings are in contrast to a recent study involving attending physicians that found the risk of major bleeding to be the most important attribute when prescribing OAC. Interestingly in the same study, patients were also asked to rank their preferences and the risk of major bleeding was rated low, a finding that was consistent with the behavior of residents in our study.[10]

Lack of reversal agents for the NOACs remains one of the major barriers to their use.[11] We found that the residents who ranked the desire for a reversal agent highly were about 50% less likely to choose a guideline-preferred OAC in all clinical scenarios except the patient with stable stage 3 chronic kidney disease in which it was not a significant factor. There are now many studies and meta-analyses showing NOACs having a favourable risk-benefit profile compared with warfarin, with a significant reduction in rates of stroke, intracranial hemorrhage, mortality and with a major bleeding risk profile similar to warfarin.[12-15] In our prior study, we found that about two thirds of resident physicians would switch from warfarin to a NOAC should a reversal agent became available.[6] This finding is in contrast to survey assessing attending physicians' factors that found presence of an antidote to be a less important attribute when prescribing OAC.[10] Interestingly, our findings are more congruent with patient preferences in that study, as they rated the availability of an antidote as an important attribute.[10] Idarucizumab, a monoclonal antibody fragment, was recently approved in the United States for the reversal of direct thrombin inhibitor dabigatran.[16] Idarucizumab completely reverses the anticoagulant effect of dabigatran within minutes. Reversal agents for factor Xa inhibitors are currently in various stages of development.[17] Nevertheless, it is not yet known whether reversing the effects of NOACs will change patient's morbidity or mortality. What becomes clear from this analysis is that the existence of a reversal agent increases the level of guideline-preferred practices amongst the residents.

Another interesting and paradoxical finding of this study was that although the desire for the presence of a reversal agent was a strong negative predictor of choosing a NOAC, the fear of adverse events was not. This is in contrast to attendings' who had the opposite preference in that they valued adverse events much higher than the presence of an antidote.[10] This may be due to resident's misunderstanding the value of reversal and patient outcomes.

Although, the Canadian Cardiovascular Society recommends the use of NOACs in preference to warfarin for stroke prevention in AF, the adoption of these drugs have not been uniformly accepted and this may be, in part, due to a lack of alignment with reimbursement systems.[18] Valuing cost consideration was not a significant predictor in any of the clinical scenarios which may reflect the general prescribing patterns of OACs in Canada. As indications for the use of NOACs expand, which now include venous thromboembolism and pulmonary embolisms, more provinces may adopt reimbursement plans that can lead to wider adoption of NOACs.[19]

Limitations

Some limitations of our study are worth mentioning. First, our findings are subject to limitations with survey-based designs. Although this was a good method to assess the choices of anticoagulation of a large number of residents, we cannot tell the extent to which the self-report is related to what is done in practice. Second, resident physician roles and responsibilities vary between residency programs and centers and it is unclear the extent of the influence attending physicians have on junior residents' decisions. However, our findings were consistent uniformly across all training years. It would also be interesting to see how the factors influencing resident decisions may change if other co-morbidities that were barriers to anticoagulation by attending physicians were added to the clinical scenarios such as cognitive impairment, frequent falls and poor patient adherence.[20]

Conclusions

Factors that increase the likelihood that Canadian residents will select a non-vitamin K oral anti-coagulant for a patient with non-valvular atrial fibrillation have been identified.

1.Self-reported comfort level with oral anticoagulants is the most significant predictor across all patient scenarios.

2.Each additional year of training led to an increased likelihood of prescribing a NOAC.

3.Desire for the presence of a reversal agent was generally a strong negative predictor of choosing a NOAC.

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Validation Of The HAS-BLED Tool In Atrial Fibrillation Patients Receiving Rivaroxaban

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Abstract

Background: Atrial fibrillation (Afib) patients are at an increased risk of stroke. Patients at moderate to high risk of stroke typically receive antithrombotics, placing them at an increased risk of bleeding. The HAS-BLED tool has been validated in Afib patients receiving warfarin for prediction of major bleeding events. Although HAS-BLED has been researched in patients receiving warfarin, this tool has not been validated with the novel anticoagulant rivaroxaban.

Methods: The trial design was retrospective case-control approved by the Institutional Review Board at University of Tennessee Medical Center. Patients who were identified as having a bleeding event were cross-referenced with a list of patients receiving rivaroxaban. Inclusion criteria were adult patients with atrial fibrillation who were taking rivaroxaban for at least six months, with a CHA2DS2-VASc score greater than or equal to 2 OR CHADS2 score greater than or equal to 1. The primary endpoint is the predictive ability of HAS-BLED as measured through the c-statistic. Secondary endpoints include correlation of HAS-BLED and bleeding risk.

Results: After reviewing 9621 medical records, 15 patients met the inclusion criteria for major bleeding. Ninety patients were randomly selected for inclusion as the matched control group. The predictive ability of HAS-BLED was not statistically significant (c statistic = 0.68; p = 0.07), but did show some diagnostic ability to predict major bleeding events. Patients with major bleeding were more likely to have a history of bleeding and use concomitant antiplatelet agents. There were significantly more patients with a HAS-BLED score greater than or equal to 3 in the patients that experienced a major bleeding event.

Conclusion: HAS-BLED demonstrated some diagnostic ability to predict major bleeding events in patients receiving rivaroxaban but this was not statistically significant due to limited sample size.

Introduction

Atrial fibrillation patients are at a five-fold increased risk of ischemic stroke.[1] With the aging population, the incidence of atrial fibrillation increases annually, putting more patients at risk for stroke. $CHADS_2$ and CHA_2DS_2-VASc are proven risk assessment tools to determine a patient's annual risk of ischemic stroke. $CHADS_2$ includes congestive heart failure, hypertension, age greater than 75, diabetes and prior stroke or transient ischemic attack. The 2012 CHEST guidelines recommended anticoagulation in patients with a $CHADS_2$ score greater than or equal to one indicating an annual stroke risk of at least 2.8%.[2] Two years later, $CHADS_2$ was updated to include vascular disease, female sex and age greater than 65; this became the $CHADS_2$-VASc scoring system. The AHA/ACC atrial fibrillation guidelines recommend anticoagulation when a patient's annual stroke risk is greater than 1.3%, i.e. CHA_2DS_2-VASc greater than or equal to 2.[3] When determining the best anticoagulation option for these patients, it is imperative to weigh the risk of stroke with the risk of bleeding. Historically, bleeding risk was determined by subjective opinion of a practitioner. The European Heart Survey determined that many patients were denied guideline recommended anticoagulation due to perceived increased bleeding risk, despite no objective evaluation.[4] Insufficient anticoagulation in atrial fibrillation patients leads to a significant increase in stroke risk.[5] Subsequently, several bleeding risk assessment tools were derived for atrial fibrillation patients.

The HAS-BLED bleeding risk assessment tool has been proven to be more clinically useful in predicting major bleeding as compared to other bleeding risk schemas.[6-11] The criteria making up HAS-BLED are listed in table 1. A HAS-BLED score greater than or equal to 3 indicates a high risk of major bleeding. HAS-BLED has been validated in patients with atrial fibrillation receiving warfarin, but there is inadequate evidence in the novel anticoagulants.[7] There is a retrospective review of patients receiving dabigatran which found to have a higher risk of bleeding when the HAS-BLED score was greater or equal to three.[12] To our knowledge, the present study is the first to evaluate HAS-BLED in patients receiving rivaroxaban. This retrospective analysis was designed to identify if the HAS-BLED bleeding risk assessment tool can be used in atrial fibrillation patients receiving rivaroxaban to determine major bleeding risk.

Key Words:

Atrial Fibrillation, HAS-BLED, Rivaroxaban.

Disclosures:
None.

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Table 1:

H	Hypertension	1 point
A	Abnormal renal or liver function	2 points possible
S	Stroke or TIA	1 point
B	Bleeding or predisposition	1 point
L	Labile INR	1 point
E	Age greater than or equal to 65	1 point
D	Drugs or Alcohol concomitantly	2 points possible

Methods

This study was a single center, retrospective case-control study designed to identify the predictive ability of the HAS-BLED bleeding risk assessment tool in patients receiving rivaroxaban. This study was approved by the University of Tennessee Medical Center (UTMC) institutional review board (IRB). For the case patients, adult UTMC patients were eligible for inclusion if they had atrial fibrillation and a major bleeding event while on rivaroxaban. Major bleeding was defined by the following criteria: primary reason for hospitalization as a bleeding event, need for red blood cell transfusion of 1 unit or more or hemoglobin drop of at least 2 g/L.[7] Patients were included if they were also a patient within the University Cardiology electronic medical record (EMR) and had their major bleeding event between October 2011 – October 2014. Once the patients with major bleeding were identified, a control group of atrial fibrillation patients receiving rivaroxaban were matched based on $CHADS_2$ and $CHADS_2$-VASc. These patients were identified by a report generated from the University Cardiology EMR of patients receiving rivaroxaban during the pre-defined timeframe. Patients were excluded if they were pregnant, had another indication for anticoagulation, or if they were missing any information necessary to calculate HAS-BLED, $CHADS_2$, or CHA_2DS_2-VASc scores. Dosing of rivaroxaban was up to the discretion of the provider.

The primary endpoint was the predictive ability of HAS-BLED for bleeding, as defined by the c-statistic. The secondary endpoints included demographic predictors of bleeding and the predictive ability of $CHADS_2$ and CHA2S2-VASc for major bleeding. Secondary endpoints and baseline characteristics were analyzed with the chi square test, Fisher's exact test, Student's t test, and Wilcoxon rank sum test. All p values were two-sided and considered statistically significant if less than 0.05. Statistical analyses were performed using the SPSS Version 21 software (Armonk, NY: IBM Corp.).

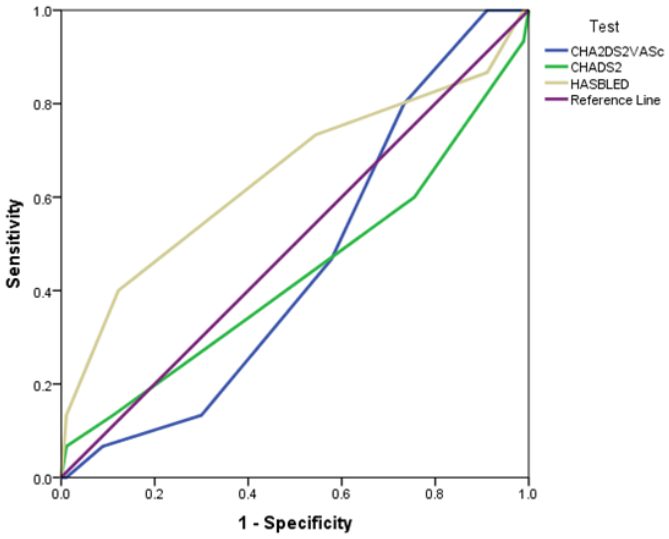

Figure 1: Receiver operator characteristic (ROC) for three scoring systems

Results

Between October 2011 and October 2014, there were 85 patients identified to have experienced a non-traumatic bleeding event and also found in the University Cardiology EMR. Fifteen patients met the inclusion criteria and were included in the analysis. 887 patients were identified as having received rivaroxaban during the study period. Ninety patients were randomly selected as atrial fibrillation patients without bleeding events. The primary reason for exclusion was prior treatment with dabigatran. All control patients received rivaroxaban for at least six months. Baseline characteristics are summarized in table 2. Baseline characteristics were not significantly different regarding age, gender, weight, serum creatinine or rivaroxaban dose. There were significantly more patients with hypertension in the non-bleeding group as compared to the bleeding group (67% vs 89%, p = 0.023). Patients who bled had a significantly lower hemoglobin as compared to the control group (9.46 g/L v. 13.25 g/L p < 0.001).

For the primary endpoint, the c-statistic of 0.68 was not statistically significant but this was highly indicative of a type II error (table 3). There were significantly more patients with a HAS-BLED score greater than or equal to three in the bleeding group.

Table 2: Group characteristics

Characteristic	Bleeds (n=15)	No Bleeds (n=90)	P Value
Age in yrs (SD)	73.3 (11.9)	72.04 (10.52)	-
Gender (% males)	8 (53)	43 (47.78)	-
Weight in kg (BMI in kg/m^2)	87.2 (30.3)	88.85 (25.4)	-
Serum creatinine in mg/dL (SD)	1.01 (0.31)	0.96 (0.32)	-
Estimated GFR in mL/min (SD)	57.79 (21.83)	65.48 (27.02)	-
Antiplatelet use (%)	11 (73)	37 (41.11)	0.02
Hemoglobin (SD)	9.46 (2.36)	13.25 (1.96)	<0.001
Hematocrit (SD)	29.46 (6.84)	44.34 (5.22)	<0.001
Rivaroxaban dose (%)			
20 mg	8 (53.33)	56 (62.22)	-
15 mg	6 (40)	33 (36.67)	
10 mg	1 (6.67)	1 (1.11)	
Presence of drug interactions (%)	5 (33.3)	18 (20)	-
$CHADS_2$ (SD)	2.07 (1.33)	2.26 (1)	-
CHA_2DS_2-VASc (SD)	3.47 (1.13)	3.62 (1.47)	-
Heart failure (%)	5 (33.33)	26 (28.89)	-
Hypertension (%)	10 (66.67)	80 (88.89)	0.023
Age ≥ 65 years of age (%)	13 (86.67)	68 (75.56)	-
Age ≥ 75 years of age (%)	6 (40)	43 (47.78)	-
Diabetes (%)	4 (26.67)	26 (28.89)	-
Stroke (%)	3 (20)	14 (15.56)	-
Vascular disease (%)	0 (0)	12 (13.33)	-
HAS-BLED (SD)	3.13 (1.18)	2.58 (0.87)	0.035
Abnormal renal function (%)	1 (6.67)	1 (1.11)	-
Abnormal liver function (%)	0 (0)	2 (2.22)	-
Bleeding history (%)	4 (26.67)	5 (5.56)	0.023
Labile INR (%)	1 (6.67)	7 (7.78)	-
NSAID use (%)	3 (20)	11 (12.2)	-
Alcohol use (%)	1 (6.67)	8 (8.89)	-
HAS-BLED ≥ 3	6 (40)	11 (12.22)	0.015

Table 3: C-statistics for scoring systems

Predictive Ability of Scoring System	C Statistic	P Value
HAS-BLED	0.65	0.07
$CHADS_2$	0.44	0.43
CHA_2DS_2-VASc	0.45	0.57

There were significantly more patients on an antiplatelet agent in the bleeding group as compared to the non-bleeding control group (73% v. 41.11%; p = 0.02). The average HAS-BLED score was significantly higher in the bleeding group as compared to the non-bleeding group (3.13 [SD 1.18] v. 2.58 [SD 0.87]; p = 0.035). The bleeding group was five-times more likely to have a history of bleeding as compared to the control group (26.67% v. 5.56%; p = 0.023). As compared to $CHADS_2$ and CHA_2DS_2-VASc, HAS-BLED was the scoring system which showed a trend toward predicting major bleeding events in patients receiving rivaroxaban (figure 1).

Discussion

Findings from this study indicate the HAS-BLED score for patients on rivaroxaban has some diagnostic ability to predict major bleeding, but this was not statistically significant. The calculated c-statistic in this study was similar and in some cases higher than previously published studies.[6,7] Patients were more likely to have a HAS-BLED score greater than or equal to three in the bleeding population. Based on the results of Lip et al., a HAS-BLED score greater than 3 is indicative of a high risk of bleeding.[6] To our knowledge, this is the first study to evaluate the predictive ability of HAS-BLED in atrial fibrillation patients receiving rivaroxaban.

Major bleeding events were found to be more likely in patients receiving antiplatelet agents or with a history of bleeding. These characteristics are not included in the $CHADS_2$ and CHA_2DS_2-VASc scoring systems, which limits their predictive abilities as a bleeding risk scoring system. This adds to the growing body of evidence that HAS-BLED should be used in conjunction with stroke assessment tools to guide anticoagulation decisions in patients with atrial fibrillation.

Conclusions

There are several limitations within this study. One of the most apparent limitations is the small sample size. This trial was a single site, retrospective analysis which may not have included major bleeding events at another institution. Future researchers should seek out a larger sample size to further validate the diagnostic ability of the HAS-BLED scoring system to predict major bleeding events. Another limitation is the fact that major bleeding was defined in accordance to the original HAS-BLED definition which is less exclusive as compared to other major bleeding criteria; therefore patients may have been included in this analysis that would have been excluded if a more stringent definition was used. In conclusion, for atrial fibrillation patients receiving rivaroxaban, the HAS-BLED scoring system demonstrated some diagnostic ability to predict major bleeding events but this was not statistically significant due to limited sample size.

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Right Ventricular Pacing for Assessment of Cavo-Tricuspid Isthmus Block

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Abstract

Background: Cavo-tricuspid isthmus (CTI) dependent atrial flutter is typically treated with cardiac ablation. Standard techniques to assess CTI block after ablation can be technically challenging. Right ventricular (RV) pacing may allow for another technique to assess CTI block after ablation.

Objective: The purpose of this study was to evaluate RV pacing as a method to assess CTI block after ablation of CTI dependent atrial flutter, and define endpoints of ablation using this technique.

Methods: 28 patients undergoing ablation of CTI dependent atrial flutter with intact ventriculoatrial (VA) conduction were prospectively enrolled in this study and underwent the RV pacing protocol, as well as standard coronary sinus (CS) pacing techniques to assess CTI block.

Results: The mean trans-isthmus conduction interval during CS pacing (TICICS) at 600 and 400ms after CTI ablation was 168 +/- 9ms and 175 +/- 18ms, respectively. The mean trans-isthmus conduction interval during RV pacing (TICIRV) at 600ms and 400ms after CTI ablation was 109 +/- 5ms and 111 +/- 5ms, respectively. A TICIRV >100ms was associated with a successful outcome after CTI ablation.

Conclusions: RV pacing may add incremental value in the assessment of CTI block in patients undergoing ablation of CTI dependent atrial flutter.

Introduction

Typical atrial flutter dependent on the cavo-tricuspid isthmus (CTI) is a common arrhythmia frequently treated with radiofrequency (RF) ablation.[1,2] Bidirectional CTI block is the standard endpoint for ablation of atrial flutter.[3] Methods to assess bidirectional CTI block, including changes in electrogram (EGM) polarity, measurement of trans-isthmus conduction interval (TICI), and an interval between double potentials (DPs) > 110ms along the ablation line can be difficult to assess.[4-6] Right ventricular (RV) pacing has been shown to be helpful in assessing CTI block, but this technique has not been validated and specific endpoints to determine CTI block have not been defined.[7] The purpose of this study was to evaluate the utility of RV pacing in patients undergoing ablation for CTI-dependent atrial flutter and to define specific endpoints associated with bidirectional CTI block.

Methods

Study Population

A total of 33 consecutive patients who underwent radiofrequency (RF) catheter ablation of CTI-dependent atrial flutter were prospectively enrolled in this study. Patients were excluded from the study if they were under 18 years of age, pregnant, or had undergone a previous CTI ablation. Patients without ventriculoatrial (VA) conduction, identified during the ablation procedure, were subsequently excluded. The protocol was approved by the Medstar Institutional Review Board. Patients provided written informed consent for all procedures.

Atrial Flutter Ablation: Study Protocol

Sedation was provided by electrophysiology (EP) laboratory nursing staff or an anesthesiologist. Access was obtained via the right femoral vein. A 7F deflectable duo-decapolar catheter (Boston Scientific, San Jose, CA; M004 20SL22025 with 2/20/2/2/2/2/2/2/2/2/2/2/25/2/25/2/25/22/2/2mm spacing) was positioned around the tricuspid annulus (TA) in the right atrium (RA) with the distal electrode pair (RA 1-2) placed in the coronary sinus (CS) ostium. Electrode pair RA 3-4 was located lateral to the planned CTI ablation line (Figure 1). Through an 8F 60cm sheath (St. Jude Medical, St. Paul, MN; RAMP, 406898), a 10mm RF ablation catheter (Boston Scientific, San Jose, CA; Blazer II XP, M004 4790THMK20) was positioned on the CTI. A 5F quadripolar catheter (St. Jude Medical, St. Paul, MN; M0045404S0) was positioned in the RV apex (Figure 1).

Patients presented to the EP laboratory in either sinus rhythm or atrial flutter. Patients in atrial flutter underwent pacing with concealed entrainment to confirm CTI dependence of the atrial flutter.[1] Patients in atrial flutter were cardioverted to sinus rhythm with a 200J synchronized shock. RV pacing was performed to ensure

Key Words:
Atrial Flutter Ablation, Cavo-Tricuspid Isthmus, Right Ventricular Pacing, Bidirectional Block.

Disclosures:
None.

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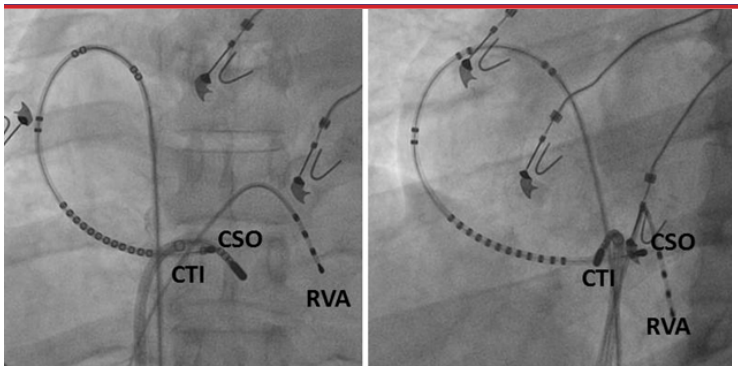

Figure 1: Anteroposterior (left) and left anterior oblique (right) fluoroscopic views of intra-cardiac catheter placement during atrial flutter ablation. The radiofrequency ablation catheter is placed along the cavo-tricuspid isthmus (CTI). The distal tip of the duo-decapolar catheter is placed in the coronary sinus ostium (CSO). The quadripolar catheter tip is placed in the right ventricular apex (RVA)

intact retrograde VA conduction.

Once in sinus rhythm, pacing at two different cycle lengths (600ms and 400ms) from the CS ostium and RV apex was performed. When pacing from the CS ostium, the trans-isthmus conduction interval ($TICI_{CS}$) was measured from the pacing stimulus to the local EGM on the pair of electrodes of the duo-decapolar catheter (RA 3-4) located immediately lateral to the planned ablation line on the CTI. When pacing from the RV apex, the trans-isthmus conduction interval ($TICI_{RV}$) was measured from the local EGM on the distal electrode pair (RA 1-2) of the duo-decapolar catheter located at the CS ostium to the pair of electrodes (RA 3-4) located immediately lateral to the planned ablation line on the CTI.

Endpoints

The $TICI_{RV}$ after CTI ablation was the primary endpoint. Secondary endpoints included the $TICI_{CS}$, differences in $TICI_{CS}$ and differences in $TICI_{RV}$ pre- and post CTI ablation, as well as differences in $TICI_{CS}$ and differences in $TICI_{RV}$ when pacing at two different cycle lengths.

Follow up

All patients were followed until hospital discharge. At one month, patients were evaluated for symptoms at an office visit, and an ECG was obtained. A Holter or event monitor was performed if symptoms suggested recurrent atrial flutter.

Statistical Analysis

28 patients undergoing atrial flutter ablation were included in the analysis. Five patients were excluded due to the absence of retrograde VA conduction during RV pacing, which is required for this diagnostic maneuver. Continuous data were expressed as the mean +/- standard deviation. Univariate comparisons were performed on all continuous variables with either unpaired T test or analysis of variance, as appropriate. Categorical variables were compared with Chi-square analysis. All statistical analyses were performed using SAS version 9.1 (SAS Institute, NC). A p value < 0.05 was considered statistically significant.

Results

Clinical Characteristics

Twenty-eight of 33 (84.9%) patients undergoing ablation of CTI dependent atrial flutter had intact retrograde VA conduction and were included in this analysis. The mean age was 60.7 +/- 15.0 years. The mean left ventricular ejection fraction was 0.50 +/- 0.16. Of 28 patients, 17 (60.7%) presented to the EP laboratory in atrial flutter and underwent cardioversion at the time of the procedure. Among these 17 patients, the atrial flutter cycle length was 255 +/- 33ms (Table 1).

Electrophysiology Findings During CS Pacing Before And After CTI Ablation

The mean $TICI_{CS}$ with a paced cycle length of 600ms pre- and post-ablation was 42 +/- 5ms (range 20-50ms) and 169 +/- 9ms (range 150-220ms; p < 0.01), respectively. The mean $TICI_{CS}$ with a paced cycle length of 400ms pre- and post-ablation was 47 +/- 9ms (range 25-65ms) and 175 +/- 18ms (range 150-225ms; p = 0.01), respectively. The difference between $TICI_{CS}$ pre- and post- ablation was 126 +/- 9ms with a paced cycle length of 600ms, and 139 +/- 25ms with a paced cycle length of 400ms (p = 0.08). A change in the pattern of activation across the lateral RA wall during CS pacing was noted post CTI ablation and was consistent with CTI block in all patients.

Electrophysiology Findings With RV Pacing Before And After CTI Ablation

The mean $TICI_{RV}$ with a paced cycle length of 600ms pre- and post-ablation was 31 +/- 4ms (range 20-50ms) and 109 +/- 5ms

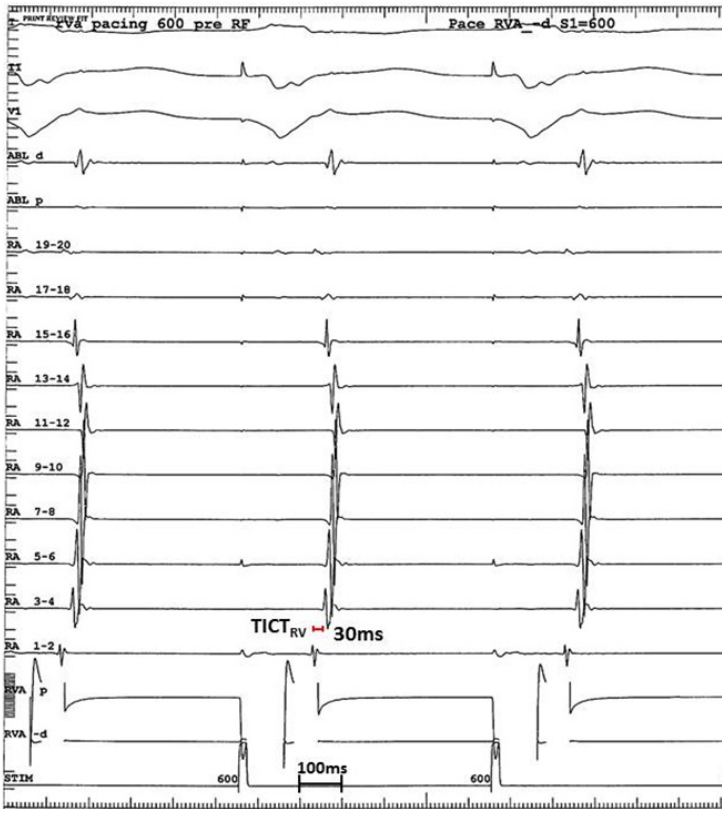

Figure 2: The trans-isthmus conduction interval during right ventricular pacing (TICIRV) was measured pre-ablation of the cavo-tricuspid isthmus (CTI). Surface ECG leads I, II, and V1 and intra-cardiac electrograms from an ablation catheter placed on the CTI (ABLd-ABL p), a duodecapolar catheter placed on the right atrium (RA) septum, to the cristae, and around the tricuspid annulus with the distal tip in the coronary sinus ostium (RA 19-20 to RA 1-2), and a quadripolar catheter placed in the RV apex (RVp-RVd) are shown. RV pacing pre-ablation of the CTI with an atrial activation sequence consistent with isthmus conduction and a TICIRV interval of 30ms, as measured between paired electrodes RA 1-2 and RA 3-4, is shown

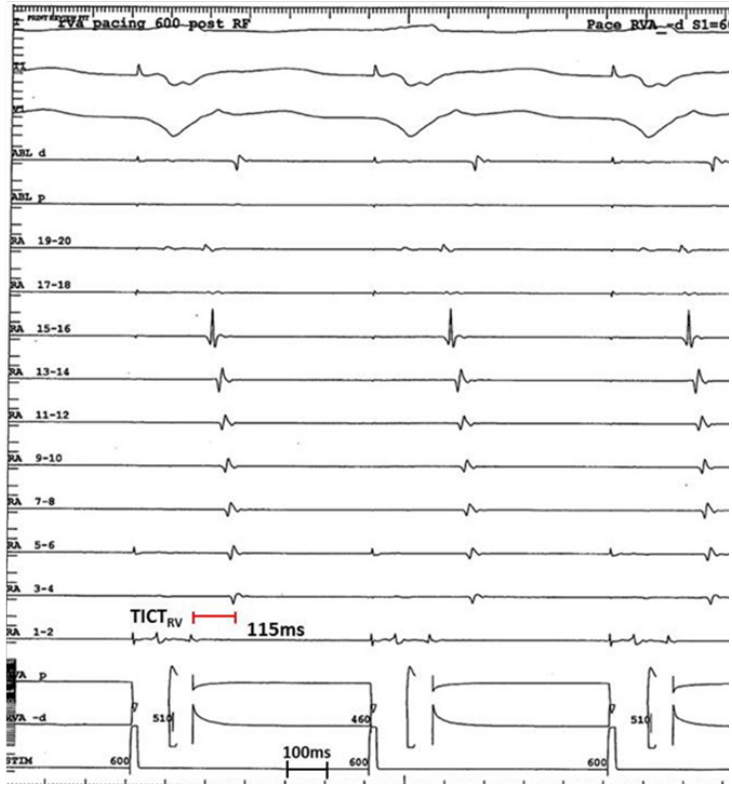

Figure 3: The trans-isthmus conduction interval during right ventricular pacing (TICIRV) was measured post-ablation of the cavo-tricuspid isthmus (CTI). The tracings are arranged as in Figure 2. RV pacing post-ablation of the CTI with an atrial activation sequence consistent with complete isthmus block and a TICIRV interval of 115ms is shown

(range 100-140ms; p < 0.01), respectively (Figures 2 and 3). The mean $TICI_{RV}$ with a paced cycle length of 400ms pre- and post-ablation was 34 +/- 9ms (range 20-60ms) and 111 +/- 5ms (range 100-125ms; p < 0.01), respectively. The difference between $TICI_{RV}$ pre- and post- ablation was 79 +/- 8ms with a paced cycle length of 600ms, and 79 +/- 12ms with a paced cycle length of 400ms (p = 0.8). A change in the pattern of activation across the lateral RA wall during RV pacing was noted post CTI ablation and was consistent with CTI block in all patients.

Short And Mid-Term Outcomes Post CTI Ablation

Bidirectional CTI block was achieved in all 28 patients. No complications were observed. The mean follow up was 8.1 +/- 6.6 months. There were no recurrences of atrial flutter.

Discussion

Major Findings

The major finding of this study is that RV pacing during ablation of CTI dependent atrial flutter is an important adjunctive tool in the assessment of CTI block. More specifically, a TICTRV > 100ms is associated with successful CTI ablation.

Ablation of CTI Dependent Atrial Flutter: Previous Studies

CTI dependent atrial flutter is a common arrhythmia, and RF ablation is first line therapy. In early studies, CTI dependent atrial flutter ablation was performed with a 4mm tip RF ablation catheter.[1-3] However, subsequent studies observed improved outcomes with CTI ablation with 8mm and 10mm tip RF ablation catheters.[8-9]

Methods to assess CTI block after ablation include measurement of the $TICI_{CS}$, and presence of DPs along the ablation line.[4-6] DPs represent the measurement of local activation on both the medial and lateral sides of the CTI ablation line, and are likely the most accurate near-field assessment of CTI conduction. The current method to assess DPs relies on pacing from the proximal CS while recording DPs with an ablation catheter along the length of the CTI ablation line. An interval between DPs > 110ms has been associated with bidirectional CTI block.[6] Challenges with this technique include poor stability of a catheter in the coronary sinus, unreliable capture of the atrial tissue, and inaccurate measurement of the first component of the split potential due to pacing artifact. Data regarding the utility of DPs have come from studies using a 4mm tip RF ablation catheter.[6,10-11] Larger 8mm and 10mm tip RF ablation catheters, functionally, have a larger "antenna" and lead to greater destruction of local tissue; both of which can prevent visualization of one or both components of the DPs along the ablation line.

The $TICI_{CS}$ is defined as the interval between the stimulus artifact and the local atrial activation recorded from the pair of electrodes positioned on the CTI just lateral to the ablation line. This method relies on pacing from the proximal CS. An increase in $TICI_{CS}$ >50% has been associated with complete CTI block).[12] Although an absolute measurement of $TICI_{CS}$ has not been found to be associated with complete CTI block, a $TICI_{CS}$ 150-180ms or greater is generally an acceptable target after CTI ablation.[12] $TICI_{CS}$ may overestimate the frequency of CTI block due to latency between CS pacing and atrial capture, and may be unable to discriminate complete block from incomplete block with very slow conduction. As with the measurement of DPs, $TICI_{CS}$ also requires stable capture of the atrium from the distal tip of the duo-decapolar catheter positioned in the CS ostium. Hence, methods to assess CTI block with CS pacing have limitations.

Comparison of $TICI_{RV}$ with Previous Endpoints

Right ventricular (RV) pacing overcomes these challenges of coronary sinus pacing, allows for stable and reliable pacing, eliminates the issue of latency with atrial capture, and provides an accurate measurement of $TICI_{RV}$; hence, it is helpful in assessing CTI block. Previous studies have shown that RV pacing can aid in the assessment of CTI block, but have not provided specific endpoints for ablation.[7]

In the current study, we defined $TICI_{RV}$ as the interval between the distal pair of electrodes on the duo-decapolar catheter located at

Table 1: Baseline clinical characteristics of patients undergoing atrial flutter ablation

Variable	Mean +/- STD
Age (years)	60.7 +/- 15.0
Male sex (%)	78.6
BMI (kg/m2)	31.2 +/-7.6
Diabetes (%)	39.3
Hypertension (%)	89.3
Coronary disease (%)	25.0
Prior CVA (%)	17.9
Ejection Fraction (%)	49.7 +/- 15.8
Medications (%)	
Aspirin	53.6
Beta-blocker	67.9
ACE-I/ARB	57.1
Warfarin	17.9
Anti-arrhythmic	10.7

the CS ostium and the pair of electrodes positioned on the CTI just lateral to the planned ablation line. Once CTI block is achieved, the distance between the medial and lateral electrodes is slightly shorter with the $TICI_{RV}$ as opposed to that of DPs, where the medial and lateral potentials are recorded on the CTI ablation line. Therefore, it is expected that with CTI block, less time is required to inscribe the medial and lateral electrodes with TICTRV than when recording DPs. In the current study, a $TICI_{RV}$ >100ms after ablation of CTI dependent atrial flutter is shorter than the duration expected with DPs, i.e., > 110ms,[6] and was associated with excellent outcomes.

Limitations

RV pacing to assess CTI block has at least three limitations. First, patients without intact retrograde VA conduction cannot utilize RV pacing in the assessment of CTI block. In this study, this occurred 15% of the time and the use of RV pacing was precluded. Isoproterenol may have improved VA conduction and allowed for the use of RV pacing in the assessment of CTI block, but was not administered to patients in this study. Second, DPs were not measured during RV pacing. Electrophysiologically, this is likely the gold standard to assess bidirectional block. However, DPs are difficult to assess after CTI ablation with a 10mm tip RF ablation catheter. Third, data regarding partial but not complete CTI block was not collected. However, a comparison of the $TICI_{RV}$ before and after the achievement of complete CTI block was performed, and as expected, was slightly less than DPs. Finally, lateral RA pacing was not performed pre- and post-CTI ablation to confirm true bidirectional block. However, after CTI ablation, unidirectional block is not common.

Clinical Implications

Data evaluating the use of RV pacing as a method to assess CTI block during ablation of CTI dependent atrial flutter have been limited. RV pacing allows for accurate assessment of $TICI_{RV}$ along the CTI ablation line. These results demonstrate that a $TICI_{RV}$ >100ms is associated with excellent outcomes after ablation of CTI dependent atrial flutter, and should be considered for verification of bidirectional CTI block.

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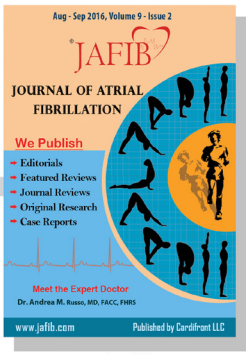

Pulmonary Vein Remodeling Following Atrial Fibrillation Ablation: Implications For The Radiographic Diagnosis Of Pulmonary Vein Stenosis

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Abstract

Background: Pulmonary vein (PV) reverse remodeling has been recognized following atrial fibrillation (AF) ablation. However, the extent of physiologic reverse remodeling after AF ablation and the potential impact of reverse remodeling on the radiographic diagnosis of PV stenosis have not been well characterized.

Methods: From January 2004 to February 2014, 186 patients underwent paired cardiac magnetic resonance imaging (MRI) to delineate PV orifice dimensions before and after (mean 109 ± 61 days) an initial AF ablation.

Results: Negative remodeling of the PV orifice cross sectional area occurred in 67.8% of veins with a mean reduction in area of 21.0 ± 14.1%, and positive remodeling was seen in the remaining PVs with an increase in area of 22.1 ± 23.4% compared to baseline. No PVs demonstrated a reduction in cross-sectional area of > 75% (maximum reduction observed was 58%). Negative remodeling of the PV long axis dimension was observed in 55.2% of veins with a mean reduction of 14.6 ± 9.2% compared to pre-ablation and positive remodeling was observed in 25.3% of PVs with a mean increase in diameter of 14.7 ± 12.6%. Only 1 PV demonstrated a reduction in orifice diameter of > 50%. There were no clinically evident or suspected cases of PV stenosis in this cohort.

Conclusions: Negative remodeling of the PV orifice area was noted in the majority of PVs following AF ablation. However, in almost all cases, the extent of negative remodeling was well below commonly used thresholds for the radiographic diagnosis of PV stenosis.

Introduction

Pulmonary vein stenosis (PVS) is an important complication of catheter ablation for atrial fibrillation (AF). Although the incidence of PVS has decreased with the evolution from ostial to more antral PV isolation and other advances in ablation technology, a recent systematic review suggested that the incidence of PVS in contemporary studies remains approximately 2%.[1] In the Second Worldwide Survey of AF ablation, the incidence of PVS requiring invasive treatment was 0.29% among patients undergoing ablation from 2003 to 2006;[2] however, this figure is likely subject to underreporting, particularly given that most operators do not routinely screen asymptomatic patients for PVS following ablation.[3] The diagnosis of PVS depends on a combination of symptoms, cross-sectional imaging such as computed tomographic (CT) or magnetic resonance (MR) angiography, functional assessment such as lung perfusion scanning and findings at diagnostic catheterization including pulmonary venography and hemodynamic assessment of stenosis severity. In patients with symptoms concerning for PVS following AF ablation, cross-sectional imaging is frequently used as an initial diagnostic step and helps guide further evaluation. Commonly cited radiographic criteria for the diagnosis of PVS include a reduction in PV long axis diameter of >50% compared to pre-ablation[1,4] or a reduction in PV cross-sectional area of >75% (corresponding to a reduction in diameter of ~50%).[5] These thresholds were defined primarily based on early series of patients presenting for evaluation of clinically suspected PVS where it was noted that

Key Words:
Atrial Fibrillation, Ablation, Pulmonary Veins, Pulmonary Vein Stenosis, Cardiac Magnetic Resonance.

