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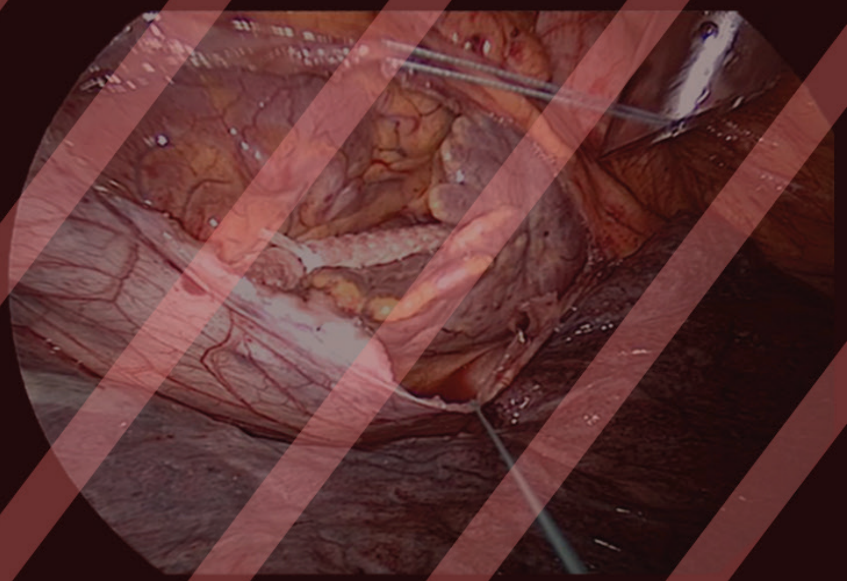

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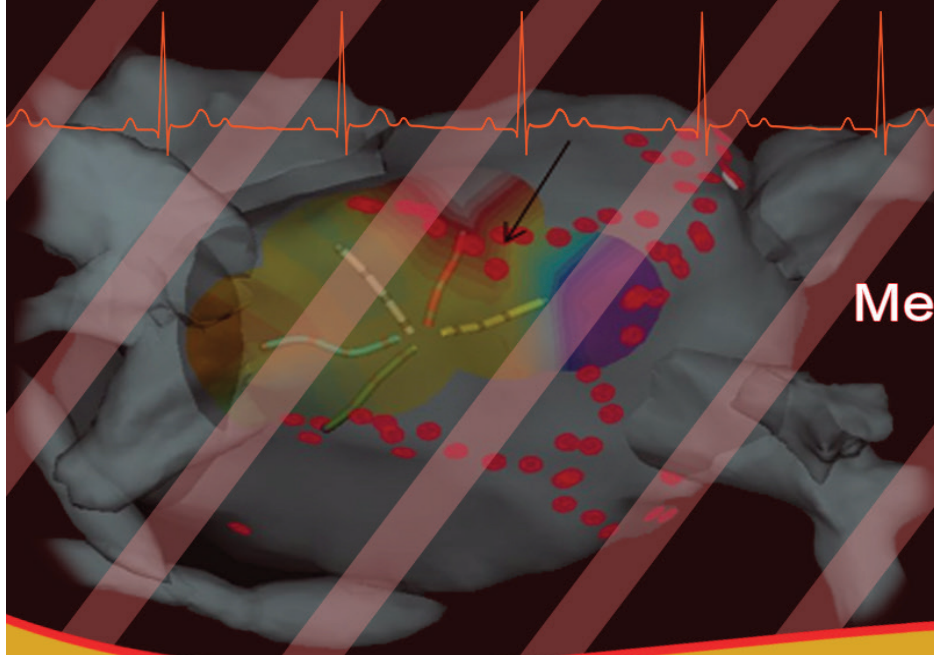

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Humanity, Service, Kindness, Innovation and Science has no Boundaries and Walls

Dear Friends and Colleagues from around the world

Hope this edition of JAFIB finds you in good health and better spirits. The journal wants to reaffirm our faith in universal readership, scientific advancement and technological innovation. The service of humanity and expression of kindness knows no boundaries and walls. We as physicians will abide by the Hippocratic Oath and be global citizens in our commitment to eradicate disease, tend to the suffering uphold the values of human dignity.

In this issue of the journal we cover a wide variety of topics that are published by some of the most brilliant cardiologists from all around the world. These contributions range from His bundle pacing to rediscovering intravenous sotalol from colleagues of all orders. Jie Cheng and group published a very interesting meta-analysis of all studies related to esophageal temperature monitoring and the pitfalls in its reliance in preventing esophageal injury. As the use of novel oral anticoagulants increases the inappropriate dosing issues continue to rise. A single institutional experience from Quebec, Canada address this particular issue well. Barmano etal from Sweden published their experience with structured AF care in improving outcomes of therapy. Several excellent review articles on electrophysiologic studies, techniques and outcomes of non-paroxysmal atrial fibrillation, oral anticoagulation management during peri-procedural state and pathogenesis of AF are highlights of this issue. A very comprehensive comparison between cardiac resynchronization therapy and His Bundle pacing in patients with left ventricular dysfunction by Pugal Vijayraman and colleagues is very thought provoking and could be a game changer in heart failure therapy.

We once again thank you for your unwavering support of the journal and your eternal belief in the humanity and kindness of the world. May sanity, humanity and kindness succeed in combating insanity, poverty and disease?

Best warm regards

Dhanunjaya (DJ)Lakkireddy
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Impact of Alcohol Consumption on Atrial Fibrillation Outcomes Following Pulmonary Vein Isolation

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Abstract

Moderate to heavy alcohol use has been shown to be associated with increased atrial fibrillation (AF) incidence. However, the relationship between alcohol use and AF recurrence after pulmonary vein isolation (PVI) is not well known.We sought to study the impact of different alcohol consumption levels on outcomes after AF ablation.A retrospective analysis was performed of 226 consecutive patients undergoing first time PVI for AF. Clinical data were collected including alcohol intake classified into 3 groups: none-rare (< 1 drink/ week), moderate (1-7 drinks/ week), and heavy (> 7 drinks/ week). Patients were followed for recurrences within the first 3 months (blanking period; early recurrence) and after 3 months up to 1 year (late recurrence) after the ablation. Paroxysmal and persistent AF had early recurrence rates of 29.1% and 32.2%, and late recurrence rates of 30.2% and 44.1%, respectively. The none-rare alcohol group had a higher frequency of diabetes mellitus (p=0.007). Neither moderate or heavy alcohol consumption, in reference to the none-rare group, was significantly predictive of early or late AF recurrence on adjusted multivariate logistic regression analysis (p>0.05).Despite known associations between alcohol and incidence of AF, alcohol consumption is not associated with early or late AF recurrence after PVI in this cohort.

Introduction

Alcohol consumption in moderation has been reported to have beneficial cardiovascular protective effect.[1], [2] Recent evidence continues to emerge on the physiologic and genetic mechanisms through which alcohol may reduce the risk of developing CVD.[3] Nonetheless, alcohol intake has been implicated with an increased incidence of atrial fibrillation.[4] The heart holiday syndrome, in fact, was first described in 1978 by Ettinger et al and linked to binge alcohol drinking behavior preceding AF occurrence.[5] Incidence of AF is also elevated in chronic levels of modest alcohol intake.[6]Abstinence from alcohol remains the optimal management of alcohol related heart disease including atrial fibrillation.[7]

Catheter ablation has become the mainstay of therapy in many symptomatic patients with atrial fibrillation. In addition, long-term control of AF requires modification of risk factors and management of associated comorbidities.[8], [9] Identifying predictors of AF recurrence after catheter ablation could help focus the management of these potential risk factors and better select patients who would likely have favorable outcomes. A recent study has shown that alcohol consumption may be an independent predictor of paroxysmal AF (PAF) recurrence after catheter ablation,[10] but the study was small and did not include persistent AF patients. In this study, we further explore the association of different alcohol consumption levels with early and late recurrence rates of AF (both paroxysmal and persistent) and AF-free survival after pulmonary vein isolation by catheter ablation.

Key Words

alcohol; arrhythmia, atrial fibrillation; catheter ablation; pulmonary vein isolation; recurrence.

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Methods

Study Subjects

This study was approved by the Institutional Review Board at the University of Colorado. In this retrospective observational study, we reviewed the medical records of 226 consecutive patients who underwent first-time PVI for symptomatic, non-valvular AF from January 2011 to April 2014 at the University of Colorado ([Figure 1]). Patient baseline characteristics and clinical data were collected. AF with self-terminated episodes within seven days prior to the catheter ablation procedure was defined as paroxysmal AF (PAF). AF that continued for more than seven days was defined as persistent AF (PsAF). Only patients who had a history taken regarding alcohol use were included in the study. Alcohol consumption habits were classified into three groups: none-rare (<1 drink per week), moderate (1-7 drinks per week), and heavy (>7 drinks per week). One drink was defined as 6 fl. oz. of alcohol. Patient data was de-identified.

Ablation Procedure

All patients underwent pulmonary vein isolation. Entrance and exit block was assessed for all veins. PAF patients underwent PVI alone; some PAF patients had additional cavotricuspid isthmus

(CTI) ablation only if clinically indicated (inducible or history of typical CTI dependent flutter). In persistent AF (PsAF) patients, at the discretion of the operator, patients underwent PVI alone or PVI with additional linear, complex fractionated atrial electrograms (CFAE), and/or non-PV trigger ablation.

Post-ablation Management and Follow up

Patients were followed monthly for the first 3 months and then every 3-6 months thereafter. All asymptomatic patients had 12 lead electrocardiograms at 1, 3, 6 and 12 months after the ablation procedure. Patients with symptoms suggestive of AF recurrence had new 12-lead electrocardiograms and/or ambulatory monitoring. AF recurrence was defined as the presence of evident tachyarrhythmia on 12-lead electrocardiogram or atrial arrhythmia lasting for 30 seconds or more on ambulatory cardiac monitor. AF recurrences were considered separately in the first 3 months (early period or blanking period) and after 3 months (late period) following catheter ablation. AF-free survival time was defined as the number of days from the date of catheter ablation to the first documented AF recurrence in the pertinent follow up period (early or late).