Disclosures:
None.

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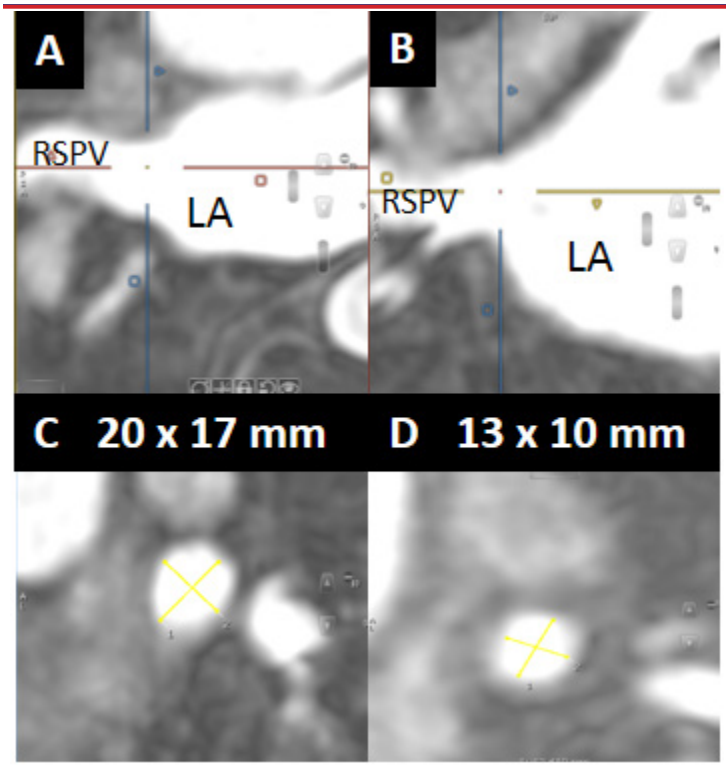

Figure 1: **A and B. Example of orthogonal projections on cardiac magnetic resonance imaging used to define the pulmonary vein (PV) orifice. C and D. Long and short axis measurements of the PV orifice used to calculate the orifice cross-sectional area. Pre-ablation (panel C), the right superior PV measured 20 x 17 mm. Post-ablation (panel D), it measured 13 x 10 mm. RSPV = right superior pulmonary vein, LA = left atrium**

symptoms typically emerged when the severity of stenosis reached a threshold of approximately 60% reduction in diameter.[6,7] However, it is well recognized that AF ablation and maintenance of sinus rhythm may result in reductions of left atrial (LA) size and pressure, with concomitant reverse remodeling of the PVs and a physiologic reduction in PV size.[8-14] However, the incidence and extent of physiologic reverse remodeling associated with AF ablation and the manner in which reverse remodeling may impact the radiographic diagnosis of PVS have not been well described.

Methods

The Emory University institutional review board approved the study protocol. Patients at Emory University Hospital Midtown undergoing initial catheter ablation for atrial fibrillation between January 2004 and February 2014 who had paired pre- and post-procedure cardiac magnetic resonance (CMR) imaging performed to delineate PV anatomy were included in this analysis. Post-procedure CMR was performed in all patients in this cohort to screen for PVS. Baseline demographic data, clinical covariates and procedural details were ascertained by review of electronic medical records. The decision to perform AF ablation along with specific details of the ablation strategy and peri-procedural management were performed at the discretion of the treating physician.

Pre- and post-ablation gadolinium-enhanced CMR scans were performed on a 1.5 tesla Philips Intera® MRI scanner (Amsterdam, Netherlands) using a 5-element phased-array cardiac coil. Turbospin echo and gradient echo images in axial and double oblique planes following the administration of gadopentetate dimeglumine (Magnevist®) or gadobenate dimeglumine (MultiHance®) (dosed at 0.075-0.10 mmol/kg) were used to delineate PV anatomy. Orthogonal projections of angiographic images were used to measure PV dimensions (Figure 1). PV orifice cross-sectional area was calculated from the ostial long and short axis dimensions assuming an ellipsoid shape.15

From the 186 patients in this cohort, 18 patients (9.7%) had a left common PV and in these cases, the left-sided veins were excluded from the analysis of PV remodeling, resulting in a total of 708 individual PV orifices for analysis.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation and categorical data are summarized as frequencies and percentages. Comparisons across groups were performed using the Student's T-test or Fisher's exact test, as appropriate. Correlations between continuous variables were performed using Pearson correlation coefficients. For all comparisons, a two-tailed $p < 0.05$ was considered to be statistically significant. Analysis was performed using STATISTICA software (Statsoft, Inc., Tulsa, OK).

Results

During the period of interest, 186 patients underwent paired pre- and post-procedure CMR scans associated with a first AF ablation procedure. Mean age of patients in this cohort was 58.3 ± 9.8 years, 82% were male and 24% had persistent AF. Other baseline characteristics are presented in Table 1. The vast majority of patients in this cohort underwent antral PV isolation with radiofrequency (RF) (n=181) and 5 patients underwent Cryoballoon ablation. There were no significant differences in baseline characteristics between patients in the 2 ablation modality groups. The post-procedure CMR was performed 109 ± 61 days following ablation. No patients in this cohort had clinically evident or suspected PV stenosis.

At baseline (prior to ablation), the mean cross-sectional areas of the four PVs were: left superior PV (LSPV) 202.6 ± 66.6 mm2; left inferior PV (LIPV) 177.9 ± 84.4 mm2; right superior PV (RSPV) 268.4 ± 114.9 mm^2 and right inferior PV (RIPV) 221.9 ± 86.6 mm^2. At the time of follow-up CMR, negative remodeling of the PV orifice

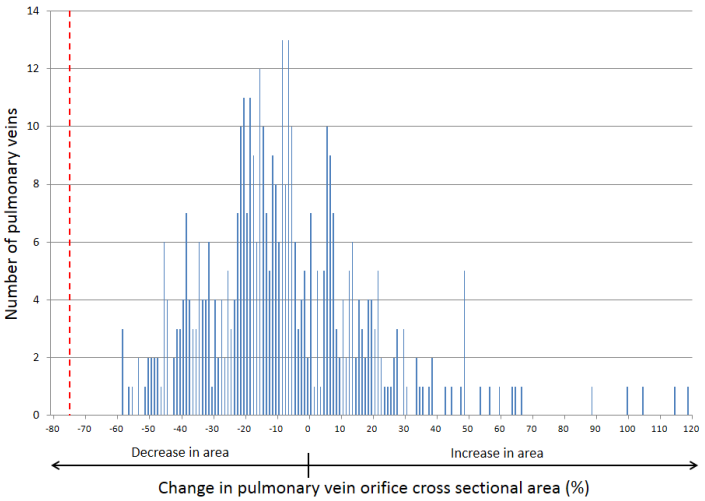

Figure 2: **Distribution of changes in pulmonary vein orifice cross sectional area observed after atrial fibrillation ablation. The dashed red line marks the 75% reduction in cross sectional area threshold which is commonly used for the radiographic diagnosis of pulmonary vein stenosis**

(defined by a reduction in cross sectional area) was observed in 67.8% of veins, with a mean reduction in area of 21.0 ± 14.1% and positive remodeling was seen in the remaining PVs with an increase in area of 22.1 ± 23.4%. Averaging all veins, the mean percent change in PV orifice cross sectional area for each of the four PVs ranged from a mean reduction of 5.1% in the RIPV to a reduction of 9.8% in the RSPV (Table 2). For all PVs, the mean change in cross sectional area is plotted in Figure 2 and approximates a bell-shaped distribution, with the peak centered in the range of roughly 5-10% reduction in orifice area across all veins. The largest decrease in orifice area in any vein observed was 58%, well below the currently used threshold of 75% for the radiographic diagnosis of PVS (marked by the dashed red line in Figure 2).

There were some statistically significant, although relatively weak correlations in the extent of negative or positive remodeling between PVs. The strongest correlation was between the LSPV and RIPV ($r = 0.247$, $p = 0.02$). Other significant correlations included the LSPV vs. LIPV ($r = 0.239$, $p = 0.03$) and LSPV vs. RSPV ($r = 0.220$, $p = 0.04$). Other correlations were not significant. At the patient level, out of 186 patients included in this cohort, 44 demonstrated evidence of concordant positive remodeling, meaning that all PVs showed an increase in orifice size following ablation whereas only 5 patients showed evidence of concordant negative remodeling. This data highlights that although over two-thirds of PVs demonstrated negative remodeling, in the vast majority of patients, at least one PV showed an increase in size, leading to lack of concordance in negative remodeling. In contrast, when positive remodeling was present, it was much more likely that all PVs increased in size leading to a concordant pattern. No significant difference was noted in the need for cardioversion in the first 3 months following ablation among patients with, compared to those without, concordant positive remodeling.

Data on PV long axis diameter are also presented in Table 2. Following ablation, approximately half of PVs demonstrated a reduction in diameter, about a quarter increased in diameter and no change was noted in the remaining patients. The distribution of changes in PV diameter following ablation is plotted in Figure 3. The maximum observed decrease in PV diameter following ablation was 51%, which is just above the commonly used threshold of 50% (marked by the dashed red line in Figure 3). With the exception of that single PV, all others demonstrated changes in diameter well below the 50% threshold.

Discussion

Our data demonstrate that AF ablation is associated with negative remodeling of the PV orifice area in about two-thirds of PVs, and the expected physiologic change in PV orifice area follows a roughly bell-shaped distribution with a mean reduction in orifice area of about 5-10%. In about one-third of PVs, positive remodeling is observed after ablation and when present, positive remodeling is more likely to affect all PVs in a concordant pattern. Importantly, the physiologic range of negative remodeling observed is well below the thresholds currently used for the radiographic diagnosis of PV stenosis.

Numerous prior studies have assessed the extent of PV negative remodeling associated with AF ablation by comparing paired baseline and follow-up imaging studies (both CT and MR), usually performed at a mean follow-up of approximately 2 - 4 months post-ablation. In these studies, the mean reduction in PV diameter following ablation has ranged from 6.5 - 16%.[10,11,13,16] In similarly designed studies, it has been noted that the percentage of PVs that can be expected to demonstrate evidence of negative remodeling ranges from 22 - 38%.[9,11,14] Our data add to this existing body of literature in several ways. First, a major difference between prior studies assessing PV remodeling after AF ablation and our analysis is that most prior studies have focused on a single PV diameter measurement rather than assessing cross-sectional area. However, it is well recognized that the PV orifice in most patients is ellipsoid, not spherical[15,17,18] and therefore, a single long-axis diameter measurement does not fully represent the orifice size or the degree of hemodynamic impact from narrowing of the PV orifice. When assessing cross-sectional area, our data suggest that nearly two-thirds of PVs demonstrate evidence of negative remodeling after ablation. In contrast, prior studies looking only at changes in diameter, but not in area, have suggested that the percentage of PVs that demonstrate negative remodeling is lower, ranging from 22 – 38%.[9,11,14] Additionally, whereas most previous studies have focused on the extent of negative remodeling, our data also incorporates the extent of positive remodeling and in doing so, we are able to demonstrate that the physiologic range of PV orifice remodeling following ablation approximates a bell-shaped distribution, with a mean change in cross-sectional area of around negative 5-10% (Figure 2).

Having demonstrated such a bell-shaped distribution, it is interesting to speculate on the potential mechanisms for negative and positive remodeling. Although the pathophysiologic mechanisms which lead to PVS have not been precisely defined, it has been speculated based on histologic studies that inflammatory injury leads to collagen deposition, intimal proliferation, fibrosis and eventually endovascular contraction.[1] However, it seems probable that the mechanisms leading to physiologic negative remodeling are likely distinct from the patterns of injury that lead to clinically relevant PVS. It has been speculated that successful catheter ablation, and the maintenance of sinus rhythm, may lead to reductions in LA volume and pressure, with a corresponding reduction in PV size. Although some studies have demonstrated a correlation between post-ablation reduction in LA volume and PV size[13] others have suggested that

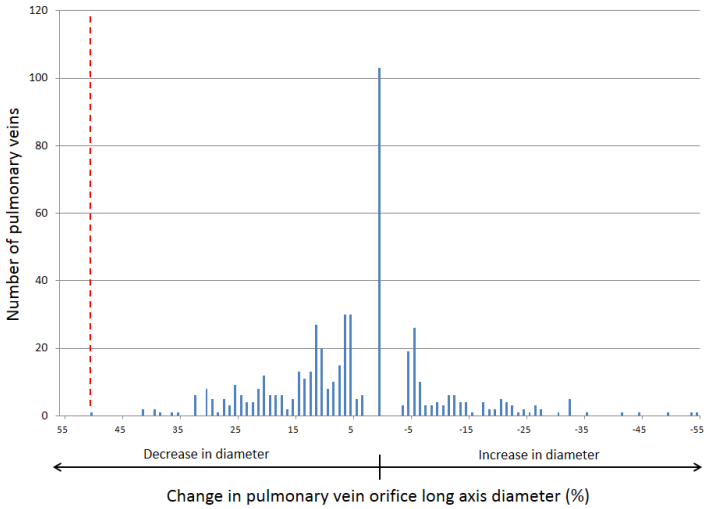

Figure 3: **Distribution of changes in pulmonary vein orifice diameter observed after atrial fibrillation ablation. The dashed red line marks the 50% reduction in diameter threshold which is commonly used for the radiographic diagnosis of pulmonary vein stenosis**

Table 1: Baseline characteristics

	n = 186
Age (years)	58.3 ± 9.8
Male gender	152 (81.7)
Hypertension	76 (40.9)
Coronary artery disease	14 (7.5)
Diabetes mellitus	7 (3.8)
Obstructive sleep apnea	20 (10.8)
Persistent atrial fibrillation	45 (24.2)
Medical therapy at the time of ablation	
Beta blockers	57 (30.6)
Non-dihydropyridine calcium channel blockers	18 (9.7)
Angiotensin antagonists	37 (19.9)
Statins	47 (25.3)
Warfarin	80 (43)
Novel oral anticoagulants	24 (12.9)
Amiodarone	12 (6.5)
Dronaderone	17 (9.1)
Sotalol	32 (17.2)
Dofetilide	9 (4.8)
Class Ic antiarrhythmics	55 (29.6)

the magnitude of PV remodeling differs between PVs and does not necessarily correspond with changes in LA volume.[12,16] Our data are more consistent with the later in demonstrating that correlations between PVs in the extent of remodeling were relatively weak and although the majority of PVs demonstrated evidence of negative remodeling, within individual patients, there was significant variability in the pattern of PV remodeling leading to a lack of concordance in negative remodeling. The correlation between maintenance of sinus rhythm after ablation, LA pressure and PV remodeling is likely complex and requires further elucidation.

Defining the expected range of physiologic remodeling after AF ablation has important relevance for the diagnosis of PVS. Although PVS has become less common with advances in ablation technology and evolution from ostial to antral lesions, a recent systematic review suggested that the incidence of PVS in contemporary studies ranges from 3-8% (mean ~2%)[1] and these figures may be an underestimate since most operators do not screen for PVS in the absence of clinical concern.[3] As such, determining the risk of PVS remains an important step in defining the safety of new ablation technologies. For instance, in a recent analysis of 50 patients undergoing ablation with the pulmonary vein ablation catheter (PVAC, Medtronic, Minneapolis, MN), mild PV narrowing (defined by a reduction in diameter of 10-24%) occurred in 35% of PVs, moderate narrowing (defined by a reduction in diameter of 25-50%) occurred in 30% of PVs and severe narrowing (defined by >50% diameter reduction) occurred in 4% of PVs,[16] leading the authors to conclude that the observed rates were "a reason for concern." Our data would suggest that mild to moderate narrowing of the PV diameter (<50%) are within the physiologic range of negative remodeling which can be expected following AF ablation. In the Clinical Study of the Artic-Front Cryoablation Balloon for the Treatment of Paroxysmal Atrial Fibrillation (STOP-AF) trial, using a definition of PVS of reduction in cross-sectional area >75%, only 10 PVs out of 228 patients in the on-treatment analysis met radiographic criteria for PVS.[5] Our data suggest that using cross-sectional area, rather than diameter, and taking into account the expected physiologic range of negative remodeling associated with AF ablation, are both likely to improve the sensitivity and specificity of radiographic criteria for determining PVS.

Lastly, it is important to note that our analysis, along with most prior studies assessing the incidence of PVS, have focused on radiographic measurements of PV area and diameter. It is conceivable that beyond area and diameter, other radiographic patterns of PV stenosis may exist, such as unexpected deformities in the shape or morphology of PVs as a result of pathologic injury. Such morphology criteria may be missed when relying on diameter or area alone. However, until such morphologic criteria have been systematically assessed and validated for the purpose of diagnosing PVS, our data suggest that some caution should be applied when using PV diameter and area to identify PVS given the expected ranges of physiologic remodeling.

Limitations

Several important limitations of our cohort should be noted. First, due to changes over time in the CMR protocol for quantifying LA volumes at our institution, we are unable to assess the relationship between changes in LA volume and PV remodeling. Additionally, although it is interesting to speculate on the relationship between success of ablation (i.e. maintenance of sinus rhythm) and the pattern of PV remodeling, we are unable to provide consistent data on the recurrence rates of AF in this cohort. At our institution, as in many others, there has been a gradual tendency to more rigorous monitoring of patients to detect sub-clinical AF episodes after ablation.[3] Therefore, temporal changes in the intensity of monitoring post-ablation would likely confound the relationship between recurrence

Table 2: Changes in pulmonary vein orifice size

	Baseline cross sectional area (mm²)	Mean change in cross sectional area (%)	Percentage of patients with change following ablation		
			Reduction	No change	Increase
Left superior pulmonary vein	202.6 ± 66.6	-6.4 ± 26.5	61.8		38.2
Left inferior pulmonary vein	177.9 ± 84.4	-7.7 ± 28.5	73.4		26.6
Right superior pulmonary vein	268.4 ± 114.9	-9.8 ± 24.5	69.8		30.2
Right inferior pulmonary vein	221.9 ± 86.6	-5.1 ± 26.8	67.5		32.5
	Baseline long axis diameter (mm)	**Mean change in diameter (%)**	**Percentage of patients with change following ablation**		
			Reduction	**No change**	**Increase**
Left superior pulmonary vein	18.0 ± 3.3	-5.1 ± 14.6	56.5	20.9	22.6
Left inferior pulmonary vein	17.5 ± 3.3	-6.0 ± 16.3	63.1	22.3	14.6
Right superior pulmonary vein	20.3 ± 4.3	-5.2 ± 15.4	53.9	20.6	25.5
Right inferior pulmonary vein	18.3 ± 3.7	-2.0 ± 13.4	49.3	21.1	29.6

Data are presented as mean ± standard

of AF and PV remodeling patterns. As noted in the Results section, we did not note any correlation between the need for cardioversion post-ablation and the pattern of remodeling.

All follow-up CMRs in this cohort were performed within the first few months after ablation, roughly corresponding to the clinical "blanking period". Therefore, we are unable to comment on longer-term impacts of ablation on PV remodeling and the extent to which the remodeling patterns observed soon after ablation may change with time. Lastly, our analysis demonstrates a range of physiologic negative remodeling which may impact the diagnosis of PVS when using PV diameter and area criteria. In the absence of histologic or functional assessments of PV remodeling and without specific radiographic criteria to differentiate pathologic injury from physiologic remodeling, we cannot exclude the possibility of overlap between physiologic negative remodeling and pathologic PV stenosis in our cohort. However, as detailed in the Results section, there were no cases of clinically suspected PVS in this analysis.

Conclusions

Pulmonary vein negative remodeling, defined by a reduction in cross-sectional area, occurs in approximately two-thirds of PVs following a first AF ablation and the extent of remodeling follows a roughly bell-shaped distribution with a mean change in PV orifice area of around negative 5-10%. These changes occur in the absence of any clinical evidence to suggest PVS. The expected physiologic range of PV remodeling should be taken into account when determining radiographic thresholds for diagnosing PV stenosis.

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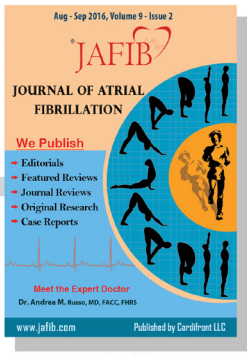

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Screening For Atrial Fibrillation In The Community Using A Novel ECG Recorder

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Abstract

Aims: MyDiagnostick (MDK) is a novel portable ECG recorder. We conducted this study to evaluate its role in screening for atrial fibrillation (AF).

Methods: The device is a cylindrical rod with metallic electrodes at both ends recording electrocardiogram (ECG) when both electrodes are held. Individuals were requested to hold the device for approximately 15 s, the device was then connected to a laptop (with proprietary software downloaded) and analysed. Anonymised ECGs were stored for further analysis. A total of 855 ECGs were recorded and analysed offline by two arrhythmia specialists assessing ECG quality, in particular the level of noise. A noise score (NS) was devised regarding ECG quality.

Results: Seven individuals were found with unknown AF (0,8%). In general ECG quality was good and rhythm diagnosis was certain with total interobserver agreement.

Conclusion: The MDK provided a rapid and accurate rhythm analysis and has potential implications in preventing ischaemic cardio-embolic stroke.

Introduction

Atrial fibrillation (AF) is the most frequently occurring arrhythmia, with a prevalence ranging from 0.7% in the age group 55–59 years to 17.8% in those aged ≥85 years.[1] More than 30% of patients with AF are asymptomatic.[2-3] These patients are at increased risk of heart failure and ischaemic thromboembolic stroke. In particular, the annual stroke risk in AF patients not treated with anticoagulants is 5%, which is two to seven times as high compared with non-AF patients.[4] Furthermore, a stroke registry by Pisters et al. demonstrated that 45% of all AF-related strokes occurred in patients with asymptomatic and unknown AF.[5] For this reason, screening for AF and initiation of anticoagulation in patients at risk is key to reducing the total number of embolic strokes as well as heart failure hospitalizations. For the diagnosis of AF an ECG showing the arrhythmia is mandatory, since pulse analysis is not accurate enough. Recently a new diagnostic device, the MyDiagnostick (MDK) (Applied Biomedical Systems BV, Maastricht, The Netherlands), has been validated enabling quick ECG recordings and easy detection of AF.[6]

Key Words:

Atrial fibrillation, Screening, MyDiagnostick.

Disclosures:
None.

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Two recent studies[6-7] have shown the accuracy of MDK in detecting AF through 60 s recordings using the automatic algorithm. The hypothesis of our study was that shorter rhythm strips (15 s) obtained through MDK and analysed by experienced personnel would allow quick and reliable mass screening for AF. This is the first use of MDK for AF screening via this method.

Material and Methods

The MDK is a cylindrical rod (length 26 cm, diameter 2 cm) with metallic electrodes at both ends that are held onto to record an ECG in lead I configuration (Figure 1). Using this novel device we screened a large population for AF during a single-day campaign for rhythm awareness in a busy shopping centre in Leeds (UK). Four MDK sticks and 2 laptops with proprietary software for the device were used. A total of 855 people were screened from 9 am to 7 pm. People of both sex and all ages were enrolled after signing a consent form. Individuals with known AF or pacemaker implanted were excluded. People enrolled were asked to hold MDK with both hands at the ends of the stick. Being a portable device people could have their rhythm checked with great simplicity, holding the device in front of them for only 15 s, until the first flashing light, corresponding to an ECG strip recorded, stopped flashing. In this way we obtained a large number of ECG lead I strips in an easy and quick manner. For people who could not keep their arms steady while standing, we asked them to have a sit and put their arms on their knees while holding the stick. Individuals were given access to their results immediately, in fact specialists or cardiologists, who were attending the AF screening campaign, plugged the device into the laptop, downloaded and

Figure 1: MyDiagnostick

analysed the ECG at all times, for each patient they had enrolled, soon after obtaining the ECG recording. Anonymous ECGs were stored electronically. Two arrhythmia specialists analysed the ECGs offline to describe and classify quality of the ECG strips despite such a short recording. Noise on ECG was described according to a noise score (NS) where NS 1 was a completely clear ECG, NS 2 was an ECG with noise but where a good interpretation was possible, NS 3 was borderline ECG for noise (analysis based on RR regularity), NS 4 was a not interpretable ECG (Figure 2). This NS was validated through an evaluation of agreement between the operators about score of noise on ECGs. A sample of 50 ECGs were analysed by two arrhythmia specialists, independently, to validate interpretation.

There was 82% agreement with regards to noise classification. However there was 100% agreement on rhythm diagnosis.

Results

Using MDK 855 people were screened in only 10 hours in a busy suburban shopping centre. We found 7 individuals with unknown AF (0.8%). Globally, the MDK showed good quality lead I strips (Table 1). Twenty-eight percent of ECG strips were completely clear and only in 7% of cases the level of noise was so high that it was impossible to interpret the ECG. In 80% of the recordings we had a NS of 1 or 2.

Discussion

For the first time we used MDK to obtain 15 s ECG recordings to screen for AF in a large population. Our results proved that short rhythm strips obtained through MDK and analysed by experienced people provided good quality ECG data, with low NS. We found 7 individuals with unknown AF (0.8%). Previous studies have shown the accuracy of MDK in AF detection through 60 s ECG recordings and using an automatic algorithm (see above). In one of these studies general practitioners screened for AF in191 patients in primary care6 using MDK. They compared the results with 12 lead ECG recordings and showed good diagnostic accuracy of the device (high sensitivity and specificity for atrial fibrillation (94% (95% CI 87-98) and 93% (95% CI 85-97) respectively). In another study MDK was used to screen a population of 676 patients attending their general practitioner for influenza vaccination: in 1.6% of patients AF had never been diagnosed before (all patients with CHA_2DS_2-VASc score >1).[7] In our study we showed high rhythm diagnostic accuracy with shorter records time. This has implication as it can allow a large number of people to be screened quickly.

The Importance Of AF Detection: Available Technologies And Addressed Populations

In almost half of the patients with an AF-related stroke, AF has been previously undiagnosed.[8] Two large randomized trials, CRYSTAL-AF[9] and EMBRACE,[10] have compared standard of care monitoring in cryptogenic stroke patients to invasive and non-invasive monitoring strategies, respectively, documenting a higher detection of AF in the intervention group and subsequently a higher rate of anticoagulant treatment.

Clearly, as the method of detecting AF has been heterogeneous, the optimal approach is still debated.[11] Several strategies for detection of this arrhythmia in patients with a previous stroke include: in-hospital monitoring,[12] serial ECGs,[13-14] ECG Holter monitoring,[15] monitoring with the use of external event or loop recorders,[16] long-term outpatient monitoring,[17] and monitoring by means of implantable cardiac monitors.[18]

Other technologies to screen for AF on a large scale and assess people with silent AF exist. An automatic oscillometric sphygmomanometer incorporating an algorithm for detecting AF was tested in a study enrolling 405 unselected outpatients seen in two cardiology clinics. This device showed a sensitivity of 95% and a specificity of 86% for AF detection at each blood pressure measurement.[19] A recent study, 'SEARCH-AF', screened 1000 pharmacy customers aged ≥65 years using an iPhone electrocardiogram, identifying 1.5 % people with undiagnosed atrial fibrillation.[20]

Of course, dealing with screening addressed to large populations, cost-effectiveness of the devices used must be considered.

Recently, the CADTH (Canadian Agency for Drugs and Technologies in Health) conducted a systematic review (36 studies) about very topic issues: the clinical effectiveness and cost-effectiveness of outpatient cardiac monitoring devices for AF monitoring after an ischemic stroke/TIA. They showed that to ensure cost-effective use of cardiac monitoring, the incremental cost compared with standard practice must be relatively small, the diagnostic yield must be substantial, the patient cohort must be relatively healthy and the initiation of OAC in newly diagnosed patients must be high. To achieve a high diagnostic yield, the patient cohort must be one with a high expected prevalence of AF based on their medical history, type of stroke and stroke symptoms, their recent discharge after their stroke and few investigations for AF in hospital.[21]

Also in terms of costs MDK can be considered a convenient technology, likely to be offered to a larger population.

Limitations

The MDK has shown to be an easy and accurate technology to screen large populations for AF. However this technology has some limitations. First of all it provides a single lead ECG and in some patients with a very vertical cardiac axis, distinguishing a p wave can be difficult. Secondly, ECG interpretation can be affected by muscle tremor. Furthermore, the automatic algorithm could not identify

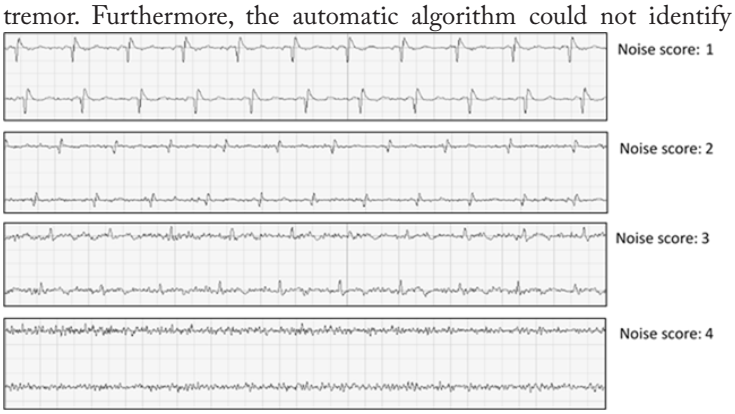

Figure 2: Examples of lead I ECG recordings for noise score

Table 1: Results of MDK use for AF screening

	MDK ECG recordings	%
AF	7/855	0.8
NS 1	240/855	28
NS 2	446/855	52
NS 3	107/855	13
NS 4	62/855	7

sinus arrhythmia or very frequent extra beats, erroneously classifying those rhythms as AF. However we were not affected by this limitation because we did not rely on the automatic algorithm. Moreover, as QRS regularity is used as a surrogate of sinus rhythm when it is not possible to clearly distinguish a p wave, in patients with AF with little RR interval variation, sinus rhythm could be misdiagnosed. Finally, although a 15 s ECG recording is shorter than the usual 60 s, it is longer than the 10 s conventional 12 lead ECG.

Conclusions

During a single-day screening for AF in a large population, MDK resulted to be an easy-to-use new technology, with very good diagnostic accuracy for AF detection. We obtained clear ECG recordings in only 15 s, with a low interobserver variability, supporting the reliability of this novel device. Using MDK general practitioners could regularly screen all patients >65 years, at higher risk for ischaemic thromboembolic stroke, more frequently. This easy to use and portable device has a potentially important role in population screening for AF.

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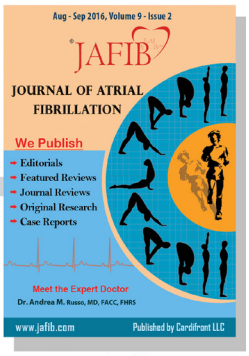

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Efficacy And Safety Of Implantable Loop Recorder: Experience Of A Center

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Abstract

Introduction: Symptoms like syncope or palpitations frequently present a diagnostic challenge. An implantable loop recorder (ILR) is an important aid in the management of these patients.

Methods: A retrospective study of patients that underwent ILR implantation from November 2007 to 2014. For each patient the indication for implantation, baseline characteristics, previous study, complications, recorded tracing and interventions were evaluated.

Results: A total of 62 patients were included, 50% men, with a mean age of 62.5±18.8 years old. Previously to ILR implantation 88.7% of patients had performed Holter, 17.7% external events recorder, 33.9% Tilt test and 29% an electrophysiological study. The implantation indications were recurrent syncope in 90.3%, palpitations 8.1% and ischemic stroke in one patient. Mean follow-up time was 17.1±16.3 months. Symptoms were reported in 66.1% of the patients, 46.8% of those yielding a diagnostic finding. In all cases of palpitation complaints with diagnosis we found atrial fibrillation (AF). In patients with syncope atrioventricular conduction disturbance was demonstrated in 19.6%, sinus node dysfunction in 16.1%, paroxysmal supra-ventricular tachycardia 7.1% and AF in 1.8%. These finding resulted in 19 pacemaker and one CRT-D implantation, introduction of anticoagulation in five patients and one ablation of accessory pathway. There were no major complications.

Conclusion: ILR proved to be safe and efficient. It has enabled the identification or exclusion of serious rhythm disturbances in more than half of patients and provided a targeted therapeutic intervention.

Introduction

Symptoms like syncope or palpitations are common conditions in clinical practice, thus having a significant impact on the patient's quality of life. They are frequent causes of cardiology referral and even hospitalization.[1] Due to the variety of underlying possible mechanisms, the precise diagnosis relies on the correlation between symptoms and electrocardiography evidence at the time of episodes. However, given the paroxysmal and unpredictable nature of these symptoms, they frequently present a diagnostic challenge.

The choice of monitoring technique in different clinical situations should be driven by the stratification risk and predicted rate of symptom recurrence.[1,2] Conventional Holter monitoring and external loop recorders are known to have low diagnostic yield, and even after an extensive evaluation many patients remain undiagnosed.[3,4] A long-term monitoring through an implantable loop recorder (ILR) is an important aid in the management of these patients.

In recent years, significant advances have been made in diagnosing and understanding the mechanisms of rhythm conditions, with an increased number of patients having a final diagnosis. This increment has been greatly enhanced by the development and widespread use of the ILR. It is a small subcutaneous device for continuous electrocardiographic monitoring that can be extremely useful in the diagnosis of syncope of undetermined origin after the initial assessment, in patients with unrecorded palpitations that occur occasionally, in detection of atrial fibrillation and study of cryptogenic stroke.[5] The efficacy and safety of the ILR as a diagnostic tool has already been demonstrated in several studies.[6,7,8]

The aim of this study was to describe the experience of a tertiary center with the use of ILR.

Material and Methods

A retrospective, observational, single-center study of consecutive patients that underwent ILR implantation during a seven years period. All patients had a Cardiology evaluation and at least a basic study with an ECG and transthoracic echocardiogram previous to the procedure.

We collected clinical and electrocardiographic data from a prospective database and from medical electronic and ILR records.

We used the Reveal DX/XT/LINQ ILR device (Medtronic) a subcutaneously implantable device for long-term continuously

Key Words:
Atrial Fibrillation, Implantable Loop Recorder, Therapeutic Intervention.

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cardiac rhythm monitoring for up to three years. The device was subcutaneously implanted in the left parasternal region, under local anesthesia. Events could be recorded by two methods: manually activated by the patients in case of symptoms or automatically triggered when arrhythmic events satisfied the pre-programmed cut-off criteria for asystole, brady or taquiarrhythmias and atria or ventricular fibrillation. Generally, the device memory can automatically store between 27 to 29 automatically activated events with 30 seconds of pre-activation and 27 seconds of post-activation and 3 patient-activated events with 6.5 minutes of pre-activation and 1 minute of post-activation, with few variances according to the type of arrhythmic event and program design. Patients had a first follow-up visit in three months, in six months intervals thereafter, and after every event activated. Sixteen patients had CareLink remote monitoring system that transmits the information of the arrhythmic event or activated episodes at distance to a web server that can be accessed by the assistant doctor or arrhythmic unit staff.

In the present study, the implantation indication, baseline characteristics, study previous to ILR implantation, complications of procedure, recorded monitoring tracings and subsequent interventions, were evaluated for each patient

The statistical analysis was performed with SPSS 20 version.

Results

Between November 2007 and November 2014 a total of 62 patients were included, 50% were men, with a mean age of 62.5±18.8 years old. The demographic and clinical characteristics of patients are presented in Table 1. All patients had a baseline echocardiogram and ECG, with 95% of the patients in sinus rhythm. QRS complex and atrial ventricular conduction was normal in 63.1% of the patients. 17.3% presented with first degree atrioventricular block, 12.9% had right bundle branch block and 6.7% left bundle branch block. Further ECG characteristics are described in Table 2. In 19.4% structural heart disease was identified and 88.7% of the patients had a normal left ventricular ejection fraction.

Previously to ILR implantation, 88.7% of the patients had performed at least one Holter monitoring, 17.7% an external event recorder, 33.9% a Tilt table test and 29% an electrophysiological study. Thus, 23.3% of patients underwent more than two different types of complementary exams before IRL implantation without a clear diagnosis.

Regarding the implantation indications, 90.3% were for recurrent syncope/presyncope, 8.1% for palpitations complaints and in one case, ischemic stroke with suspected cardioembolic origin after initial assessment. Mean follow-up time was 17.1±16.3 months (IQR 4-30). During follow-up, symptoms were reported in 66.1% (n=41) of the patients and from those, 29 (46.8%) yielded a diagnostic finding (44.5% of the patients with syncope, 60% of patients with palpitations symptoms and in the ischemic stroke case), with a mean time of 12.8 ± 14.4 months (IQR 1.5-21.5) from device implantation to diagnosis. In all cases of palpitations symptoms with diagnosis AF with ventricular rapid response was found.For patients with syncope, atrioventricular conduction disturbance was demonstrated in 19.6%, sinus node dysfunction in 16.1%, paroxysmal supra-ventricular tachycardia in 7.1% and AF with slow ventricular rate in 1.8%. In the ischemic stroke case AF was detected after 5 months of monitoring (Table 3). There were no significant differences in the baseline ECG characteristics (rhythm disorders, intra-ventricular or atrioventricular conduction disturbance) or findings in the previous study, when compared to the group in which no diagnosis was obtained.

Subsequently to the diagnosis obtained by the ILR, the following therapeutic interventions were pursuit: 19 patients received a permanent pacemaker, one a cardiac resynchronization therapy device, in five patients anticoagulation was introduced, and one was submitted to ablation of an accessory pathway.

There were no major complications reported during the implantation procedure or follow-up time. The mortality rate was 4.8% (n = 3) all from non-cardiac causes.

Discussion

The objective of this study was to describe our center's experience with the use of ILR and establish its safety and efficacy in real world practice.