Statistical Analysis

on ECG All data were analyzed using SPSS software version 22.0. Normality of continuous variables was tested using Shapiro-Wilkins test. Continuous variables following Bayesian normal distribution were presented as mean ± SD and analyzed using unpaired t-test of independent samples. Continuous variables not following normal distribution were presented as median (25th to 75th interquartile range) and compared using Mann-Whitney U test. Categorical variables were tested using Fisher's exact test. Univariate logistic regression analysis was performed to test each individual potential variable for the prediction of early or late AF recurrence. Variables that have p<0.2 were entered in a multivariable logistic regression analysis to test the independence of AF recurrence prediction. A Kaplan-Meier estimation with a log-rank test was performed comparing the study groups. All probability values were 2-sided, and a P of <0.05 was considered significant.

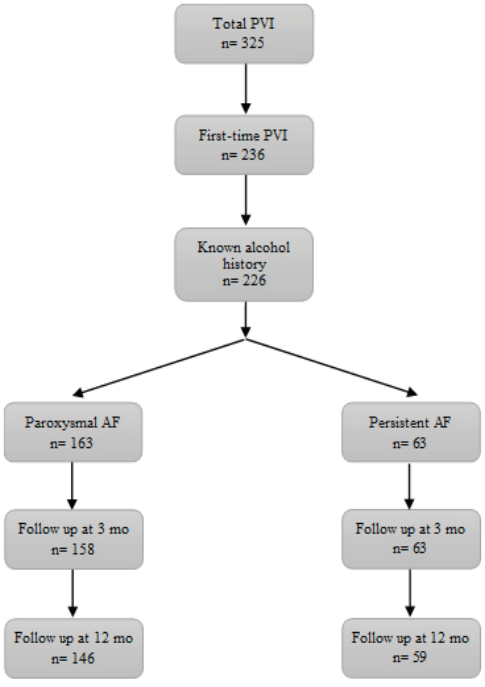

Figure 1: **Schematic diagram of the study population. Patients who underwent PVI for the first time and had documented alcohol consumption levels were included. Patients who were lost to follow up were excluded from subsequent analyses.**

Results

Patient Population and Ablation Procedure

Two hundred twenty six consecutive patients with symptomatic, non-valvular AF underwent their first PVI in the period of January 2011 to April 2014. Baseline characteristics of patients in each group are summarized in [Table 1]. The only significant difference was the higher prevalence of diabetes mellitus in the none-rare alcohol group. For all patients, mean age was 62.1 +/- 9.9 years (range 31-84, median=63 years) and 153 (67.7%) were men. PAF was present in 163 (72.1%) patients. The prevalence of PAF was higher as the level of alcohol consumption increased; however, this was not statistically significant among the alcohol groups. Mean AF history was 4.1 +/- 4.9 years (range 2 months to 46 years). Most patients (56.2%) had one drug failure history while 15.0% had 2 or more drug failures.

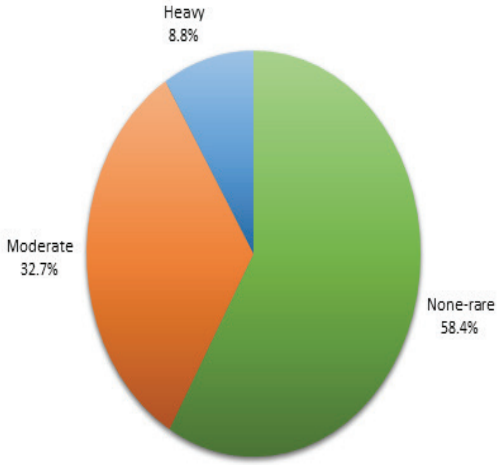

Figure 2: **Distribution of study population (patients undergoing first time PVI) demonstrated by alcohol consumption levels**

All of the patients were undergoing PVI for the first time; however, prior catheter ablation had been performed in 23 patients for atrial flutter (AFL), 1 for AVNRT and 2 for VT. Eleven patients had a history of sick sinus syndrome. Pacemakers were present in 22 patients (20 dual chamber, 1 single chamber, and 1 biventricular pacemaker). An alcohol use survey on admission showed that the majority of patients, 132 (58.4%), had none to rare (<1 drink per week) alcohol use, while 74 (32.7%) and 20 (8.8%) patients reported moderate (1-7 drink per week) and heavy (>1 drink per week) alcohol use, respectively ([Figure 2]).

Of those presenting for AF ablation, 63 (27.9%) patients had PsAF. PVI was performed using radiofrequency ablation in most patients, except in 9 patients where cryoballoon ablation was used. Additional linear, CFAE and non-PV trigger ablation was performed, in 54.9%, 8.4%, and 10.2% of patients, respectively.

Characteristics of Patients by Alcohol Consumption Levels

Increased alcohol consumption levels are positively correlated with older age, male sex, higher rate of PAF, greater left atrial volume

index (LAVi) and further need of additional linear, CFAE and non-PV trigger ablation ([Table 1]).

Follow up and Outcomes

In the blanking period (0-3 months), 5 PAF patients were lost to follow up. In the following 3-12 month follow up period, an additional 12 PAF patients and 4 PsAF patients were lost to follow up. Early and late recurrence rates were 29.1% and 32.2% in the PAF group, and 30.2% and 44.1% in the PsAF group, respectively. For PAF patients, early recurrence rates were 30.7%, 29.1% and 29.4% (p=1.000) and late recurrence rates were 34.6%, 33.3% and 25.0% (p=0.846) in the none-rare, moderate and heavy alcohol groups, respectively ([Figure 3A]). In PsAF patients, early recurrence rates were 33.3%, 27.8% and 0.0% (p=0.640) and late recurrence rates were 42.9%, 47.1% and 0.0% (p=0.398) in the none-rare, moderate and heavy alcohol groups, respectively ([Figure 3B]). Among those patients who had an early recurrence, 68.4% developed late recurrences. The presence of early recurrence was independently predictive of late recurrence after catheter ablation based on multivariable logistic regression models adjusting for linear ablation, AF type, and DM (OR 7.797, 95% CI 3.815-15.937, p<0.001).

On univariate logistic regression analysis, none of the alcohol groups showed any significant association with early or late AF recurrence ([Table 2]). Among the baseline characteristics, only age and the absence of diabetes mellitus were significantly associated with higher early and late AF recurrence rates, respectively [age (OR 1.032, 95% CI 1.000-1.065, p=0.050) and absence of DM (OR 0.300, 95% CI 0.110-0.818, p=0.019)].

With multivariable regression models, after adjusting for potential confounding covariates, none of the alcohol levels were independently predictive of early or late AF recurrence ([Figure 4]). Paroxysmal AF and the absence of DM were the only two parameters that remained independently predictive of late AF recurrence [PAF (OR 0.410, 95% CI 0.205-0.820, p=0.012) and absence of DM (OR 0.242, 95% CI 0.085-0.688, p=0.008)].

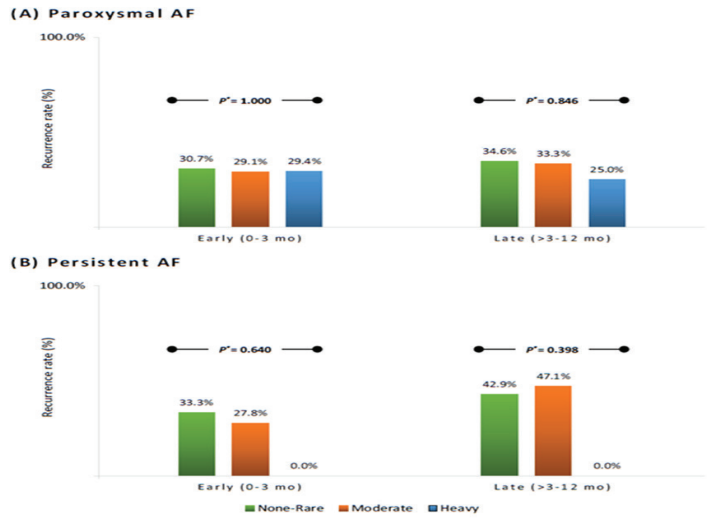

Figure 3: Recurrence rates of PAF (A) and PsAF (B) after catheter ablation in the none-rare, moderate and heavy alcohol consumption groups in the early and late follow up periods. *P value for statistical difference among the three groups of alcohol consumption.

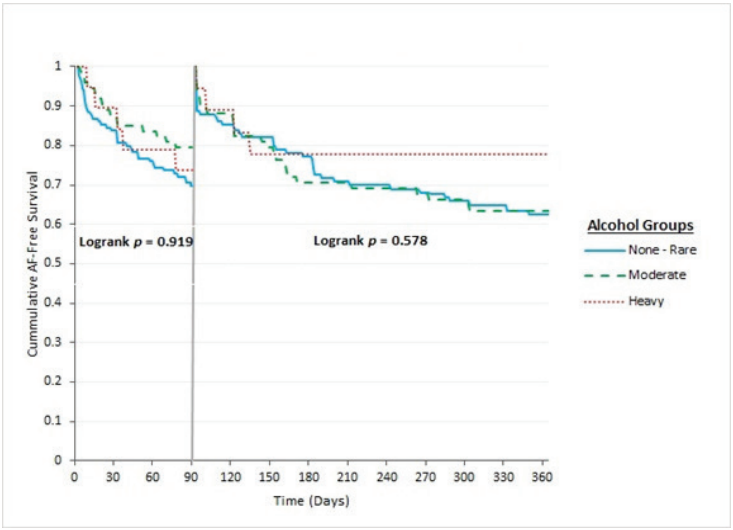

Figure 4: Kaplan-Meier curve demonstrating time to first AF recurrence in early and late follow up periods after catheter ablation according to alcohol consumption groups

Discussion

In this study, we hypothesized that different alcohol consumption levels will have different effects on outcomes after PVI ablation for AF. However, the main finding of our study was that alcohol consumption was not associated with a higher likelihood of early or late AF recurrence in the first year after pulmonary vein isolation by catheter ablation. To the best of our knowledge, this is the first study exploring the impact of alcohol consumption on early and late catheter ablation outcomes of both paroxysmal and persistent atrial fibrillation.