Current guidelines for the management of patients with syncope,[2] palpitations[9] and AF[10] recommend the use of prolonged electrocardiogram monitoring techniques to better establish a correlation between the symptoms and a specific ECG finding, so as to achieve a precise diagnosis. Its indication was also expanded to different clinical scenarios like the study of cryptogenic stroke or after myocardial infarction.[3,11,12] However, the 2014 European Heart Rhythm Association survey, which assessed the use of different monitoring techniques in the evaluation of patients with these clinical situations (unexplained syncope, palpitations and diagnosis

Table 1: Patient demographic and clinical characteristics. * Left ventricular function quantification according to Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from American Society of Echocardiography and the European Association of Cardiovascular Imaging. Journal of the American Society of Echocardiography. January 2015

Baseline characteristics	
Age (years old)	62.5 ± 18.8
Male gender	50.0 %
Hypertension	64.5%
Dyslipidemia	37.1%
Diabetes	16.1%
Ischemic heart disease	9.7%
Left ventricular function *	
Normal	88.7%
Mildly abnormal	3.2%
Moderately abnormal	6.5%
Severely abnormal	1.6%

Table 2: Electrocardiography characteristics. AV: atrioventricular; RBBB: right bundle branch block; LAFB: Left anterior fascicular block; LBBB: left bundle branch block

ECG baseline characteristics	
Sinus Rhythm	95.2%
Atrial Fibrillation	4.8%
Normal QRS and AV conduction	63.1%
First degree AV block	12.5%
RBBB	4.9%
RBBB+ LAFB	8.0%
LAFB	1.6%
LAFB + First degree AV block	3.2%
LBBB	5.1%
LBBB + First degree AV block	1.6%

AF) in different European centers, found discrepancies and poor adherence to the guidelines regarding the use of IRL, specially in the management of patients with unexplained syncope, in which only a minority of non high-risk patients seemed to receive an IRL as part of theirs diagnostic practice.[1]

In our study, the main indication for ILR use was recurrent syncope/pre syncope (90.3%) and only a minority implanted ILR for palpitations complaints or in stroke investigation. This data demonstrate that clinicians are still reluctant to use ILR in situations like unexplained palpitations, cryptogenic stroke or AF. Moreover, in our study, IRL was only used after a previous extensive evaluation with several non-invasive and even invasive techniques, with 23.3% of the patients being submitted to more than two different types of complementary exams without a clear diagnosis before IRL implantation was considered. This approach is indubitably associated to higher costs and resources consumption, with longer period of time from symptoms to diagnosis. In the PICTURE registry that enrolled 570 patients, the median number of tests performed per patient was 13, being ECG, transthoracic echocardiogram, ambulatory ECG monitoring, in hospital ECG monitoring, exercise tests and orthostatic blood pressure measurement the tests most frequently performed.[8] The reason for this late referral to ILR implantation, shown in several studies and confirmed in our study, is unknown, especially after ILR had proven to be able to provide an earlier diagnosis of the underlying rhythm disturbance, along with a reduction in the number of advanced cardiac tests performed.[8] Recent studies showed that ILR monitoring is likely to be a cost effective strategy especially in patients who present infrequent symptoms suspected to be arrhythmic.[13]

In our study the diagnostic yield of the ILR was 46.8% over a period of 12.8 ± 14.4 months and provided useful information in another 19.3% in which arrhythmic events were excluded as symptoms cause. These results are in accordance with other published data describing similar diagnostic rates.[6,7,8] Several randomized studies that compared the use of prolonged ILR monitoring to conventional tests in the study of unexplained syncope, demonstrated the efficacy and safety of the ILR as a diagnostic tool. The study of Krahn et al that included 60 consecutive patients with unexplained syncope randomized to IRL monitoring or conventional investigation, described a diagnostic yield of 52% vs 20% (p=0.012).[7] The FRESH study presented a diagnostic rate of 46.2% with IRL monitoring for patients with unexplained syncope and the study of Farwell DJ. et al, a single center study that evaluated the diagnosis yield of IRL compared with conventional strategy showed that an ECG diagnosis was identified in 33% of ILR group in contrast with only 4% in the other patients.[14,15] Similar efficacy rates were also described for patients with palpitations. The RUP study, that included 50 patients with unexplained palpitation, compared the diagnostic rate and the costs of ILR implantation with the use of conventional strategy (24 hours Holter recording, a 4-week period of ambulatory ECG monitoring with an external recorder, and electrophysiological study). This study demonstrated the superiority of the IRL approach with a diagnosis rate of 73% vs 21% in conventional group (p<0.001) and costs of 3.056 ±363 euro vs 6.768±6.672 euro (p= 0.012).[16]

The majority of our patients with episodes of syncope of arrhythmic origin had bradyarrhythmic events, with atrioventricular conduction disturbances or sinus node dysfunction as main causes. This data was in accordance with diagnostic findings in ISSUE study.[2,17]

Table 3: Diagnostic findings according to ILR implantation reasons

ILR implantation reason	Diagnostic finding	
Syncope (90.3%)	Atrioventricular conduction disturbance	19.6%
	Sinus node dysfunction	16.1%
	Paroxysmal supra-ventricular tachycardia	7.1%
	Atrial fibrillation	1.8%
Palpitations (8,1%)	Atrial fibrillation	100%
Ischemic stroke (1.6%)	Atrial fibrillation	100%

An interesting feature in our study was that all patients with palpitations complains in which a diagnosis was achieved had paroxysmal episodes of AF as cause of their symptoms. This is possibly explained by the paroxysmal nature of this arrhythmia, frequently presented by short but symptomatic episodes, most of which very difficult to diagnose with other monitoring methods. In RUP study the main diagnostic findings for palpitations symptoms were supraventricular tachycardia and AF/atrial flutter both in 6 of a total of 19 patients with a final arrhythmic diagnose.[16] Several data showed that AF detection increases with monitoring intensification. However the use of ILR in AF setting has some limitations especially related to their limited storage capacity and problems on the detection channel, with either undersensing or oversensing that can triggering storage of ECG data that have no clinical significance.[18,19]

The AF detection algorithm operates through an assessment on the regularity of RR intervals within a 2 minutes time window. It requires at least 2 minutes of AF for the device to recognize the rhythm as AF and automatically store the episode. Shorter episodes can only be captured manually activated by patients. Once AF is diagnosed, it is stored as a sustained AF episode within the automatic episode counter, showing date and time of occurrence as well as episode length. However, when storage is exhausted, older EGMs are overwritten with newer ones and only the final events are kept in the memory as EGM. Considering these limited storage capacity, the diagnostic accuracy of ILR may be lower in patients with a high number of false positive episodes.[20,21]

The initial study of Hindricks G. et al that access the performance of the ILR with a dedicated AF detection algorithm found a high sensitivity of 96.1% for AF detection and a high negative predictive value, while specificity was limited by falsely stored AF episodes in 15% of the patients.[20] Also in the study of Eitel C. et al, interrogations with automatically stored AF episodes containing only EGMs with sinus rhythm and artefacts leading to AF misdetection could be found in 22% in the group with conventional AF detection algorithm. The reasons found for AF misdetection were the occurrence of myopotentials/noise in 35%, T-wave oversensing in 1.5%, frequent premature ventricular or atrial complexes in 15% and R-wave undersensing in 4%.[21]

In order to supplant these limitations specific AF detection algorithms with a software upgrade have been developed. The mentioned upgraded software aims a reduction of noise induced false-positive AF episodes by reducing the noise rejection threshold from 60 to 5 seconds. Furthermore the patient can check whether EGM storage capacity is exhausted.[21]

The previous referred study of Eitel C.et al, had as main objective to analyse the performance of the implantable continuous AF detection device in a clinical setting before and after introduction of a software upgrade. The results demonstrated that the introduction of

the new software significantly reduced the number of patients with a misdetection of AF (72% vs 44% p=0.001), mainly attributable to a significantly reduction of false AF detection due to myopotentials or noise. The number of patients with clinically non-diagnostic interrogations was also reduced from 38% to 16%.[21]

Additional to software developments, several other measures and follow-up strategies were proposed to increase the ILR accuracy: the need of confirmation on manual EGM analysis of all automatically detected episodes; prevention of EGM storage overcrowding with remote monitoring techniques, individual device programming and follow-up schedules or the presence of an alarm signal indicating full storage thus leading to a visit to the device clinic. Other possible measure could be prolongation of the detection period for sustained AF in order to prevent episodes of misdetection, but shorter AF episodes will then be unrecognized. However additional data are needed to assess the impact of these measures on ILR diagnostic accuracy in the clinical setting.[18,19,21]

Regarding the use of ILR on detection or in confirmation of absence of AF during long-term follow-up, especially after AF ablation procedures, ILR is also able to measure AF burden. In our study AF burden is not described, as data beyond the first detection of AF was not collected for study purpose. However, recent studies of pacemaker data have shown that morbidity is dependent on the burden of AF, supporting the value of its measurement.[22]

In our study, the baseline ECG characteristics or findings from previous exams were not predictive of diagnostic achievement in IRL. Predictive factors for ILR diagnosis have not been adequately investigated. In a recent study of Ahmed N et al. the authors studied predictors for pacemaker implantation in the IRL population with unexplained syncope. From a total of 200 patients with ILR for unexplained syncope, a pacemaker was implanted in 33 patients due to significant bradycardia. The predictive factors for occurrence of bradycardia necessitating pacemaker were predominantly clinical characteristics as history of injury secondary to syncope and female sex, with or without ECG conduction abnormalities.[23]

In the present study, no major adverse complications or events were reported during the implantation or follow-up period thus confirming the safety of this method.

The main limitations of our study were inherent to its design. It was a retrospective, observational, single-center study involving a small number of patients.

Conclusions

In our experience, the ILR proved to be a safe and useful complementary diagnostic method, with a significant additional efficacy compared to other routine electrocardiographic monitoring methods. In our study, ILR has enabled the identification or exclusion of serious rhythm disturbances in more than half of patients and provided a targeted therapeutic intervention. These results are in accordance with published data and emphasize the early use of IRL in the investigation of symptoms with suspected arrhythmic basis.

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Ajmaline Challenge To Unmask Infrahisian Disease In Patients With Recurrent And Unexplained Syncope, Preserved Ejection Fraction, With Or Without Conduction Abnormalities On Surface ECG

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Abstract

Background: Pharmacological challenge with class I antiarrhythmic drug is a recommended diagnostic test in patients with unexplained syncope only in the presence of bundle branch block, when non-invasive tests have failed to make the diagnosis. Its role in patients with minor or no conduction disturbances on 12-leads ECG has not been evaluated yet. It is also not clear which are the values of His-Ventricular interval to be considered diagnostic. We sought to evaluate the role of ajmaline challenge in unmasking the presence of an infrahisian disease in patients with recurrent and unexplained syncope, regardless of the existence of conduction disturbances on surface ECG.

Materials And Methods: Patients with history of recurrent syncope, preserved EF and a negative first level workup were enrolled. Conduction disturbances on ECG were not considered as an exclusion criteria. During EPS, basal HV conduction was determined. In the presence of a HV >70 msec the study was interrupted and the patient was implanted with a pacemaker. If the HV was ≤ 70 msec, ajmaline was infused and HV was reassessed. The maximum value of HV was considered. A prolongation ≥ 100 msec was considered as diagnostic and indicative of conduction disease, and the patient underwent pacemaker implantation. Patients with an HV <100 msec were implanted with an ILR.

Results: Sixteen consecutive patients were studied (age 76±5.2 years). Nine patients had conduction disturbances at baseline ECG (group ECG+). Among them, 5 had a basal diagnostic HV interval and 4 had a non-diagnostic HV interval. In the latter group, abnormal response to ajmaline was observed in 3 patients. In this group only one patient was implanted with an ILR, 8 patients were implanted with a pacemaker. Among the seven patients without conduction disturbances (group ECG-), no one had a diagnostic basal HV interval. After drug administration, 4 patients had a non-diagnostic response and were implanted with an ILR, while 3 patient had a pathological response and were implanted with a pacemaker. No difference was found in the values of maximum HV interval prolongation after ajmaline between the two groups (P = 0.89). During a mean follow up of 13±3 months, no patient has developed a syncopal episode. One patient in group ECG- and negative drug test was implanted after 3 months with a permanent pacemaker because of a two to one asymptomatic AV block at ILR interrogation.

Conclusions: Ajmaline challenge is a useful tool to unmask the presence of a infrahisian disease in patients with preserved EF, unexplained syncope and negative workup, even in the absence of conduction disturbances on 12-leads ECG. It is a simple and safe test that may disclose the detection of the disease. In these patients, an earlier pacemaker implantation of a pacemaker, may avoid the consequences of a syncopal recurrence. Values of HV interval > 70 msec in basal conditions and ≥ 100 msec after ajmaline administration seem appropriate to unmask infrahisian disease. Larger population is required to validate this hypothesis.

Introduction

Unexplained and recurrent syncope represents a diagnostic challenge for cardiologists and electrophysiologists. It is known to affect quality of life, to cause physical injuries and to be a harbinger of sudden death. The current management 1 suggests implantation of an ILR (Implantable Loop Recorder) in the presence of a normal ejection fraction, no or minimal structural heart disease, normal 12-lead ECG and negative first level work-up. Conversely, Electrophysiological Study (EPS) before implantation of an ILR is recommended only in the presence of sinus bradycardia and/or conduction disturbances on surface ECG. So far, the conduction disturbances liable of an EPS were the bundle branch block or the bifascicular block.[2] EPS is a useful tool to detect atrio-ventricular conduction abnormalities, although with very low sensitivity.[3,4,5,6,7] To overcome this limitation, class 1A and 1C drugs have been introduced into clinical practice.[8,9,10,11,12]

Ajmaline is a class 1A drug, a very powerful sodium channel blocker with relative short half-life.[13] Its role in diagnostic testing is confined to two fields of application: to unmask the diagnostic electrocardiographic pattern of Brugada syndrome in the case of non-

Key Words:

Electrophysiological study, Ajmaline, His-Ventricular interval.

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None.

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diagnostic basal ECG or as diagnostic testing to identify patients with paroxysmal atrio-ventricular blocks.[8] It has a predominant extra-renal metabolism,[13] thus it can be used with safety also in patients with advanced renal disease.[14]

In order to detect patients with paroxysmal AV block, ajmaline has been widely used in the past in subjects with surface ECG abnormalities, but standardized diagnostic values of His-Ventricular time are still missing .[15, 16, 17, 18, 19, 20, 21] Another unanswered issue is the use of EPS with drug test in subjects with minor conduction abnormalities, as proposed in recent new diagnostic algorithms.[22]

So far, there is no data available in the literature about the role of the test in patients with minor or even without conduction disturbances on surface ECG.

Given these premises, we sought to evaluate the feasibility, utility, safety and diagnostic role of ajmaline challenge in unmasking the presence of an infrahisian disease in patients with recurrent and unexplained syncope, with preserved ejection fraction, regardless of the existence of conduction disturbances on surface ECG.

Methods

Study Population

All consecutive patients referred to our institution between September 2014 and March 2015 were included in this study. Inclusion criteria were: a history of recurrent and unexplained syncopal episodes (2 or more syncopal episodes per year), or a single episode with severe trauma or physical injury and/or patients with syncope in high risk setting; a negative first level workup (biochemical analysis, 24-hour Holter monitoring, tilt table testing, carotid sinus massage, stress test and neurological work-up). The term "unexplained" refers to a transient loss of consciousness with abrupt onset and offset of unknown cause. Medical history, physical examination, baseline ECG and transthoracic echocardiography were obtained before any invasive procedure. Relevant structural cardiac abnormalities or severe left ventricular dysfunction were excluded. Conduction abnormalities on 12-leads ECG or the presence of atrial fibrillation were not considered as an exclusion criteria. Patients with syncope and known ischaemic heart disease underwent to coronary angiography in order to exclude the presence of new significant coronary artery disease.

Study Protocol

Patients were divided into two groups: those with a conduction disturbance on 12-leads ECG (group ECG+) and those without any conduction abnormality (group ECG-). Conduction disturbances on 12-leads ECG were defined as the presence of at least a prolongation of the PR interval above 200 msec and/or the presence of a QRS duration superior to 100 msec.

Figure 1 shows the study flow-chart. A basal EPS was performed in all cases. If the latter did not show any abnormal finding on AV conduction (HV > 70 msec, development of intra- or infra-hisian block on incremental atrial pacing) drug test with ajmaline was then performed. In any case the patient, according to the results of the previous tests, was implanted with a permanent cardiac pacemaker (PM) or an Implantable Loop Recorder (ILR).

Electrophysiological Study

Figure 1: Study flow-chart

Antiarrhythmic drugs, were discontinued for at least 5 half-lives before the procedure, except for amiodarone. After obtaining informed consent, two 6 French diagnostic quadripolar electrode catheters (S. Jude Medical, Minnetonka, MN, USA) were introduced via the right femoral vein using the Seldinger technique and advanced under fluoroscopic guidance to the high right atrium (HRA) and across the tricuspid valve to record the His Bundle potential. The surface electrocardiographic recordings and intracardiac electrograms were continuously recorded and stored on a digital recording system (EP-Workmate 4.2 System, S. Jude Medical, Minnetonka, MN, USA). Bipolar intracardiac electrograms were filtered between 30 and 500 KHz. Baseline conduction intervals (AH and HV) were recorded and measured at a speed of 300 mm/s. The electrophysiologic evaluation of sinus node function (if patient was in sinus rhythm) included measurements of sinus node recovery time (SNRT), corrected SNRT (cSNRT = SNRT – sinus node cycle length) and sino-atrial conduction time (SACT) estimated by the protocol described by Narula et al.[24] Anterograde conduction was also tested with atrial incremental pacing and a programmed atrial stimulation was performed at HRA with 2 basic cycle length (500 and 400 msec) and 1, 2 or 3 atrial extrastimuli with a minimum coupling interval of 200 msec.

The quadripolar catheter at HRA was then moved into the right ventricular apex and bipolar pacing from the distal pair of electrodes was performed in order to test the capture threshold. The stimulation amplitude was set at twice the capture threshold to permit emergency stimulation, if required during the subsequent test. Retrograde conduction was tested with ventricular incremental pacing and a programmed ventricular stimulation was performed with 2 basic cycle length (500 and 400 msec) and 1, 2 or 3 ventricular extrastimuli with a minimum coupling interval of 200 msec.

Regardless of the measured basal values of the various parameters, an HV interval value was considered diagnostic only if greater than 70 msec, otherwise ajmaline challenge was performed.

lAjmaline Challenge

Ajmaline was administered intravenously at a dose of 1 mg/Kg over a 2 minutes period. Ajmaline infusion was promptly interrupted before reaching the target dose if QRS prolongation exceeded 30% compared to baseline duration, in the occurrence of frequent premature ventricular contractions (PVCs), or appearance of a type 1 Brugada ECG in right precordial leads, or in the case of development of high degree atrio-ventricular block. By the end of the infusion HV interval was constantly monitored and assessed at the 1st, 2nd, 3rd, 4th, 5th minute and then every five minutes until half an hour.[25] The longer HV time interval at a speed of 300 mm/sec was then taken. A prolongation of the HV interval ≥100 msec was considered diagnostic and the patient was implanted with a PM. A prolongation less than 100 msec was considered non-diagnostic and the patient was implanted with ILR.

ECG And Intracardiac Recordings

All ECG tracings and intracardiac recordings were analyzed before and after ajmaline infusion by two experienced electrophysiologists and, in case of disagreement, a third physician was consulted. Heart rate, PQ interval, QRS duration, AH and HV interval, SNRT and cSNRT were measured in milliseconds.

Statistical Analysis

Data are expressed as mean ± standard deviation (SD) or as absolute

values and percentages as appropriate. The Fisher's exact test was used to compare categorical variables. Continuous variables between two groups were analysed using the unpaired Student's t-test. A P-value less than 0.05 was considered for statistical significance. Statistical analyses were conducted using the SPSS software (SPSS v22, IL, USA).

Results

Baseline Characteristics

A total of 16 consecutive patients were enrolled in the study. Table 1 summarizes the baseline clinical characteristics of the population. Mean age was 76 ± 5 years (ranging from 68 to 86) and 7 were male (44%). All patients showed preserved left ventricular function on transthoracic echocardiogram, with a mean EF of 57 ± 5 %. Six patients (37%) had minimal structural heart disease (defined as the presence of mild valvular disease and/or mild left ventricular hypertrophy and/or mild dilatation of the aortic bulb). One patient had history of paroxysmal atrial fibrillation. All patients were in sinus rhythm at the time of enrolment and during the EPS. One patient had history of coronary artery disease and a coronary angiography excluded the progression of new significant disease. Nine patients (56%) had a conduction disturbance and were included in the group ECG+.

Table 2 shows the type of conduction disturbances on 12-leads ECG found in this group of patients. The most common was the first degree AV block associated with the left bundle branch block (3 patients, corresponding to 33%). Two patients (22%) presented with isolated right bundle branch block. There was a patient with isolated left bundle branch block and two patients with two kind of bifascicular block, respectively: one with first degree AV block associated to left anterior fascicular block and one patient with left bundle branch block. An isolated first degree AV block was present only in one patient.

Seven patients (44%) had no conduction disturbance on surface 12-leads ECG and were included in the group ECG-.

Table 3 highlights the baseline clinical characteristics of the two groups. They did not differ for the mean age (75 ± 6 years and 76 ± 5 years, P=0.96) and the mean ejection fraction (57 ± 4% and 59 ± 2%, P=0.18).

Males were more likely to have a conduction disturbance on surface ECG, although the difference was not statistically significant (P=0.06).

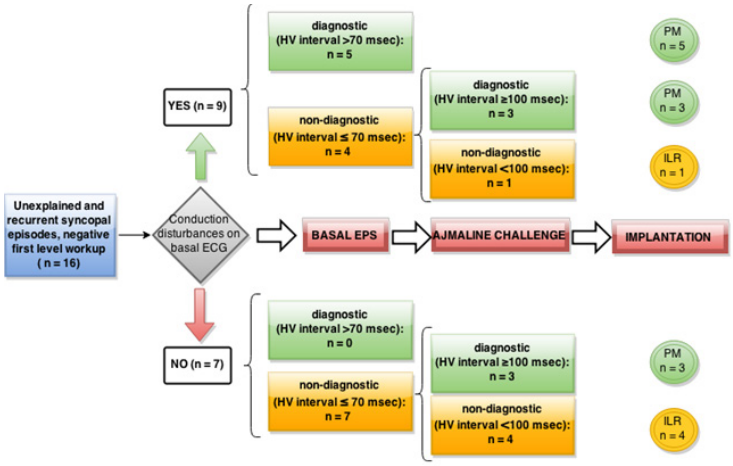

Figure 2: Results

Mean QRS duration was significantly different between the two groups (133 ± 30 msec and 90 ± 7 msec, P <0.01) while there was a trend toward a difference in the PR interval duration (234 ± 79 msec and 174 ± 22 msec) though it did not reach a statistical difference (P= 0.07).

Evidences From Basal EPS

All 16 patients underwent the basal EPS (figure 2 and table 4). No patient had abnormal cSNRT (group ECG+ 372 ± 140 msec, group ECG– 365 ±151 msec, P=0.67) or developed intra or infrahisian block during incremental atrial pacing. All patients showed a normal response after atrial and ventricular programmed electrical stimulation. AH intervals were statistically different between the groups: mean AH intervals in group ECG+ were 155 ± 58 msec while they were 86 ± 16 msec in group ECG- (P=0.02). Basal mean HV intervals were statistically different between the two groups: they were 68 ± 12 msec in group ECG+ and 56 ± 7 msec in group ECG- (P=0.036).

Table 5 summarizes the comparison of the results of diagnostic basal HV interval between the two groups. In the group ECG+, 5 patients (56%) had a basal diagnostic HV interval with a mean value of 76 ± 6 msec, while 4 patients (44%) had a non-diagnostic HV interval (58 ± 8 msec). The difference between this baseline values reached a significant statistical difference (P < 0.01).

In the group ECG-, none had a diagnostic basal HV interval, with a mean value of 56 ± 7 msec. Of note, these values were not statistically different from those registered in the group ECG+ with non-diagnostic basal HV interval (P=0.74).

Response To Ajmaline Challenge And Side Effects

Eleven patients, of which 4 in the group ECG+ and 7 in the group ECG-, underwent drug test with ajmaline. All patients were tested with the maximal dose required to complete the challenge, and there was no premature interruption of the drug infusion. No side effects were recorded during drug administration. Of the four patients in the group ECG +, 3 (75%) developed a diagnostic interval with a mean HV of 108 ± 2 msec (Table 5). In the group ECG -, three patients (43%) showed a diagnostic HV interval, with a mean value 108 ± 8 msec. It is noteworthy that the mean maximum value of HV interval reached during a positive challenge is not statistically different between the two groups (P=0.89).

Finally, when properly evaluable, no patients developed a Brugada type 1 on right precordial leads during the test.

Implantation

After the protocol application (EPS + drug challenge), a total of eleven patients (69%) were implanted with a permanent pacemaker while five patients (31%) underwent an ILR implantation.

Among the patients implanted with a PM: 8 belonged to the group ECG +, of which 5 after a basal EPS and 3 after the drug challenge; and 3 belonged to the group ECG-. The protocol unmasked an infrahisian disease in 89% of patients with ECG+ and in 43% of patients in group ECG-. Finally, five patients were implanted with a ILR (31%): 1 in the group ECG+ and 4 in the group ECG-.

Patient implanted with a pacemaker received appropriate devices for their conditions. Some patients in the group ECG+ and all patients in the group ECG- were implanted with pacemakers equipped with algorithms aimed at reducing the ventricular pacing percentage, such as the Managed Ventricular Pacing[26] and the SafeR.[27] In the latter case, it is possible to review retrospectively, into pacemaker memory,

Table 1: Baseline clinical characteristics of study population (N = 16)

Age (years), mean ± SD	76±5
Males	7 (44)
Associated structural heart diseases:	
Any abnormality	10 (62.5)
Ischemic	1 (6.25)
Valvular	5 (31)
Hypertensive	2 (12.5)
Other	2 (12.5)
LV ejection fraction (%), mean ± SD	57 ± 5
ECG conduction disturbances	9 (56)
Sinus Rhythm at EPS	16 (100)
History of paroxysmal/persistent AF	1 (6.25)

Data are expressed as No. (%) unless otherwise specified

all the block types for which ventricular pacing is activated.

Follow-Up

A mean follow up of 13 ± 3 months was available for all patients. Follow-up was not statistically different among the two groups (P=0.85). Patients in the group ECG+ had no recurrence of syncopal episodes and one patient died because of a cerebral neoplasia.

In the group ECG – there was no recurrence of syncope in any patient. One of them showed, on ILR memory, an asymptomatic episode of two to one AV block and was consequently implanted with a permanent pacemaker.

Analysis of stored pacemaker data in patients implanted in both groups demonstrated the occurrence of various types of paroxysmal AV block (type 2, advanced and complete AV block). In particular, among the patients belonging to the group ECG-, the retrospective analysis of the EGM stored into pacemaker memory showed that all of them (n = 3, 100%) had the occurrence of the above mentioned types of AV block, with regular activation of ventricular pacing back-up algorithms.

Discussion

To the best of our knowledge, this is the first report of the use of ajmaline challenge in unmasking the presence of an infrahisian disease in patients with recurrent and unexplained syncope, preserved ejection fraction and no conduction disturbances on surface ECG.

The use of drug stress test during EPS in current guidelines[1] is a class IIb level B indication in patients with 12-lead ECG bundle branch block, when non-invasive tests failed to make the diagnosis. In patients with normal ECG, no structural heart disease and no palpitations, EPS is a Class III Level B indication. However, very recently, Rosanio et al[22] proposed a diagnostic algorithm according to which the presence of a Type 1 AV block can be considered an indication to perform EPS. Consequently, it can be noticed a trend toward a theoretical extension of the use of the EPS. However, nowadays only 2% of patients with unexplained syncope assessed by cardiologists undergo to EPS, and even fewer if they are evaluated by other specialists.[1,28]

Another thorny issue is represented by the lack of standardized diagnostic values of HV time during a basal EPS or after a drug stress test.[15,16,17,18,19,20,21] Moreover, some of these studies were conducted before the era of primary prevention of sudden cardiac death, and consequently patients with left ventricular dysfunction were included. Enormous clarity and great strides have been made in the ISSUE Study,[29] where Moya and colleagues enrolled patients with unexplained syncope after a complete negative workup, including an EPS. Patients were implanted with an ILR and divided into four groups according to their basal condition: syncope alone, syncope alone and positive tilt test, syncope associated to bundle branch block and negative EPS and, at last, patients with structural heart disease and negative EPS. The group with bundle branch block and negative EPS[4] consisted of 52 patients. Criteria to consider diagnostic the EPS were a basal HV interval ≥ 70 msec and the development of 2nd or 3rd degree infrahisian block after ajmaline infusion. During the follow-up authors recorded 21 asystolic pauses, of which 17 were AV blocks and four were sinus pauses. This means that 1/3 of patients were false negative at EPS, as expected by the low sensitivity of the exam but also taking into account the high specific values considered in that study. Still in the ISSUE study, if we consider the group of isolate syncope and the tilt positive group,[30] only 66% of patients had undergone an EPS. After a mean follow-up of 9 ± 5 and 10 ± 5 months, of the 16 asystolic pauses detected, 14 were sinus arrests and only 2 (1.8%) were AV blocks. Here EPS seems to be more sensitive than the third group, especially towards the AV block. But it has to be kept in mind that only 2/3 of patient underwent an EPS with the aforementioned criteria of positivity.

In a recent study,[31] Conte and colleagues used ajmaline challenge in elderly patients to unmask atrio-ventricular conduction disease and/or the typical Brugada ECG pattern. No values of basal HV interval to be considered diagnostic for conduction disease are reported. After ajmaline infusion they considered a response abnormal only when the prolongation of HV exceeded 100 msec.

In our study, the application of the protocol with less severe diagnostic criteria during ajmaline challenge, ensured a prompt diagnosis in the group ECG+ in 8 over 9 patients (89%). With the same criteria, in 3 over 7 patients (43%) in the group of patients with normal ECG, a diagnosis was reached. The instrumental follow-up at pacemaker interrogation, with events of various kinds of paroxysmal AV block stored, including complete AV block, demonstrates that the mechanism of the syncopal episodes occurring before EPS and PM implantation were cardiogenic and caused by severe brady-arrhythmias. Although the very small population studied in the group ECG-, no false positives emerged during the follow-up.

As expected, the sensitivity of the EPS without ajmaline was very low in patients with ECG conduction abnormalities. The use of ajmaline significantly improved the sensitivity of the EPS in this group. This is in line with what has been described previously.[3,4,5,6,7] Fujimura and colleagues3 reported that sensitivity of basal EPS is 37.5% in patients with paroxysmal sinus pause and 15.4% in patients with paroxysmal AV block. The introduction of class 1A and 1C agents during EPS improves sensitivity of the test up to 50-80%.[10]

Table 2: Type of conduction disturbances on surface ECG in the group ECG+ (PR interval ≥ 200 msec and/or QRS duration > 100 msec)

First degree AV Block	1 (11.1)
RBBB	2 (22.2)
LBBB	1 (11.1)
First degree AV block + LAFB	1 (11.1)
RBBB + LAFB	1 (11.1)
First degree AV block + LBBB	3 (33.3)

Data are expressed as No. (%)
RBBB = Right Bundle Branch Block
LBBB = Left Bundle Branch Block
LAFB = Left anterior fascicular block

Table 3: Baseline characteristics in the group with (ECG +, N = 9) or without (ECG -, N = 7) conduction abnormalities on 12-leads ECG

	ECG + (n = 9)	ECG – (n = 7)	P-value
Age (years), mean ± SD	75±6	76±5	0.96
Males	6 (67)	1 (14)	0.06
Associated structural heart diseases:			
Any abnormality	5 (56)	5 (71)	
Ischemic	0 (0)	1 (14)	
Valvular	3 (33)	2 (29)	
Hypertensive	1 (11)	1 (14)	
Other	1 (11)	1 (14)	
LV ejection fraction (%), mean ± SD	57 ± 4	59 ± 2	0.18
ECG conduction disturbances	9 (100)	0 (0)	
QRS duration (msec), mean ± SD	133 ± 30	90 ± 7	0.0037
PR interval (msec), mean ± SD	234 ± 79	174 ± 22	0.07

Data are expressed as No. (%) unless otherwise specified

However, we intentionally included in the group ECG+ patients with any conduction abnormality on surface ECG. According to our inclusion criteria, we studied some patients that, considering the last guidelines, would have directly implanted an ILR. In the light of this result, it seems that the sensitivity reported here is higher than that reported up to now in the literature, and it exceeds 95%. In fact, in the group ECG+, the only patient implanted with an ILR showed an isolated PR prolongation on surface ECG.

The results in patients without any conduction disorder (ECG -) are rather surprising. First of all, the sensitivity of the EPS without ajmaline verges on zero. Ajmaline helps improving the sensitivity and unmasks the presence of an infrahisian disease, which could not have been proved in any other way. Furthermore, the most surprising result is that the mean maximum value of HV interval reached during a positive ajmaline challenge is not statistically different between this group of patients and that registered in the group ECG+. In other words, it seems to be independent of the presence of a conduction disturbance on surface ECG.

These findings allow us to speculate that diagnostic HV interval values considered here are provided with sufficient sensitivity and specificity, but further studies with larger population are required to support this speculation.

One possible explanation of our results was the selection during the anamnesis, with considerable attention to the clinical features of syncopal episodes. We enrolled patients with two or more syncopal episodes per year, or patients with a single episode but with physical injury. In both cases, and with the limits and difficulties often correlated with anamnesis, it was assumed that with some specific clinical features, the syncope was of cardiogenic nature.

Furthermore, we are aware that the diagnostic role of this test is highly dependent on the basis of the clinical features of syncopal episodes.[23] In fact, from a clinical point of view, we found that the presence of a previous history of injury secondary to syncope and patients of female sex were more likely to have a positive result and therefore to implant a pacemaker, regardless of the presence of ECG conduction disturbance. This findings confirm those of a recent retrospective study.[32] Ahmed and colleagues studied the clinical predictors of pacemaker implantation in 200 patients suffering from unexplained syncope receiving an ILR. Of the 33 patients with clinical significant bradycardia requiring PM implantation, history of injury secondary to syncope was found to be the strongest independent predictor for PM implantation, regardless of the presence of 12-lead ECG conduction abnormalities. Female sex was another strong predictor, but only in patients with ECG conduction disturbances.

Table 4: Parameters at basal EPS (N = 16)

BASAL EPS	ECG + (n = 9)	ECG – (n = 7)	P-value
cSNRT (msec)	372 ± 140	365 ± 151	0.67
AH (msec)	155 ± 68	86 ± 16	0.02
HV (msec)	68 ± 12	56 ± 7	0.036

Data are expressed as mean ± SD, unless otherwise specified

Despite in the ISSUE study[30] only 1% of patients experienced a severe injury due to syncopal relapse, a potential advantage of EPS in this setting is to unmask infrahisian disease, avoiding the implantation of an ILR and thus the traumatic consequences of syncope recurrence.

In our study, ajmaline challenge proved to be a safe procedure. Ajmaline has a very rapid effect, usually in the first 2-3 minutes after the end of infusion. Pharmacokinetics studies13 show that the duration of electrophysiological effects is short (about 30 minutes), in comparison with the slow decay of plasma concentrations (half-life of 7.3 ± 3.6 hours), so that it is believed that a threshold concentration exists under which no drug effect can be detected. We did not record any ventricular arrhythmias during the drug challenge nor any transient second or third degree AV block. Nevertheless, ajmaline infusion has to be performed in an appropriate environment, with advanced life-support facilities available, as external defibrillator and ventricular back-up pacing.

Table 5: Comparison of basal HV interval (A) and stress HV interval (B)

Basal HV interval	ECG +	ECG –	P-value
DIAGNOSTIC (N = 5)	76 ± 6 msec	-	
NON-DIAGNOSTIC (N = 4+7)	58 ± 8 msec	56 ± 7 msec	0.74

Data are expressed as mean ± SD

Stress HV interval	ECG +	ECG –	P-value
DIAGNOSTIC (N = 3+3)	108 ± 2 msec	108 ± 8 msec	0.89
NON-DIAGNOSTIC (1+4)	75 ± 0 msec	80 ± 6 msec	-

Data are expressed as mean ± SD

Study Limitations

This study has several limitations. First, this is a monocentric observational study. Second, the study population is too small to draw final conclusions. Therefore, the present study can be considered only as preliminary.

Conclusions

Ajmaline challenge is a useful tool to unmask the presence of an infrahisian disease in patients with preserved EF, unexplained syncope and negative workup, even in absence of conduction disturbances on basal ECG. It is a simple and safe test that may advance the detection of the disease. With the early placement of a pacemaker instead of a loop recorder the consequences of a syncopal recurrence, as severe physical injuries, may be avoided. Additional studies, multicentric and with larger population, are required to confirm this hypothesis.

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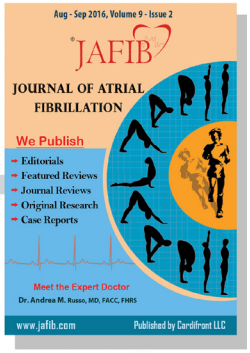

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Implantable Loop Recorder: Diagnostic Yield And Possible Therapeutic Effect In Patients With Neurally Mediated Reflex Syncope

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Abstract

Through a retrospective study concerning the experience of our center in patients affected by Neurally Mediated reflex Syncope (NMS) we wanted to verify not only the diagnostic yield of the Implantable Loop Recorder (ILR) but its possible placebo therapeutic effect.

In the context of patients affected by a severe clinical presentation of NMS identified through a careful clinical evaluation, we selected those who followed a diagnostic iter using the ILR.

We analysed 84 patients (39 male and 45 female, mean age 71 years), during the period 2009-2013. 34 patients (40.5%) had no recurrences after a mean follow-up (FU) of 35 months, among these 17 concluded a FU of 4 years. 50 patients (59.5%) had recurrences and a specific diagnosis after an average period of 7 months.

We found an important number of patients who showed a disappearance of syncope during an observation period of 2-3 and 4 years. At first glance this results could be explained considering the possible placebo therapeutic effect of ILR.

Introduction

The ILR represents the golden standard in syncope work-up according to the ESC 2009 guidelines.[1] It plays an important and unique role in the context of uncertain diagnosis in high risk patients and in moderate risk after all the invasive and non-invasive diagnostic procedures have been performed but there is not sufficient information to treat the patient. The ILR is also used in certain or suspected NMS with severe clinical presentation: invalidating recurrences of episodes, unpredictable forms, traumatic effects or syncope occurring during high risk activities.

In the past a carefully selected group of patients with severe clinical presentation of likely neurally mediated reflex syncope was stratified following a specific diagnostic path guided by Tilt Table Test (TTT). After a careful initial evaluation (clinical history, physical examination, electrocardiogram and echocardiogram) a TTT was performed to investigate the underlying physiopathological mechanism: cardioinhibitory or vasodepressive form. In most cases patients with a documented cardioinhibitory activity by TTT underwent a pacemaker implantation (PM) but the efficacy of cardiac pacing for prevention of syncopal recurrences is still controversial. It was already questioned approximately 15 years ago: two important randomized, multicenter, open label studies (SYDIT[1] and VASIS[2]) showed results in favour of pacing, but in the same period other two randomized, multicenter, double-blind studies (VPS-[2,3] SYNPACE[4]) failed to demonstrate the superiority of cardiac pacing to over placebo.

ISSUE-2 Trial[5] changed the medical history in the context of reflex syncope. It showed the capacity of ILR to guide the specific therapy and confirmed that there is not always a clear correlation between the results of TTT and the mechanism documented by ILR at the time of the syncope. The main objective was to verify the value of ILR in assessing the mechanism of syncope and the efficacy of ILR-guided therapy after syncope recurrence. ISSUE 2 was set up to verify risk stratification and diagnosis of NMS based on initial evaluation; early implantation of an ILR (irrespective of the results of tilt testing and the adenosine triphosphate ATP test), and therapy delayed until after ILR documentation of the apparent basis of the syncope with a FU period of 2 years.