Cutoffs for the 3 levels of alcohol consumption were chosen to better define terms such as none, rare, moderate and heavy that are used in the literature to describe alcohol consumption behavior. Moderate drinking was defined by National Institute on Alcohol Abuse and Alcoholism (NIAAA) as the following: for women, low-risk drinking is no more than 3 drinks on any single day and no more than 7 drinks per week. For men, it is defined as no more than 4 drinks on any single day and no more than 14 drinks per week. Applying this definition to our study would have required further data collection, which is not feasible in a retrospective study. Therefore, we defined moderate drinking, for both men and women, as 1-7 drinks per week to reflect a weekly habit of drinking but not more than daily.

Our main findings are in contrast to a recently published prospective study that shows a significantly lower success rate after catheter ablation in patients with alcohol use, when compared to the abstainer group, and a possible detrimental dose-dependent effect of alcohol consumption on catheter ablation outcomes of PAF.[10] In their 122-patient study, Qiao et al had a predominantly male population, and the authors used the definition of the NIAAA for daily alcohol consumption levels in their study. This is an important distinction since those patients with rare alcohol use, who would have been classified in the none-rare group according to our definition, were actually included under the moderate alcohol group. Despite this, the size of their moderate alcohol group was smaller (10.6% vs. 32.7%), compared to our study. In addition, the size of their heavy alcohol group was larger (32.0% vs. 8.8%).

Table 1: Patient baseline characteristics by alcohol groups

Parameter	None – Rare (n=132)	Moderate (n=74)	Heavy (n=20)	P value
Age, years	61.3 ± 10.7	62.7 ± 9.0	64.3 ± 6.9	0.361
BMI, kg/m2	30.0 ± 6.0	28.8 ± 6.6	28.0 ± 4.9	0.219
Paroxysmal AF, n (%)	89 (67.4%)	56 (75.7%)	17 (90.0%)	0.081
History of EPS or ablation not for AF, n (%)	18 (15.8%)	15 (21.7%)	2 (12.5%)	0.574
AF history duration, years	4.07 ± 4.06	3.99 ± 6.52	4.98 ± 3.74	0.775
HTN, n (%)	79 (59.8%)	35 (47.3%)	12 (60.0%)	0.222
DM, n (%)	28 (21.2%)	4 (5.4%)	3 (15.0%)	0.007
CAD, n (%)	28 (21.2%)	10 (13.5%)	4 (20.0%)	0.397
$CHADS_2$ score	1.4 ± 1.3	1.0 ± 1.0	1.3 ± 0.9	0.060
Number of failed AADs	1.2 ± 0.8	1.1 ± 0.8	1.4 ± 0.9	0.376
Ablation of additional linear ablation, n (%)	71 (53.8%)	40 (54.1%)	13 (65.0%)	0.693
Ablation of additional CFAE, n (%)	11 (8.3%)	6 (8.1%)	2 (10.0%)	0.874
Ablation of additional non-PV trigger, n (%)	10 (7.6%)	9 (12.2%)	4 (20.0%)	0.152
LAVi, ml/m2	31.9 ± 13.3	33.0 ± 18.7	38.7 ± 15.0	0.302
LVEF ≥ 50%, n (%)	98 (89.9%)	64 (94.1%)	15 (93.8%)	0.724
LVEF 41 – 49%, n (%)	6 (5.5%)	3 (4.4%)	1 (6.3%)	0.894
LVEF 36 – 40%, n (%)	1 (0.9%)	1 (1.5%)	0 (0.0%)	1.000
LVEF ≤ 35%, n (%)	4 (3.7%)	0 (0.0%)	0 (0.0%)	0.392
Early AF recurrence, n (%)	39 (30.2%)	21 (28.8%)	5 (26.3%)	0.974
Late AF recurrence, n (%)	44 (37.0%)	25 (36.8%)	4 (22.2%)	0.500

BMI: body mass index; EP: electrophysiology study; AF: atrial fibrillation; HTN: hypertension; DM: diabetes mellitus; CAD: coronary artery disease; $CHADS_2$ score: congestive heart failure, hypertension, age, DM, stroke/transient ischemic attack score for the thromboembolic risk assessment; AADs: antiarrhythmic drugs; CFAE: ablation of complex fractionated atrial electrograms; PV: pulmonary vein; LAVi: left atrial volume index; LVEF: left ventricular ejection fraction

Alcohol Consumption and Risk of Atrial Fibrillation

There is a considerable volume of evidence today to support the observations linking alcohol consumption patterns and levels to cardiovascular effects, including higher incidence of atrial fibrillation. Alcohol-induced cardiac dysrhythmias are supported by several studies demonstrating various electrophysiologic alterations of the cardiac substrate. Since its description in 1978, the "holiday heart" has shed light on the association of alcohol and cardiac dysrhythmias, specifically atrial fibrillation.[5] Although the pathogenesis of (acute) alcohol-induced dysrhythmias remains poorly delineated, direct and indirect effects on heart rhythm disturbances are implicated.[11]-[16]

Chronic alcohol drinking, especially, has been associated with increased risk of AF even with a lack of alcoholic cardiomyopathy.[17], [18] Several pathologic mechanisms and electrophysiologic changes of the underlying cardiac substrate have been described.[19]-[25] Furthermore, chronic alcohol can be associated with other traditional risk factors, such as hypertension, and promote atrial fibrosis and subsequently AF.[26]

Conflicting Evidence Regarding Alcohol Consumption and Atrial Fibrillation

Several studies have shown a deleterious relationship between the increased daily amount of consumed alcohol and the incidence of AF.[27]-[29] Although there is a significant amount of research showing the relationship of binge alcohol drinking and holiday heart syndrome, the relationship for a full range of alcohol consumption with the risk of AF is less certain.[30],[31] A large number of studies have reported that ethanol intake, of various amounts, was not associated with occurrences of AF.[11], [17], [32] In addition, a recent analysis from the Framingham study did not observe a link between alcohol consumption and AF.[33]

The prevalence of moderate-heavy alcohol drinking in this study population is high (41.6%). The lack of association that we have found between alcohol consumption groups and AF recurrence after ablation adds further understanding to this complex relationship between alcohol consumption and incidence of AF. Nevertheless, the influence of alcohol on cardiovascular health, and specifically AF, remains an area of active debate and research.

Catheter Ablation of Atrial Fibrillation in Alcohol Consuming Patients

With increasing advanced therapies for AF, namely catheter ablation, assessing ablation success rates after these procedures is critical for patients, institutions and physicians. Though the outcomes of these procedures are becoming more promising, the success rates are still below what medical providers and patients hope them to be. Several factors can influence procedural success rates including, but not limited to, patient selection, operator-dependent and procedure-related factors, current technology, ablation lesion durability and the underlying AF pathophysiology. As several risk factors have been linked to the incidence of atrial fibrillation, risk factor modification

Table 2: Univariate logistic regression analysis of early and late AF recurrence by patient characteristics

Parameter	0 – 3 month			3- 12 month		
	OR*	95% CI	P value	OR*	95% CI	P value
Age	1.032	1.000–1.065	0.050	1.019	0.989–1.050	0.223
Sex (female)	0.889	0.477–1.658	0.711	1.319	0.718–2.422	0.372
BMI	1.036	0.990–1.085	0.129	1.020	0.973–1.069	0.418
AF type (PAF vs. PsAF)	0.951	0.502–1.801	0.878	0.603	0.324–1.120	0.109
AF history duration	1.030	0.969–1.094	0.344	1.032	0.957–1.114	0.414
HTN (presence vs. absence)	1.010	0.565–1.808	0.972	0.851	0.480–1.510	0.581
DM (presence vs. absence)	0.842	0.370–1.919	0.683	0.300	0.110–0.818	0.019
CAD (presence vs. absence)	0.544	0.236–1.255	0.153	1.027	0.485–2.173	0.945
CHADS2 score	1.062	0.840–1.343	0.617	0.965	0.782–1.267	0.969
Number of failed AADs	1.036	0.717–1.497	0.849	1.006	0.699–1.447	0.976
Alcohol use	71 (53.8%) 11 (8.3%) 10 (7.6%)		40 (54.1%) 6 (8.1%) 9 (12.2%)	13 (65.0%) 2 (10.0%) 4 (20.0%)		0.693 0.874 0.152
Additional (presence): Linear ablation CFAE ablation Non-PV trigger	 0.818 2.346 1.319	 0.458–1.461 0.906–6.078 0.530–3.283	 0.497 0.079 0.551	 0.679 1.682 1.127	 0.382–1.205 0.620–4.566 0.444–2.859	 0.186 0.307 0.802
LAVi	0.983	0.955–1.011	0.224	1.004	0.980–1.029	0.723
LVEF ≥ 50%, n (%) LVEF 41 – 49%, n (%) LVEF 36 – 40%, n (%) LVEF ≤ 35%, n (%)	1.883 0.575 – 0.767	0.515–6.881 0.118–2.801 –... 0.078–7.547	0.339 0.494 – 0.820	1.196 1.115 – 0.836	0.390–3.664 0.302–4.108 – 0.074–9.415	0.754 0.870 – 0.885
Early AF recurrence (presence)				7.265	3.691–14.299	<0.001

BMI: body mass index; PAF: paroxysmal AF; PsAF: persistent AF; EP: electrophysiology; AF: 379 atrial fibrillation; HTN: hypertension; DM: diabetes mellitus; CAD: coronary artery disease; 380 $CHADS_2$ score: congestive heart failure, HTN, age, DM, stroke/transient ischemic attack score 381 for the thromboembolic risk assessment; AADs: antiarrhythmic drugs; CFAE: ablation of 382 complex fractionated atrial electrograms; PV: pulmonary vein; LAVi: left atrial volume index; 383 LVEF: left ventricular ejection fraction. *OR refers to odds ratio of recurrence of AF versus 384 remaining in sinus rhythm after catheter ablation.

was shown to significantly help manage AF and reduce its recurrence, with or without catheter ablation. Risk reduction after catheter ablation may potentially boost the chances of AF-free survival and greatly reduce the costs associated with recurrences after these procedures. However, from our study, it does not appear that alcohol consumption is a major risk factor after ablation that can be altered to reduce recurrences.

Limitations

This is an observational retrospective study that investigates the relationship of alcohol consumption behavior reported at the time of the ablation procedure with early and late recurrence following the ablation procedure. Alcohol consumption in the follow up period was not tracked. Hence, we are assuming that the patients' alcohol consumption patterns remain the same in the follow up period after their ablation. The number of patients in the heavy alcohol group is relatively smaller, and thus the sample size may not have sufficient power to detect differences. Under reporting or recall biases during the alcohol use survey are also possible and are limitations of survey and retrospective studies. In addition, some patients may have a subtype of atrial fibrillation that is more alcohol sensitive. However, the retrospective nature of this study was not able to better define this population in our cohort and may be an area of further research in terms of their outcomes and response to ablation.

Conclusions

Alcohol use is common among patients undergoing catheter ablation of AF. Contrary to known associations of alcohol consumption and incidence of AF, different levels of alcohol consumption were not associated with significantly different rates of AF recurrence after catheter ablation in our cohort of patients undergoing pulmonary vein isolation. Further research is needed to study the effects of alcohol consumption, if any, on outcomes following catheter ablation for atrial fibrillation.

Disclosure

Drs. Sauer and Nguyen receive significant research grants from Biosense Webster and CardioNXT and educational grants from St Jude Medical, Boston Scientific, and Medtronic. Drs. Sauer and Nguyen have a provisional patent on partially insulated focused catheter ablation. Drs. Nguyen and Sauer have non-public equity interests/stock options in CardioNXT.

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Structured Care Of Patients With Atrial Fibrillation Improves Guideline Adherence

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Abstract

There are many reports of lack of guideline adherence in the treatment of patients with atrial fibrillation (AF), and AF affects health-related quality of life (HRQoL) negatively. The aim of this study was to investigate whether structured care compared to standard care of a general AF population could improve guideline adherence and HRQoL, and reduce symptoms, anxiety and depression.In total, 176 patients were recruited to the intervention and 146 patients to the control group. The intervention consisted of a structured follow-up program, while patients serving as controls received standard care. The primary outcome was guideline adherence evaluated through: appropriate use of oral anticoagulants (OAC) and antiarrhythmics, whether echocardiogram and thyroid lab tests were performed, and patient-reported outcome measures (PROMs), assessed with the questionnaires SF-36, EQ-5D, HADS and ASTA at baseline and after one yearGuideline adherence was significantly better in the intervention group, 91% vs. 63% ($p < 0.01$), mainly due to appropriate OAC treatment 94% vs. 74% ($p < 0.01$). Symptoms assessed with ASTA were less frequent and the negative impact of AF was reduced in the intervention group after one year/ at follow-up. Five scales in SF-36, and the visual analogue scale for current health status in EQ-5D (EQ-VAS), improved significantly in both groups.structured care of patients with AF significantly improved guideline adherence and patients reported fewer symptoms and a reduced negative impact on disease-specific HRQoL compared to standard care at one year follow-up.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia with a prevalence of approximately 3% in the Swedish population, and increases with age.[1] Due to an aging population, the number of patients with AF will increase, which implies great demands on the healthcare services. AF is associated with heart failure, disabling symptoms, decreased health-related quality of life (HRQoL), increased mortality and risk of ischaemic stroke.[2] Approximately 15% of all strokes are due to AF and among octogenarians as many as 25%[3]. Ischaemic stroke due to AF leads to higher mortality and greater disability than a stroke caused by other reasons.[3] Although it is well-known that treatment with oral anticoagulants (OAC) in high risk patients significantly reduces the risk for stroke, there are many reports of its underuse[4]. Studies have shown that other factors than well-known risk factors for stroke are often involved in the decision on whether to prescribe OAC or not.[4] There is a lack in guideline adherence in other areas as well, especially echocardiography.[5]

Secondary to stroke prevention, the care of patients with AF should focus on symptom relief and improvement in HRQoL, since AF often leads to more or less severe symptoms and a reduced HRQoL[6]. Anxiety and depression are particularly strong predictors of HRQoL in patients with AF.[6, 7] Symptoms, anxiety, depression and HRQoL can be evaluated by patient-reported outcome measures (PROMs). PROMs provide a way to gain insight into how patients perceive their health and offer a way to measure the effects of healthcare interventions, most commonly through self-completed questionnaires.[8]

The aim of this study was to investigate whether structured care compared to standard care of a general AF-population could improve guideline adherence and HRQoL and decrease symptoms, anxiety and depression.

Methods

Study design

The study had a non-randomised prospective design. The intervention took place at the Ryhov county hospital in Jönköping, Sweden, while patients in the control group were enrolled at three county hospitals in the same area (Kalmar, Eksjö and Norrköping, Sweden). All patients were asked to fill out questionnaires at inclusion and after one year, and their medical records were examined one year after inclusion. There was no study-related contact with

Key Words

Atrial fibrillation, Guideline Adherence, Anticoagulants, Health-related Quality of life, Symptoms, Anxiety.

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patients in the control group, while patients in the intervention group were followed at the AF clinic as described below. Educational level, occupation and cohabitation was registered. The first patient was included in December 2009 and the last follow-up was made in April 2014. Ethical approval was obtained from the Regional Ethical Committee in Linköping (Dnr. M145-09). The study complies with the declaration of Helsinki.

Study population

All patients ≥ 18 years who visited the emergency room (ER) due to AF were eligible for participation. Written informed consent was obtained prior to enrolment. Exclusion criteria were unwillingness to participate, unstable coronary artery disease, sepsis or other severe infection, AF early after thoracic surgery, acute pulmonary embolism, known hyperthyroidism, malignant disease with expected survival less than one year, dementia or insufficient knowledge of the Swedish language making it difficult to independently fill out the questionnaires.

Norm population

In 2006, a survey of the population in south-eastern Sweden was conducted, including assessment of HRQoL measured with, among others, SF-36. In total, 7 238 individuals responded to the survey, and the individuals aged 65-74 years were used for comparison.

Enrolment

Eligible patients were informed of the study at the ER or at the cardiac ward. Enrolled patients were then scheduled for an outpatient visit at the AF outpatient clinic (see below) within two weeks. Patients enrolled at the hospitals serving as control centres were only asked to fill out the questionnaires and then received "care as usual".

Structured care of atrial fibrillation

Education and preparations

Prior to study onset, physicians at the emergency care unit at the intervention centre were educated concerning current guidelines. A pocket sized laminated algorithm was presented, containing recommendations for treatment with oral anticoagulants (OAC) and with suggestions for outpatient management.

Atrial fibrillation outpatient clinic

The AF outpatient clinic was active one day weekly and manned by two cardiologists and two nurses. All patients included in the study were followed at the AF outpatient clinic for one or two weeks after discharge and then after three and 12 months. Data was entered in the Swedish National quality AF registry (Auricula) at the first and last visits. The nurses` perspective was information and education in order to increase the patients' knowledge about AF. They also provided information on lifestyle with focus on overweight/obesity, the amount of alcohol and coffee use, stress and psychological distress. In addition to the orally given information, an information booklet from the Swedish Heart and Lung Foundation was handed out, containing general information about AF including basic anatomy, physiology, symptoms and treatment. The physician's evaluation was made aided by a checklist to ensure that treatment was given according to guidelines. If OAC was not prescribed when indicated, an explanation was mandatory. Increased availability was also a part of the structured AF outpatient clinic. Patients could reach a nurse every weekday morning.

Outcomes

The primary outcomes were the effect of structured care on guideline adherence, symptoms, anxiety, depression and HRQoL. Adherence to guidelines was evaluated by five criteria: a) appropriate prescription of OAC according to the $CHADS_2$ and CHA_2DS_2-VASc criteria (table 1), b) echocardiogram performed, c) thyroid laboratory tests performed, d) no antiarrhythmic drugs (AA) prescribed to patients in permanent AF, and e) no class 1c-AA prescribed in the presence of structural heart disease. At the onset, the recommendation in the guidelines were based upon the $CHADS_2$ classification scheme and suggested the use of OAC when $CHADS_2$ ≥2 in patients without contraindications. During the study, new guidelines were published recommending the use of the CHA_2DS_2-VASc classification scheme and treatment with OAC for scores ≥1. Symptoms, anxiety, depression and HRQoL were assessed by the following questionnaires:

The Medical Outcomes Study 36-Item Short-Form Health Survey

The Medical Outcomes Study (MOS) 36-Item Short-Form Health Survey (SF-36) is a generic questionnaire designed to measure an individual's physical and mental health. It comprises 35 items grouped into eight scales and one question concerning changes in health outside the scales. The eight scales are physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH). For each of the eight scales scores were coded, summed, and transformed to a scale from 0 (worst possible health) to 100 (best possible health). The scoring of the SF-36 data was carried out as described by Ware and colleagues[9]. SF-36 has been widely used in research, including studies of patients with arrhythmias[6, 10].

The EuroQol Health Questionnaire, five dimensions and EuroQol Health Questionnaire, Visual Analog Scale

In The EuroQol Health Questionnaire, five dimensions (EQ-5D) and EuroQol Health Questionnaire, Visual Analog Scale (EQ-VAS) questionnaire was used to characterize health state. The EQ-5D questionnaire assesses five dimensions; patient mobility, self-care, activity, pain/discomfort, and mood, each with three levels of severity. The UK EQ-5D index tariff was used to obtain a weighted index, with a range from -0.59 to 1.0, where 1.0 represents full health[11]. The EQ-VAS records the respondents' self-rated health status on a vertically graduated (0–100) visual analogue scale with 100 (best imaginable health state) at the top and 0 (worst imaginable health state) at the bottom. EQ-5D/EQ-VAS has been extensively validated and is one of the most used generic HRQoL instruments in AF studies [10].