Out of an initial enrollment of 392, about 143 (36,5%) of patients had recurrence of syncope, 57 (40%) of whom had asystole.

Starting from the important experience of the ISSUE-2 Trial a new international, multicenter, controlled, double blind study was organized: the ISSUE-3 Trial.[6] It showed that pacing is effective in reducing recurrence of syncope in patients in the category of 40 years and above and severe asystolic NMS documented by ILR. There was 32% absolute risk reduction and 57% relative risk reduction, with evidence of a clear, statistical difference between the two groups: Pm

Key Words:
Neurally Mediated Reflex Syncope, SYNPACE, Cardioinhibitory.

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None.

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on and Pm off arm. Concerning the two-year diagnostic yield of ILR in the ISSUE-3 Trial it was found that about a half of patients who received an ILR had a specific diagnosis within two years of observation, of these about an other half (25%) underwent a PM implantation due to a documented significant pause.[8]

Aim of the Study

Through a retrospective study concerning the experience of our center in patients affected by severe clinical presentation of NMS, we wanted to verify not only the diagnostic yield of ILR but its possible placebo therapeutic effect.

Methods

The selection of patients was made according to the ISSUE-3 criteria: certain or suspected reflex syncope (except of "Carotid Sinus Syndrome" because this is an already accepted indication for cardiac pacing), age more than 40 years, and severe clinical presentation. The severity of the clinical presentation was based on the definition of high frequency or risk provided by guide lines: invalidated quality of life because of the recurrences, unpredictable syncope, syncope exposing patients to risk of trauma, occurence of syncope during "high risk activity".

The exclusion of patients involved cardiac abnormalities which suggested cardiac syncope, symptomatic orthostatic hypotension, non-syncopal loss of consciousness.

All patients followed a diagnostic iter guided by ILR and were followed till the first documented syncopal recurrence or an occurrence of a diagnostic arrhythmic event. Events were classified according to the ISSUE classification[9] as: type 1 (asystole > 3 s and recurrence of syncope or > 6 s without recurrence of syncope or presyncope), type 2 (bradycardia), type 3 (slight o no rhythm variations) and type 4 (tachycardia).

Results

We analysed 84 patients (39 male and 45 female, mean age 71 years), during the period 2009-2013. 34 patients (40.5%) had not recurrences after a mean follow-up (FU) of 35 months, among these 17 patients concluded a FU of 4 years. 50 patients (59.5%) had recurrences and a specific diagnosis after an average period of 7 ±8 months.

The prevalent form of neurally mediated syncope was the cardioinhibitory form (26 patients, 31%), followed by vasodepressive NMS (21 patients, 25%).

Tachyarrhythmias were diagnosed in 2 patients (2,4%) and 3rd degree- AV- Block (2 patients, 2,4%).

Discussion

In our clinical experience we have found an important number of patients with disappearance of syncope during an observation period of 2,3 and 4 years. At first glance this results may suggest a possible placebo effect of the ILR and can be disappointing in the everyday clinical setting.

Still, this is the most controversial explanation for this phaenomenon.

The ISSUE-2 experience gave us the possibility to use ILR as therapy- guiding device.

From one hand we have learnt that ILR is able to warrant a specific diagnosis in about a half of patients during a follow-up period of 2 years, and among these another half undergo a PM implantation because of evidence of an asystolic event as cause of syncope.

On the other hand we must bear in mind that there is about half of patients without diagnosis at the end of this period. We are talking about patients selected maintaining the same inclusion criteria: frequent recurrences and invalidated quality of life. The question is what happened at these patients and why patients with frequent recurrences of syncope haven't had any more episodes after the ILR implantation.

In our study we have not found important differences prolonging the follow-up until the 4th year: about 40% of patients haven't had recurrences after a mean follow-up (FU) of 53 months.

At first glance this result could be explained considering the possible placebo therapeutic effect of ILR. The way we see things is that we should investigate and interpret the results using common sense and applying larger scientific considerations.

Recently the SUP-2 Study[10,11] has been completed; it is a multicenter, prospective, observational study which wanted to verify the utility of a standardized algorithm for cardiac pacing in older patients affected by severe unpredictable reflex syncope. The Syncope Unit Project 2 (SUP 2) showed the benefit of cardiac pacing at 3 years in patients selected according to the ESC-guide lines: carotid sinus massage (CSM) , followed by Tilting Table Test (TTT) if CSM was negative, followed by implantation of an Implantable Loop Recorder (ILR), if TTT was negative; those who had an asystolic response to one of these tests received a dual-chamber pacemaker. The 3-years recurrence of syncope in the treated group was 20% and was significantly lower than in the group of patients who did not receive the pacemaker and were observed by ILR.

Focusing on the total syncope burden of the SUP-2 we observed that it fell dramatically in the year before and after cardiac pacing. The number of syncopes also decreased in the ILR group (Figure A). It is likely that other mechanisms contributed to this reduction.

First of all it is necessary to remember that the syncopal recurrence is not constant because of an important feature of NMS that is the "cyclicity": in the typical subject affected by NMS during the life-time there are phases of concentrated frequent recurrences of syncope, a long period without events and then an important high burden of syncope again.

Second point could concern the potential, possible placebo effect of device implantation, in this case of ILR. This is a delicate point at which we have to pay particular attention. As mentioned before,

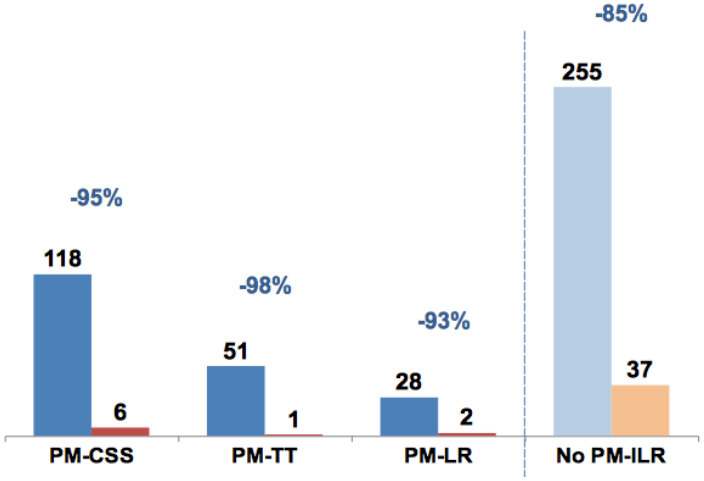

Figure A:

starting from the "cyclicity" characterising the NMS, what we need is only the opportunity to follow the patient for a very long period (decades); if we take in count the high number of syncope – free survival already Sheldon and Rose[12] had observed in 2001, where by following a group of patients with severe quality of life reduction by neurally mediated syncope a big part (40-60%) of the patients had not had any recurrence in 2 years of follow up. The patients were not implanted and had similar recurrence rates to our implanted patients. We are not mistaken affirming that we would have obtained a higher number of recurrences of syncope in the ILR group (control group) if we had monitored our patients for a longer and longer period. The suspect is that actually what we call possible placebo effect in observing relatively limited samples in size and time is simply the statistical "regression to the mean". It is the phaenomenon which occurs when natural events are followed up for a too short period of time or in a too little sample size, not allowing the observed event to occur spontaneously within statistical expectation of the mean.

After these considerations and according to the findings of the scientific literature and our study, we can affirm that the ILR mantains its important diagnostic role, related to the capacity to focus on the electrocardiographic detection at the moment of the clinical loss of counsciousness. Controversial is its potential placebo effect, considering the fact that, according to the natural history of NMS, we should monitor patients for a very long period, activity that is not necessary considering the benign condition of this form. For this reason it will be difficult to discriminate between a potential placebo effect of ILR and the statistical "regression to the mean".

Conclusions

The high rate of undiagnosed syncopes despite ILR implantation are most probably attributable to a combination of regression to the mean with not enough long FU- time and the main feature of syncope itself: the cyclicity of syncope.

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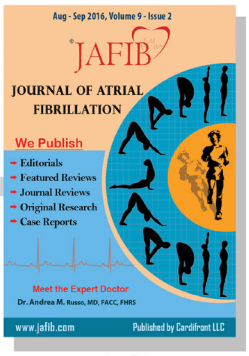

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Emergency Department Readmission in Elderly Patients After Acute Rhythm or Rate Control Treatment for Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) is an age-related increasing disease, characterized by a high number of relapses frequently leading the patients to Emergency Department (ED). Despite AF relapses may be clinically heterogeneous, a proper management requires either a fast and effective restore of the sinus rhythm or a satisfactory control of the ventricular rate. Whether the strategy adopted in the ED could affect the course of disease is still debated.

Therefore, the aim of our study was to evaluate the number of ED readmission for AF related symptoms and the event-free period in patients older than 70 years previously treated in ED for an AF recurrence, in order to assess a possible relationship with the acute strategy.

An overall number of 302 recurrences of AF were drawn randomly, regarding 102 patients (mean age 78 years). We found that 206 cases (68.2%) were treated with rhythm restoration strategy (RR) whereas 96 (31.8%) with rate control strategy (RC). The median following event-free period was 118.6 +/- 15.5 and 212.9 +/- 37.1 days ($p < 0.05$) for RR and RC strategy, respectively. Within 6 months, 124 (60.1%) out of RR group patients and only 44 (45.8%) out of RC group patients had to be readmitted to ED for AF related symptoms (whether a recurrence or inefficient rate control symptoms) ($p< 0.05$). This advantage was substantially confirmed (79.1% vs 65.6% respectively, $p < 0.05$) after a 12 months follow-up. Our results indicate that acute treatment of AF may affect the long-term outcome of the disease and the ED readmission rate of the patient. Ventricular rate control seems to be associated with a longer event-free period if compared to the rhythm control strategy in the elderly patients. This suggests an age-based work-up of patients admitted to the ED, preferentially using ventricular rate control in elderly subjects.

Introduction

Atrial fibrillation (AF) is the most frequent arrhythmic disorder in Western countries and may occur in more than 1% of general population,[1,2] its incidence raising up 18% in over 80 years people.[3,4] Ageing process in the general population will reasonably increase such prevalence, so that about 18 millions of European people are estimated to be affected by AF within the next 4-5 decades.[5,6,7]

The natural course of AF is often characterized by a sequence of relapses leading to a final condition of established chronic arrhythmia.[8] Moreover, the clinical manifestations of AF relapses very often force patients to refer themselves to Emergency Department (ED), thus representing a common clinical issue for emergency physicians. Notably, the relapse rate after the first episode of AF is about 10% in the first 12 months and 5% in the following years.[9]

Currently, AF relapses overall account for 3% of the ED readmissions, but it is easy to suppose that this feature will be substantially increased in the next few years as well the economic burden linked to the management of this disease.[10,11,12]

Despite clinical presentation of AF is heterogeneous and ranges from the isolated recognition of abnormal heart rhythm up to severe life-threatening conditions, all patients admitted to ED require a fast effective reversal of the arrhythmic disorder or, at least, the control of ventricular rate aimed to reassure satisfactory functional status and quality of life. For this reason, essential tasks for the Emergency Physician are

1.safe and effective management of the acute arrhythmia in order to obtain the recovery of the previous steady-state in relatively short time,

2.starting of adequate treatment able to prevent future AF related

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Atrial Fibrillation, Rate Control, Rhythm Control, Recurrences.

Disclosures:
None.

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Table 1: Associated diseases

	RR (n = 206) %	RC (n = 96)%	p-value
Sex			0.802
Male	84 (40.8)	41 (42.7)	
Female	122 (59.2)	55 (57.3)	
Age	78 (74 – 82)	78 (75 – 83)	1.000
Onset			0.034
< 12 h	167 (81.1)	42 (43.8)	
12 – 24 h	18 (8.7)	10 (10.4)	
24 – 48 h	20 (9.7)	7 (7.3)	
48 – 96 h	1 (0.5)	37 (38.5)	
Onset symptoms			
Dyspnoea	9 (4.4)	8 (8.3)	0.184
Fatigue	25 (12.1)	34 (35.5)	0.001
Chest pain	14 (6.8)	5 (5.2)	0.800
Hypertension	187 (90.8)	88 (91.7)	1.000
Cronic Heart Failure	14 (6.8)	5 (5.2)	0.800
Ischemic heart disease	38 (18.4)	13 (13.5)	0.326
Cardiomyopathy	2 (1.0)	2 (2.1)	0.594
Valvular heart disease	44 (21.4)	21 (21.9)	1.000
Diabetes	13 (13.5)	20 (9.7)	0.327
Dyslipidemia	49 (23.8)	27 (28.1)	0.477

readmission to the ED.[13]

Currently, two approaches are available to achieve such goals: the first strategy is aimed to restore sinus rhythm (SR) either by electrical or pharmacological intervention; the second one is limited to gain a good ventricular rate control leaving the patient in chronic stable AF. The lack of reports comparing the different approaches and the several outcomes examined makes the best choice still uncertain.[14] Particularly, whether the number of AF relapses and the disease-free period could depend on the strategy adopted in ED still remains an unsolved question.[15,16]

Therefore, we reviewed of all AF recurrences treated in our ED in the last five years in order to assess a possible relationship between the different strategy, rhythm or rate control, and the following relapses. In this report, we present the preliminary results obtained on a small subset of recurrences drawn randomly (n = 302). The aim of this preliminary study is to evaluate whether the rhythm or rate control strategies could influence the number of AF relapses in ED and then the event-free period.

Methods

"Index Events" and Inclusion Criteria

In this preliminary study we retrospectively evaluated 302 AF recurrences randomly drawn from all episodes of AF observed in the Emergency Department (ED) of General Hospital of Verona (Italy) from January 2010 to December 2014. We considered as "index event" any AF recurrence with a clearly inferable recent onset of the arrhythmia (< 96 hours).

The inclusion criteria were the following:

1.age > 70 years;

2.clinical history of previous AF episode already treated in our ED, in order to surely exclude a first diagnosed AF;

3.evidence of stable sinus rhythm (SR) before the present AF recurrence (index event);

4.well proven and datable ED readmission after the "index event" for AF-related symptoms, due either to symptomatic recurrence or unsatisfying rate control (relapse event).

We excluded from the analysis all patients with a permanent pacemaker or previously submitted to percutaneous transcatheter ablation procedures (Fig. 1).

Statistical analysis was performed on all index events included in the dataset (n= 302).

Data Collection

Clinical reports of the AF recurrence (index event) of each patient enrolled in the study were examined. We collected data regarding previous clinical history and chronic therapy, the well-defined onset of symptoms, the electrocardiogram registered both at admission and discharge time and the treatment administered in ED.

All recorded index events were divided into two groups according to ED treatment:

1.strategy aimed at restoring the normal sinus rhythm (Rhythm control group – RR group);

2.strategy only aimed at controlling the ventricular rate without restoration of sinus rhythm (Rate control group – RC group).

All patients were treated with anticoagulant drugs.

Thereafter in each considered index event we verified:

1.the heart rhythm registered within a week from admittance;

2.following ED readmission either due to a new AF recurrence or symptoms related to an unsatisfying ventricular control (relapse event).

The time interval between the index event and the relapse event was defined as "event-free period" and considered as the outcome of this preliminary study.

Statistical Analysis

Statistical analysis was performed using SPSS 22.0 (IBM Inc., Chicago, Illinois, USA). Quantitative values were compared by Student's t-test for unpaired data, and expressed as means ± standard deviation or 95% interval confidence (95% CI); when necessary, logarithmic transformation was applied to obtain normal disribution and variability of the data was expressed as 95% confidence interval. Categorical variables were compared by chi squared test or Wilcoxon-Mann-Whitman test.

Comparison between the event-free time of the different treatments was performed by using Kaplan-Maier and Long Rank Test (statistical significance when $p < 0.05$). Relapses and ED readmission rates were compared by Fisher's exact test.

Results

According to the preliminary study protocol and the inclusion and exclusion criteria, an overall number of 302 clinical folders regarding ED admissions for AF datable recurrence were finally evaluated. The study population consisted of 102 patients (mean age 78 years, range

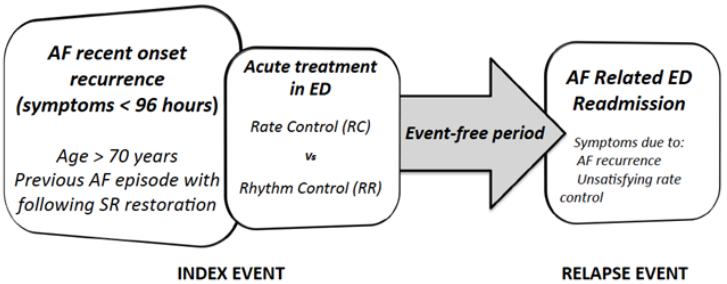

Figure 1: Schematic summary of the study protocol

Table 2: Drug history

	RR (n = 206)	RC (n = 96)	p
Beta blocker	71 (34.5)	48 (50.0)	0.012
Ca-Antagonist	38 (18.4)	24 (25.3)	0.220
ACE inhibitors / ARBs	143 (69.4)	65 (67.7)	0.894
Antiarrhythmic	114 (55.3)	33 (34.4)	0.001
Digital	2 (1.0)	3 (3.2)	0.168
Diuretics	97 (47.1)	48 (50.5)	0.620
ASA	78 (37.9)	46 (48.4)	0.101
Anticoagulant	70 (34.0)	28 (29.5)	0.509

70-93), with a median of 2 events for patient (range 1-9).

In 144 (47.7%) out of these events, the onset of symptoms lasted within three hours, in 120 (39.7%) between 3 and 24 hours, and in 39 (12.6%) between 48 and 72 hours. The main clinical features including details of the previous home therapy of these patients are reported in Table 1 and 2.

As regards the therapeutic strategy adopted, in 206 (68.2%) out of 302 recurrence it was aimed to restore SR by means of either electrical or pharmacological interventions (RR), whereas in the remaining 96 (31.8%) ED treatment strategy was limited to heart rate control (RC).

A stable restoration of normal sinus rhythm before discharge was obtained in 181 recurrences out of 302 (59.9%), 151 of which in the RR group and 30 in the RC group ($p < 0.05$).

At one week evaluation from discharge SR was reported in 191 of 206 (92.7%) in the RR group and 65 of 96 (67.4%) in RC group ($p < 0.05$).

Notably, all the 12 early relapses (< 7 days) occurred in subjects treated according to the RR strategy.

As regards the following ED readmission for any AF related symptoms (either AF recurrence or unsatisfactory rate control) the median event–free period without AF related ED admission was 212.9 +/- 37.1 days for RC and 118.6 +/- 15.5 days for RR strategy ($p < 0.05$). In the Fig. 2 are shown the Kaplan-Meier time curves for both these strategies.

There were no substantial differences in terms of ED readmission between RC and RR strategies during the first month (16.7% vs 20.9% respectively, $p > 0.05$), as shown in fig. 2, but we found a significant difference after 6 and 12 months (Table 3): particularly, 6 months later, the 60.1 % of the patients in RR group whereas only the 45.8% of those in RC group had to be readmitted to ED due to AF ($p < 0.05$). Within a 12 months follow-up period, this trend was substantially confirmed (79.1% vs 65.6% respectively, $p < 0.05$).

In the subgroup of patients who experienced restoration of the sinus rhythm either during the ED stay or within the following week (as verified by means of a Cardiologist visit), the median period of well-being was 103.4 days +/-14.5 for RR group and 165.3 days +/- 30.1 for RC group ($p < 0.05$).

Discussion

Our preliminary results suggested that in over 70 years-old patients the rate control management of AF recurrences in ED could lead to a wider event-free period.

In a recent long-term follow-up study AF is reported to have a slow progression from an isolated form ("lone AF") to a sustained ones, since many years could lapse within the first and the second episode.[8] However, when the underlying structural disease has worsened, AF episodes occur as a cluster of more or less near recurrences, forcing the patients to several admittances in ED.[2,8]

Therefore we though convenient to exclude all the first episodes of AF and to consider the recurrences only. A better understanding of the natural history of AF could improve the management of recurrences and reduce the need for acute treatment.

Our study is retrospective and moreover preliminary, being carried out on a small number of patients, and thus the apparent larger effectiveness of rate-control strategy in reducing AF relapses in elder population has to be confirmed in a wider series.

However, to the best of our knowledge, this is one of the first study evaluating in elder patients observed in Emergency Department (ED), a setting where a fast therapeutic response is needed, the long-term results of rhythm control versus rate control strategy, not only in terms of AF recurrences but also of symptoms related to an inadequate ventricular rate control.

Moreover, for the very first time the event-free period has been considered as an outcome in the acute management of AF recurrences. This could represent a novel key to assess the best treatment for AF in elder patients, where the requirement of stable circulatory performance is often a priority in comparison with the need for restoring sinus rhythm.

Main international trials, like AFFIRM,[17] STAF,[18] and RACE,[19] that compared rate to rhythm control in AF management, considered patients clinically stable and followed-up by a cardiologist in settings other than the ED. Instead, AF recurrence develop within hours, can be heavily symptomatic and therefore require the rapid intervention of the emergency physician.[20] Our study focused on patients managed in the ED for a " recent onset" recurrence of AF. Most of the enrolled patients (87.4%) were admitted to ED within 24 hours from the onset of symptoms and over 47% of them within 3 hours. On the contrary, the AFFIRM trial mostly enrolled patients with AF lasting more than 48 hours (69.2%), and other studies like PIAF, RACE, STAF, HOTCAFE' only patients suffering from persistent AF (> 7 days).[17,18,19,20,21,22] The elder age is another distinctive feature of the patients considered in our study. As matter of fact, AF represents an age-related disease and in the "real word" mean age of the affected individuals has been continuously increasing. This epidemiological

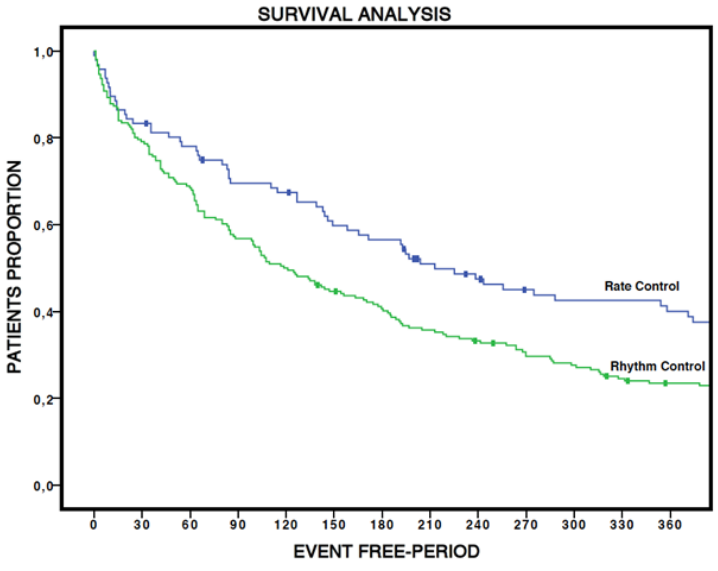

Figure 2: Atrial Fibrillation related event-free period (months) after an AF recurrence

Table 3: Recurrence rate

Recurrence rate	RR (n = 206)	RC (n = 96)	p
Recurrences 1 month	43 (20.9)	16 (16.7)	0.438
Recurrences 3 months	90 (43.7)	31 (32.3)	0.077
Recurrences 6 months	123 (60.1)	44 (45.8)	0.025
Recurrences 12 months	143 (79.1)	63 (65.6)	0.015

observation made us to focus our attention to older people, aged at least 70 years (mean age 78 years), thus drawing a further difference from above mentioned international trials where a younger population was studied, generally in the sixth decade of life.

Also the endpoint considered in the present study was quite different from previous trials. AFFIRM considered the overall mortality,[17] AF-CHF cardiovascular mortality[21] and PIAF symptoms improvement. Other studies like RACE, STAF, J-RHYTM[22] had different composite endpoints. Our main endpoint was the event-free period, defined as the period ranging from the acute treatment in ED for an AF recurrence to the following relapse of any symptom associated with not (or poorly) controlled underlying arrhythmia.

The primary outcome of the present study resulted to be clearly applicable since the patients undergoing rate control strategy showed an event-free period significantly longer than those treated with rhythm control strategy (212.9 vs 118,6 days respectively, $p < 0.05$). Moreover, the former is burdened by lower hospitalization rates if compared to the latter group.

Our findings appeared to be consistent with the results achieved by Chatterjee et al.[23,24] Similarly, Shariff et al.[25] reported that in population aged > 70 years the rate control is superior to the rhythm control in terms of mortality and hospitalization, suggesting that an adequately stable ventricular rate may allow a better quality of life in elderly patients and probably reduce the related health care costs.

For long time, rhythm control with fast restoration of sinus rhythm was considered the strategy of choice,[26,27] in order to delay the evolution toward a permanent AF.[28,29,30] This assumption, probably correct in younger patients, seems disputable in older individuals because of pre-existing structural heart alterations and subsequent relative ineffectiveness of antiarrhythmic drugs.[31]

For these reasons, a longer well-being state in the elderly population may not necessarily require the restoration of sinus rhythm, being a controlled ventricular rate sufficient for this purpose. On the contrary, the sequential changes of rhythm by itself or the use of specific preventive drugs could paradoxically facilitate the AF relapses and thus consequent hospitalizations.

Although these hypothesis are speculative and need to be demonstrated, the results in the event-free period within ED readmissions is of main importance, mainly from the emergency physicians point of view.

However, this study is burdened by some remarkable limitations.

Firstly, this is a retrospective study with several difficulties common to such type of investigations and so the relevance of the present conclusions has to be carefully confirmed by appropriate, prospective, well controlled studies.

Secondly, the adherence to the home therapy in the event-free periods was far to be fully evaluated and possible drug changes or interferences (for example by "pill-in-the-pocket" approach) cannot be ruled out.

Finally, it has also been reported that recurrent episodes occur in approximately 90% of AF patients but many of these remain asymptomatic;[32] we were unable to record such episodes that nevertheless did not appear to have any substantial or evident impact on the quality of life of the patients.

In spite of all these limitations, the study shows a picture of the "real world" ED population and the main end-point represents an outcome of objective importance for its related clinical and economical implications.

As matter of fact, if confirmed, these findings suggest an age-based stratification and work-up for the patients admitted to the ED for AF relapse, preferably addressing elderly people to rate control strategy while reserving the most challenging protocols of sinus rhythm restoration to the younger patients. Such approach should result more effective not only in terms of patient health but also in saving time and costs for the Emergency Department.

Conclusions

In a context of progressive ageing of the general population, AF relapses in elderly people probably will lead to an exponential increase of the number of ED admissions and a consequent increasingly economic burden for the public Health System in the next future. Thus, emergency physicians should be able to rapidly and safely manage acute AF symptoms and to restore the previous steady state of the patient.

Our preliminary study indicates that the acute treatment started by the emergency physician will probably affect the long-term outcome of the disease and the following hospital readmission rate of the patient. Ventricular rate control seems to be associated with a longer event-free and well-being period for the elderly patients if compared to the rhythm control strategy. This suggests an age-based work-up of the patients admitted to the ED, with a preferential choice of controlling the ventricular rate in elderly subjects, while reserving the most challenging protocols of cardiac synchronization to the younger patients.

Further prospective studies will be needed to definitely confirm possible advantages of such approach in the acute setting.

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Influence Of Inter Electrode Atrial Lead Distance On Acapconfirm™ Viability

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Abstract

Introduction: The AcapConfirm™ feature available with the Zephyr pacemaker family (St. Jude Medical) is designed for monitoring patient's atrial capture threshold periodically, and automatically adjusting the atrial pulse amplitude. Previous studies showed a relative low proportion of patients at three months follow-up with recommended automatic atrial capture after the AcapConfirm™ viability test. The purpose of the present study is to evaluate the effect of inter electrode distance on the viability of the AcapConfirm™ algorithm.

Methods and Results: 132 patients (66 woman and 86 men; 71, 08 ± 8, 04 years old) were enrolled into this prospective evaluation. Sixty six bipolar leads (models 1882 (54p) and LPA1200M (12p)) with an inter electrode distance of 10 mm (Group A) were compared with sixty six bipolar leads (model 1999) with an inter electrode distance of 1,1mm (Group B). Set-up test AcapConfirm viability and manual step-down atrial threshold test as well as automatic threshold testing by AcapConfirm™ were performed at 3 months after implantation. A positive viability of the AcapConfirm™ algorithm was much lower in Group B (37, 9%; 95% confidence interval, 10, 3% – 65, 4%) versus thirty two patients (48, 5%; 95% confidence interval, 20, 9% - 76%) in Group A. However, the difference was not statistically significant ($\chi 2=1, 51$; p=0, 33). The most frequent reason to reject the AcapConfirm activation was a too small evoked response to polarization ratio (N9).At 3 months, threshold results from the AcapConfirm™ positive test were: 0, 53 ± 0, 13 V in Group B versus 0, 67 ± 0, 18 V in Group A (p< 0, 01). The differences between automatic and manual measurements were ≤0.25V in all patients.

Conclusion: We observed that a short inter electrode distance (1,1mm) is more likely correlated with a lower frequency of AcapConfirm™ viability and threshold that a standard inter electrode distance (10mm). A small evoked response to polarization ratio was the most common cause of a negative test of AcapConfirm™ viability.

Introduction

The AcapConfirm™ feature available with the Zephyr pacemaker family (St. Jude Medical) is designed for monitoring patient's atrial capture threshold periodically, and automatically adjusting the atrial pulse amplitude. ACapConfirm™ use pacing depolarization inte¬gral to calculate atrial-evoked response.[1] ¬ Previous studies showed a relative low proportion of patients at three months follow-up with recommended automatic atrial capture after the AcapConfirm™ viability test.[2]

The purpose of the present study is to evaluate the effect of inter electrode distance on the clinical viability of the AcapConfirm™ algorithm. Viability of atrial threshold monitoring algorithm is defined as the percentage of patients who had atrial threshold monitoring enabled.

Key Words:

Acapconfirm, Automatic Threshold, Interelectrode Distance.

Disclosures:
None.

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Study Design

This observational, prospective data collection study included 142 consecutive patients with right atrial leads (bipolar) and right ventricular leads (bipolar) admitted for dual chamber pacemaker implantation. The intervention was performed by a single operator with experience in atrial and ventricular lead placement, under local anaesthesia and conscious sedation using a combination of intravenous midazolam and fentanyl. All patients received prophylactic intravenous antibiotics just before the procedure. Both leads were inserted via the left or right subclavian venous approach. The atrial and ventricular lead position choice was left to the discretion of the operator. After the device was implanted and before the patient was discharged from the hospital, the pacemaker was interrogated and the patient underwent chest radiography and standard 12-lead electrocardiography. Set-up test AcapConfirm™ viability and manual step-down (2,5 to 0,25V @ 0,4ms) atrial threshold test as well as automatic threshold testing by AcapConfirm™ were performed at implant, and 3 months after implantation. Data from participants who successfully completed both an automatic and manual capture thresholds test during follow-up at three months, were compared.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation range, while categorical data were expressed as frequency and

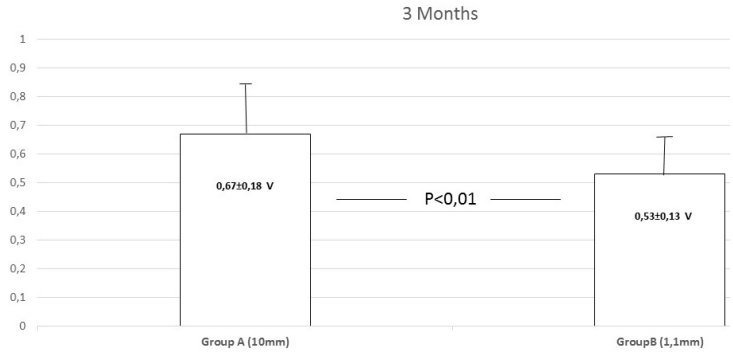

Figure 1: Automatic Atrial Threshold ACapConfirm™

percentage. To compare the proportion of AcapConfirm™ between the two groups, we performed χ^2 test for categorical variables. Continuous variables were compared using t-test for normally distributed data or Mann Whitney U test for nonnormally distributed data as deemed appropriate.

Results

Between July 2011 and August 2014, 142 patients were enrolled. Lead implantation was successful in all patients. The reasons for failure to reach the three months follow-up were atrial perforation (1p), atrial fibrillation (1p) death (3p), and loss (5p).Consequently, 132 patients (66 women and 86 men; 71, 08 ± 8, 04 years old) completed the 3-month follow-up. Regarding to interelectrode bipolar leads distance, patients were divided in 2 groups. Group A (10mm) included 54 patients with models 1882 and 12 patients with model LPA 1200M. Group B (1,1mm) included 66 patients with model 1999. Set-up test AcapConfirm viability and manual step-down atrial threshold test as well as automatic threshold testing by AcapConfirm™ (pulse width setting of 0.4 ms) were performed at 3 months after implantation.

A positive viability of the AcapConfirm™ algorithm was much lower in Group B (37, 9%; 95% confidence interval, 10, 3% – 65, 4%) versus thirty two patients (48, 5%; 95% confidence interval, 20, 9% - 76%) in Group A. However, the difference was not statistically significant (χ^2=1, 51; p=0, 33).

The most frequent reason to reject the AcapConfirm activation was a too small evoked response to polarization ratio (100% in Group A vs 87, 8% in Group B). (Table 1). At 3 months, threshold results from the AcapConfirm™ positive test were: 0, 53 ± 0, 13 V in Group B versus 0, 67 ± 0, 18 V in Group A (p< 0, 01). (Fig. 1) The differences between automatic and manual measurements were ≤0.25V in all patients.

Discussion

Beat-to-beat verification of atrial pacing is problematic, owing to the small amplitude of atrial-evoked response (AER), which would make an algorithm prone to underdetecting effective stimulation The ACapConfirm™, an atrial threshold monitoring algorithm (Zephyr™ pacemaker family), uses pacing depolarization integral to calculate atrial-evoked response in order to decrease the influence of artifact during measurement1. This optimization of pacing output may increase patient safety and therapy efficacy by ensuring continuous therapy, reduces follow-up burden, allows ambulatory and remote threshold measurement, and may increase battery longevity.[3,4,5]

Unlike ventricular Autocapture™, ACapConfirm™ algorithm is not beat-by-beat. Once the automatic atrial pulse amplitude is adjusted, it will stay in effect until the next threshold search. Threshold searches are run every 8 or 24 hours, as programmed, and the atrial threshold is determined by overdrive pacing the atrium if necessary. The overdrive rate is determined using the average atrial sensed rate and variance. If the algorithm is set to "ON", once the threshold is determined, the atrial pulse amplitude is set to a fixed voltage above the threshold, ensuring a safety margin of at least 1.7x until the next threshold search. In order to enable ACapConfirm™, the pacing pulse configuration must be programmed to bipolar and the ACap Confirm setup test must be run. Like ventricular Autocapture™, the setup test will determine the amplitude of the evoked response compared to the measured lead polarization to ensure that there is an appropriate safety margin. If an appropriate safety margin exists, the test will recommend that ACapConfirm™ can be programmed "ON".[6]

During an implant procedure, the current of injury associated with lead placement is typically the highest and the measured evoked response is typically lower until the lead matures. Clinical evaluations have shown that the ACapConfirm™ feature is more likely to be recommended as the lead matures, specifically at one and three months.

In our unselected population of patients, a relationship ER to polarization too small in the two groups studied was the most common reason to reject the AcapConfirm™ activation.

We found that a short interelectrode distance (1, 1 mm) can be associated with a lower likelihood (non-statistically significant) of automatic atrial capture than typical interelectrode distance (10 mm) using an evocated response based algorithm (AcapConfirm™). However, the automatic atrial threshold by AcapConfirm™ were significantly lower in the group with short interelectrode distance.

The ability to consistently and accurately detect capture depend on the relative magnitudes of the stimulated cardiac signal (evoked response) and the pacing-induced afterpotential (polarization). Ways to reduce the pacing polarization include increasing electrode surface area, reducing electrode polarization by coating (IROX, Pt Black, or TiN),[7,8] or using smaller coupling capacitance in the stimulation circuit.[9] When the polarization amplitude was low, the ER and AERI did not change appreciably with stimulus voltage. With a high-polarization electrode, the evoked-response waveform and AERI changes significantly with variations in the stimulus voltage. The stimulus duration does not affect the capture-evoked response, but influences the magnitude of the polarization signal.[10]

When the polarization signal is large in proportion to that of the evoked response, capture detection is impossible.[10] Other factors can influence the viability of AcapConfirm™ feature: a periodic amplitude

Table 1: ACapConfirm not recomended(codes)

	Group A (1,1 mm distance)	Group B (10 mm distance)
Gain adjustment failed-satured at min gain	X	X
Gain adjustment failed-ER too small at max gain	X	X
Capture threshold too high	X	X
Capture threshold not found	3p	X
ER too low	1p	X
ER to polarization too small	36p	44p
Variability Safety Margin	1p	X

modulation associated with respiration can affect the IEGM signal and fusion of a paced atrial depolarization with a spontaneous P wave often results in a small or even nonexistent ER, myopotential noise induced by various maneuvers has a demonstrable impact on AER sensing and, for certain exercises, cardiac beats exhibit a signal-to-noise ratio less than 2.[11]

Limitation

This study represents observational data from a single centre and thus should be considered exploratory. The major limitation is the small number of patients included, which means that the results will have to be confirmed by other groups as well.

Conclusions

According to our data, a short inter electrode distance (1,1mm) is more likely correlated with a lower frequency of AcapConfirm™ viability and lower threshold than a standard inter electrode distance (10mm). A small evoked response to polarization ratio was the most common cause of a negative test of AcapConfirm™ viability. Larger prospective studies are necessary to confirm our findings.

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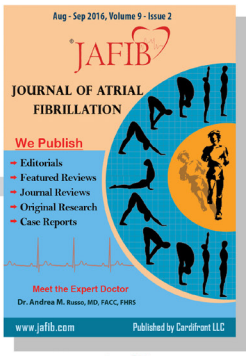

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Achieving Bidirectional Long Delays In Pulmonary Vein Antral Lines Prior To Bidirectional Block In Patients With Paroxysmal Atrial Fibrillation (The Bi-Bi Technique For Atrial Fibrillation Ablation)

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Abstract

Background: Pulmonary Vein Antral isolation (PVAI) is currently the standard of care for both paroxysmal and persistent atrial fibrillation ablation. Reconnection to the pulmonary vein is the most common cause of recurrence of atrial fibrillation. Achieving the endpoint of bidirectional block (BDB) for cavotricuspid isthmus dependant flutter has improved our outcomes for atrial flutter ablation. With this we tried to achieve long delays in the pulmonary veins antral lines prior to complete isolation comparable to those delays found in patient with bidirectional block of atrial flutter lines.

Study Objective: The objective of this paper was to evaluate feasibility and efficacy of achieving Bidirectional long delays in pulmonary vein antral lines prior to Bidirectional Block in patient with paroxysmal atrial fibrillation.

Method: A retrospective analysis was performed on patients who had paroxysmal atrial fibrillation procedures at Unity Point Methodist from January 2015 to January 2016. 20 consecutive patients with paroxysmal atrial fibrillation who had AF ablation using the Bi-Bi technique were evaluated.

Result: Mean age was 63, number of antiarrhythmic used prior to ablation was 1.4, mean left atrial size was 38 mm. Mean chads score was 1.3. Mean EF was 53%.

Long delays in the left antral circumferential lines were achieved with mean delay of 142 milliseconds +/-100. Also long delays in the right antral circumferential lines were achieved with mean delay of 150 milliseconds +/-80.

95 % (19/20) of patients were free of any atrial arrhythmias and were off antiarrhythmic medications for AF post procedure. There was only one transient complication in one patient who developed a moderate pericardial effusion that was successfully drained with no hemodynamic changes. The only patient who had recurrence was found to have asymptomatic AF with burden on his device <1%, this patient was also found to have non PV triggers for his AF. In patients with only PV triggered AF success rate was 100%.

Conclusion: Achievement of Bidirectional long delays in pulmonary vein antral lines prior to Bidirectional Block in patient with paroxysmal atrial fibrillation is feasible and highly effective technique in this small cohort of patients studied. We also outlined the procedure in details.

Introduction

Pulmonary Vein Antral isolation (PVAI) is currently the standard of care for both paroxysmal and persistent atrial fibrillation ablation.[1] The success rate for PVAI is still modest about 70-75% with first procedure and improves to 80-85% with multiple procedures in patients with paroxysmal Atrial Fibrillation.[2,4]

Reconnection to the pulmonary vein is the most common cause of recurrence of atrial fibrillation. The ability to achieve a durable PVAI with transmural lesions can be difficult. Various modalities have been done to improve outcome including injection of adenosine to look for latent conduction, pacing on the antral line and further ablation for areas of capture. Contact mapping has improved our understanding of lesion formation with care to apply enough power, time and contact.[3,8] Despite all of these efforts we still are at modest outcome for recurrence.

Achieving a bidirectional block (BDB) is currently the standard of care for typical atrial flutter ablation. Achieving the endpoint of BDB for cavo-tricuspid has revolutionized our understanding and improved our outcomes for atrial flutter ablation. Currently, success rates for atrial flutter ablation are close to 95% when BDB is achieved.[4]

Verma et al has studied patients who have had atrial fibrillation ablation with a repeated electrophysiological procedure.[2] He found

Key Words:

Ablation, PVI, Bidirectional Delay, Bidirectional Block.

Disclosures:
None.

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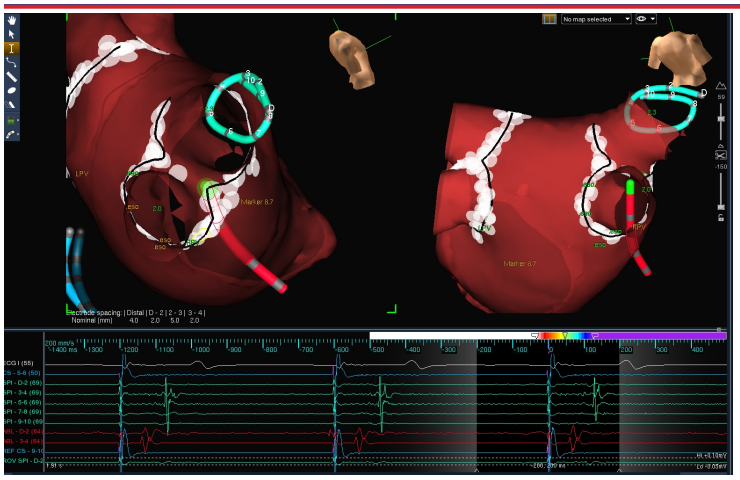

Figure 1: ABL (ablation catheter), SPI (Spiral catheter in RUPV), REF CS (coronary sinus catheter) During pacing form CS proximal we noticed a significant delay in spiral catheter located in RUPV

EAM (electro anatomical map) using Ensite. illustrating the intentional gap left at the superior aspect of RUPV to help evaluate for BD delay prior to closing the GAP. The Black line is the line drawn prior to ablation and the white dots are the ablation lesions done

that patients who maintained sinus rhythm with no recurrence had significant delay from pulmonary vein to the atrium or no conduction i.e. exit block from the veins. He also noted that patients who had a longer delay are more likely to maintain sinus rhythm with or without anti-arrhythmic. Therefore, we hypothesized that if we are able to achieve this delay in the first procedure in both antral lines prior to complete isolation of the veins then this may lead to more favorable effects on outcome. With this we tried to achieve long delays in the PV antral lines prior to complete isolation comparable to the delays found in patient with bidirectional block seen in Atrial flutter cases Fig 1,2.

Pulmonary vein antral lines are circular lines and therefore it is possible to pace both sides of each line and look for conduction delay. We proposed that pacing from distal coronary sinus while watching for delay in the left upper pulmonary vein (LUPV) with the aim of achieving long bidirectional delay before complete isolation of the left antral line. This is done by leaving a small gap in the superior

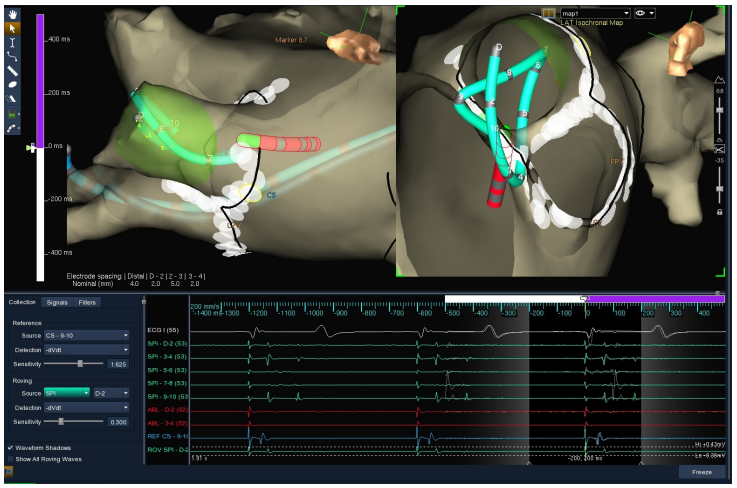

Figure 2: ABL (ablation catheter), SPI (Spiral catheter in LUPV), REF CS (coronary sinus catheter) During pacing form CS Distal we noticed a significant delay in spiral catheter located in LUPV with a double potential , significant delay between potentials is noted

EAM (electro anatomical map) using Ensite illustrating the intentional gap left at the superior aspect of LUPV to help evaluate for BD delay prior to closing the GAP. The Black line is the line drawn prior to ablation and the white dots are the ablation lesions done

aspect of the line(by the roof)and only close this gap after achieving enough delay, preferably >135, in the line.

Likewise for the right sided antral line we paced from the proximal coronary sinus while watching for signal delay in the spiral catheter inserted in the right upper pulmonary vein (RUPV) Fig 1,2.

Procedure Protocol

Patients with paroxysmal atrial fibrillation who have failed antiarrhythmic medications were asked to stop their antiarrhythmic medications 5 days prior to the procedure or longer for amiodarone cases. After detailed information was given to patients about the procedure, and informed consent was obtained the patients were then brought into the EP lab. Venous access was attained with ultrasound guidance using three 8 French sheaths inserted into the right common femoral vein. Next, 9 French sheaths were inserted into the left common femoral vein and 7 French sheaths were inserted into the right internal jugular vein.

Transesophageal echocardiogram and a 64-slice CAT scan was obtained on all patients prior to the procedure. The anatomy obtained from both transesophageal echocardiogram and 64-slice CAT scan was integrated with electro-anatomical mapping anatomy obtained from the EnSite Velocity System (St. Jude Medical) Figure 1.

All patients were anticoagulated with Coumadin or new oral anticoagulants with target INR between 2 and 3 both before the procedure as well as after the procedure, for at least three months. Periodic INRs were done before and after the procedure.

All patients underwent general anesthesia with hemodynamic monitoring by the anesthesia teams. Arterial lines were inserted through the femoral arteries to confirm hemodynamic stability.

An 8 French ACUSON AcuNav intracardiac echo catheter (Siemens Medical USA, Malvern, PA) were inserted into the left common femoral veins and placed into the right atrium. They were then used to monitor transseptal punctures, confirm catheter stability and position, and lastly, used to evaluate catheter contact during ablation and provide safety guards for early detection of complications.

Duodecapolar catheters were inserted through the right internal jugular vein into the coronary sinus with the proximal poles in the high right atrium.

Two transseptal punctures were performed with intracardiac echo as well as fluouroscopic guidance using the ACross™ Transseptal

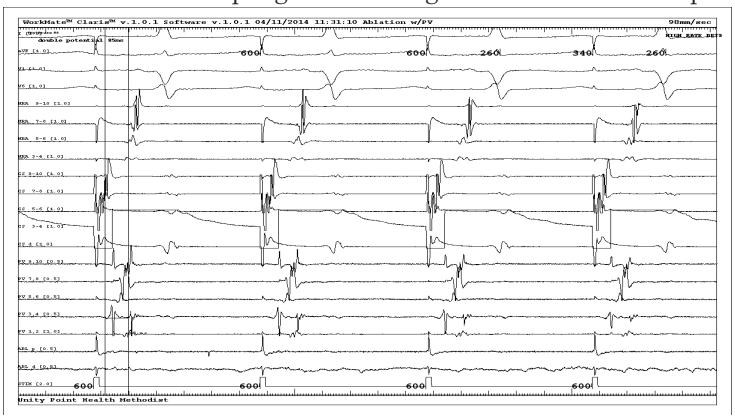

Figure 3: ABL (ablation catheter), PV (Spiral catheter in LUPV), CS (coronary sinus catheter), HRA (high right atrial catheter). STIM (stimulation channel)

During pacing form CS Distal we noticed a significant delay in spiral catheter located in LUPV with a double potential , delay between potentials are 85 ms

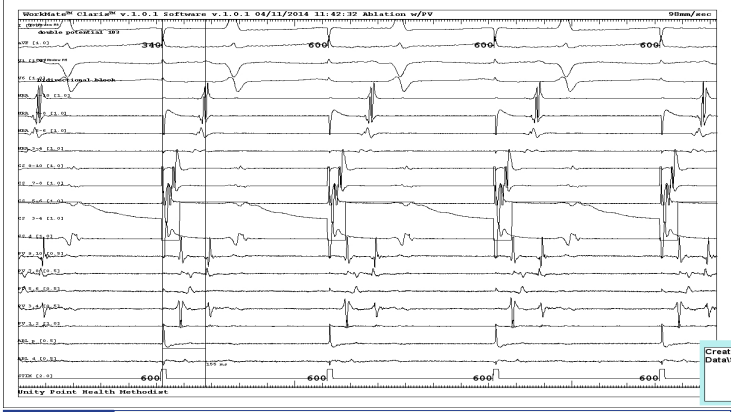

Figure 4: ABL (ablation catheter), PV (Spiral catheter in LUPV), CS (coronary sinus catheter), HRA (high right atrial catheter). STIM (stimulation channel)

During pacing form CS Distal we noticed a significant delay in Spiral (PV) catheter located in LUPV with a delay of 155 ms in the left antral line.

Access System (St. Jude Medical). The SafeSept™ Transseptal Guidewire (Pressure Products, Inc., San Pedro, CA) was used to avoid through and through punctures.

Next, a spiral catheters were used to obtain electroanatomical mapping of the left atrium, which was later merged with CT imaging anatomy.

An esophageal temperature probe was advanced into the esophagus and intermittently repositioned in close proximity to the ablating catheter for each patient. Considering the importance esophageal temperature change during ablation; any significant rise of more than 0.5° was enough to consider lowering the wattage output or moving to another area. Power was titrated at 20 watts with an irrigation catheter in areas close to the esophagus.

Peri-procedural anticoagulation was obtained with heparin bolus, as well as heparin drip to maintain ACT more than 350 and less than 400. ACTs were checked every 15 minutes, and heparin was readjusted until ACTs remained stable.

Left atrial pressure, as well as patient input and output, were continuously monitored throughout the procedure. Ablation was performed using saline irrigation catheters with power of 30-35 watts. In areas close to the esophagus or inside the veins the power was titrated down to 20 watts. Care was taken to avoid ablation inside veins and do large antral lines.

Steps Done for Achieving Long Bidirectional Delays for Pulmonary Veins Antral Lines (Fig 1-7)

1.Electroanatomical map of the left atrium was obtained for each patient.

2.Two wide antral lines with were drawn with a small gaps left at the superior aspect of the line on each side, leaving also the carina open.

3.Ablation was done on top of the drawn lines while pacing from distal CS for left antral line and proximal CS for right antral line,

4.Evaluation of the delay to pulmonary vein potential was intermittently measured till we achieve a delay of at least 135 ms or more on each antral line while pacing from the coronary sinus catheter.

5.If the ablation was completed without achieving antral delay then we try look for gap in the line and do further ablation in area of gaps or persistent signal.

6.If delay was still not achieved then we pace at line for area of capture and ablate at area of capture or viable myocardium.

7.If delay was still not achieved then we look for signal inside the line and target areas with narrowest delay as a sign of a gap.

8.Once we achieved the delay we paced from inside the veins to ensure that the delay is bidirectional, and then we closed the gap at the superior aspect of each line.

9.We then paced from the spiral catheter inside each of the four veins to ensure exit block

10.We insured entrance block by evaluation of absence of signal inside the veins or this was done with pacing in the left atrial appendage or right atrium to make sure that the remaining signals left were only far field.

11.We then put some lesions at the carina on each side for completion purposes.

Isuprel was then started with decremented atrial pacing down to a cycle length of 200 for 6 seconds to insure the veins are disconnected with no further induction of AF.

Protamine 40 mg was given, and catheters were removed at the end of the procedure. Hemostasis was achieved by manual pressure at venous access sites. The patient then was transferred to the floor where they stayed overnight and was sent home the next day.

The patient was followed up with holter monitor done for 24 hours every 3 months till 1 year, and an event monitor for any symptoms of recurrence during the first year and thereafter. Patients were also

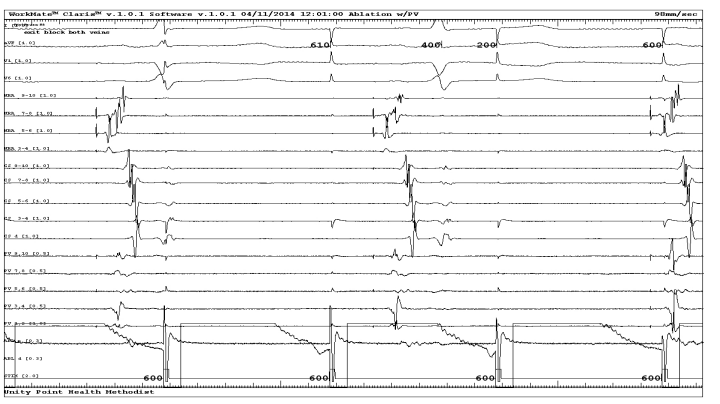

Figure 5: ABL (ablation catheter), PV (Spiral catheter in LUPV), CS (coronary sinus catheter), HRA (high right atrial catheter). STIM (stimulation channel)

During pacing form ablation catheter inside LUPV we noticed evidence of Exit block from the vein.

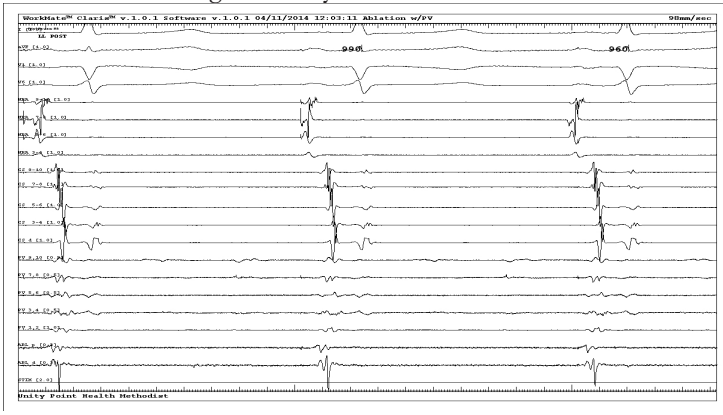

Figure 6: ABL (ablation catheter), PV (Spiral catheter in LLPV), CS (coronary sinus catheter), HRA (high right atrial catheter). STIM (stimulation channel)

PV potentials are gone as evidence of entrance block into the vein.

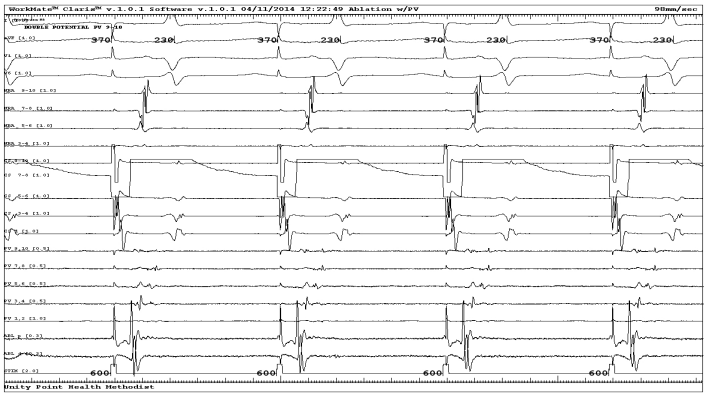

Figure 7: ABL (ablation catheter), PV (Reflexion catheter in RUPV), CS (coronary sinus catheter), HRA (high right atrial catheter). STIM (stimulation channel)

During pacing form CS proximal we noticed a significant delay in Spiral (PV) catheter located in RUPV also douple potentials and significant delay between potential in right antral line

followed closely with a visit every 3-6 months since procedure with frequent EKGs. 4 patients had dual chamber devices which were used to evaluate for recurrence of AF every 3 months post procedure.

Any atrial arrhythmias >30 seconds after the 90 days waiting period were considered as failure or recurrence.

Results

20 consecutive patients were analyzed. Mean age was 63, number of antiarrhythmic used prior to ablation were 1.4, mean left atrial size was 38 mm. Mean chads score was 1.3. Mean EF was 53%.

Delays Achieved

Of the 20 patient that underwent atrial fibrillation ablation with the new technique we were able to obtain an average delay of 142 +/- 100 milliseconds. Also long delays in the right antral circumferential lines were achieved with mean delay of 150 +/-80 milliseconds.

Outcome

95 % (19/20) of patients were free of any atrial arrhythmias and were off antiarrhythmic medications for AF post procedure. There was only one transient complication in this group related to moderate pericardial effusion that was successfully drained with no hemodynamic changes. The only patient who had recurrence was found to have AF burden on his device <1%, this patient was also found to have non PV triggers for his AF triggers as demonstrated with the presence of frequent non Pulmonary Veins PACs during Isupril infusion.

In patients with only PV triggered AF success rate was 100%.

Mean total ablation time was only 71 min. Mean fluoroscopy was only 2.8 min. 20 patients stopped their antiarrhythmic medications for AF.

Mean follow up for all patients' were12 months (6 to 18).

Discussion

In this study we demonstrated the feasibility of achieving long delays into the pulmonary veins antral lines prior to complete isolation. These delays are somewhat comparable to the delays we usually see in the typical flutter lines. We also found no recurrence of AF in all patients who achieved long delays and had pulmonary veins triggers for AF suggesting the durability of isolation.

All patients were free of symptoms post ablation and there was no need for repeat ablation in any patient.

To our best of our knowledge this is the first report of ablation to achieve such a high success 95% with clinical success of 100 %. Other meta-analysis showed that the single-procedure freedom from atrial arrhythmia of 53.1 % in patients with paroxysmal AF with the average number of procedures per patient of 1.51.[6]

We believe that Bi-Bi technique for AF ablation may improve our term treatment of paroxysmal AF and it may be a step closer towards the cure.

We noticed our total ablation time is short and comparable to other studies using the standard technique.[9]

The new technique does not seems to add significant complication as there is no added ablations or no deviation from the standard technique except for paying more attention to the signal delay during the same procedure. We had only one complication which compares favorably with the updated worldwide survey of AF ablation rate of major complications of 4.54%.[7]

Also note our fluoroscopy time is very low compared with other studies we are getting closer to achieve near zero fluoroscopy, this is done with the help of 3 D mapping and intra-cardiac echo.

Limitations

This is a single center, single operator experience with limited number of patients and limited follow up. Further studies will be needed to substantiate the findings.

Conclusions

Achievement of bidirectional long delays in pulmonary vein antral lines prior to bidirectional block in patient with paroxysmal atrial fibrillation is feasible and highly effective technique in this small cohort of patient studied. We hope that the Bi-Bi technique for AF ablation may translate to a true Bye -Bye for AF in patients with paroxysmal AF.

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Association Between Left Atrial Compression And Atrial Fibrillation: A Case Presentation And A Short Review Of Literature

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Abstract

This case report describes a patient who developed palpitations and chest pain and was found to be in atrial fibrillation. This was likely due to the presence of an extra-cardiac mass, which was compressing the left atrium. The mass was related to small cell carcinoma, which decreased significantly in size after chemotherapy. Resolution of the atrial fibrillation correlated temporally with reduction in the size of the mass and alleviation of the left atrial compression.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia characterized by irregular, disorganized and rapid atrial activation leading to an irregular ventricular rhythm.[1] Almost any cardiovascular condition can predispose to AF, common causes being hypertension, coronary artery disease, heart failure, valvular heart disease, cardiomyopathy, pericarditis. Extra-cardiac causes include thyrotoxicosis, chest trauma, thoracic surgery, obstructive sleep apnea, pulmonary embolism, medication use, alcohol excess and withdrawal etc.[1,2,3]

The left atrium (LA) is highly susceptible to compression by extra-cardiac structures. There have been reports of LA compression by bronchogenic cysts,[4] esophageal cancer,[5] achalasia,[6] diaphragmatic hernia,[7] aorta[8] etc. Such compression usually leads to hemodynamic instability, decreased cardiac output, pulmonary congestion and hypoxia.[8]

In this paper, we report a case of LA compression and new onset AF, wherein the AF resolved after chemotherapy and discuss the possible association between LA compression and new onset AF.

Case Report

66 year old female with a past medical history including hypertension, COPD, interstitial lung disease (ILD) and peripheral neuropathy presented to the emergency room (ER) with complaints of worsening shortness of breath for one week and substernal chest pain radiating to back, 9/10 on intensity, which began after drinking soup. The pain lasted for 3 hours and was relieved by sublingual nitroglycerin in the ER. Her troponins were negative all along. Initial EKG showed sinus rhythm without any acute changes. The patient also reported that she had been nauseated and felt as if solid food was sticking in her chest for about 3 weeks. CT chest was done that showed an infracarinal mass (6.2x7.7x8.9 cm) that had increased in size, moderate mediastinal lymphadenopathy, right lower lobe masses and nodule in the right upper lobe along with pulmonary changes consistent with emphysema and ILD.

On the second day, patient had persistent chest discomfort and was found to be tachycardic. An EKG showed AF with a rapid ventricular response (137 bpm). This was new with no known previous history of AF. CT angiogram of the chest ruled out pulmonary embolism and reconfirmed the presence of enlarged mediastinal and hilar lymph nodes along with an 8.0 cm mass/node in the subcarinal space (see figure #1 below) that was occluding the right lower lobe bronchus. Echocardiogram done early in the presentation showed that there was an echogenic mass located outside of the lateral free wall of the left atrium causing partial compression of the left atrial cavity (see figure #2 below).

A biopsy of the lung masses revealed small cell lung cancer. The patient received four cycles of chemotherapy, which included carboplatin and etoposide. Atrial fibrillation converted to sinus rhythm without electrical or pharmacological cardioversion. A follow-up chest CT four months later and after receiving chemotherapy showed a decrease in the size of the mediastinal and subcarinal nodes (2.3cm and 4.3cm in size)(see figure #3) with an increase in size of the right lower lobe mass. Patient remained in sinus rhythm.

In summary, this was a patient who developed new AF, palpitations

Key Words:
Atrial Fibrillation, Compressing, Mass, Left Atrium, New Onset.

Disclosures:
None.

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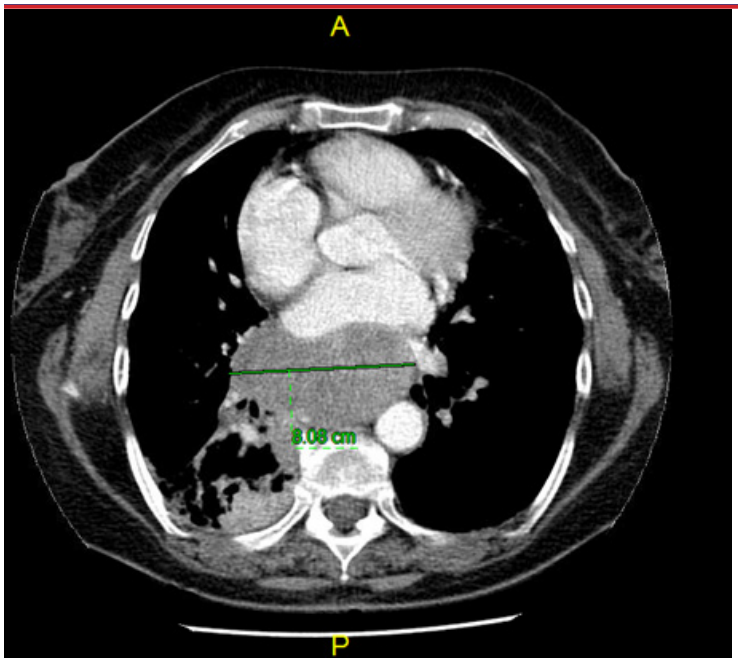

Figure 1:

and chest pain, which was likely due to the presence of an extra-cardiac mass, which was compressing the LA. The mass was related to small cell carcinoma, which decreased significantly in size after chemotherapy. Resolution of the AF correlated temporally with reduction in the size of the mass and alleviation of the LA compression.

Discussion

Although a causal relationship is difficult to establish, several case reports have tried to show an association between external compression of the LA and AF.[8] Upile et al described a case where AF was attributed to external compression of LA by an enlarged esophagus due to achalasia. The AF resolved after removal of food debris from the esophagus.[6] Bayraktar et al reported a case of a patient with a mid esophageal mass (squamous cell carcinoma on biopsy) who was found to have one episode of AF. Chest CT showed subcarinal lymphadenopathy and esophageal thickening resulting in compression of the LA. While the patient has had HTN for 5 years, an echocardiogram revealed a structurally normal heart. Hence it

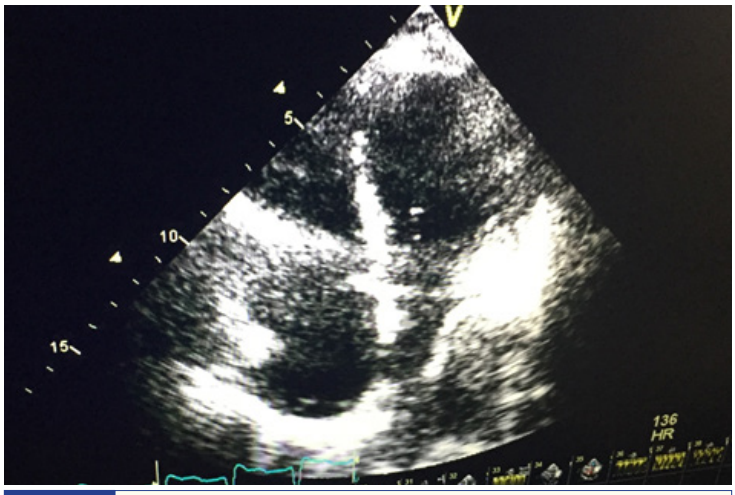

Figure 2:

Table 1: This table shows several reported cases of compressing masses and their association with atrial fibrillation

Clinical scenario	Association	Ref
36 years old man with unremarkable past history presented with palpitation, AF found on EKG. CT scan and echocardiography showed a mediastinal cystic mass (later diagnosed as bronchogenic cyst) that was compressing the LA.	No apparent cause of AF other than external compression. The case report does not mention if the patient stayed sinus after the mass was surgically removed.	4
58 years old man presented with dysphagia, later diagnosed with esophageal carcinoma. His initial EKG was sinus, later developed AF that converted to sinus spontaneously. CT scan showed subcarinal lymphadenopathy and esophageal thickening that compressed LA.	No other cause of AF identified. AF was short-lived and did not recur.	5
84 years old woman presented with dysphagia, later diagnosed as achalasia. She was found to have AF.	Patient reverted back to sinus rhythm after about 300 ml food debris was removed from esophagus.	6
75 years old woman presented with palpitation was diagnosed with AF. CT scan and echocardiography showed descending aorta compressing LA.	Possible causes of AF include external compression, hypertension and heart failure (ejection fraction 44%).	8
38 years old woman without significant medical history presented with palpitation during swallowing. She was found to have AF during deglutition.	Esophageal manometry with simultaneous EKG showed AF occurring with deglutition. No other cause of AF was found.	9

was proposed that AF was precipitated by the esophageal carcinoma compressing the LA or pulmonary veins.[5] Volpi et al described a case of a patient with a bronchogenic cyst compressing the LA leading to reduced LA cavity size on echocardiogram and associated AF. The authors postulate that the AF was probably due to mechanical stretching of atrial myocardial fibers.[4] One case report describes a non-aneurysmatic segment of the descending aorta compressing the LA which was felt to be a possible cause of significant hemodynamic compromise, pulmonary congestion and AF in that patient.[8] Malik et al reported on a patient who had palpitation during swallowing and was shown to have AF induced by deglutition.[9] In our case, the patient did not have a previous history of AF; it is very likely that both AF and difficulty in swallowing were related to the subcarinal mass.

Conclusions

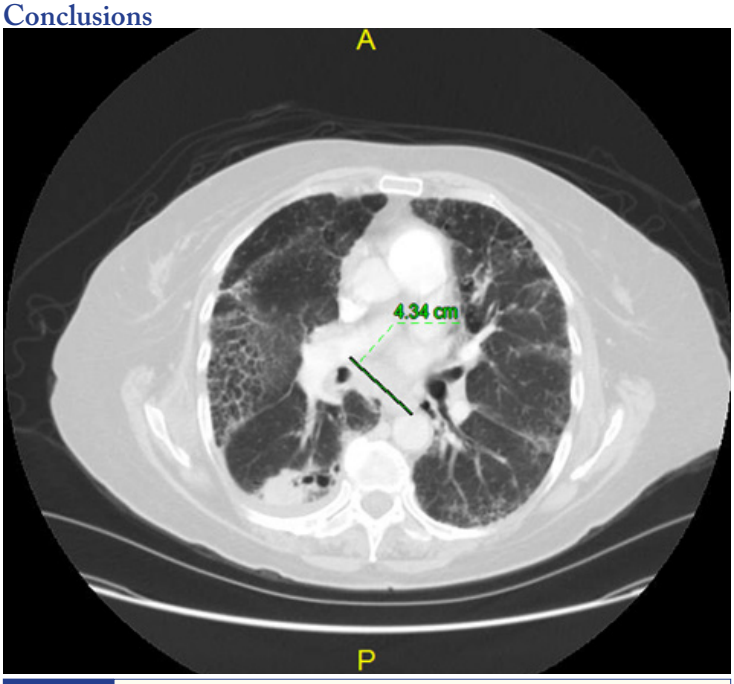

Figure 3:

While a definite causal relationship has not been established, multiple case-reports have shown a possible association between mechanical compression of the LA and AF. It is possible that such compression may cause ectopic beats in susceptible individuals leading to AF. Echocardiography is a nice modality through which to demonstrate compression of the LA. Further study is needed to establish a causal relationship and predict the pattern of AF in cases of LA compression. Further understanding of the electrical and mechanical mechanisms underlying this entity may have significant therapeutic implications.

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Diagnostic and Management Difficulties of Complete Atrioventricular Block In Children in Marrakech: A Report of Three Cases With a Review of the Literature

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Abstract

Complete atrioventricular (AV) block is a rare affection in children. It is the consequence of abnormal conduction tissue within a cardiac malformation or it is due to cardiac injury.

Yet the etiology of late complete atrioventricular block in child remains mostly unknown. The treatment of children's Complete atrioventricular block is the implantation of a pacemaker with immediate results satisfactory in the absence of associated cardiomyopathy. In this observation we will treat three cases.

Cases

A 11-year-old boy was admitted to the hospital following a syncopal episode. He denied chest pain, palpitations, or dyspnea. No story of fever, emesis, diarrhea, rhinorrhea, or sore throat. He had no history of significant medical illnesses prior to this event and no family history of heart disease or sudden death.

An initial EKG performed in the field showed a high-degree atrioventricular (AV) block with a ventricular rate of 33 bpm (Fig.1). He was afebrile, and his blood pressure was 100/60 mmHg, with normal respiratory rates oxygen saturation. He was awake and responsive, and no abnormalities were detected upon complete physical examination.

Laboratory studies were unremarkable for a troponin level of 2.64 µg/L, a white blood cell count of 7,400 µL with 48% lymphocytes, mildly elevated aspartate aminotransferase of 53 U/L, and normal C-reactive protein at 3.3 mg/L. Serum electrolytes and brain natriuretic peptide levels were within normal limits. A chest x-ray showed an appropriate cardiac size and silhouette. Echocardiogram demonstrated normal anatomy and function. Multiple laboratory studies were ordered (for the child and his mom), but a causative pathogen was not identified. her Holter monitor confirmed the diagnosis of persistent CAVB. Permanent pacemaker placement was required.

The second, was a 9-year-old girl, presented with history of recurrent lower respiratory tract infections since the age of 2 months. Physical examination was normal. Baseline 12-lead electrocardiogram (EKG) showed normal sinus rhythm with no conduction delays. Transthoracic echocardiography showed a 16 mm ostium secundum ASD with dilated right atrium. Pulmonary arterial pressure was normal. She underwent a total repair of the ASD. EKG monitoring during the procedure was within normal limits. Post procedure 2D echocardiography showed no residual shunt. EKG monitoring at 12 h showed complete heart block (CHB) with a ventricular rate of 61 beats per minute. The patient was asymptomatic and hemodynamically stable. temporary pacing was required. She was started on a course of oral prednisolone at 2 mg/kg/day to decrease the inflammation and edema around the AV node thought to cause the conduction problems. Her rhythm was checked at 12-h intervals by shortly turning off the pacemaker and recording the patient's ECG. On day 16, patient reverted to normal sinus rhythm with no conduction delays or blocks. No permanent pacemaker placement was required and patient was discharged to home with frequent visit for follow up. She continues to remain asymptomatic and in normal sinus rhythm with no recurrence of heart block.

The third patient is a 7-year-old girl was brought to the emergency department (ED) after a 3 episodes of syncope within the past 2 days without palpitations or prodromal symptoms. The patient had

Key Words:
Complete Atrioventricular Block, Children, Pacing, Myocarditis.

Disclosures:
None.

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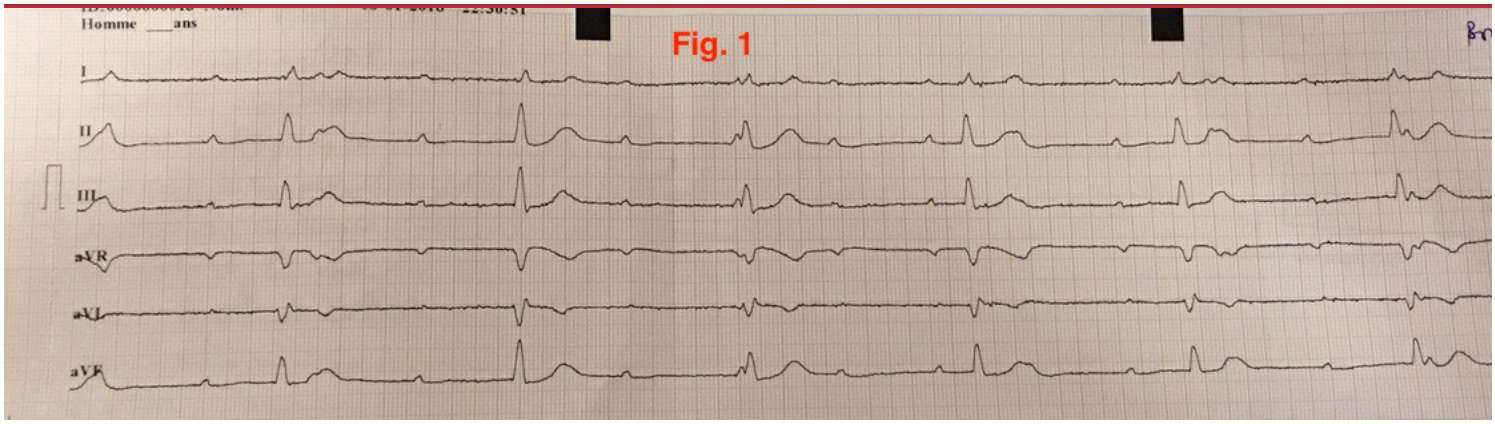

Figure 1: The electrocardiogram demonstrates the complete atrio-ventricular block with ventricular escape beat rate 31 beats/min on the day of admission. The flat P waves in lead I and negative P waves in lead aVL suggested left atrial rhythm which may be related to myocarditis

no significant medical or family history without any complaints of dizziness, dyspnea, palpitations, or chest pain. She had recent symptoms (fever, rhinorrhea, and sore throat) suggestive of a viral illness. She was taking Paracetamol for her fever and Amoxicillin for 5 days. The patient was awake and oriented, with a normal blood pressure of 110/60 mm Hg, heart rate of 75 beats per minute, respiration rate of 20 breaths per minute, and temperature of 38.4°C.

Results of laboratory tests, including serum electrolyte levels, complete blood cell counts, were normal. Serum cardiac markers were abnormal: creatine phosphokinase, 1064 U/L (normal, 150 U/L); troponin T, 61.2 mg/L (normal, less than 0.05 ng/mL), CRP, 52mg /L; VS, 110 in the first hour. A chest film showed no cardiomegaly or pulmonary congestion, and transthoracic echocardiography showed pericardiac effusion with no other abnormalities.

The parents refused MRI with gadolinium contrast and endomyocardial biopsy. The child was treated with prednisone. Permanent pacemaker was necessary for persistent bradycardia. Follow up showed a normal heart function on echocardiography (Fig. 2).