The Hospital Anxiety and Depression Scale

The domain specific questionnaire Hospital Anxiety and Depression Scale (HADS) is used to evaluate symptoms of anxiety and depression. It consists of two subscales, where seven questions assess anxiety (HADS-A) and the remaining seven assess depression (HADS-D). Responses are scored from 0 to 3 with higher scores denoting more psychological distress. The score for each subscale can range from 0 to 21. The scores are categorized as normal (0-7), mild (8-10), moderate (11-14) and severe (15-21) anxiety and/or depression respectively[12]. HADS has previously been used in AF studies[13].

The Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia

The disease-specific Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia (ASTA) is divided into three separate parts where part I evaluates the patient's latest episode of arrhythmia, current medication and the patients' subjective feeling of any

existence of arrhythmia. Part II evaluates symptom burden including frequency and duration of arrhythmia episodes, and contains a 10-item symptom scale with four response alternatives: "(0) No, (1)Yes, to a certain extent, (2) Yes, quite a lot and (3) Yes, a lot. Outside of the Symptom scale there are two questions concerning "near syncope" and "syncope" with the response alternatives Yes/No. Part III assesses the influence on HRQoL and consists of a 13-item scale with seven physical subscale items and six mental subscale items. The response alternatives are the same as for the symptom scale in part II[14, 15]. In order to evaluate experiences of achieved freedom from arrhythmia-specific symptoms and negatively influenced HRQoL after one year , the variables were dichotomized to the responses "Yes" or "No".

Statistics

In order to detect a five-point difference in the scales in SF-36 between the groups using an alpha of 0.05 and a power of 0.80, 200 patients in each group were required. Normally distributed variables are presented as means ± standard deviations, whereas categorical variables are presented as percentages and numbers. Differences between the two patient groups for normally distributed variables were tested with independent t-test, and paired t-test for differences over time within the groups. For non-normally distributed variables the Mann-Whitney U test was used for testing differences between two groups, and Wilcoxon's signed rank test within groups over time and McNemar's test was used for dichotomous variables. For categorical variables the Chi-square test or Fischer's exact test were used between groups, and for proportions the z-test with continuity correction was used. All calculations were made with SPSS statistical software version 20.0 (Armonk, NY: IBM Corp). P-values <0.05 were considered as statistically significant.

Results

Patient characteristics

The intervention group consisted of 199 patients and the control group of 162, and patients available for analysis were 176 (88%) and 146 (90%), respectively. (Figure 1). The two groups differed at baseline concerning educational degree, number of patients with $CHADS_2$ 0 p, and the number of patients having their first episode of AF (Table 2).

Guideline adherence

At baseline, there was no difference in treatment with OAC according to guidelines between the intervention group and the control group, 27 (65 %) vs. 17 (63 %, p = 0.88) using $CHADS_2$, and 51 (61 %) vs. 42 (55%, p = 0.43) using CHA_2DS_2-VASc. The number of patients treated according to guidelines after one year, in terms of adherence to all five criteria investigated, was significantly better in the intervention group, 152 (93%) vs. 105 (74%, p < 0.01). The difference in total adherence to guidelines was greater using the CHA_2DS_2-VASc in favour of the intervention group after one year, 148 (91%) vs. 89 (63%, p < 0.01). This was mainly due to an improvement in OAC treatment ([figure 2]). There were also significant differences in whether thyroid function was tested or not, 175 (99%) vs. 126 (86%, p < 0.01). However, there were no differences in investigations with echocardiogram, 164 (93%) vs. 133 (92%, p = 0.62), in whether patients were treated with AA although in permanent AF (none in both groups), or whether a class Ic-AA drug was used despite presence of structural heart disease (two patients in each group).

During follow-up, stroke, transient ischemic attack or peripheral embolus occurred in five patients (3%) in the intervention group and three patients (2%) in the control group. Two patients in the intervention group suffered from intracerebral bleeding, while one patient in the intervention group and one patient in the control group suffered from gastrointestinal bleeding.

The number of patients with CHA_2DS_2-VASc 0 p after one year was 21 (12 %) and 11 (8 %) in the intervention group and control group, respectively. However, seven (33 %) and five (46 %) of those patients were treated with OAC (n.s.) and the reasons were recent or planned ablation or DC-conversion, patients' own will to continue, close to reaching 65 years of age and in one patient a second echocardiography was planned since the left ventricular function was hard to evaluate due to arrhythmia in the first echocardiography.

Patient-reported outcome measures

The number of enrolled patients that did not return the questionnaires at follow-up was seven (4%) in the intervention group and 48 (33%) in the control group. There were also a number of missing answers within the questionnaires, hence the numbers of patients not included in the analyses of PROMs were greater for some scales.

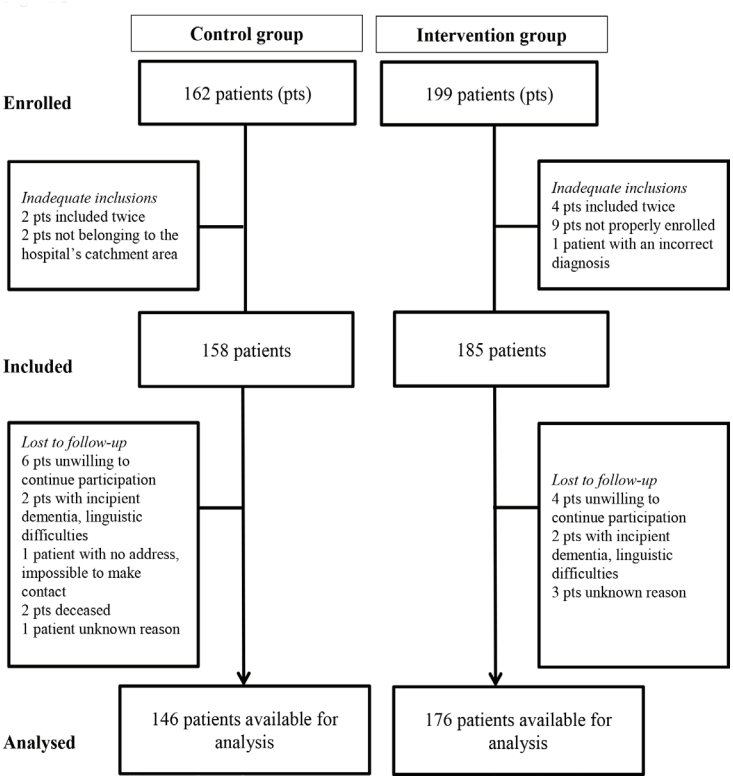

Figure 1: **Study inclusion flowchart**

Symptoms

Compared to the intervention group, patients in the control group reported more dizziness (p =0.01), cold sweat (p = 0.03), weakness (p = 0.02) and tiredness (p = 0.04) at baseline, and after one year more weakness (p = 0.04) and fatigue (p = 0.03), as assessed with ASTA. Over the year, significantly fewer patients were feeling pressure in the chest in the intervention group (figure 3) while no significant change was seen in the control group.

Anxiety and depression

The degree of anxiety assessed with HADS was normal atbaseline, e.g. ≤7 in 120 (75 %) patients in the intervention group and in 96

(79 %) patients in the control group. The degree of depression was normal in 128 (81%) and 106 (86 %) patients, in the intervention group and control group, respectively. There were no significant differences between the groups.

The degree of anxiety was reduced after one year in both groups, while depression did not change significantly (table 3). The scoring did not differ between the groups at the one year follow-up.

Health-related quality of life

At baseline, measured with the ASTA questionnaire, there were more patients in the control group who reported that they were

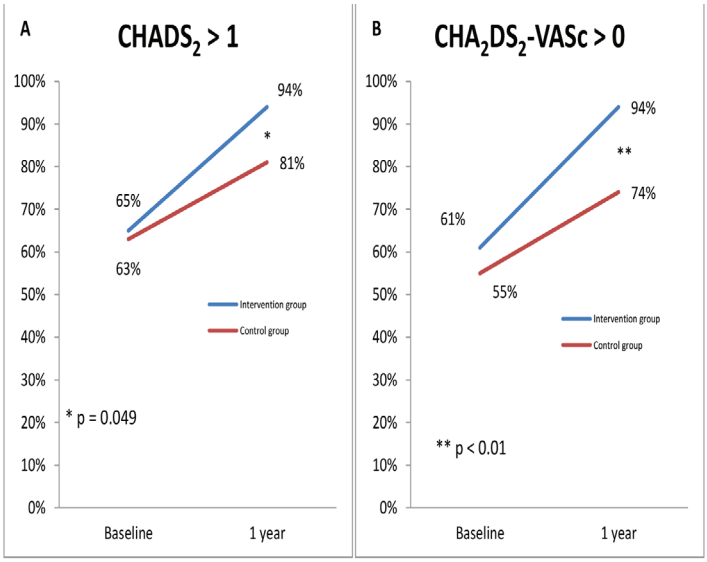

Figure 2: **The proportion of patients in the intervention and control groups treated with oral anticoagulation (OAC) according to guidelines using the $CHADS_2$-criteria (A) and the CHA_2DS_2-VASc-criteria (B) at baseline and at follow-up after one year.**

unable to work (p=0.01), more who avoided spending time with acquaintances (p=0.03) and family/relatives (p=0.03). After one year the patients in the intervention group were to a higher degree free from a negative influence on HRQoL compared to patients in the control group, where more patients were unable to work (p = 0.01).

There were differences between the two groups at baseline also in SF-36 (table 3). Patients in the intervention group scored higher in four scales (PF, RP, SF and RE) compared to patients in the control group. After one year there was significant improvement in both groups in the scales RP, VT, SF, MH and additionally RE in the control group. Both patient groups improved in their scoring in EQ-VAS while there were no differences in the EQ-5D index. There were no significant differences between the groups at the one year follow-up (table 3).

Comparisons with the norm population

When comparing the two patient groups at baseline with a norm population assessed by SF-36, the patients in the intervention group scored significantly worse (p<0.05) in six out of eight scales (RP, GH, VT, SF, RE, MH) while the patients in the control group scored worse in seven of the scales (PF, RP, GH, VT, SF, RE, MH) (figure 4).

After one year, the patients in the intervention group improved in two scales (SF and MH) and scored similar to the norm population, and even better than the norm population in the scale BP. The patients in the control group still scored worse in seven out of eight scales, i.e. in all except BP, equal to the situation at baseline.