Discussion

The aim of permanent pacing therapy in patients with complete AV block is to restore heart rhythm and rate, relieve the patient from bradycardia-related symptoms, provide haemodynamic stability, and thereby improve patient well-being and clinical outcome.[1] Selecting a pulse generator and pacing lead for a child who needs life-long pacing for complete AV block depends on several important factors.[2] The psychological impact of pacemaker implantation in a child must be taken into account. This is especially true of the adolescent who may have to significantly alter his or her lifestyle as a result of this intervention.[3]

The CAVC is a cause of postoperative cardiac morbidity following repair of congenital heart disease, Current practice dictates implantation of permanent pacemaker (PPM) when post-op CAVB persists > 9 days.[2]

Congenital complete atrioventricular block (CCAVB) has described by Morquio in 1901, it has been of interest in the past primarily because of the risk of sudden cardiac death This complication may be the initial manifestation of congenital AV block, even in previously asymptomatic patients3 In this case, there are specific indications for implantation of a pacemaker. Some observations support the hypothesis that late progression to CAVB can be the result of an immune-mediated pathogenetic mechanism during foetal life. An autoantibody-associated diagnosis after the neonatal period is therefore possible, and testing of maternal serology at the time of diagnosis is recommended.[4]

Myocarditis complicated with complete atrioventricular block (CAVB) is rare in children. The clinical symptoms of acquired CAVB related to myocarditis are often characterized by acute onset of symptoms of low cardiac output due to a slow ventricular rate that may even lead to hypotension or Stokes-Adams seizures.[5] The cardiac enzyme may be abnormal. At disease onset, patients may report various specific or non-specific symptoms, such as fever, general malaise, dyspnea, chest pain, abdominal pain, nausea or vomiting. The development of CAVB probably followed the severe acute inflammation of the bundle branches.[6] The severity of the pathological changes of the AV conduction system may reflect the extent of reversibility of the CAVB.

Previous pediatric reports regarding the clinical course of CAVB after myocarditis were mostly case reports or small case series, some review tried to summarize them (Mei-Hwan Wu) but stile non suffisent to optimize the outcome.[7]

Conclusions

In general, AV block refers to a conduction delay or interruption of the impulses generated in the atrium before they reach the ventricles. AV block may be transient or permanent, and the anatomic level at which it occurs varies. These features determine the clinical significance of this condition, which may range from minimal to

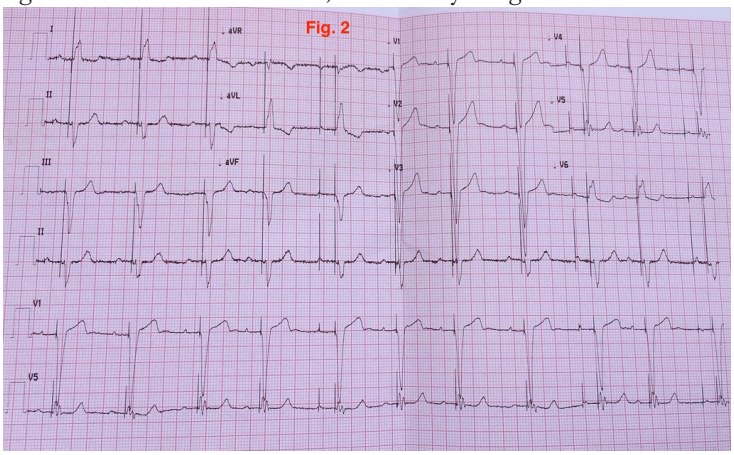

Figure 2: ECG after pacing with beat rate 62/min

severely symptomatic, including syncope, congestive heart failure, or sudden death.

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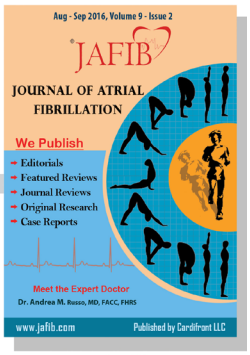

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Reducing The Risk Of Stroke In Patients With Nonvalvular Atrial Fibrillation With Direct Oral Anticoagulants. Is One Of These Not Like The Others?

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Abstract

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and increases risk of stroke by nearly 5-fold. While warfarin has been employed successfully to reduce the risk of stroke in these patients, there are a number of challenges with therapy. These include the need for therapeutic monitoring due to variability in patient response, frequent dose adjustments, numerous drug-drug, drug-food, and drug-disease interactions, and a heightened risk of thrombosis and bleeding due to these issues. Current guidelines recommend that the vitamin K antagonists (VKA) or direct oral anticoagulants (DOACs) should be used for thromboprophylaxis in patients with nonvalvular AF at risk for stroke or systemic embolic events. The DOACs include the direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors rivaroxaban, apixaban, and edoxaban. In clinical trials these agents consistently demonstrated a reduction in the risks of hemorrhagic stroke and intracranial hemorrhage compared to VKA. Clinicians now must decide if there are meaningful differences between these agents in order to prescribe the best agent for an individual patient. Therefore, it is critical for clinicians to go beyond information provided in manuscript abstracts, and gain an understanding of the similarities and differences in clinical trial design, patient enrollment, and statistical analysis.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and is associated with a 4- to 5-fold increased risk of ischemic stroke.[1] The incidence of AF increases with age and presents with a wide spectrum of symptoms and severity. The forms of AF; paroxysmal, persistent, and permanent, all require individualized management, which may range from medical therapy to interventional procedure to device implantation. Atrial fibrillation is estimated to afflict as many as 6 million patients in the Unites States and as many as 34 million patients worldwide. Its prevalence is projected to double over the next 25 years, magnifying the management burden to health care providers.

Although stroke is the most feared complication of AF, stroke rates have declined over the last decade by virtue of patients taking oral anticoagulants.[1] Vitamin K antagonists (VKAs) were the cornerstone of stroke prevention for over 50 years. While VKA administration can effectively reduce the stroke rate by two-thirds, registry and hospital level data suggest they are frequently under prescribed, reaching only about 50% of eligible patients.[2-3] Furthermore, the stroke reduction benefit and bleeding risk are directly associated with the percentage of time the International Normalized Ratio (INR) is within a targeted range. Both registry and clinic level data suggest time in therapeutic range (TTR) is suboptimal and often associated with poor outcomes and higher healthcare costs.[4-7]

In the past several years direct acting oral anticoagulants (DOACs) have emerged as alternatives to VKAs. Collectively, they have been shown to provide better efficacy in stroke reduction and intracranial hemorrhage with at least a similar incidence of major bleeding when compared to VKAs.[8] In addition, they require no laboratory monitoring, can be administered in fixed doses, and improve long term persistence.[9] There are, however, differences in their pharmacokinetic profiles and specifics in the individual trial design that are important for clinicians to consider in their prescribing.[10] This review is intended to highlight the important similarities and differences of these agents as they relate to use in AF.

Phase 3 Clinical Trials

Each of the four currently available DOACs has a phase 3 clinical trials evaluating its efficacy and safety compared to a VKA, mainly warfarin, in patients with nonvalvular atrial fibrillation (NVAF). These studies include the evaluation of dabigatran, rivaroxaban,

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Atrial Fibrillation, DOACs, Warfarin, NVAF.

Disclosures:
Dr. Dobesh has served as a consultant for Boehringer Ingelheim, Janssen Pharmaceuticals, BMS/Pfizer, Daiichi-Sankyo, and Portola Pharmaceuticals.
Dr. Fanikos has served as a consultant for Boehringer Ingelheim and Baxalta.

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Table 1: Comparison of clinical trial design for DOAC clinical trials in patients with NVAF[11-14]

	RE-LY (dabigatran)	ROCKET AF (rivaroxaban)	ARISTOTLE (apixaban)	ENGAGE AF-TIMI 48 (edoxaban)
Study Design	Randomized, dabigatran dosage-blinded, open-label warfarin, parallel-arm, noninferiority study	Randomized, double-blind, double-dummy, event-driven, parallel-arm, noninferiority study	Randomized, double-blind, double-dummy, parallel-arm, noninferiority study	Randomized, double-blind, double-dummy trial, parallel-arm, noninferiority study
Primary Endpoint (analysis population)	Stroke or systemic embolism (ITT)	Stroke or systemic embolism (PP)	Stroke or systemic embolism (ITT)	Stroke or systemic embolism (mITT)
Dosage	Dabigatran 110 mg or 150 mg BID, or warfarin dose-adjusted to a target INR of 2.0 to 3.0	Rivaroxaban 20 mg once daily or warfarin dose-adjusted to a target INR of 2.0 to 3.0	Apixaban 5 mg BID or warfarin dose-adjusted to a target INR of 2.0 to 3.0	Edoxaban 30 mg or 60 mg once daily, or warfarin dose-adjusted to a target INR of 2.0 to 3.0
Dose reduction	None	15 mg once daily for patients with a CrCl of 30 to 49 mL/min	2.5 mg BID in a subset of patients with 2 or more of the following criteria: age ≥80, body weight ≤60 kg, or serum creatinine ≥1.5mg/dL	50% dose reduction was given to patients with CrCl 30-50 mL/min, body weight ≤60 kg, or concomitant use of verapamil, quinidine, or dronedarone at randomization or during study

DOAC = direct oral anticoagulant; NVAF=nonvalvular atrial fibrillation; ITT = intention to treat population; PP = per protocol as-treated population during treatment; mITT = modified intention to treat; BID = twice daily; INR = international normalized ratio; CrCl = creatinine clearance

apixaban, and edoxaban in the RE-LY (Randomized Evaluation of Long Term Anticoagulant Therapy with Dabigatran etexilate) trial,[11] the 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) trial,[12] the ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation) trial,[13] and the ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation – Thrombolysis in Myocardial Infarction 48) trial,[14] respectively. All patients included in these trials were at an increased risk of stroke due to one or more additional risk factors, such as previous stroke or transient ischemic attack (TIA), heart failure, diabetes mellitus, hypertension, or age ≥ 75 years. All four trials were noninferiority trials, which are typically designed to evaluate a per-protocol or modified intention to treat (mITT) population (Table 1). Use of intent-to-treat population (ITT) compared to an on-treatment populations for noninferiority study is controversial and the Food and Drug Administration (FDA) recommends that results for noninferiority analyses be reported for both populations.[15,16] The inclusion of all patients randomized to treatment in the ITT population avoids biases associated with switching treatment, dropout patterns, or patient selection. However, these analyses also include patient outcomes that occur after patients have ceased treatment, including patients with poor compliance. There were differences in the reported populations analyzed for the primary efficacy endpoints: RE-LY and ARISTOTLE reported noninferiority for their ITT populations,[11,13] ROCKET AF reported for the per-protocol population,[12] and ENGAGE AF analyzed the mITT population.[14]

Primary efficacy endpoint in all of these trials was the incidence of stroke (ischemic or hemorrhagic) and systemic embolic events (SEE) (Table 1). All studies used an adapted version of the International Society of Thrombosis and Hemostasis (ISTH) criteria for major and clinically relevant nonmajor (CRNM) bleeding.[17] Major bleeding was the primary safety outcome in the RE-LY, ARISTOTLE, and ENGAGE AF trials, while the ROCKET AF trial use the composite of major and CRNM as the primary safety endpoint. The RE-LY, ROCKET AF, and ARISTOTLE trials had a median follow up time of about 2 years, while the ENGAGE AF trial had a median follow up period of 2.8 years.

Dabigatran

The first trial to evaluate the efficacy and safety of a DOAC compared to warfarin for the reduction of risk of stroke and SEE in patients with NVAF was the RE-LY trial.[11] Patients (n=18,113) were randomized to either dabigatran 110 mg twice daily, dabigatran 150 mg twice daily, or dose-adjusted warfarin. While dabigatran was administered in a blinded fashion, dose-adjusted warfarin was administered in a non-blinded fashion.

Compared to dose-adjusted warfarin, dabigatran 110 mg twice daily demonstrated noninferiority in prevention of the primary endpoint [relative risk (RR) 0.91, 95% confidence interval (CI) 0.74 – 1.11; p <0.001 for noninferiority), while dabigatran 150 mg twice daily proved to be superior in the prevention of the primary endpoint (RR 0.66, 95% CI 0.53 – 0.82; p <0.001 for superiority) (Table 2).11 While both doses of dabigatran significantly reduced the risk of hemorrhagic stroke compared with warfarin (RR 0.31, 95% CI 0.17 – 0.56; p <0.001 for dabigatran 110 mg; RR 0.24, 95% CI 0.14 – 0.49; p<0.001 for dabigatran 150 mg), ischemic stroke was also significantly reduced with the use of dabigatran 150 mg twice daily compared to warfarin (RR 0.76, 95% CI 0.60 – 0.98; p = 0.03).[11] It should be noted that event rates for dabigatran were updated following publication of the primary data to reflect inclusion of events potentially related to stroke, as well as the addition of patients who did not undergo randomization and several deaths that occurred after the end of the study.[18,19]

The rate of major bleeding was similar in patients randomized to dabigatran 150 mg twice daily compared to adjusted-dose warfarin (RR 0.93, 95% CI 0.81 – 1.07; p = 0.31), and lower in patients who received dabigatran 110 mg twice daily compared to warfarin (RR 0.80, 95% CI 0.69 – 0.93, p = 0.003) (Table 3).[11] There was a significantly higher rate of major gastrointestinal bleeding with dabigatran 150 mg twice daily compared to warfarin (RR 1.50, 95% CI 1.19 – 1.89; p <0.001). The rate of intracranial bleeding was significantly reduced in patients receiving dabigatran 150 mg (RR 0.40, 95% CI 0.27 – 0.60; p <0.001) or dabigatran 110 mg (RR 0.31, 95% CI 0.20 – 0.47; p <0.001) compared with warfarin.[21] The incidence of other adverse events were similar between groups, except the rate of dyspepsia. Dyspepsia was significantly more common in patients receiving dabigatran 110 mg twice daily (11.8%) and 150 mg twice daily (11.3%) compared with warfarin (5.8%; p <0.001 for both comparisons).[11]

While a renally-adjusted dose of dabigatran was not evaluated in the RE-LY trial, pharmacokinetic data support the use of a 75 mg twice daily dose in patients with a creatinine clearance (CrCl) of 15 to 30 mL/min.[20] Efficacy and safety data are not available for this dose of dabigatran.

Rivaroxaban

The ROCKET AF trial was a double-blind, double-dummy trial in which patients with NVAF were randomized to rivaroxaban 20

Table 2: Efficacy of DOACs compared with warfarin in phase 3 trials in patients with NVAF[11-14]

	RE-LY			ROCKET AF		ARISTOTLE		ENGAGE AF – TIMI 48		
	Dabigatran							Edoxaban		
Outcome (%)a,b	110 mg	150 mg	Warfarin	Rivaroxaban	Warfarin	Apixaban	Warfarin	Low Dose	High Dose	Warfarin
Stroke or SEE (ITT) p-value	1.54 p=0.27	1.11 p<0.001	1.69	2.1 p=0.12	2.4	1.27 p=0.01	1.60	2.04 p=0.10	1.57 p=0.08	1.80
Stroke or SEE (PP or mITT)c p-value	NR	NR	NR	1.7 p=0.015	2.2	NR	NR	1.61 p=0.44	1.18 p=0.02	1.50
Total stroke p-value	1.44 p=0.41	1.01 p<0.001	1.57	1.65 p=0.092	1.96	1.19 p=0.01	1.51	1.91 p=0.12	1.49 p=0.11	1.69
Ischemic stroke p=value	1.34 p=0.35	0.92 p=0.03	1.20	1.34 p=0.581	1.42	0.97 p=0.42	1.05	1.77 p<0.001	1.25 p=0.97	1.25
Hemorrhagic stroke p-value	0.12 p<0.001	0.26 p<0.001	0.38	0.26 p=0.024	0.44	0.24 p<0.001	0.47	0.16 p<0.001	0.26 p<0.001	0.47
SEE p-value	NR	NR	NR	0.04 p=0.003	0.19	0.09 p=0.70	0.10	0.15 p=0.43	0.08 p=0.19	0.12
Total mortality p-value	3.75 p=0.13	3.64 p=0.051	4.13	1.87 p=0.07	2.21	3.52 p=0.047	3.94	3.80 p=0.006	3.99 p=0.08	4.35

DOAC=direct oral anticoagulant; NVAF=nonvalvular atrial fibrillation; SEE=systemic embolic event; ITT=intention to treat; PP=per protocol; mITT=modified intention to treat
a All p values for superiority.
b Event rate for RE-LY, ARISTOTLE, and ENGAGE AF are in %/year; for ROCKET AF, number/100 patient years
c ROCKET AF evaluated data in the per protocol safety analysis and ENGAGE AF-TIMI 48 evaluated data in the modified intention to treat analysis

mg daily or dose-adjusted warfarin.[12] Patients with a CrCl of 30 to 49 mL/min and randomized to rivaroxaban received a 15 mg daily dose instead of 20 mg daily.

At the end of follow up, rivaroxaban demonstrated noninferiority to warfarin for the prevention of the primary endpoint (HR 0.79, 95% CI, 0.66 – 0.96; p <0.001 for noninferiority).[12] Rivaroxaban demonstrated superiority in the on-treatment analysis (p = 0.015), but not in the ITT analysis (p = 0.12) (Table 2). The rate of hemorrhagic stroke was significantly reduced in the rivaroxaban group compared with the warfarin group, but with no statistical difference in the rate of ischemic stroke (Table 2).

Major bleeding was similar between patients receiving rivaroxaban and warfarin (HR 1.04, 95% CI 0.90 – 1.20) (Table 3).[12] While patients receiving rivaroxaban experienced significantly less intracranial hemorrhage (ICH) (HR 0.67, 95% CI, 0.47 – 0.93; p = 0.02) and fatal bleeding (HR, 0.50, 95% CI, 0.31 – 0.79; p = 0.003) compared to patients receiving warfarin, there were more major GI bleeding (3.2% vs. 2.2%; p <0.001) and a higher need for transfusion (2.6% vs 2.15%; p=0.04) with the use of rivaroxaban compared to warfarin. Major and CRNM bleeding rates were similar between groups (HR 1.03, 95% CI 0.96 – 1.11). Rates of other adverse events were similar between groups.

The reduced dose of rivaroxaban (15 mg once daily) or rivaroxaban placebo, for patients with moderate renal insufficiency, was used in 21% of patients in both groups. The primary efficacy and safety outcomes were consistent with the outcomes demonstrated with those who received full dose rivaroxaban.[12]

Apixaban

The ARISTOTLE trial represents the Phase 3 trial comparing the efficacy and safety of apixaban compared to warfarin in patients with NVAF.[13] Patients (n=18,201) were randomized in a double-blinded, double-dummy fashion to apixaban 5 mg twice daily or adjusted-dose warfarin. Patients considered to be at a high risk of bleeding based on at least two of the following risk factors; age ≥80 years, body weight ≤60kg, or serum creatinine ≥1.5 mg/dL, received a reduced dose of apixaban of 2.5 mg twice daily.

Patients receiving apixaban demonstrated a lower annualized rate of the primary endpoint compared to patients receiving warfarin (HR 0.79, 95% CI 0.66 – 0.95; p < 0.001 for noninferiority; p = 0.01 for superiority; Table 2).[13] Similar to the ROCKET-AF trial, there was a significant reduction in risk for hemorrhagic stroke among patients who received apixaban compared to warfarin without a reduction in ischemic stroke.

Major bleeding rates were lower in the apixaban group compared with the warfarin group (HR 0.69, 95% CI (0.60 – 0.80; p <0.001) (Table 3).[13] Similarly, major or CRNM bleeding occurred less frequently in patients who received apixaban than patients who received warfarin (HR 0.68, 0.61 – 0.75; p <0.001). Rates of other adverse events were similar between groups.

The reduced dose of apixaban of 2.5 mg twice daily was administered in 4.7% of patients in the apixaban group. The primary efficacy and safety outcomes were not significantly different for patients who received the 2.5 mg twice-daily dose compared to those who received the full dose.[13]

Edoxaban

Two doses of edoxaban were evaluated for efficacy and safety in patients with NVAF in the ENGAGE AF-TIMI 48 trial.[14] Patients (n=21,105) were randomized in a double-blind, double-dummy fashion to either high dose edoxaban (60 mg once daily), low dose edoxaban (30 mg once daily), or dose-adjusted warfarin. Patients randomized to edoxaban with moderate renal insufficiency (CrCl 30-50 mL/min), body weight of 60 kg or less, or concomitant use of a potent P-glycoprotein inhibitor, received 50% of their group allocation dose.

Both doses of edoxaban demonstrated noninferiority to warfarin in prevention of the primary endpoint (HR 0.79, 95% CI 0.63 – 0.99; p <0.001 for high dose, and HR 1.07, 95% CI 0.87 – 1.31; p = 0.005 for low dose) (Table 2).[14] Furthermore, edoxaban 60 mg daily demonstrated superiority (p = 0.02) to warfarin when the mITT population was analyzed, but this superiority was not maintained when the ITT population was tested (p = 0.08). Treatment with either dose of edoxaban led to significantly lower rates of hemorrhagic stroke compared with warfarin (HR 0.54, 95% CI 0.38 – 0.77; p <0.001 for high dose, and HR 0.33, 0.22 – 0.50; p <0.001 for low

Table 3: Safety of DOACs compared with warfarin in phase 3 trials in patients with NVAF[11-14]

	RE-LY			ROCKET AF		ARISTOTLE		ENGAGE AF – TIMI 48		
	Dabigatran							Edoxaban		
Outcome (%)a,b	110 mg	150 mg	Warfarin	Rivaroxaban	Warfarin	Apixaban	Warfarin	Low Dose	High Dose	Warfarin
Major bleeding p-value	2.71 p=0.003	3.11 p=0.31	3.36	3.6 p=0.58	3.4	2.13 p<0.001	3.09	1.61 p<0.001	2.75 p<0.001	3.43
CRNM bleeding p-value	13.2 p<0.001	14.8 p=0.005	16.4	11.8 p=0.35	11.4	2.08 p<0.001	3.00	6.60 p<0.001	8.67 p<0.001	10.2
Major or CRNM bleeding p-value	14.6 p<0.001	16.4 p=0.002	18.2	14.9 p=0.44	14.5	4.07 p<0.001	6.01	7.97 p<0.001	11.1 p<0.001	13.0
Intracranial bleeding p-value	0.23 p<0.001	0.30 p<0.001	0.74	0.5 p=0.02	0.7	0.33 p<0.001	0.80	0.26 p<0.001	0.39 p<0.001	0.85
GI bleeding p-value	1.12 p=0.43	1.51 p<0.001	1.02	3.2 p<0.001	2.2	0.76 p=0.37	0.86	0.82 p<0.001	1.51 p=0.03	1.23

DOAC=direct oral anticoagulant; NVAF=nonvalvular atrial fibrillation; CRNM=clinically relevant nonmajor bleeding; GI=gastrointestinal
a All p values for superiority.
b Event rate for RE-LY, ARISTOTLE, and ENGAGE AF are in %/year; for ROCKET AF, number/100 patient years

dose). While ischemic stroke was similar between patients receiving edoxaban 60 mg daily and adjusted-dose warfarin (1.25% for both), patients receiving edoxaban 30 mg daily demonstrated a significant increase in the incidence of ischemic stroke compared to warfarin (HR 1.41, 95% CI 1.19 – 1.67; p<0.001). This contributed to the lack of an FDA approval for the low dose edoxaban regimen.

Major bleeding was significantly decreased for both doses of edoxaban compared to dose-adjusted warfarin (HR 0.80, 95% CI 0.71 – 0.91; p <0.001 for high dose, and HR 0.47, 95% CI 0.41 – 0.45; p <0.001 for low dose) (Table 3).[14] Rates of CRNM bleeding and major plus CRNM bleeding were lower in patients receiving either dose of edoxaban compared to warfarin (Table 3). The incidence of other adverse effects were similar between the groups.

Rates of the primary endpoint in patients who received the 50% dose reduction were 2.32% for the high dose group (30 mg), 3.14% for the low dose group (15 mg), and 2.68% for patients with similar characteristics in the warfarin group.[14] These results were similar to those in the full dose groups. However, the reductions in the risk for major bleeding were significantly greater for patients in the high dose and low dose edoxaban groups who received a 50% dose reduction compared to those who did not (p = 0.02 and p <0.01 for interaction, respectively). Major bleeding rates for reduced-dose edoxaban patients were 3.05% for high dose group (30 mg) and 1.50% for low dose group (15 mg) compared to 4.85% for patients randomized to warfarin with similar characteristics. Additional post hoc analyses were performed with patients stratified by renal function. The rate of ischemic stroke increased with the use of edoxaban compared to warfarin in patients with CrCl >95 mL/min, likely due to lower plasma concentrations of edoxaban.[21] Therefore, edoxaban should not be used in patients with AF and a CrCl >95 mL/min.

Controversies and Discussion

A superficial review of the DOAC trial results may lead clinicians to conclude that one or more of these agents are a better selection compared to others when prescribing for patients. While this may be a tempting conclusion, it is critical that clinicians understand that details about differences in the study designs and study populations make comparisons extremely difficult.

Dosing is sometimes a reason for prescribing one agent over another. While the four currently available DOACs have a pharmacokinetic half-life of approximately 12 hours, dabigatran and apixaban are dosed twice daily, and rivaroxaban and edoxaban are dosed once daily.[20,22] For the vast majority of drugs used in clinical practice, the dosing regimens follow the pharmacokinetics. Therefore, a drug with a 12 hour half-life is dosed twice daily and a drug with a 20 hour half-live is dosed once daily. Despite the 12 hour pharmacokinetic half-live of rivaroxaban and edoxaban, these agents provide 24 hours of anticoagulant activity.[23-25] This is because the pharmacodynamic effect, the anticoagulant effect, is longer than the pharmacokinetic half-live. The ability of once daily dosing is most likely attributed to different target binding kinetics and volume of distribution between agents. Similarly, enoxaparin has a half-live of four to six hours, but is only dosed once or twice daily.[26,27] It has been assumed that the only way to get 24 hours of anticoagulant effect with a drug that has a 12 hour half-life is to provide much higher drug peak concentrations, and that these higher concentrations are then associated with higher risk for bleeding. Peak drug concentrations are relative to each individual agent, and are not comparable across agents. It has also been demonstrated in this class of agents that bleeding risk comes with agents having higher trough concentrations, and is not related to higher peak concentrations.[28,29]

The issue of dosing frequency can play an important role in patient adherence. It is unlikely that if a patient is nonadherent to therapy with warfarin that they would be adherent with a DOAC. Although, DOACs may be advantageous in patients where nonadherence is linked with the frequency of warfarin monitoring. One study across 103 anticoagulation clinic managed patients found that 11 patients were found to be nonadherent within 3 months of initiation of twice daily dabigatran. Adherence was defined as taking >80% or required doses.[30] There were also 30% of patients who reported missing doses during this time frame, with one reporting missing a dose every day. In a study of 5,736 Veterans Affairs patients, adherence of twice daily dabigatran demonstrated a connection to clinical outcomes.[31] Using the same definition of adherence as the previous study, 28% of patients were found to be nonadherent to twice daily dabigatran therapy. For every 10% decrease in adherence there was a corresponding 13% increased risk of stroke and all-cause mortality. Therefore, once daily DOAC therapy may be preferred to twice daily therapy in patients in whom adherence with a more complex regimen is unattainable. While there are no comparable data to evaluating adherence with once compared to twice daily DOAC therapy, adherence with once daily cardiovascular medications are typically better than twice daily medications.[32]

Renal elimination and perceived safety in patients with chronic kidney disease are cited as important differences among DOACs.

Table 4: Patient demographics and characteristics in the phase 3 clinical trials[11-14]

	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF-TIMI 48
Study Drug	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Patients (n)	18,113	14,264	18,201	21,105
Median age (years)	71 (mean)	73	70	72
Male sex (%)	64	60	65	62
Mean weight (kg)	83	28 kg/m^2 (BMI)	82 (median)	NR (10% ≤60 kg)
Low body weight (%)a	2.0	28	11	10
Paroxysmal AF (%)	33	18	15	25
Persistent or permanent AF (%)	67	81	85	75
CHADS2 score				
Mean	2.1	3.5	2.1	2.8
0-1 (%)	32	0b	34	–
2 (%)	36	13	36	77 (≤3)
3-6 (%)	32	87	30	23 (4-6)
Previous stroke or TIA (%)	20	55	19	28
Heart failure (%)	32	63	35	57
Diabetes mellitus (%)	23	40	25	36
Hypertension (%)	79	91	87	94
Previous VKA use (%)	50	62	57	59
Previous aspirin use (%)	40	37	31	29
Mean TTR (%)	64	55	62	65
Median TTR (%)	NR	58	66	68
Median follow-up (y)	2.0	1.9	1.8	2.8

AF = atrial fibrillation; NR = not reported; TIA = transient ischemic attack; VKA = vitamin K antagonist; TTR = time in therapeutic range
aFor RE-LY, <50kg; ROCKET AF, ≤70kg
b3 patients had a score of 1

The DOACs have varying dependence of renal function for their elimination. Dabigatran has the highest level of renal elimination at approximately 80%, followed by edoxaban at approximately 50%, rivaroxaban at approximately 36%, and apixaban at approximately 27%.[22-24] Importantly, the RE-LY, ROCKET AF, and ENGAGE AF trials[11,12,14] excluded patients with a CrCl < 30 mL/min, and the ARISTOTLE trial excluded patients with a CrCl < 25 mL/min.[13] Data in patients with lower CrCl is based on pharmacokinetic studies, and no patient outcome data is available. For some time it has been thought that apixaban was a safer agent in patients with renal disease due to the existence of data in patients receiving hemodialysis. This was a single dose study in eight patients that demonstrated a Cmax and area under the curve (AUC) that was not significantly different compared to patients without renal failure.[33] Similar data also exist with rivaroxaban. A single dose study of rivaroxaban 15 mg in eight patients undergoing chronic hemodialysis.[34] The findings demonstrated that the Cmax and AUC of this dose of rivaroxaban is not significantly different compared to patients with moderate renal insufficiency receiving the same dose. Clinicians should consider that these are both single dose studies without any clinical outcome information before using any of these agents in patients requiring hemodialysis.

In the individual studies, dabigatran and apixaban demonstrated superiority over warfarin in the ITT analysis, while rivaroxaban and edoxaban only demonstrated noninferiority in this analysis. So does this mean that, for example, apixaban should be used instead of rivaroxaban? A detailed understanding of the differences in study evaluation, design, and populations should be understood before considering the answer to this question. Rivaroxaban and edoxaban did demonstrate superiority over warfarin in the per-protocol and mITT analysis, respectively.[12,14] The difference between these analyses and the ITT analysis was only 28 patients in the ROCKET AF trial (0.2% of the total study population) and only 47 patients in the ENGAGE AF trial (0.3% of the total study population.[12,14] Small numbers of patients had an important impact of the statistical interpretation of results.

Differences demonstrated in the individual trials may also be simply an issue of trial size. While the trials with dabigatran, rivaroxaban, and edoxaban had approximately 6,000 to 7,000 patients per arm,[11,12,14] the ARISTOTLE trial with apixaban had over 9,000 patients per arm.[13] When evaluating the absolute difference in the primary endpoint between the ARISTOTLE and ROCKET AF trials, using the ITT analysis, the absolute difference is 0.3% in both trials (Table 2).[12,13] Therefore, was this same absolute difference superior for apixaban, and not for rivaroxaban, because apixaban is a better drug, or possibly due to the fact the ARISTOTLE trial had approximately 4,000 more patients than the ROCKET AF trial to evaluate the same primary endpoint? Statistical differences can be achieved by analysis of large patient populations but clinical differences may not be meaningful.

The issue of trial size likely also impacts the mortality findings from these trials. All of these trials produced a relative reduction in all-cause mortality of approximately 10%. The p-values for this reduction did not quite make statistical significance in the RE-LY (0.051),[11] ROCKET AF (0.07),[12] and ENGAGE AF (0.08)[14] trials, but was significant in the ARISTOTLE trial (0.047).[13] It then has to be decided if these findings suggest that apixaban is a better drug than the others, or that an additional 2000 patients per arm pushes the same relative reduction to become statistically significant. Based on the pharmacology among these agents, it would seem this is likely explained by differences in trial size. The reduction in mortality claim for apixaban has also been scrutinized by the FDA research site inspections. The ARISTOTLE trial received seven "official action indicated" reports from the FDA on the study sites.[35] These included issues with protocol, record keeping, patient safety, falsification of data, and inaccurate adverse drug event reporting. One site in China was found to have altered patient records.[35] If this site is removed from the full data set, the mortality findings are no longer statistically significant.[35]

The patients enrolled in these four clinical trials were not similar in regards to their risk of stroke and systemic embolism or bleeding (Table 4). In the RE-LY and ARISTOTLE trials, the mean $CHADS_2$ score was 2.2 and 2.1, respectively.[11,13] By comparison, patients in the ROCKET-AF and ENGAGE-AF trials were higher risk subjects with mean $CHADS_2$ score of 3.5 and 2.8, respectively.[12,14] Patients with a $CHADS_2$ score of 0 or 1, that may not be candidates for anticoagulant therapy,[36] made up about one-third of the total patients in RE-LY and ARISTOTLE. Only three patients in ROCKET-AF had this low level risk. Moreover, about one-third of patients in RE-LY and ARISTOTLE were high-risk, with a $CHADS_2$ score of ≥3. The ROCKET-AF trial enrolled 87% of patients in this high-risk group. Patients in RE-LY and ARISTOTLE consistently had lower incidence of all components of the $CHADS_2$ score compared to patients in ROCKET-AF and ENGAGE-AF (Table 4). Therefore, differences in patient populations studied are important to consider when evaluating these results, and make comparisons across agents and trials challenging.

In addition to differences in the patient populations studied, a recent reinterpretation of the DOAC phase 3 trials results suggest that the failure of rivaroxaban and high dose edoxaban to demonstrate superiority over warfarin in their ITT analyses of the primary efficacy endpoint may be due an imbalance of off-treatment events in the DOAC arms compared to the warfarin arms. These high discontinuation rates, coupled with more off-treatment events, would dilute the benefits of the treatment effect in the ITT analyses.[37]

It is important to realize that the benefit of all of the DOACs in the setting of NVAF is a significant reduction in hemorrhagic stroke (Table 2). Only dabigatran provided a significant reduction in the rates of ischemic stroke compared with warfarin.[11] In RE-LY, warfarin was administered in an open-label manner and INR was monitored and adjusted locally. In the other three trials, due to their double-bind, double-dummy designs, INR monitoring was done through standardized, encrypted, point-of-care devices that provide INR readings (real or sham) to the site investigators. This difference may result in greater variability in warfarin control at the individual patient level when warfarin is administered open-label compared to blinded, as demonstrated in an analysis of the Stroke Prevention Using Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III (open-label) and V (blinded) trials.[38,39] While the rate of stroke and SEE was 1.6% for ximelagatran in both studies, the efficacy outcome occurred in 2.3% of patients receiving open label warfarin in the SPORTIF III trial, but improved to 1.2% with blinded warfarin in the SPORTIF V trial.[38,39] Therefore, open-label warfarin resulted in a stroke and rate that was almost twice that of blinded warfarin.[38-40] Thus it may be that in RE-LY, there was greater individual INR variability which may have contributed to the higher ischemic stroke rate observed in the warfarin treatment group.[40]

The level of INR control within the trials has also been raised as an issue that may have impacted outcomes or interpretation of the data. The mean TTR for VKA therapy was highest in the ENGAGE AF trial (65%) and lowest in the ROCKET AF trial (55%), with both the RE-LY and ARISTOTLE trials being above 60% (Table 4). The reason for the lower TTR in the ROCKET AF trial is due to two factors. First, while investigators in the RE-LY, ARISTOTLE, and ENGAGE trials were provided guidance on warfarin management through protocols,[11,13,14] investigators in the ROCKET-AF trial were not provided protocols and managed warfarin according to their usual practice.[12] The other reason for the lower TTR is due to the difference in risk of patients mentioned above. It is known that higher risk patients and patients with more comorbidities have a more difficult time keeping their INR between 2.0 to 3.0.[41] The main concern with a lower TTR is the impact on efficacy and safety in the trial. In the RE-LY trial, the benefit of dabigatran over VKA was most evident in patients with the lowest quartile of TTR, while those in the highest quartile of TTR did not demonstrate a difference between the groups.[42] This was not evident with the direct Xa inhibitors rivaroxaban and apixaban. In both the ROCKET AF and ARISTOTLE trials, there was no correlation between the quartiles of TTR and efficacy and safety.[43,44] Therefore, the level of INR control did not impact the results of the trials, and the overall TTR should not be a factor when evaluating these trials.

The point of care INR monitoring device used in the ROCKET AF trial was recalled by the US FDA in December of 2014 after receiving almost 19,000 reports of malfunctions.[45] The device was found to report falsely low INR values for patients with anemia (hematocrit less than 30%), conditions associated with elevated fibrinogen levels (acute and chronic inflammatory conditions, severe infection, advanced cancer, or renal disease requiring dialysis), or patients bleeding or with unusual bruising.[46] The concern is that doses of warfarin could have been unnecessarily increased, putting these patients at higher risk of bleeding and making rivaroxaban appear safer than it really was.

Of the total safety population of the ROCKET AF trial (n=14,236) 37% of patients had at least one of the conditions mentioned in the device recall.[47] Therefore, the ROCKET AF investigators re-evaluated the data from the trial based on the presence or absence of one of these conditions to assess if patients with one of these conditions had an exaggerated safety response to rivaroxaban compared to warfarin. For major bleeding, the HR for all patients was 1.04 and was 1.18 for patients with any one of the recall conditions.[47] The results for ICH was similar, with a HR of 0.67 for all patients and 1.03 for those with any one of the recall conditions. If the device had led to unnecessary increases in warfarin dosing, then the HRs for the patients with any one of the recall conditions should have been lower than the overall study. That was not the case for any of the bleeding outcomes in the trial.[47] The European Medicines Agency has since concluded that "There is sufficient evidence to conclude that the benefit/risk balance remains unchanged and favourable for treatment with rivaroxaban in the prevention of thromboembolism in non-valvular atrial fibrillation".[48]

As mentioned above, the benefit of all of the DOACs compared to warfarin is a significant reduction in hemorrhagic stroke, which is counted as an efficacy and safety outcome in all of trials. When evaluating overall major bleeding, it is important to understand that the trials calculated the outcome of major bleeding over different periods of time. Apixaban and either dose of edoxaban significantly reduced major bleeding rates compared to warfarin, whereas rivaroxaban and dabigatran demonstrated similar rates of major bleeding compared to warfarin (Table 3). While this may be due to truly better safety with apixaban and edoxaban, it may also be due to how bleeding events were accrued. In the ARISTOTLE and ENGAGE-AF trials, bleeding events were only included if they occurred 2 or 3 days, respectively, after last dose.[13,14] In the RE-LY and ROCKET-AF trials, bleeding events were recorded over the duration of the study for both dabigatran and rivaroxaban.[11,12] Therefore, there is reason to question if there is truly a difference between the agents, or once again, is this more an issue of trial design.

Based on the controversies discussed here, it seems difficult to suggest that one agent has a defined benefit in efficacy or safely over another in patients with NVAF. Therefore, a collective review of these data as a class of agents may be most appropriate. A meta-analysis of all 71,683 participants in the RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF trials compared DOACs to warfarin.[8] Stroke or SEE were reduced by 19% by DOACs compared with warfarin (RR 0.81, 95% CI, 0.73 – 0.91; p <0.0001). DOACs significantly reduced all-cause mortality (RR 0.90, 95% CI, 0.85 – 0.95; p = 0.0003) and intracranial hemorrhage (RR 0.48, 95% CI, 0.39 – 0.59; p <0.0001), but increased gastrointestinal bleeding (RR 1.25, 95% CI, 1.01 – 1.55; p = 0.04).[8] Finally, in an analysis of the net clinical benefit of the DOACs compared to warfarin based on the phase 3 clinical trials, each of the drugs evaluated had a favorable net clinical benefit in comparison to warfarin.[49] All four DOACs had significant net clinical benefit for the composite of disabling stroke plus life

threatening bleeding.[49]

Conclusions

Current guidelines for the management of AF from the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) recommend DOACs or warfarin for reduction of risk of thromboembolism in NVAF patients with a CHA_2DS_2-VASc score ≥2, with consideration of risk of stroke, risk of bleeding, and patient preferences.[50] These guidelines recommend a DOAC over warfarin only for patients who have difficult to manage INRs. In addition, the European Society of Cardiology ESC recommends that a DOAC be selected rather than a dose-adjusted VKA for most patients when oral anticoagulation is recommended.[51] This recommendation is based on the consistent reduction in hemorrhagic stroke demonstrated with all DOACs compared to therapy with a VKA.

When selecting a DOAC for reducing the risk of stroke in patients with NVAF, it is critical that clinicians have an in-depth understanding of the trial design, patient populations, and statistical evaluations. Based on existing data, it does not seem justified to claim that any agent has an efficacy or safety benefit compared to another. There are other individual patient factors to consider including risk factors, tolerability, patient preference, potential for drug interaction, and other clinical characteristics that may help with agent selection. Otherwise, only future prospective head-to-head clinical trials will answer this question.

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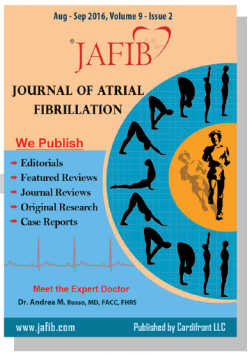

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A Comparison Between NOACs and Warfarin on Time to Elective Cardioversion

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Abstract

Cardioversion of atrial fibrillation is a procedure that has been commonly performed for over half a century. There is known to be an elevated risk of thromboembolism around the time of cardioversion, which has been shown to be drastically reduced with oral anticoagulation. The consistency of therapeutic anticoagulation in the weeks leading up to elective cardioversion is an important factor in the safety of the procedure. Until recently, the only option for oral anti-coagulation was Warfarin. The challenges of dosing Warfarin to achieve a therapeutic INR are well documented. In recent years, novel oral anticoagulant medications have been developed, which are thought to provide a consistent intensity of anticoagulation and do not require routine monitoring or dose adjustment. The purpose of this review is to examine the literature pertaining to a comparison of Warfarin versus novel oral anti-coagulants with respect to time of elective cardioversion.

Introduction

Atrial Fibrillation is the most common cardiac arrhythmia in the general population.[1] Cardioversion (electrical or pharmacological) is performed in patients with AF to restore sinus rhythm in the appropriate clinical setting.[2] Cardioversion was first performed and described in this population in the mid-1950s.[3] Cardioversion in patients with AF is associated with an increased risk (5-7%) of thromboembolic events without anticoagulation.[4] The risk of thromboembolism is magnified around the time of cardioversion, due to atrial stunning which occurs immediately post-cardioversion and persists for several weeks.[5,6] This peri-procedural stroke risk is reduced with the use of anticoagulant drugs prior to cardioversion. In one of the first studies (conducted during the mid-1960s) examining the effect of anticoagulation on thromboembolic episodes after electrical cardioversion, 437 patients were enrolled; 228 patients received anticoagulant therapy and 209 control patients did not. The atrial arrhythmia was successfully converted to sinus rhythm in 348 patients. Embolic episodes occurred in 2 patients (0.8 percent) in the anticoagulant group and in 11 patients (5.3 percent) in the control group. This difference was statistically significant. This early study paved the way for modern anti-coagulation guidelines pertaining to cardioversion of AF.[7]

Guidelines recommend that 3 weeks of therapeutic international normalized ratio (INR) are achieved before cardioversion; additionally, the oral anticoagulant should be continued for a minimum of 4 weeks post cardioversion.[1] The cut-offs of 3 weeks of anticoagulation prior to cardioversion and 4 weeks of anticoagulation post-cardioversion are based on data from non-randomized observational and retrospective studies; clinical guideline documents acknowledge the arbitrary nature of these cut-offs.[5,8] Importantly, cardioversion can be safely performed with less than 3 weeks of anticoagulation if guided by trans-esophageal echocardiography.[9]

Until recently, the only available oral anticoagulant was Warfarin. Over the past few years, newer anticoagulant drugs (NOACs) have been approved for prevention of stroke in patients with AF; these agents have all proved to be non-inferior to Warfarin with respect to rates of stroke and embolism. In the most recent ACC/AHA/HRS guidelines, anticoagulation with Dabigatran, Rivaroxaban or Apixaban at least 3 weeks before and 4 weeks after cardioversion is considered reasonable.(Class IIa – Level of evidence: C)[1]

In this review, we examine the evidence relating to the relative efficacy of NOACs compared to Warfarin with respect to the prevention of thromboembolism around the time of cardioversion.[10] We focus on the limited available data related to "time to cardioversion" comparisons between NOACs and Warfarin. The majority of the available literature regarding NOAC use in this regard focuses on Dabigatran.

Cardioversion and Dabigatran Efficacy

In a small single center study of the general efficacy of NOAC therapy prior to cardioversion in relatively low risk patients, a cohort of patients with a mean $CHADS_2$ score of 1.2±1.1 were treated with

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NOACs, Warfarin, Elective Cardioversion.

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None.

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Rivaroxaban or Dabigatran prior to DCCV. Average anticoagulant treatment time pre-cardioversion was 38±9 days. Roughly 20% of patients underwent TEE prior to DCCV. Of the 30 patients that were treated with Dabigatran, no patients experienced any adverse clinical neurologic events or major bleeding events at 60 days post-cardioversion.[11]

The safety of using Dabigatran in converting persistent atrial arrhythmias to sinus rhythm without transesophageal echocardiography was studied by Cozma et al; 82 patients (of which 45 had persistent atrial fibrillation and 37 had atrial flutter) were included. Dabigatran was used for 3 weeks before and 6 months after cardioversion. Mean age was 63.1±10.4 years. Forty-nine patients underwent uncomplicated electric cardioversion and 11 patients were pharmacologically cardioverted. The mean CHA_2DS_2-VASc score was 3.0 ± 1.4. No major cardiac or neurologic events occurred during the follow up period of 19.4 ± 9.5 months.[12]

Dabigatran and Time to Cardioversion

A post hoc analysis of the landmark RE-LY trial was performed with special focus on cardioversion. A total of 1983 cardioversions performed in 1270 patients were considered (647 on Dabigatran 110mg BID, 672 on Dabigatran 150mg BID and 664 on Warfarin). Cardioversions performed on protocol assigned drug taken for more than 3 weeks were 76.4% in the D110 group, 79.2% in the D150 group, and 85.5% in the Warfarin group. Such "delays" in cardioversion were statistically more frequent in the Warfarin group; however, it should be noted that the rate of TEE-guided cardioversion was higher in the Dabigatran group (25.5% in D110, 24.1% in D150 and 13.3% in Warfarin). Stroke and systemic embolism rates at 30 days were 0.8%, 0.3% and 0.6% in the D110 group, the D150 group, and the Warfarin group respectively (these differences were not statistically significant); there was no significant difference in thromboembolic event rate in patients with and without transesophageal echocardiography.[13]

In a retrospective analysis, the adequacy of 1 month of Dabigatran therapy prior to cardioversion in preventing thromboembolic episodes was studied in 631 patients. Of the cohort, 570 were oral anticoagulant naïve when Dabigatran was initiated. A Warfarin control group consisted of 166 patients. The mean age was 64.2± 11.2 and the majority of patients were male (68.4%). The average CHA_2DS_2-VASc score was 2.0 ± 1.5 and the mean creatinine was 88.1± 32.4mL/min. The dose of Dabigatran was 150mg BID. In the Warfarin control group, the mean age was 71 and the average CHA_2DS_2-VASc score was 2.5. A total of 705 cardioversions were performed; 121 patients underwent more than one cardioversion. The median time from initiation of Dabigatran to first cardioversion was 32 days. Sinus rhythm was established in 91.1 % after cardioversion. In the Warfarin control group, 166 patients underwent 172 cardioversions. The median time from initiation of Warfarin to first cardioversion was 74 days. In the 570 patients who were anticoagulant naïve, there were three events of thromboembolism within 30 days after cardioversion, an incidence of 0.53%. In the Warfarin comparison group, one transient ischemic attack occurred within 30 days, an incidence of 0.60%.[14]

Anticoagulant naïve patients with a first time discharge diagnosis of non valvular atrial fibrillation and plans for elective cardioversion on anticoagulation were included in a study using data from the nationwide Danish registries. Authors compared the proportion of patients undergoing cardioversion within the first 4 weeks of starting anticoagulation on Warfarin versus Dabigatran. In this study, a composite end point of stroke, major bleeding and death within 30 weeks after cardioversion was employed. A total of 1230 patients were included with 37% in the Dabigatran group (n=456) and 63% in the Warfarin group (n=774). The study population consisted of mostly men. Of note, patients prescribed Warfarin were slightly older and had a higher prevalence of chronic heart failure (D 11.0% vs W 19.1%, p<0.001), ischemic heart disease (D 8.3% vs W 13.8%, p = 0.005), and hypertension (D 63.8% vs W 70.5%, p = 0.017). The median time to cardioversion was 4 weeks (IQR 2.9-6.5) in the Dabigatran group and 6.9 weeks (IQR 3.9-12.1) in the Warfarin group. The adjusted odds ratio of cardioversion within the first 4 weeks was 2.3 (95% CI 1.7-3.1, p<0.005) in favor of Dabigatran treatment. TEE was performed prior to cardioversion in 6% of patients in the Dabigatran group and 5% of patients in the Warfarin group. The composite endpoint of stroke, major bleeding or death within 30 weeks after cardioversion occurred in 3 patients (0.7%: bleed 0, stroke 1, death 2) in the Dabigatran group and in 13 patients (1.4%: bleed 0, stroke 1, death 12) in the Warfarin group. The time dependent Cox regression analysis found a non-significant difference [hazard ratio 1.33; 95% CI 0.33 to 5.42) for the composite endpoint in the Warfarin group compared to the Dabigatran group.[15]

Dabigatran Dosing

There have been case reports of thromboembolic episodes after cardioversion of patients taking inappropriate doses of uninterrupted Dabigatran. A recently published case report described a 66 year-old male taking the 110mg BID dose of Dabigatran for new onset atrial fibrillation experiencing a ST elevation myocardial infarction from a thromboembolic coronary occlusion 48 hours after elective DCCV. The patient had been on Dabigatran for 23 days prior to cardioversion. This patient was on a lower dose of Dabigatran (110mg, not approved for use in US) despite his young age and normal renal function.[16]

In a retrospective survey of the incidence and fate of left atrial thrombus during Dabigatran therapy in patients with AF, a total of 198 patients underwent TEE to rule out the presence of left atrial thrombus before cardioversion. Dabigatran 150mg BID and 110mg BID were given to 98 and 100 patients respectively. Dabigatran was administered for <3 weeks in 21%, for 3-6 weeks in 24% and for ≥ 6 weeks in 55% of patients prior to TEE. Left atrial thrombus was found in eight patients (4%); these individuals tended to be older, had higher $CHADS_2$ score and had a higher prevalence of prior stroke or transient ischemic attack. One patient had been on Dabigatran 150mg BID for ≥ 3 weeks while the remaining seven were on 110mg BID. A second TEE was performed in six of the eight patients; these studies revealed complete resolution of the thrombus in five patients with the earliest resolution within 23 days after the first TEE. Of these five patients, one was receiving a prolonged 150mg BID dose, two had an increase in dosage from 110mg to 150mg BID and the remaining two were switched to Warfarin. Two patients (1%) had a stroke at days 3 and 15 after cardioversion while on Dabigatran 110mg BID, despite the fact that LA thrombus was not detected before cardioversion.[17]

Rivaroxaban and Apixaban – Efficacy and Time to Cardioversion

In the X-VeRT trial , an exploratory prospective randomized trial in patients undergoing elective cardioversion,1504 patients

were assigned to Rivaroxaban or VKA therapy in a 2:1 ratio; 1002 patients were assigned to Rivaroxaban and 502 to VKA. Patients were scheduled to undergo early (1-5 days) or delayed (21-25 days) cardioversion. TEE was performed in 564 of 872 (Rivaroxaban: 377; VKA:187) patients scheduled to undergo early cardioversion and in 64 of 632 (Rivaroxaban:33; VKA:31) patients scheduled for delayed cardioversion. The decision to perform a TEE and the timing of TEE was at the investigator's discretion, but the intention to perform a TEE was declared before randomization. The primary efficacy outcome (which included composite of stroke, TIA, peripheral embolism, MI and cardiovascular death) occurred in 5 of 978 patients (0.51%) in the Rivaroxaban group and in 5 of 492 patients (1.02%) in the VKA group (risk ratio 0.50; 95% CI 0.15 – 1.73). The primary safety outcome was major bleeding, which occurred in 6 patients (0.6%) in the Rivaroxaban group and 4 patients (0.8%) in the VKA group (RR 0.76; 95% CI 0.21-2.67). The patients randomized to the early cardioversion arm had a target of receiving cardioversion within 5 days of enrollment; the target for patients in the delayed cardioversion arm was 21-25 day post enrollment. In the delayed group (where most patients did not have a TEE), Rivaroxaban was associated with a significantly shorter time to cardioversion compared with VKAs (median 22 days vs. 30 days; P<0.001).[18,19]

Other published work supports the assertion that Rivaroxaban is safe and effective for use in patients with AF prior to cardioversion.[11]

There is limited data available comparing Apixaban to VKAs prior to cardioversion. In a comparison of 743 cardioversions in 540 patients (265 on Apixaban and 275 on Warfarin) from the ARISTOTLE trial, no stroke or systemic emboli occurred in the 30-day follow up period. Major bleeding occurred in 1 patient (0.2%) receiving Warfarin and 2 patients receiving Apixaban (0.6%).20

Summary

Though there are no prospective randomized controlled trials comparing the efficacy of anticoagulation and time to cardioversion with Dabigatran compared to Warfarin, it appears from the above evidence that anticoagulation with Dabigatran for at least 3 weeks prior to cardioversion is associated with similar thromboembolic risks as compared to Warfarin.[2,10] The pharmacology of Dabigatran, allowing for therapeutic anticoagulation 2 hours after the first dose, would explain the shorter times from anticoagulant initiation to cardioversion noted with Dabigatran as compared to Warfarin, which requires the achievement of a therapeutic INR with subsequent maintenance in the therapeutic range for 3-4 consecutive weeks. It should be noted that left atrial thrombus has been noted in patients on reduced doses of Dabigatran and a TEE prior to cardioversion might be reasonable in these patients. Furthermore, inappropriate dose reduction of Dabigatran is well described in the literature and may be a risk factor for thromboembolism.

The newer NOACs (Rivaroxaban, Apixaban, and Edoxaban) have limited data with respect to safety/efficacy related to the cardioversion of AF. Data is even more sparse regarding time from initiation of these medications to cardioversion. Existing data suggest that the use of Rivaroxaban and Apixaban peri-cardioversion is safe and that Rivaroxaban is associated with shorter times to cardioversion than Warfarin, particularly when TEE guidance is not used.

A prospective randomized trial comparing cardioversion with Edoxaban versus Warfarin – the ENSURE-AF study – is currently underway.[21]

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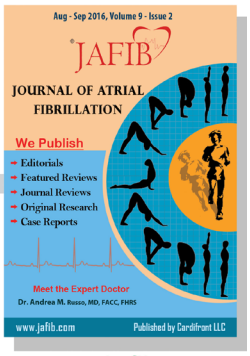

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Search For The Ideal Antithrombotic Drug: Utopian Task Likely Is Implemented Already

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Abstract

Atrial fibrillation is the most prevalent cardiac arrhythmia with a high risk of ischemic stroke. Thromboprophylaxis plays a key role in prevention of cardioembolic and non-cardioembolic events. Oral antithrombotic drugs are most often used to reduce hypercoagulable state. Patients may suffer from both under- and overtreatment compromising the outcomes. Medication peculiarities at large are well-known and widely debated. Non-adherence to antithrombotic drug regimen poses a significant risk of stroke. There is a pressing need for more detailed delineation of risk factors, namely by incorporation of the letter "N" (meaning "Non-adherence to drug therapy") into the well-known risk score alphanumeric display: CHA2DS2N-VASc. Better delineation of risk factors related to antithrombotic treatment as well as those related to treatment for congestive heart failure, hypertension, diabetes are desirable. Similarly, the bleeding risk score formula HAS-BLED might be improved by an additional risk factor, marked as the symbol "E", meaning "Excessive antithrombotic dosing" i.e. HAS-BLEDE. Improved formulas would help raise the predictive scores value and awareness for clinicians facing the problem of non-adherence to treatment regimen. If patients properly followed the prescribed drug therapy regimen it would potentially reveal that we already have ideal or near ideal antithrombotic drug(s). These drugs, herein non-specified, are widely used, but due to non-adherence they are not categorized as the best ones. That is why considerable efforts are focused on continued research and new developments.

Introduction

Atrial fibrillation (AF) affects millions of people worldwide and is one of the most common causes of stroke.[1,2] Up to 15-30% of ischemic strokes are caused by cardiac sources of emboli being associated with poor prognosis.[3] Non-paroxysmal AF is associated with a highly significant increase in thromboembolism and death.[4,5] Ischemic stroke is a heterogeneous entity with diverse causes, including lacunar infarction, cerebrovascular stenosis, and emboli of sundry types, including fat, air, atheromata, septic vegetations, and calcific debris from left-sided heart valves in addition to thromboemboli originating from variety of sources.[6,7]

Thromboprophylaxis with oral anticoagulants is the mainstay for stroke prevention, reducing the annual incidence of stroke in AF patients by more than 60%.[8] Some studies have shown that for people with AF and previous transient ischemic attack, anticoagulant use can reduce recurrent stroke by two-thirds, and all vascular events can be reduced by one-half.[9] Long-term ischemic stroke risk however, coexists in this group of patients. Thromboembolic complications are not fully preventable even by careful protection of double, triple or multiple drug therapy.[10] Any intense antithrombotic therapy, however, generates bleeding complications. Nevertheless, favorable, acceptable and even excellent clinical results might be achieved by old/conventional or novel drug therapy. In this regard collaboration and discipline from patients is much needed. We have noticed that irregular intake of antithrombotic drugs is often accompanied by the impairment of clinical outcomes in patients with AF or with other risks of ischemic events. Many patients are prone to empirical approach and to their own motivation on dosage. In general, adherence to long-term therapies in any chronic disease is poor.[11] That is why we focus on a newly emerged clinical problem medication non-adherence being associated with undue risk of clinical or subclinical ischemic events and/or hemorrhage. It deserves attention, starting by its proper identification, or in the words of Bosworth and colleagues[12] – a call for action!

Key Words:
Atrial Fibrillation, Antithrombotic Therapy, Stroke, Bleeding Complications, Risk Score Acronym, Adherence, Non-Adherence.

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None.

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Requirements for Antithrombotic Medication

The ideal antithrombotic drug should inhibit thrombosis without affecting hemostasis.[13] In terms of practical drug development for an ideal anticoagulant Kunitada and colleagues[14] pointed out three minimum requirements – oral availability, minimum bleeding propensity, and a mechanism based on direct inhibition of an activated coagulation factor. There are a number of other requirements: drugs should possess a long half life, absorbed after oral administration, provide wide therapeutic range, high degree of safety and efficacy

profile, high tolerability, predictable antithrombotic effect, devoid of side effects or regular laboratory control, fixed regular dosage, low rate of bleeding complications, little or no interaction with plasma proteins, food and other drugs, prompt partial or complete reversibility as needed during and post interventional procedure and last but not the least comprise low cost.[4,13,15] Oral anticoagulants should prevent ischemic stroke in AF, especially among patients at moderate to high risk of thromboembolic events.[10,16,17] This goal might be achieved if drugs were used regularly as prescribed.

There are controversies associated with clinical use of various drugs – antithrombotics, antiplatelet agents and/or novel oral anticoagulants.[18-21] In this analysis we will not tackle the issue of establishing ratings of specific drug(s) or identifying ideal ones. It is very likely that we already have very effective antithrombotic(s). However, a large proportion of ischemic patients are still managed in a chaotic manner by their own "strategies". It hampers accurate determination of drug capabilities and the clinical efficacy of antithrombotic drugs. Further patient education might help discourage deviation from prescribed dosage of antithrombotics.

Quality of Treatment: Problems Related to Medication Non-Adherence

In order to establish an adequate preventive strategy it is crucial to identify the cause of the embolism.[3] After a complete diagnostic workup up to 30% of strokes remain with undetermined cause, and most of them are attributed to an embolic mechanism suggesting a cardiac origin.[22]

According to Cate and other clinicians[23,24] non-adherence to medication is a potential threat to the safe use of oral anticoagulants. Consensus is that with cardiovascular medication for chronic use the non-adherence rate adds up to 50%, translating to about 125,000 deaths in the USA annually.[12,25] There are reports which postulate that as many as 40% of patients still do not adhere to their treatment regimens.[26,27] Almost 50% of chronically ill patients do not take their medication as regularly as prescribed even though it is obligatory for a successful medication therapy.[25,28] This makes non-adherence to medications one of the largest and most expensive disease categories.[29] Recently Kim and colleagues[30] have stated that a substantial proportion of patients with AF are not treated optimally including inappropriateness of antithrombotic use, especially before stroke.

Stroke patients are potentially at high risk for medication non-persistence because they require long-term therapy, are more likely to have cognitive or physical impairments, and are often depressed.[31] Obviously, we face age-related behavioral peculiarities – forgetfulness, ignorance, indifference, empirical/intuitive self-dose readjustment etc. In the absence of certain symptoms and of reason for patients' motivation, adherence drops and this may occur with novel oral anticoagulant therapy, where symptoms are absent, most apparently in AF patients.[23] It can be expected that in the management of novel anticoagulants non-adherence may reach comparable figures (± 50%) if no measures to boost adherence are being taken.[23] Our unpublished data show that this phenomenon merits further investigation.

Adherence (compliance) is the degree to which a patient follows a treatment regimen;[32] adherence requires that the prescription is obtained promptly and the drug is taken as prescribed in terms of dose, dosing interval and duration of treatment. However, only about half the people who leave a doctor's office with a prescription take the drug as directed.[32] Factors for non-adherence can be categorized into 3 major groups: socioeconomic, communication-related, and motivational.[33] Bosworth et al.[12] have indicated that multifactorial basis for non-adherence calls for multifaceted solution.

The problem of poor patient adherence has been extensively researched, but the rates of non-adherences have not changed much in the past 3 decades.[29] The AF Investigators found that, despite appropriately prescribed, and one in the three was not taking any anticoagulants at all at the time of their stroke.[34] AF patients deliberately, carelessly or occasionally fail to protect themselves from serious complications. The propensity to ignore doctor's instructions leads to the impairment of quality of treatment.

Recently Ullman[24] has stressed that adherence in AF falls into two categories. The first is physician adherence to published guidelines while the other one is the rigor with which patients follow their prescribed treatment. A noteworthy fact is that healthcare providers play a unique and important role in assisting patients' healthy behavior changes.[29] As with physician non-adherence to guidelines, patient non-adherence to treatment increases morbidity, mortality and health care costs.[34] Obviously the physicians and pharmacists deal with uncertainty from this point of view. That is why serious antithrombotic therapy strategies are compromised. Although the strategies to enhance patient adherence exist in the literature, they are often too complex and not practicable for busy practicing physicians.[29]

Uncertainty remains over optimal antithrombotic treatment of patients with AF.[35] There are two major hurdles to achieve absolute clinical efficacy: thrombosis/thrombembolism, and hemorrhage. In rare cases it can also be drug intolerability. Real practice however differs from clinical trials and from anticoagulation clinics also from the safety point of view;[18] discrepancies in clinical outcomes are elucidated with investigations of antithrombotic efficacy under strict medical control. The rate of major bleeding, for example, in real life was more than double than that reported in anticoagulation clinics.[19,20] Such outcomes are attributed to iatrogenic and patient-dependent reasons.

More recent studies have shown, that appropriate anticoagulation rates of high risk patients as high as 80% are attainable.[36] Hypothetically clinicians already do have optimal (if not ideal) antithrombotic drug(s) likely enabling full control of the clinical entity. Difficulty in estimation of drug efficacy incorporates the uncertainty of whether the ischemic complication occurs due to under-treatment or due to an atherothrombotic event. Secondly and most importantly, both ischemic and bleeding complications may take place due to under-treatment and over-treatment: it depends largely on patients' behavioral peculiarities. "Medicine won't work if you don't take them" – a statement of the World Health Organization (WHO, 2003) related to the medication adherence.[37] That is why patients do not achieve maximum clinical benefit.[25] Such cases underscore the benefit of antithrombotic drugs while at the same time question their efficacy.

When choosing the appropriate therapeutic approach, it is relevant to balance the degree of ischemic protection provided by antithrombotic therapy with the "iatrogenic" bleeding risk.[38] The use of warfarin, antiplatelets, novel anticoagulants, double and triple therapy (dual antiplatelet plus anticoagulant) are widely discussed.[10,18,38] Nevertheless, the abovementioned risks persist. Cate in 2013[23] has stressed that adherence should become a major topic

of discussion; policy makers, consumers, physicians and insurers should take their responsibility and start discussing the options for maximizing adherence, preferably in a patient centered manner.

Considerations According to Supplementation of Risk Factors in Acronymic Scheme CHA_2DS_2-VASc

AF confers an excess risk of stroke, but this risk is not homogeneous, and depends on the presence or absence of various risk factors.[39] Some of these factors were properly selected, compacted and declared in 2001.[38,40] The CHA_2DS_2-VASc score (Congestive heart failure, Hypertension, Age ≥ 75 years [Doubled], Diabetes, Stroke/transient ischemic attack/thromboembolism [Doubled], Vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plaque], Age 65-75 years, sex category [female]) is used clinically for stroke risk stratification in AF.[41]

Since 2001 an initial risk scoring system $CHADS_2$[39] underwent evolution. Currently adopted risk score formula CHA_2DS_2-VASc might be supplemented by an indication of non-adherence to antithrombotic drug regimen as follows: CHA_2DS_2N-VASc, where "N" means "Non-adherence" risk factor. Better delineation of risk factors related to antithrombotic treatment as well as those related to treatment for congestive heart failure, hypertension, diabetes are desirable. The symbol "N" actually reflects both physician (care provider) and patient adherence to given guidelines. Thus, both parties share the responsibility of lege artis therapy.

The additional risk factor incorporated into the formula potentially contributes to more accurate stroke risk stratification and more effective stroke prevention. "N" risk factor emerges when drug treatment is initiated and established. Last but not least, this new ingredient will likely allow to better identify risk criteria (low/moderate/high) in AF patients. Finally, the eligibility of "N" risk factor in the risk score stratification scheme is open for discussion.

Overanticoagulation-Related Risk

Many risk factors for stroke are also risk factors for bleeding on oral anticoagulation.[42] Currently, clinical scores for bleeding risk estimation are much less well validated than stroke risk scales.[43] Singer et al.[44] have provided quantitative assessments of the net clinical benefit of warfarin anticoagulation among patients with AF; by comparison of outcomes of intracranial hemorrhage and AF-related ischemic stroke they weighted intracaranial hemorrhage being 50% worse than ischemic stroke. In general, overanticoagulation is considered to be an alarming clinical problem.

Importantly, risk factors for bleeding include patient-related and treatment-related factors.[45] Patient-related factors include age, previous episodes of bleeding, anemia (hematocrit less than 30%), hypertension, heart disease, cerebrovascular disease, history of gastrointestinal hemorrhage, active peptic ulcer or liver disease, recent or imminent surgery, trauma, excessive alcohol intake, unreliability, frequent or significant anti-inflammatory (NSAIDs), and use of other medication or natural remedies.[16,45] Hylek and colleagues[46] have declared that 26% of patients stopped warfarin within the first year, mostly due to perceived safety issues. Reportedly, treatment related factors are as follows: duration, intensity and variability of warfarin treatment, concomitant use of aspirin, and support patients received from their providers and home environments.[10,19,45]

On the basis of a nationwide cohort study Lamberts and co-authors[35] have declared their main finding – an immediate high risk of bleeding with recommended triple therapy; the risk was continually elevated in comparison with less intense antithrombotic regimens. They also added that triple therapy has no safe therapeutic window. Hemorrhagic risk however should not prevent antithrombotic drug prescription but should focus medical attention on the patient.[18]

Some selective and most important risk factors were incorporated into the bleeding risk stratification acronym HAS-BLED.[42] HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile International Normalized Ratio, Elderly, Drugs/alcohol concomitantly) bleeding risk schema has been proposed as a simple, easy calculation to assess bleeding risk in AF patients, whereby some caution and regular review of the patient is needed, following the initiation of antithrombotic therapy, whether with oral anticoagulation or antiplatelet therapy.[47] Wan and colleagues[48] have emphasized that bleeding risk is multifactorial and also intimately related to quality of anticoagulation control.

Enhancement of the HAS-BLED scheme by the involvement of supplementary bleeding risk factor is highly desirable. The definition "excessive antithrombotic dosing", marked by symbol "E" potentially might represent this relevant clinical problem. Thus, the modified acronym reflecting unduly designed and/or implemented therapy might be delineated as follows: HAS-BLEDE with an assumed one additional risk score. It could indicate an enhanced vigilance to ill-performed antithrombotic therapy and clinical threats. Again, both parties, i.e. the physician (health professional) and the patient take on the responsibility of lege artis therapy. Eventually, consensus on a proposal could be attained and validated.

If the patients were precisely following the prescribed well-designed therapy regimen it would perhaps reveal that we already have ideal or near ideal antithrombotic drug or drugs. These drugs likely are widely used, but due to non-adherence/non-compliance they are not categorized as the best ones. That is why the research and new developments continue.

Conclusions

Antithrombotic therapy in AF patients in respect to stroke prevention is considered to be an important strategic approach. Some inadequacies and poor compliance to medication or medical instructions are trailed; this conceals the real antithrombotic efficacy and clinical outcomes of patients, suffering from atrial fibrillation and ischemic stroke threats. More effective prevention of ischemic events may be reached by the careful use of antithrombotic drugs currently available. An overall estimation of their efficacy is limited and hampered by non-adherence to medication. This suggests the need for the incorporation of an additional risk factor "N" (meaning "Non-adherence to medication") into the alphanumeric risk score system, i.e. CHA_2DS_2N-VASc. This will increase the visibility of existing risk factor and allow to achieve better clinical results. Similarly, bleeding risk score formula might be enriched by the symbol "E" (meaning "Excessive antithrombotic dosing"), i.e. HAS-BLEDE. Improved formulas should raise the predictive scores value and awareness for clinicians facing the problem of non-adherence to treatment regimen. The value and clinical applicability of new alphanumeric developments are to be debated. Further efforts are required to minimize the risks of AF treatment preferably by more accurate adherence to medication.

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Brugada Syndrome:Risk Stratification And Management

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Abstract

The Brugada syndrome (BrS) is an arrhythmogenic disease associated with an increased risk of ventricular fibrillation and sudden cardiac death. The risk stratification and management of BrS patients, particularly of asymptomatic ones, still remains challenging. A previous history of aborted sudden cardiac death or arrhythmic syncope in the presence of spontaneous type 1 ECG pattern of BrS phenotype appear to be the most reliable predictors of future arrhythmic events. Several other ECG parameters have been proposed for risk stratification. Among these ECG markers, QRS-fragmentation appears very promising. Although the value of electrophysiological study still remains controversial, it appears to add important information on risk stratification, particularly when incorporated in multiparametric scores in combination with other known risk factors. The present review article provides an update on the pathophysiology, risk stratification and management of patients with BrS.

Introduction

The Brugada syndrome (BrS) is an inherited arrhythmogenic disease characterized by ST-segment elevation in right precordial leads on surface electrocardiogram (ECG), the absence of overt structural heart disease, and an increased risk of ventricular fibrillation (VF) and sudden cardiac death (SCD).[1-5] There is increasing evidence suggesting that mild structural abnormalities seen in the right ventricular outflow tract provide the arrhythmia substrate in BrS.[2,6,7] The BrS is definitively diagnosed when a type 1 ST-segment elevation (coved type) ≥2 mm is observed either spontaneously or after intravenous administration of a sodium channel blocking agent (ajmaline, flecainide, procainamide or pilsicainide) in at least one right precordial lead (V1 and V2), which are placed in a standard or a superior position (up to the 2nd intercostal space).[8] The BrS is a genetically heterogeneous channelopathy. Up to now, mutations in 19 genes have been identified in subjects with BrS phenotype.[4] These mutations cause either a decrease in inward sodium or calcium current or an increase in outward potassium currents resulting in an outward shift in the balance of current active during the early phases of the action potential.[4]

The BrS typically manifests with cardiac arrest or syncope, occurring in the third and fourth decade of life.[3-5] The majority of BrS patients are asymptomatic, usually diagnosed incidentally. The risk stratification of BrS patients, and particularly of asymptomatic ones, still remains challenging. Currently, subjects with spontaneous type 1 ECG pattern and aborted SCD or syncope of arrhythmic origin are at highest risk for future arrhythmic events, and are advised to receive an the implantable cardioverter defibrillator (ICD).[3-5] Emerging evidence clearly underscore our inability to stratify patients with BrS.[9] Several markers has been proposed for risk stratification, but the majority of them have not been tested in a prospective manner. The present study focus on current risk stratification markers as well as on the management of high risk BrS patients.

Risk Stratification Of Individuals With Brugada Syndrome

It is widely accepted that symptomatic BrS patients are at increased risk for future events.[4,5] However, in a post-mortem study, the majority of SCDs related to BrS occurred in asymptomatic individuals (72%). Based on the Second Expert Consensus Conference on BrS,[3] 68% of this population would have been categorized as low risk.9 Asymptomatic BrS patients display an annual event rate of arrhythmic events between 0.5 and 1%.[10-12] This event will occur in about 50% of cases as VF without any warning symptoms.[13] Although, it is currently impossible to estimate the evolution of arrhythmic risk

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Brugada Syndrome, Risk Stratification, Electrophysiological Study, Sudden Cardiac Death.

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over time, assuming an annual event rate of 1%, a 10% event rate at 10-year follow-up in otherwise healthy patients is extremely high. Proper risk stratification of BrS patients, particularly of asymptomatic ones, is therefore of paramount importance. Several clinical, echocardiographic, electrocardiographic and electrophysiological markers have been proposed as risk stratifiers (figure 1).

Clinical Markers

A history of aborted SCD has been consistently associated with the highest risk of future arrhythmic events in all studies, and thus has a major prognostic impact.[10-12,14-20] In a recent meta-analysis, the incidence of arrhythmic events (sustained ventricular arrhythmia or appropriate ICD therapy or SCD) was 13.5% per year in patients with a history of SCD, 3.2% per year in patients with syncope and 1% per year in asymptomatic patients.[21] The arrhythmic risk among patients with a history of aborted SCD is 35% at 4 years,[10,15] 44% at 7 years,[12] and 48% at 10 years.[21]

A history of syncope has been associated with an increased incidence of future arrhythmic events in several studies, including a meta-analysis.[10,11,14,16-23] However, Priori's group have initially demonstrated that the association of syncope and spontaneous ST-segment elevation has the best predictive value to identify individuals at high risk, and not a history of syncope as a single risk factor.[24] Kamakura et al. showed that patients presenting with aborted SCD had a grim prognosis, while those presenting with syncope or no symptoms had an excellent prognosis irrespective of their ECG pattern.[15] Conte et al. from P. Brugada's group have recently demonstrated that patients with a history of syncope display a similar clinical course with asymptomatic ones. In particular, 11% of patients with syncope and 13% of asymptomatic subjects received appropriate shocks during a long term follow-up period of 83.8 ± 57.3 months.[12] This inconsistency possibly reflects our difficulty to differentiate arrhythmic from neurally-mediated syncope. A high incidence of neurally-mediated susceptibility in asymptomatic individuals with BrS ECG pattern has been previously shown.[25] In Conte's study, after ICD placement, 21 patients (11.9%) experienced episodes of syncope. Of them, 5 patients had neurally-mediated syncope. In 8 patients with recurrent syncope after ICD implantation, the rate of ventricular pacing was <1%, and no ventricular arrhythmias were detected.[25] This possibly explains why some patients with a previous history of undetermined syncope display an excellent prognosis.

The majority of large studies on BrS have demonstrated that a family history of SCD is not predictive of future arrhythmic events.[10,12,24,26] In the largest registry, a family history of SCD was not predictive of arrhythmic events in either symptomatic (3.3% vs. 3.0%) or asymptomatic patients (0.5% vs. 0.6%).[10] On the contrary, Kamakura et al. have demonstrated that a family history of SCD occurring at age <45 years is an independent risk factor of poor prognosis irrespective of ECG type. Delise et al. have shown that family history of SCD may be of prognostic significance only in combination with other risk factors.[17]

In a previous meta-analysis accumulating data on 1.545 patients, male gender has been associated with a malignant clinical course.[20] In FINGER registry, male gender tended to be associated with a shorter time to first event, but this difference did not reach statistical significance (mean event rate per year, 3.0% for men versus 0.9% for women).[10] Similarly, in Conte's study, males displayed a near 3-fold higher risk for appropriate shocks during follow-up.[12] Data from S. Priori's group showed that there is a non-significant excess of events in males (13%) as opposed to females (9%).[24] These data suggest that females with BrS ECG pattern should not be regarded as a low risk group.