Discussion

The main finding in this study on structured care given through an AF outpatient clinic was the significant improvement in guideline adherence. At the one-year follow-up the patients reached the HRQoL scores of a norm population to a higher degree compared to patients in the control group. Arrhythmia-specific symptoms were less frequently experienced in the intervention group and HRQoL improved, measured with the arrhythmia-specific questionnaire.

Several studies have shown a discrepancy between guidelines and everyday clinical practice in the management of AF[5, 16]. A Swedish study from 2002 showed that about 50 % of AF patients with indications for OAC actually received it[17]. Since the introduction of a risk factor-based approach for stroke prevention, i.e. $CHADS_2$/CHA_2DS_2-VASc-scores, there has been a considerable improvement in guideline adherence concerning OAC treatment[16].

However, contemporary data still indicate significant both under- and over-treatment with OAC in patients with AF, which is associated with poorer outcome and emphasizes the importance of guideline implementation[16]. Although appropriate antithrombotic treatment was higher in the control group at follow-up than shown in the results from older studies[5] and consistent with new promising reports[16], the structured care resulted in a greater improvement in adequate use of OAC. Studies show that guideline adherence concerning AF management and especially antithrombotic treatment, is improving worldwide[16], but this study shows the importance of structured care in order to improve guideline adherence.

The structured care in this study resulted in improved guideline adherence. The results are consistent with a study conducted by Hendriks et al., which showed a significant improvement in guideline

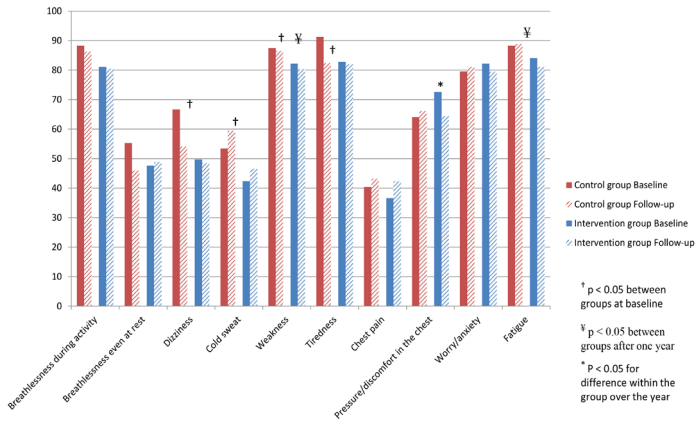

Figure 3: **Percentage of patients with any degree of symptoms, assessed with the Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia (ASTA) at baseline and after one year in the control and the intervention groups.**

adherence leading to a significant reduction in cardiovascular mortality and hospitalisation[18]. Another similarity between these two studies is the patients' reported measurements, where the patients in the control group had lower scores in symptom burden and HRQoL at baseline. In both studies, the scores of the generic SF-36 questionnaire improved in both groups, with no significant difference between the groups at follow-up[13]. Both studies suffer from a relatively large number of patients lost to follow-up, particularly regarding patients in the control group. However, in this

study, the SF-36 scores were to a greater extent improved to the level of the norm population in the intervention group.

Furthermore, in the disease-specific instrument, the intervention group improved more in HRQoL than the control group. Using the ASTA questionnaire allows both detection and reflection of disease-specific changes between patients and over time. The well-known SF-36 and EQ-5D questionnaires, which are often used in AF studies, are generic and thereby reflect general health, which is influenced by comorbidities, commonly present in patients with AF. Recommendations urge the use of disease-specific instruments, especially when measuring changes in symptom burden and HRQoL over time[19].

The degree of anxiety was significantly reduced in both groups. The fact that anxiety is a strong predictor of HRQoL[6,7] and that HRQoL can predict hospitalisation and mortality, emphasizes the importance of focusing on reducing anxiety in patients with AF. Treatment of patients with AF should thus focus on reducing symptoms, anxiety, depression and enhancing HRQoL in addition to being compliant with guidelines[19] .

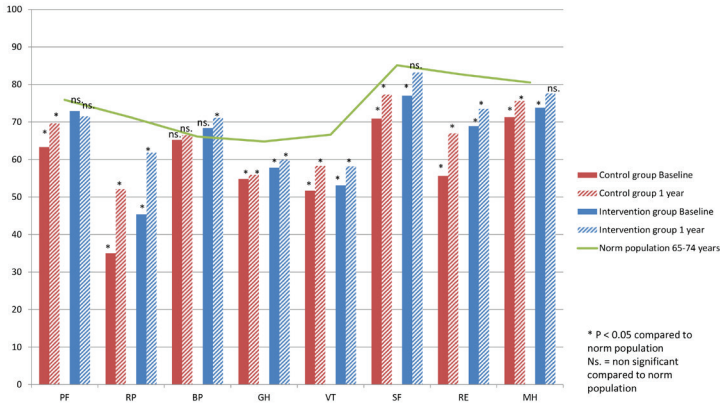

Figure 4: **SF-36 scores (means) in the control and intervention groups at baseline and after one year compared to a Swedish norm population, aged 65 to 74 years.**

Due to the complexity of the care of patients with AF, The Atrial Fibrillation Network and the European Heart Rhythm Association have recently highlighted the importance of development of structured patient-centred care, guided by risk profiling and symptom assessment. They also note that interdisciplinary dedicated AF services that incorporate lifestyle interventions are likely to facilitate such a structured model. They recommend the development of integrated and structured approaches to AF care led by interdisciplinary teams to improve the quality of care, and list the evaluation of structured care compared to current care as a research priority for the next five years[20]. Many of the recommendations mentioned above were carried out in this study, and the structured management was shown to improve the quality of care in patients with AF.

Study limitations

One important limitation is the non-randomised design of the study with the intervention group treated at one hospital while three other hospitals served as controls. This is probably the main reason for the observed differences at baseline. This design was probably also the reason for the relatively large number of patients not returning the questionnaires for follow-up, rendering the study underpowered to a certain extent.

Inclusion in the study was not consecutive for logistical reasons.

Conclusion

The study showed improvement in guideline adherence in the intervention group with structured AF care, mainly driven by improvement in OAC prescription. The degree of anxiety was reduced after one year and the scoring concerning HRQoL was improved in both patient groups. The arrhythmia-specific symptoms were less frequently experienced in the intervention group and HRQoL improved, and the SF-36 scores were more similar to the norm population compared to the control group at follow-up.

Disclosure

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Natural History Of Implantable Cardioverter-Defibrillator Implanted At Or After The Age Of 70 Years In A Veteran Population A Single Center Study

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Abstract

The median age of patients in major Implantable Cardioverter-defibrillator (ICD)trials (MUSTT, MADIT-I, MADIT-II, and SCD-HeFT) was 63-67 years; with only 11% ≥70 years. There is little follow-up data on patients over 70 years of age who received an ICD for primary/secondary prevention of sudden cardiac death, particularly for veterans. The aim of this study was to study the natural history of ICD implantation for veterans over 70 years of age. We retrospectively reviewed single center ICD data in 216 patients with a mean age at implantation 76 ± 4 years. The ICD indication was primary prevention in 161 patients and secondary prevention in 55 patients. The ICD indication was unavailable in 4 patients. Mean duration of follow up was 1686 ± 1244 days during which 114 (52%) patients died. Of these, 31% died without receiving any appropriate ICD therapy. Overall, 60/216 (28%) received appropriate therapy and 28/216 (13%) received inappropriate therapy. Patients who had ICD implantation for secondary prophylaxis had statistically more (p= 0.02) appropriate therapies compared to patients who had ICD implantation for primary prevention. Indication for implantation and hypertension predicted appropriate therapy, while age at the time of implantation and presence of atrial fibrillation predicted inappropriate therapies. Overall, 7.7% had device related complications. Although 28% septuagenarians in this study received appropriate ICD therapy, they had high rates of mortality, inappropriate therapy, and device complications. ICD implantation in the elderly merits individualized consideration, with higher benefit for secondary prevention.

Introduction:

Implantable cardioverter-defibrillator (ICD) is associated with reduction in arrhythmic death when implanted for either primary or secondary prevention of sudden cardiac death. [1], [2], [3], [4], [5]. More than 100,000 ICDs are implanted in the United States (US) annually, [6] with the majority of these (about 75%) implanted for primary prevention. [6] The mean age of patients receiving newimplants is 66 + 13 years and 43% of the new implants occur in patients > 70 years of age; [6] however, patients >70 years of age are underrepresented in the large clinical trials that have shown ICD benefit as a whole. A subgroup analysis of MADIT-II trial showed mortality benefit of ICD in patients > 70 years of age in multivariate analysis (HR 1.57, 1.02–2.41, p= 0.042). [7]

Key Words:
Implantable Cardioverter-Defibrillator,primary prevention,secondary prevention

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However, other studies have not shown consistent mortality benefit in this population .[8],[9],[10] This is also true in patients receiving an ICD for secondary prevention. [11] With advancing age and comorbidity burden, the relative contribution of noncardiac or non-arrhythmic causes of death [12], [9] may increase compared to younger patients, potentially attenuating the benefits of ICD therapy in older patients. This might be true even for those who have ICD implanted for secondary prevention. The ratio of sudden death to all cause death has been shown to fall steadily from 0.51 before age 50, to 0.26 after age 80, [9] especially in patients with heart failure orfollowing myocardial infarction. Thus, one would expect that elderly survivors of cardiac arrest may benefit less from the ICD than younger patients. This might be especially true in the veteran patient population, which has increased cardiovascular risk factors when compared to the general population.