The prevalence of atrial fibrillation in BrS patients is higher than in the general population of the same age. In a large study of 560 BrS patients, 48 (9%) had atrial fibrillation/flutter.[18] In 176 BrS patients with an ICD, 18% of patients developed paroxysmal AF during a long-term follow-up period of 83.8 ± 57.3 months.[12] A higher incidence of atrial tachyarrhythmias (fibrillation/flutter) (24%) has been demonstrated in our BrS series.[27] Spontaneous atrial fibrillation has been associated with higher incidence of syncopal episodes (60.0% vs. 22.2%) and documented VF (40.0% vs. 14.3%). In patients with documented VF, higher incidence of spontaneous atrial fibrillation (30.8% vs. 10.0%, $p < 0.05$), atrial fibrillation induction (53.8% vs. 20.0%), and prolonged interatrial conduction time was observed.[28] Siera et al. have recently reported that asymptomatic BrS subjects with history of sinus node dysfunction display an 8-fold increased risk for future arrhythmic events.[29]

Genetic Markers

A genetic defect on the SCN5A gene has not been associated with a higher risk of future arrhythmic events in several studies, suggesting that genetic analysis is a useful diagnostic parameter but it is not helpful for risk stratification.[10-12,24,26]

Echocardiographic Markers

A reduced right ventricular ejection fraction and an increased right ventricular end-diastolic volume were independently associated with history of syncope or SCD at the time of diagnosis.[30] Using tissue velocity imaging, Van Malderen et al. have demonstrated that a previous history of malignant events is associated with prolonged right ventricular ejection delay.[31]

Electrocardiographic Markers

A spontaneous type 1 ECG pattern of BrS has been consistently associated with a worse outcome in large studies,[10-12] and thus should be considered as a malignant marker. A meta-analysis showed that individuals with spontaneous type 1 ECG features exhibit a 3- to 4-fold increased risk of events compared to those with a drug-induced ECG pattern.[20] We recently demonstrated that asymptomatic subjects with spontaneous type 1 ECG pattern of BrS exhibit a 3.5 higher risk of future arrhythmic events.[32] It is therefore

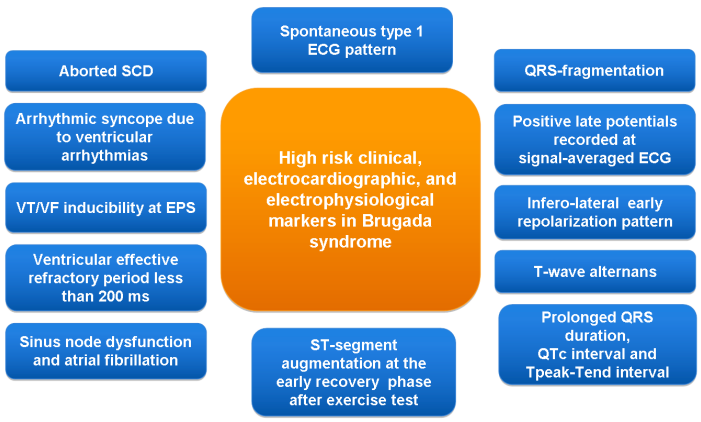

Figure 1: Clinical, electrocardiographic and electrophysiological markers proposed for risk stratification in BrS

very important to establish or not the presence of spontaneous type 1 ECG pattern in BrS patients. In patients with drug-induced type 1, spontaneous type 1 BrS can be more frequently detected with twelve lead Holter monitoring compared with conventional follow-up with periodic ECGs. Twelve lead Holter recording might avoid 20% of the pharmacological challenges with sodium channel blockers, which are not without risks, and should thus be considered as the first screening test, particularly in children or in the presence of borderline diagnostic basal ECG.[33]

Apart from the spontaneous type 1 ECG pattern, several other ECG parameters have been proposed for risk stratification of subjects with BrS phenotype. Among these ECG markers, QRS-fragmentation in twelve-lead ECG appears very promising. Morita et al. have initially demonstrated that QRS-fragmentation is more commonly seen in BrS patients with VF (85%) and syncope (50%) compared to asymptomatic ones (34%).[34] The PRELUDE study confirmed these findings and showed that QRS-fragmentation is an independent predictor of future arrhythmias.[11] Tokioka et al. have recently demonstrated that the presence of QRS-fragmentation lead to a 5-fold increase of arrhythmic events.[23] A prospective study using signal-averaged ECG suggested that positive late potentials may have predictive value of malignant arrhythmic events in BrS.[35] Ajiro et al. have showed that symptomatic subjects with BrS display significantly lower RMS40, longer LAS40, and longer filtered QRS duration compared to the asymptomatic ones.[36] The positive predictive value, negative predictive value, and predictive accuracy of late potentials were 92.0%, 78.9%, and 86.4%, respectively. Daily fluctuations in ECG and SAECG characteristics could be useful for distinguishing between high- and low-risk patients with BrS.[37]

First degree atrioventricular block has been independently associated with SCD or appropriate ICD therapies.[38] A prolonged QRS duration in leads II, V2 and V6[39,40] as well as a prolonged QTc interval >460 ms in lead V2[41] have been associated with life-threatening arrhythmic events in BrS. The Tpeak-Tend interval, a marker of transmural dispersion of repolarization, has been linked to malignant ventricular arrhythmias in various clinical settings including the BrS. Castro Hevia et al. were the first to link increased Tpeak-Tend interval as a risk factor in patients with BS.[41] Maury et al. has been recently demonstrated that the Tpeak-Tend interval from lead V1 to lead V4, the maximum value of the Tpeak-Tend interval, and the Tpeak-Tend interval dispersion in all precordial leads were significantly higher in symptomatic patients (aborted SCD, appropriate ICD therapy, syncope) than in asymptomatic patients. In multivariate analysis, a max Tpeak-Tend of >100 ms was independently related to arrhythmic events.[38] We have previously shown that the Tpeak-Tend interval and Tpeak-Tend interval/QT ratio were associated with VT/VF inducibility in BrS.[42] A more negative T-wave in lead V1 has been also associated with poor prognosis.[43] Finally, the appearance of T-wave alternans after pilsicainide administration was predictive for spontaneous VF.[44]

Masrur et al. performed a systematic review including 166 BrS patients undergoing exercise testing.[45] ST-segment augmentation was observed in 95 of 166 (57%) BrS patients. The ST augmentation occurred during early recovery after exercise in 93 Brugada patients, whereas 2 patients developed ST augmentation during the effort phase of exercise. Exercise unmasked the BrS ECG pattern in 5 patients. Three patients developed ventricular arrhythmias with exercise: 2 developed ventricular tachycardia, and 1 developed multiple ventricular extrasystoles. All 3 arrhythmias occurred during early recovery after exercise testing and resolved spontaneously. Makimoto et al. showed that ST-segment augmentation at early recovery was specific in BrS patients, and was significantly associated with a higher cardiac event rate, notably for patients with previous episode of syncope or for asymptomatic patients.[46] On the contrary, Amin et al. failed to show significant differences in the ECG variables and their changes during exercise between symptomatic (prior syncope) and asymptomatic (no prior syncope) BrS patients.[47]

An infero-lateral early repolarization pattern has been shown to be predictive of arrhythmic events.[47,49] Tokioka et al. have recently shown that the combination of QRS-fragmentation and early repolarization pattern enables the identification of high risk patients.[23] In a previous study, including 290 individuals with BrS, an early repolarization pattern manifested as notched or slurred J-point elevation mainly in lateral leads was observed in 35 subjects (12%). However, in this study, the presence of early repolarization pattern was not associated with arrhythmic events during follow-up.[50] Finally, the aVR sign, defined as R wave ≥0.3 mV or R/q ≥0.75 in lead aVR, has been associated arrhythmic events during follow-up.[51]

Electrophysiological Markers

Conflicting evidence exists on the prognostic value of electrophysiological study (EPS) in asymptomatic BS subjects. Previous studies have demonstrated an excellent negative predictive value of EPS.[17,52] On the contrary, in the PRELUDE registry, a negative EPS was not associated with a low risk of an arrhythmic event.11 Disagreement also exists regarding the positive predictive value of EPS. Data from the Brugada's series have shown that VT/VF inducibility is predictive for future events.[14,52,53] However, data from other studies do not support the use of EPS in risk stratification.[10,12,18,19]

Important data on the prognostic significance of EPS in BrS are coming from Pedro Brugada's group.[29] In their series, patients with VF inducibility presented a hazard ratio for events of 8.3. Event free survival for the non-inducible group was 99.0% at 1 year and 96.8% at 5, 10 and 15 years. Among the inducible patients it was 89.0% at 1 year, 78.4% at 5 years and 75.0% at 10 and 15 years. Among asymptomatic patients, those without EPS inducibility had an event free survival of 100.0% at 1 year, and 99.2% at 5, 10 and 15 years. Inducible subject's event free survival was 90.6% at 1 year and 79.5% at 5, 10 and 15 years. EPS inducibility was also significant for the asymptomatic subjects. Sensitivity of EPS for predicting arrhythmic events was 64.0% and specificity was 86.6%. Positive predictive value was 21.6% and negative predictive value 97.7%. If restricted to asymptomatic patients, these values increased to a sensitivity of 75.0% and a specificity of 91.3% and predictive values to 18.2% and 98.3% respectively.

Based on recent meta-analyses, EPS inducibility appears to have a prognostic role in risk stratification of BrS. Faucher et al. performed a meta-analysis of 13 studies evaluating the prognostic role of EPS in BrS patients according to clinical presentation.[21] In the whole population of BrS patients, VF inducibility was associated with a non significant higher risk of arrhythmic events during follow-up. However, induction of sustained ventricular arrhythmia was significantly and homogeneously associated with an increased risk of arrhythmic events during follow-up in patients with syncope (odds ratio of 3.30). Similarly, the asymptomatic patients with inducible

VF had an increased risk of arrhythmic events during follow-up (odds ratio of 4.62) with homogeneous results across the different studies. In Sroubek's et al. meta-analysis, VF induction was associated with cardiac events during follow-up with a hazard ratio of 2.66, with the greatest risk observed among those induced with single or double extrastimuli.[54] We have recently conducted a meta-analysis of 12 studies comprising 1,104 asymptomatic subjects with BrS who underwent EPS. During follow-up, arrhythmic events occurred in 3.3% of cases. Inducible ventricular arrhythmias at EPS were predictive of future arrhythmic events with an odds ratio of 3.5.[32]

VF inducibility by programmed electrical stimulation, abnormal restitution properties, and ventricular effective refractory period <200 ms.[11] Finally, EPS may establish the presence of sinus node dysfunction, clarify the cause of syncope or treat supraventricular arrhythmias that can mislead the diagnosis or eventually lead to inappropriate ICD therapies.

Multiparametric Risk Stratification Scores

The relationship of these markers and the usefulness of their combination have not been sufficiently examined. Brugada et al. have shown that patients with a spontaneously abnormal ECG, a previous history of syncope, and inducible sustained ventricular arrhythmias had a probability of 27.2% of suffering arrhythmic events during follow-up.[16] Similarly, Priori et al. have demonstrated that the combined presence of spontaneous type 1 ECG pattern and the history of syncope identifies subjects at risk of cardiac arrest.[24] In the same line, Delise et al. have recently proposed that subjects at highest risk are those with spontaneous type 1 ECG pattern and at least two additional risk factors (syncope, family history of SCD, or positive EPS).[17] Okamura et al. have shown that syncope, spontaneous type 1 ECG pattern, and inducible ventricular arrhythmias at EPS are important risk factors and the combination of these risks well stratify the risk of later arrhythmic events.[55] When dividing patients according to the number of these 3 risk factors present, patients with 2 or 3 risk factors experienced arrhythmic events more frequently than those with 0 or 1 risk factor.[55]

Management Of Patients With Brugada Syndrome

Based on 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD, ICD implantation is recommended in BrS patients with aborted SCD or with documented spontaneous sustained ventricular arrhythmias (Class I, LOE C).[8] ICD implantation should be considered in patients with a spontaneous diagnostic type 1 pattern and history of syncope (Class IIa, LOE C).[8] ICD implantation in BrS patients with inducible VF at EPS receives a weak recommendation in the new 2015 ESC Guidelines (Class IIb, LOE C). However, based on recent long term follow-up data[12,29] as well as on two meta-analyses,[21,32] asymptomatic individuals with spontaneous type 1 ECG and inducible VF at EPS are possibly at high risk. Nevertheless, the decision to implant an ICD in asymptomatic patients should be made weighing the potential individual risk for future arrhythmic events against risk of complications and quality of life.[14] In a recent study, a significant number of young BrS patients experience device-related complications (15.9%).[12] Complications consisted of fracture of the ventricular electrode and lead dislocation, and less commonly device infection and pulse generator migration.[12] In this series, 18.7% of patients suffered inappropriate shocks.[12]

Quinidine may be considered as an alternative therapy in patients who denied ICD as well as for treatment of supraventricular arrhythmias.[6,56,57] Low doses of quinidine are effective to prevent the recurrence of VF, including arrhythmic storm, in subjects with BrS with an ICD.[58] Furthermore, quinidine effectively prevents VT/VF induction in patients with BrS at EPS.[56,57] Belhassen et al. have recently reported the long-term outcomes of BrS patients with initially inducible VF at EPS who received quinidine (n=54), disopyramide (n=2) or both (n=4) and underwent a second EPS procedure. Fifty four patients (90%) were responders to ≥ 1 anti-arrhythmic drugs and became non-inducible. No arrhythmic events occurred during class 1A anti-arrhythmic drugs therapy in any of EPS-drug responders and in patients with no baseline inducible VF during a very long follow-up period of 113.3±71.5 months.[59]

Isoprenaline infusion is effective in the management of repeated ICD shocks and arrhythmic storms.[60] Cilostazol and milrinone that boost calcium channel current and quinidine, bepridil and the Chinese herb extract Wenxin Keli that inhibit the transient outward current may be used to suppress the triggers for VF in BrS.[6] Nademanee et al. initially showed that catheter ablation of fractionated electrograms in the epicardial right ventricular outflow rendered VF non-inducible and normalization of the BrS ECG pattern.[61] Long-term outcomes were excellent, with no recurrent VF in all patients off medication. Similarly, in a recent study, following catheter ablation and elimination of the functional substrate in right ventricular outflow tract, all patients became non-inducible during programmed electrical stimulation using up to 3 extrastimuli, while repeated flecainide infusion failed to unmask the diagnostic BrS ECG pattern.[8] Although these findings have to be confirmed in future studies, they provide new important information regarding the therapeutic management of BrS patients.

Conclusions

Risk stratification of BrS patients represents a great challenge for the treating physician. Despite the lack of evidence, it is of major importance to make the best risk stratification using every available tool/modality that has been shown to display any prognostic significance. The diagnostic yield may be therefore increased if we use the current tools properly. Although single risk factors display limited prognostic value, multiparametric scores appear to improve risk stratification.

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Patient Specific Induced Pluripotent Stem Cell-Derived Cardiomyocytes for Drug Development and Screening In Catecholaminergic Polymorphic Ventricular Tachycardia

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Abstract

Catecholaminergic polymorphic ventricular tachycardia (CPVT), an inherited arrhythmia often leading to sudden cardiac death in children and young adults, is characterized by polymorphic/bidirectional ventricular tachycardia induced by adrenergic stimulation associated with emotionally stress or physical exercise. There are two forms of CPVT: (1) CPVT1 is caused by mutations in the RYR2 gene, encoding for ryanodine receptor type 2. CPVT1 is the most common form of CPVT in the population, and is inherited by a dominant mechanism. (2) CPVT2 is caused by mutations in the CASQ2 gene, encoding for cardiac calsequestrin 2 and is inherited by recessive mechanism.

Patient-specific induced Pluripotent Stem Cells (iPSC) have the ability to differentiate into cardiomyocytes carrying the patient's genome including CPVT-linked mutations and expressing the disease phenotype in vitro at the cellular level. The potency for in vitro modeling using iPSC-derived cardiomyocytes (iPSC-CMs) has been exploited to investigate a variety of inherited diseases including cardiac arrhythmias such as CPVT.

In this review we attempted to cover the majority of CPVT patient specific iPSC research studies previously published. CPVT patient-specific iPSC model enables the in vitro investigation of the molecular and cellular disease-mechanisms by the means of electrophysiologycal and Ca^{+2} imaging methodologies. Furthermore, this in vitro model allows the screening of various antiarrhythmic drugs, specifically for each patient, also known as "personalized medicine".

Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmia which may lead to syncope and sudden cardiac death in children and young adults. The arrhythmia is characterized by polymorphic/bidirectional ventricular tachycardia induced by adrenergic stimulation associated with emotional stress or physical exercise.[1-4] CPVT is manifested in one of two forms depending on the mutated gene.

1.CPVT1 is caused by mutations in the RYR2 gene encoding the ryanodine receptor type 2, it is inherited by a dominant mechanism and constitutes 70% of the CPVT cases.

2.CPVT2 is caused by mutations in the CASQ2 gene encoding for cardiac calsequestrin 2,[5-8] it is inherited by a dominant mechanism.

There are residual cases of CPVT that are caused by mutations either in TRDN, encoding for triadin or by mutations in CALM1, encoding for calmodulin; these residual CPVT cases are inherited by a recessive/dominant mechanism, respectively.[10,11] RYR2, a homotetramer comprised of 4 pore-forming monomers, regulates Ca^{2+}-induced Ca^{2+} release process (CICR) during excitation-contraction (EC) coupling by acting as a Ca^{2+} channel in the sarcoplasmic reticulum (SR) membrane.[9,12,13] CASQ2 also regulates SR Ca^{2+} release by acting as a buffering factor with a high-capacity low-affinity Ca^{2+} binding function.[5,8,9,12,13] RYR2 and CASQ2 are both involved in the EC coupling, operating as regulators of the Ca^{2+} handling machinery in cardiomyocytes.[6,14,15] In both CPVT1 and CPVT2, the mutations cause spontaneous SR Ca^{2+} release leading to intracellular Ca^{2+} overload, which in turn can generate delayed afterdepolarizations (DADs). If these spontaneous oscillatory depolarizations reach the activation threshold, triggered arrhythmia occur, and can culminate into lethal ventricular fibrillation.[6] High intracellular Ca^{2+} level which may result in triggered activity is

Key Words:
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triggered by one of two mechanisms:

1.RYR2 mutations resulting in a gain-of-function cause increased Ca^{2+} sensitivity of RYR2, and thus leads to increased probability and duration of the open state of ryanodine receptor channel, which in turn leads to SR Ca^{2+} leak.

2.CASQ2 mutations decrease the binding efficiency of CASQ2 to SR Ca^{2+}, thus leading to SR Ca^{2+} leak from to the cytoplasm.[1,8,16-20]

There are two mechanisms by which high intracellular Ca^{2+} levels are reduced:

1. sarcoplasmic endoplasmic reticulum calcium (SERCA) pumps Ca^{2+} back into the SR.

2. Activation of sodium–calcium exchanger (NCX) that extrudes Ca^{2+} to the extracellular space and generates a net inward current (so called transient inward current) leading to membrane depolarization and DADs.

Modeling CPVT in a Dish with Induced Pluripotent Stem Cells (iPSCs)

Despite tremendously high mortality rate in CPVT patients (about 35%) the mechanisms of action are not completely clear and the current treatments are limited. Regardless of their mutation, CPVT patients are treated with insufficient efficiency, mostly with β-blockers; hence, patients still experience life-threatening episodes which may require implantable cardioverter defibrillators (ICD).[6,22,23] Therefore, research models for drug screening of new therapeutic agents are encouraged. The recent technology of iPSC offers an innovative approach to study the molecular mechanism of CPVT and to test specific drug targets.

Embryonic stem cells (ESC) derived from the inner cell mass of a blastocyst, are pluripotent stem cells carrying the ability of self-renewal and differentiation into each one of the three germ layers. In 2006, Yamanaka and Takahashi have discovered a series of essential embryonic genes (OCT4, SOX2, KLF4, c-MYC) that if introduced into a mature fully-differentiated somatic cell, reboot a reprogramming process resulting in the generation of iPSCs. Several research groups have exploited this emerged technology to generate iPSCs for the investigation of inherited diseases such as neurodegenerative, metabolic and cardiac syndromes.[24,25] Particularly, in the field of inherited arrhythmias several groups[5,6,33,39] have demonstrated the ability of mutated iPSC-CMs to recapitulate the clinical symptoms, and to serve as a superb in vitro cell model for testing effective antiarrhythmic drugs. Additionally, the iPSC technology has been successfully employed to investigate dilated cardiomyopathy,[34,35] hypertrophic cardiomyopathy[34,36,37] and other channelopathies such as long QT syndrome as well as CPVT.[1,5,6,16,33,34,38-40]

CPVT patient-specific iPSCs carry the ability of differentiating into cardiomyocytes while holding the patient's genome, including CPVT-linked mutation, thereby CPVT-iPSC-CMs express the disease phenotype in vitro at cellular levels.[24-30] CPVT patients carry different mutations in RYR2 or in CASQ2 genes that lead to different impaired protein-activities while causing for resembling clinical phenotypes. Despite the resembling phenotype in CPVT patients, the involved mechanism in each patient requires unique treatment for each specific mutation. iPSC-CMs benefit as in vitro model for investigation of each mechanism and allows the patient-specific personalized drug screening.

This review paper aims to cover most of the published investigations in the field of iPSC-CMs associated with CVPT by shedding light on the known mechanisms of CPVT, and on the explored pharmacological modalities that are suitable for patients carrying various CPVT mutations.

Cell Origin and Reprogramming Method

Different methods have been employed by research groups for cell origin production and reprogramming. While most research groups have used fibroblasts for the infection of pluripotent markers in order to generate iPSCs, Binah's group was the first to produce CPVT-iPSCs from patient's hair keratinocytes. Whereas most (9/11) have harnessed Yamanaka's 4 pluripotent factors: OCT4, SOX2, KLF4 and c-MYC or a reduced combination (OCT4, SOX2 and KLF4), Priori's group has reprogrammed somatic cells using an altered factor-set: OCT4, SOX2, NANOG and LIN-28 as described before by Yu et al.[41] Despite the different methods used for reprogramming, all groups reported that the CPVT iPSC-CM recapitulated the disease specific phenotype.

Cardiomyocytes Differentiation

To date, there are several known differentiation methods towards the cardiac linage. In the described scientific investigations 2 major methods can be found:

1.Embryoid body (EB) – spontaneous differentiation.

2.Differentiation on murine visceral endoderm-like cell line (END2).

The EB spontaneous differentiation method includes detachment of iPSCs colonies by Collagenase type IV and suspension growth for a period of 7 days prior to gelatin coated plating as described before;[42] in contrast, differentiation with END2 cell line requires 3 weeks of co-culture before separation. There is a time difference for cardiac differentiation in each method affecting the cardiomyocytes maturity and thus may create electrophysiological variability. With respect to CPVT research, the new standard of cardiac directed differentiation method was not yet introduced. In the directed

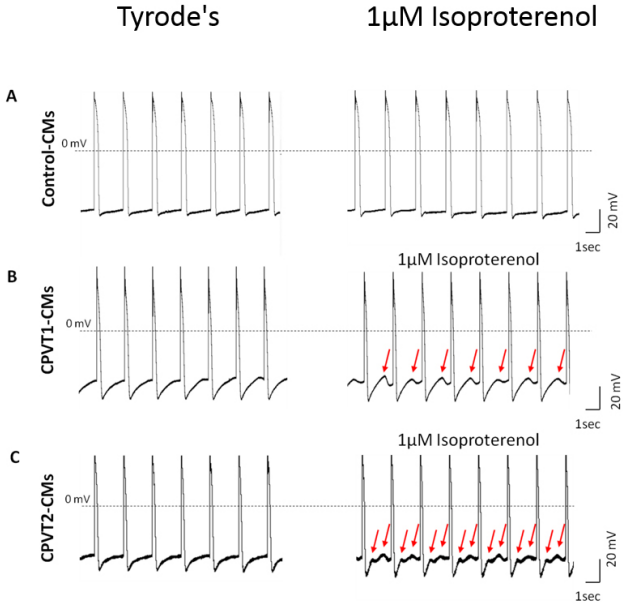

Figure 1: **Isoproterenol induced DADs in CPVT1 and CPVT2 iPSC-CM. Representative action potentials recordings from healthy control (A), CPVT1 (B) and CPVT2 (C) iPSC-CM before and after exposure to 1μM isoproterenol with 0.5 Hz external pacing. Red arrows indicate on isoproterenol-induced DADs in CPVT iPSC-CMs**

method, the differentiation is achieved either by small molecules modulating the activity of GSK-3β and Wnt signaling pathway or by inducible β-catenin shRNA.[43] The directed differentiation does not only provide a more uniform cardiac population, but also affects the cardiomyocytes maturity. As shown before, iPSC-CMs have a more developed SR while achieved by directed compared to spontaneous differentiation;[44,45] accordingly affecting age range selection for electrophysiological/EC-coupling experiments. It will be of great interest to observe CPVT results from iPSC-CMs differentiated by a directed method that is calibrated to generate mature and enriched cardiac population.

CPVT-iPSC-CMs Recapitulate Disease Specific Phenotypes

Several groups have explored CPVT phenotypes in patient-specific iPSC-CMs by the following commonly used electrophysiology and Ca^{+2}-contraction imaging methods:

Patch Clamp

Action potential recordings, by whole cell patch clamp configuration, have shown that CPVT-iPSC-CMs present DADs, early afterdepolarizations (EADs – during phase 2,3), oscillatory prepotentials and triggered arrhythmia (TA). Arrhythmias have been catecholaminergic-linked and increased during exposure to isoproterenol (a β-adrenergic agonist). While in control-cells, isoproterenol had caused positive chronotropic effect; in CPVT-CMs, it led to negative chronotropic effect and to the appearance of DADs and TA (Fig. 1). [5,16,38,39,46] Most groups have reported on similar electrical features (Maximum diastolic potential, action potential amplitude and maximal rate of depolarization (dV/dtmax)) between CPVT-CMs and control-cells.[5,6,16,39] DADs and TA have been also generated by exposure of CPVT-iPSC-CMs to forskolin (an adenylyl cyclase activator) and by the end of a pacing-train, immediately after the last pulse. Thapsigargin – SERCA inhibitor, which causes for depletion of intracellular Ca^{2+} stores, has reduced the appearance of DADs post pacing or during the exposure to forskolin. This phenomenon suggests for another involved mechanism in the generation of DADs: store-overload-induced Ca^{2+} release (SOICR). SOICR manifests the necessity to reach a certain threshold of the SR over-load for spontaneous release via RYR2 through depolarization-independent SR release.[39] It was also demonstrated that DADs may prevent the next emerging action potential, thus decreasing the cardiomyocytes beating rate, or may reach action potential threshold and initiate triggered activity. In addition to DADs, oscillatory pre-potentials were observed during action potential recordings. Unlike DADs, oscillatory pre-potentials appear during late diastolic depolarization, last for longer period and its amplitude grow progressively until reaching the action potential threshold.[5,47,48]

Calcium Handling Measurements

CICR mechanism is the key regulator of Ca^{2+} handling in cardiac muscle and is responsible for the EC coupling process. Researchers in this field measure Ca^{2+} transients either by Fura-2 or Flou-4; regardless the transient-recording method, all experiments have reported on a deranged Ca^{2+} handling machinery seen in CPVT-iPSC-CMs: multiple peaks, oscillations, varying amplitude and local Ca^{2+} release events interspersed within beats.[1,5,38,46] Abnormalities have been manifested in base line of CPVT-iPSC-CMs Ca^{2+} measurements, and increased in response to adrenergic stimulation, such as isoproterenol exposure. Ca^{2+} handling abnormalities may cause arrhythmias, expressed as electrophysiological abnormalities

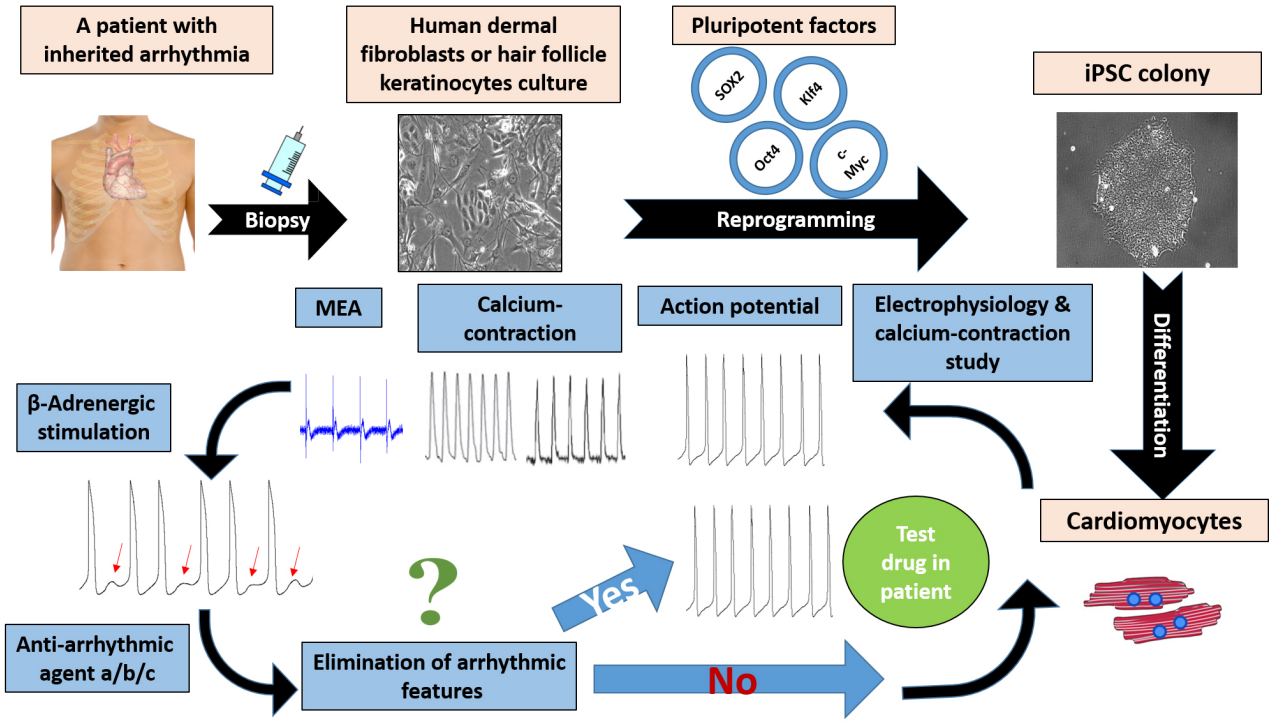

Figure 2: Representation of the personalized medicine concept in CPVT investigation. The process begins with obtaining skin or hair follicles biopsy from patient followed by reprograming procedure to generate iPSC cell-line holding the ability of differentiating into functional cardiomyocytes. To evaluate the effect of different anti-arrhythmic drugs on patient specific iPSC-CMs the scheme continues with electrophysiology and calcium-contraction study, involving external β-adrenergic stimulation resulting in arrhythmia represented as DADs. Subsequently the model allows the assessment of different anti-arrhythmic drugs for elimination of in vitro arrhythmias. Prominent agents should be tested for their effect within the patient

such as DADs, EADs or oscillatory prepotentials that eventually lead to dissimilar beat-to-beat intervals and TA; these electrophysiological abnormalities are mirrored and explained by Ca^{2+} and contraction measurements.[34] It was also indicated that Ca^{2+} handling abnormalities increase in exposure to isoproterenol or forskolin and could be reversed by addition of a beta-blocker (propranolol or metoprolol).[5,39,46] Studies have shown that in caffeine-induced calcium release experiments, mutated cells had lower SR Ca^{2+} load in base line and during adrenergic stimulation; these results represent the enhanced average open period of mutated RYR2.[16,38,40,46] Specifically in CPVT2, CASQ2-mutated cells exhibit marked diastolic [Ca^{2+}]i rise in response to adrenergic stimulation, likely to be due to decreased binding efficiency of Ca^{2+} by CASQ2.[5] Screening for antiarrhythmic treatments in CPVT-iPSC-CMs could be well studied by combining Ca^{2+} transient measurement, contraction and electrophysiological investigation.

Antiarrhythmic Pharmacological Candidates for CPVT Treatment

Studies suggested different antiarrhythmic agents for CPVT treatment, depending on the specific point mutations in RYR2 or CASQ2 and on its location. RYR2 is comprised of more than 100 exons and contains about 5000 amino acids, leading to a variety of mutations that can be found in this gene, including point mutations and deletions with varying locations from the C-terminal to the N-terminal of ryanodine receptor. It is clearly understood that mutations in different locations have dissimilar effects on protein dysfunction, resulting in the necessity of different agents to interact with different parts of RYR2 in order to compensate for function loss. The emerging field of personalized medicine acknowledges the importance of patient-specific drug screening and could be thoroughly employed using iPSC-CMs as in vitro model, as demonstrated in Fig. 2. Some progress has been done with few drug candidates linked to specific RYR2 mutations, as proof of concept, presenting the feasibility of this approach.

Dantrolene

Dantrolene, a muscle relaxant is used as a treatment for malignant hyperthermia, caused by skeletal ryanodine receptor (RYR1) mutations.[49] Datrolene stabilizes the closed state of RYR1 and hence its therapeutic effect; it has also been demonstrated to interact with RYR2.[50] In order to explore its therapeutic effects on CPVT phenotype caused by RYR2 mutation, researchers have generated iPSC-CMs from CPVT1 patient with an autosomal dominant missense RYR2 mutation: S406L. RYR2 dislocation due to its mutation has been excluded by comparing immunefluorescent stainings of CPVT1 and healthy control iPSC-CMs. As expected, increased diastolic Ca^{2+} levels have been induced by isoproterenol in CPVT-iPSC-CMs, but not in control cells. Furthermore, SR Ca^{2+} load has been increased in response to isoproterenol in control iPSC-CMs, but not in mutated iPSC-CMs. The investigators have concluded that during chatecholamine stimulation, the increased luminal Ca^{2+} caused by S406L mutation is due to diastolic Ca^{2+} leak from the SR. It has been proposed that S406L increases Ca^{2+} sensitivity of RYR2 and produces diastolic spontaneous activity due to a lower threshold. Ca^{2+} leak by hyperactive RYR2 under catecholaminergic stress elevated diastolic Ca^{2+} and decreased SR Ca^{2+} load in CPVT-iPSC-CMs. Diastolic Ca^{2+} leak can generate arrhythmia by NCX activation, causing for depolarizing currents, represented as DADs.[51] DADs and TA have been observed in 89% of mutated cells in comparison to 34% in control cells. Stress-induced diastolic Ca^{2+} leak from the SR via RYR2 could be explained by one of 2 mechanisms:

1. RYR2 mutations destroy essential inter-domain interactions that stabilize the closed state.[52,53]
2. RYR2 mutations abolish significant interactions with its modulating proteins.

It has been shown that S406L mutation is located in an inter-domain position, hence the validity of the first mechanism for this RYR2 mutation. Binding of dantrolene to the N-terminal end of skeletal and cardiac RYRs has restored normal Ca^{2+} handling in CPVT-iPSC-CMs during basal and chatecholamine-stimulation conditions. Furthermore, dantrolene has eliminated the appearance of DADs and TA, and has reestablished the wild-type phenotype, supporting the hypothesis that abnormal inter domain interactions are involved in this RYR2 mutation. Dantrolene has been proved as effective for S406L mutation; probably by restoring essential inter domain interactions within RYR2. To determine its effect on different mutations, the process should be repeated for each unique mutation. In a clinical study for dantrolene-treatment in CPVT1 patients, it markedly reduced arrhythmias in a subgroup of patients, depending on the mutation site within the RYR2 protein.[1] Dantrolene has antiarrhythmic effect only on patients with mutations in the N-terminal or in the central region of the protein; however, it has no antiarrhythmic effect on CPVT-iPSC-CMs with mutations in the trans-membrane region. The researchers disclaimed that exceptional cases have been observed and that the antiarrhythmic effect of dantrolene could not be well determined by the mutation location solely, illustrating the significance of patient-specific drug screening model for CPVT.[1] Furthermore, the results of this research on human subjects, alongside with patient-specific iPSC-CMs, indicate on similar dantrolene effect both in the clinical setting and in the corresponding in vitro model; these findings support the feasibility of in vitro drug screening while avoiding unnecessary side effects in the patient. Dantrolene binding site is a part of the domain switch region, implying for the involved mechanism in restoring defective unzipping and in stabilizing inter-domain interactions, eventually leading to inhibition of Ca^{2+} leak.[1,5,14,38,54,55]

Flecainide

Flecainide is categorized as class Ic antiarrhythmic drug and may contribute to the most common yet insufficient CPVT beta-blocker treatments. Its contributing effect originates, probably, from the reduction in the availability of membrane sodium channels and the increase of TA threshold[16,38,56,57] or from the blockade of RYR2 in the SR membrane, which decreasing its opening probability.[16,38,58-60] It eliminated DADs and TA in CPVT-iPSC-CMs.[16]

β-Blockers

A side from commonly used β-blockers and the regarding in vitro studies (such as: metoprolol and bisoprolol), the development of new modalities and the patient-specific in vitro screening of existing antiarrhythmic drugs is encouraged before it could be introduced to a CPVT patient. VK-II-86, a synthetic analog of carvedilol, acts as β-blockers and had prevented stress-induced arrhythmia in CPVT mice model, yet has not been tested on human CPVT-iPSC-CMs.[38]

CaMKII Inhibitors

The inhibition of Ca^{2+}/calmodulin-dependent serine–threonine protein kinase II (CaMKII), which phosphorylates main components

of calcium handling machinery, has been shown to prevent β adrenergic-induced arrhythmias. KN-93 (2-[N- (2-hydroxyethyl)]-N-(4methoxybenzenesulfonyl)]-amino-N-(4-chlorocinnamyl)-N-methylbenzylamine), a CaMKII inhibitor has prevented arrhythmogenic features in CPVT-iPSC-CMs.[6] It has eliminated isoproterenol-induced DADs and has restored normal calcium handling within cardiomyocytes. In 3D contracting EBs of CPVT-iPSC-CMs multiple sites have been observed for the initiation of calcium transients that, later on, have collided during propagation. KN-93 treatment has resulted in a single initiation site similarly to healthy control-iPSC-CMs.[6]

Conclusions

iPSC-CMs generated from CPVT patients recapitulate the disease specific phenotypes and by this, act as an applicable model for the investigation of key feature phenotypes as well as for the disease mechanism. The most promising ability of this model is with screening and developing of new modalities for patient specific personalized pharmacological treatments. We believe that in the following future, research of iPSC-CMs from CPVT patient, taking the advantages of this well-established model, will give new meaning for the bench to bed-side transition. Using patient specific iPSC-CMs the screening of existing alongside to newly developed pharmacological-agents will spare unnecessary exhausting and risky exploration within the patient's body. The most prominent drugs to be screened are those previously proven effective in CPVT-mice models such as: ranolazine and propafenone.[61] The currently most used therapeutic treatments including pharmacological β-blockers, implantable cardioverter-defibrillators (ICD) and left cardiac sympathetic denervation must be improved by the developing of new modalities in order to minimize the events of ICD-firing, resuscitation and mortality in CPVT patients.

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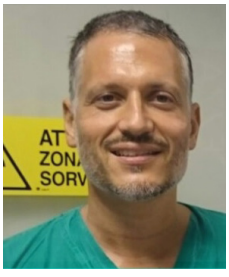

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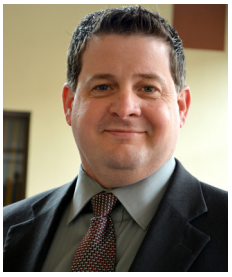
I am an interventional cardiologist and the head of the Unit of Cardiac Electrophysiology at San Paolo Hospital in Savona, Italy, since 2014. My clinical and research interests range from cardiac electrophysiology to electrocardiology, from cardiac device implantation to arrhythmias diagnosis and ablation. I have a special interest for zero/near-zero fluoroscopy ablations, and I consider myself an expert in this field. I am an AIAC regional councilor (Liguria, years 2016-2018). I own the AIAC Certification in cardiac electrophysiology (2012).



Dr. Paul P. Dobesh, Pharm.D

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Electrophysiology Fellow at Northwestern University in Chicago. Research interests include the management and prevention of post-operative atrial fibrillation and the use of novel oral anti-coagulants.

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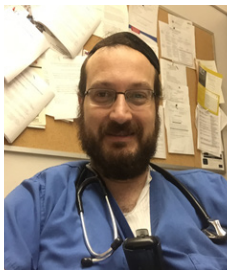

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