Procedural outcomes reported in the ≥70 yr age group have also varied considerably with some studies showing increased risk of complications in the elderly [13] while others have contradictory findings. [14]Current guidelines do not address the criteria or prognosis of ICD implantation with advancing age. [8], [9], [10] Given the considerable variation in the reported data, and lack of specific guidelines for ICD implantation at an advanced age, we sought

Table 1: Baseline Characteristics of the Study Population

Parameters	Baseline Values (N= 216)
Age (years)	76 ± 4
Male	99%
Primary Prophylaxis Indication	75%
Secondary Prophylaxis Indication	25%
Diabetes	55%
Hypertension	96%
Coronary Artery Disease	86%
Atrial fibrillation	35%
Left ventricular Ejection Fraction at time of Implantation	28 ± 12 %
NYHA Class II	27.3%
NYHA Class III	39.3%
GFR at the time of implantation	59 ± 24 ml/min
Beta Blockers	78.2%
ACE-inhibitors/ARB	79.2%
Spironolactone	9.7%
Diuretics	61.5%
Aspirin	79.2%
Dual Antiplatelet Therapy	20%
Anticoagulation	29.1%

to look into the long-term survival and procedural outcomes after ICD implantation in the elderly (age > 70 years) veteran population.

Methods

Study Population

We retrospectively studied 4800 patients who were enrolled in the device clinic at the Richard L Roudebush, Veterans Affairs (VA) Medical Center, in Indianapolis, IN. Patients with pacemakers were excluded from the study, leaving 1660 patients who had an ICD, of which 268 had ICD implanted at or after the age of 70 years. Data was incomplete in 48 patients who were excluded from further analysis. Thus, a total of 220 patients were included in the study for analysis. Patients underwent ICD implantation between 1995 and 2014. During the analysis of primary versus secondary indication, four patients were further excluded because data for indication for implantation was missing. The computerized patient record system (CPRS) database was reviewed for comorbidities at the time of implantation. This also included reading through the scanned data in CPRS for outside medical records. Device recordings of patients who had ICD therapies were reviewed by an electrophysiologist at the time of clinic visit and then adjudicated by a second electrophysiologist (RJ) during the review of records for this study. To clarify disagreement in categorization of stored events those recordings were presented in the morning conference and the consensus agreements were used for analysis.

Data Collection

Cormorbidities

Comorbidities from the CPRS database were recorded at the time of initial implantation (or within 6 months thereafter). Ejection fraction data was collected through echocardiographic, nuclear medicine, or cardiac catheterization reports within 6 months prior to the date of ICD implantation.

Outcomes

The primary outcomes were all-cause mortality and appropriate ICD therapy (anti-tachycardia pacing {ATP} orshock). Secondary outcomes include inappropriate therapy (ATP or shock), and device-related complications at ≤ 30 days and > 30 days post-implant. Mortality data was collected through CPRS. The European community and the International standards organization have provided standard criteria for adverse events observed during trials with implantable medical devices, defining an adverse event as any undesirable clinical occurrence and taking into account the severity and relationship to the implanted device. [15] In our study, we excluded inappropriate therapies as device related complication (analyzed separately). Adverse events post device implantation included lead or device revisions, infections, hematoma, lead fracture, and device recalls. This was further subdivided into procedure related complications where device recalls were not included.

Statistical Analysis

Continuous variables were summarized by mean (standard deviation) or median (interquartile range) and compared using two-sample T test (if the normality assumption holds) or Wilcoxon rank-sum test (if the normality assumption did not hold). Normality of distribution was determined using the Kolmogorov-Smirnov goodness-of-fit test. Categorical data was summarized by frequency and percentage and analyzed using Fishers exact test. Distributions of time to death were estimated by Kaplan-Meier method and compared using log-rank test. Distributions of time to appropriate and inappropriate therapies are estimated and compared using the method of sub-distribution hazard [16] . Cox proportional hazard models (for mortality) and proportional sub-distribution hazard models [17] were used to account for baseline covariates. A risk score for total mortality was created using risk factors in the multivariate Cox model, where the score is the linear sum of the products of the risk factor values and corresponding regression coefficients. The score was then rescaled to have a range of 0-100, where a higher score indicates a higher risk of death.

Calculation of risk score

x is the covariate of patient and includes six variables (Age at implant, DM, Hyperlipidemia, Atrial Fibrillation, CAD, COPD). β is the coefficient vector of the cox model for mortality.

The linear predictor for each patients is defined as lp= xβ

The constant c is defined as $C=Max_{lp}-Min_{lp}/100$

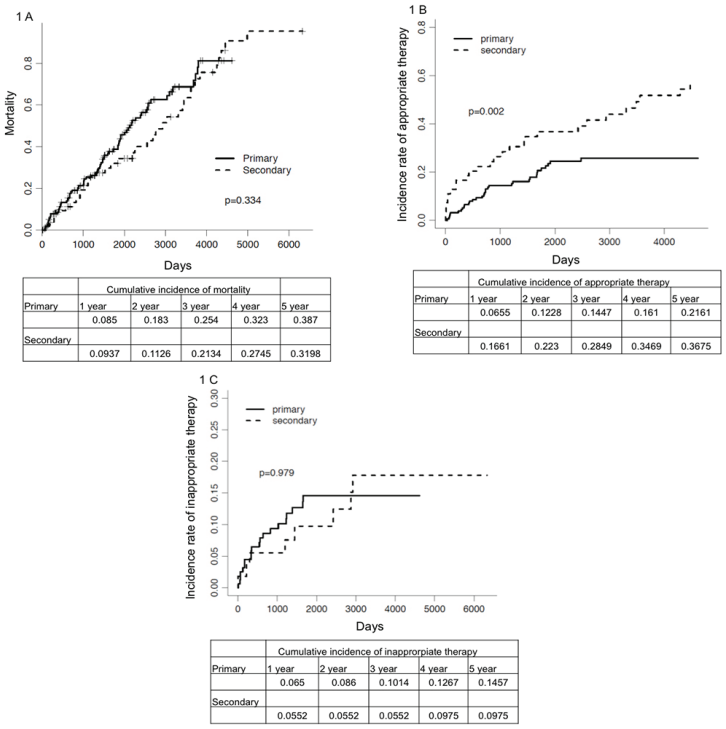
Max_{lp} is the maximum value of linear predictor for all patients in the sample set, the Min_{lp} is the minimum value of linear predictor for all patients in the sample set.

The risk score is defined as Score= $x\beta - Min_{lp}/C$. Then we can get the increment of the risk score when 1 unit increasing on the respective risk factors.

All analyses were performed using R 3.0. A two-sided p-value less than 0.05 is considered statistically significant.

Results

A total of 220 patients were included in the study. Baseline characteristics of the study population are shown in Table 1. The mean age of the study population was 76 ± 4 years. Except for one patient all were males. 161 (75%) patients had ICD implanted for primary prevention and 55 (25%) patients for secondary prevention. Overall, 119 (55%) patients had diabetes, 209 (96%) patients had hypertension, 186 (86%) patients had coronary artery disease (CAD), 76 (35%) patients had atrial fibrillation. Mean left ventricular ejection fraction (LVEF) at the time of implantation was 28 + 12%. There were 59 (27.3%) patients who had NYHA Class II heart failure



	Cumulative incidence of mortality				
Primary	1 year	2 year	3 year	4 year	5 year
	0.085	0.183	0.254	0.323	0.387
Secondary					
	0.0937	0.1126	0.2134	0.2745	0.3198

	Cumulative incidence of appropriate therapy				
Primary	1 year	2 year	3 year	4 year	5 year
	0.0655	0.1228	0.1447	0.161	0.2161
Secondary					
	0.1661	0.223	0.2849	0.3469	0.3675

	Cumulative incidence of inappropriate therapy				
Primary	1 year	2 year	3 year	4 year	5 year
	0.065	0.086	0.1014	0.1267	0.1457
Secondary					
	0.0552	0.0552	0.0552	0.0975	0.0975

Figure 1: **Kaplan Meier Curves comparing incidence of overall mortality, appropriate therapies and inappropriate therapies in primary versus secondary indication for implantation.**

(HF) and 85 (39.3%) patients had NYHA Class III HF. Mean GFR was 59 ± 24 ml/min. There were 169 (78.2%) patients taking beta-blockers, 79.2% (n= 171) on ACE-inhibitors or angiotensin receptor blockers (ARBs), 9.7% (n= 22) spironolactone, 61.5% (n= 133) diuretics, 79.2% (n= 171) aspirin, 20% (n=44) dual antiplatelet therapy and 29.1% (n=63) on anticoagulants (primarily warfarin 26.8% {n=63}). Mean follow up was 1686 ± 1244 days. 116 (53%) patients died during this period. At baseline, only atrialfibrillation was significantly different (higher in primary prevention group, 40.4% versus 20%) between the two groups. (Table 2)

Overall Data Analysis for Mortality

Out of 216 patients in the study, 114 (52%) patients died during the follow up duration. Out of 114, 35 (31%) received appropriate ICD therapy and 16 (14%) had inappropriate therapy. On univariate analysis, higher age at the time of implant (HR: 1.07, [CI: 1.03, 1.12], p = 0.002) , DM (HR: 1.66, [CI: 1.14, 2.4], p = 0.008), hyperlipidemia (HR: 1.69, [CI: 1.07, 2.67], p = 0.02), atrial fibrillation (HR: 1.54, [CI: 1.05, 2.27], p = 0.03), CAD (HR : 2.39, [CI: 1.33, 4.28], p = 0.003) and COPD (HR: 1.94, [CI: 1.31, 2.87], p = 0.001) were significantly associated with overall mortality. Age at the time of implant (HR: 1.10, [CI: 1.05, 1.15], p = < 0.00010), DM (HR: 1.62, [CI: 1.10, 2.40], p = 0.02), CAD (HR: 2.27, [CI: 1.24, 4.17], p = 0.008) and COPD (HR: 2.40, [CI: 1.60, 3.61], p = <0.0001) were significantly associated with mortality when applied to a model to develop predictors of mortality in our data.

Overall Data Analysis for Appropriate Therapy

Out of 216 patients, 60 (28%) received appropriate ICD therapies. On univariate analysis, indication for implantation (primary versus secondary) {HR: 0.41, (CI: 0.25, 0.68), p = 0.0005}, and hypertension {HR: 0.37, (CI: 0.16, 0.83), p = 0.016} were significantly associated with appropriate therapy. In a predictive model for appropriate ICD therapy, secondary prevention indication for implantation {HR: 0.43, (CI: 0.26, 0.70), p = 0.0009} and hypertension {HR: 0.37, (CI: 0.15, 0.95), p = 0.039} were the only two variables that predicted appropriate therapy. Patients with a secondary prophylaxis indication had 67 times higher risk chance of receiving appropriate therapy as compared to a primary prevention implant.

Overall Data Analysis for Inappropriate Therapy

Of the patients 216 patients, 28 (13%) received inappropriate therapies. On univariate analysis, age at the time of implantation {HR: 0.87, (CI: 0.80, 0.95), p = 0.003} and presence of atrial fibrillation {HR: 2.19, (CI: 1.05, 4.6), p = 0.04} were significantly associated with inappropriate therapies. In a predictive model for inappropriate therapy, age at time of implantation {HR: 0.87, (CI: 0.79, 0.95), p = 0.002} and atrial fibrillation {HR: 2.33, (CI: 1.11, 4.89), p = 0.025} remained significant predictors of inappropriate therapies.

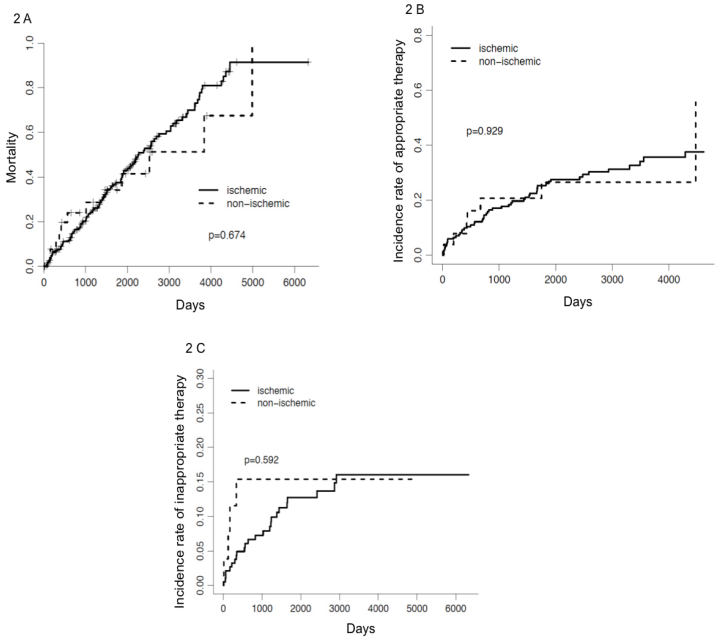


Figure 2: **Kaplan Meier Curves comparing incidence of overall mortality, appropriate therapies and inappropriate therapies in patients with ischemic versus non ischemic cardiomyopathy.**

Mortality in Primary Versus Secondary Prevention Group

There were a total of 114 (52%) deaths. Out of these, 78 (48%) had received ICD implantation for a secondary prevention indication, while 36 (66%) were primary prevention implants. In patients who had the ICD implanted for primary prevention of SCD, the 1 year mortality was 9% and 5 year mortality was 39%, not significantly different as compared to 9% and 40% in the secondary prevention group.

Appropriate ICD Therapy in Primary Versus Secondary Prevention Group

Of the 60 (27.8%) patients who received appropriate shocks, 33 (20.5%) were in patients who had secondary prophylaxis as the indication for implantation. In patients who had the ICD implanted for secondary prophylaxis, 17% received appropriate shocks in 1 year and 37% within 5 years compared to 7% and 22% respectively for patients who received the ICD for primary prophylaxis. In 55 patients who received ICD for secondary prophylaxis, 36 (65.5%) received an appropriate shock.

Table 2: Baseline Characteristics

	No. of Participants (%)			
Characteristics	**Total (n = 216)**	**Primary (n =161)**	**Secondary (n=55)**	**P Value**
Age, mean (SD), y Ischemic	76.38 (4.27)	76.40 (4.23)	76.45 (4.50)	0.94
Yes No	191 (88.0) 26 (12.0)	139 (86.3) 22 (13.7)	51 (92.7) 4 (7.3)	0.21
DM				
Yes No	119 (54.3) 100 (45.7)	91 (56.9) 69 (43.1)	28 (50.9) 27 (40.1)	0.44
Hypertension				
Yes No	209 (95.0) 11 (5.0)	156 (96.9) 5 (3.1)	51 (92.7) 4 (7.3)	0.18
Smoking status				
Current smoker Former smoker No smoking	48 (21.9) 70 (32.0) 101 (46.1)	36 (22.5) 52 (32.5) 72 (45.0)	10 (18.2) 18 (32.7) 27 (49.1)	0.78
History of Hyperlipidemia				
Yes No	169 (77.2) 50 (22.8)	126 (78.7) 34 (21.3)	42 (76.4) 13 (23.6)	0.71
GFR time, mean (SD), ml/min Chronic Kidney Disease	59.8 (21.3)	59.7 (21.6)	60.3 (20.4)	0.88
Yes No	91 (41.5) 128 (58.5)	67 (41.9) 93 (58.1)	24 (43.6) 31 (56.4)	0.8
Atrial Fibrillation				
Yes No	76 (34.5) 144 (65.5)	65 (40.4) 96 (59.6)	11 (20.0) 44 (80.0)	0.0063
Coronary artery disease				
Yes No	186 (84.5) 34 (15.5)	138 (85.7) 23 (14.3)	47 (85.5) 8 (14.5)	0.96
Chronic obstructive pulmonary disease				
Yes No	62 (28.3) 157 (71.7)	43 (26.9) 117 (73.1)	18 (32.7) 37 (67.3)	0.41
Transient ischemic attack/stroke				
Yes No	18(8.2) 201 (91.8)	15 (9.4) 145(90.6)	3 (5.5) 52 (94.5)	0.37

Inappropriate ICD Therapy in Primary Versus Secondary Prevention Group

Of the 28 patients who received inappropriate shocks, 20 (12.4%) were in patients who had primary prophylaxis as the indication for implantation and the remaining 8 (14.5%) in secondary prophylaxis patients. In patients who had the ICD implanted for secondary prophylaxis, 6% received inappropriate shocks in 1 year and 10% within 5 years compared to 7% and 15% respectively for patients who received ICD for primary prophylaxis.

Adverse events post device implantation

Twenty-three (10.4%) patients had device related complications. Out of these 23 patients, 13 died, 4 received appropriate therapy and 3 had inappropriate therapy. Two patients had both appropriate and inappropriate therapies. Six patients (23%) had complications on the day of implant, 23% had within 30 days (excluding those who had on the day of implant) and 48% had complications after 30 days of implant.

Excluding device or lead recalls, 17 had complications (7.7%). The complications included infection, hematoma, lead fracture, coronary sinus dissection, right ventricular perforation and lead revision.

New Risk Score for Overall Mortality

Based on the available data we looked at possible predictors of overall mortality in septuagenarians referred for ICD implantation. A risk score was developed based on the variables that were significant for mortality in multivariable analysis for mortality. The overall mortality based on the risk score is shown in figure 3. To better understand this we can use the following examples:

1. A 75 year old patient without any risk variables has a score of 6.2.
2. A patient who is 78 years old with diabetes mellitus, no hyperlipidemia, no atrial fibrillation, no CAD and no COPD has a score of 26.
3. A patient who is 79 years old with diabetes mellitus, hyperlipidemia, atrial fibrillation, CAD and COPD has a score of 89.

The survival curves in figure 3 can then be used to predict 1 year and 5 year mortality in the above patients.

Discussions

Life expectancy in general population at the age of 70 years is 14.2 years in males and 16.4 years in females [18]. 53% of our study population died during the follow up period of 4.6 years with 1-year and 5-year mortality being 19% and 71% respectively. This is consistent with other studies with 1-year and 5-year mortality rates of around 20-40 % and 75-80% respectively in patients with heart failure and mean age of >70 years [19], [20]. However, it is significantly different

Table 3a: Survival Analysis for all cause mortality

Parameters	Hazard ratio	95% CI	p value
Primary or secondary	1.22	(0.81 , 1.84)	0.334
Age at implant	1.07	(1.03 , 1.12)	0.00234
Ischemic	1.13	(0.62 , 2.08)	0.675
DM	1.66	(1.14 , 2.42)	0.00818
Hypertension	2.60	(0.95 , 7.15)	0.063
Smoking Status	1.37	(0.88 , 2.14)	0.159
	1.25	(0.79 , 1.97)	0.343
Hyperlipidemia	1.69	(1.07 , 2.67)	0.0243
GFR time	0.99	(0.98 , 1.00)	0.203
Chronic Kidney Disease	1.43	(0.99 , 2.08)	0.057
Atrial Fibrillation	1.54	(1.05 , 2.27)	0.027
CAD	2.39	(1.33 , 4.28)	0.00339
COPD	1.94	(1.31 , 2.87)	0.000922
TIA	0.94	(0.48 , 1.87)	0.87
LVEF	1.00	(0.99 , 1.02)	0.591

IDM: Diabetes Mellitus, GFR: Glomerular filtration rate, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, TIA: Transient ischemic attack, LVEF: Left ventricular ejection fraction.

from the 1-year and 5-year mortality in MADIT- 2 trial comparing patients with ICD and no-ICD (8% vs. 10% and 33% vs. 43%) with mean age of 64 years [21] and 5-year mortality in the Sudden Cardiac Death in Heart Failure Trial SCD-HeFT trial comparing patients with ICD and placebo (29% vs 36%) with mean age of 60 years [22].

Further, in a subgroup analysis of MADIT-2 trial evaluating 204 elderly patients (aged >75 years) with ischemic cardiomyopathy, there was a non-significant trend towards benefit with ICD therapy (HR: 0.56; 95% CI: 0.29-1.08; P= 0.08). Similarly, subgroup analysis in SCD-HeFT [22] and Comparison of Medical Therapy, pacing and Defibrillation in Heart Failure (COMPANION) studies [23] also showed little mortality benefit. This could be secondary to an increase in non-arrhythmic causes of death with increasing age, which is not prevented by an ICD. [12] , [9]

In our study, age at the time of implant, DM, CAD, COPD and atrial fibrillation was predictors of all-cause mortality. This is similar to the report of Lee et al. [12] that showed age and noncardiac comorbidities influence survival in the care of ICD recipients. They used administrative data to show that survival after ICD implantation was inversely related to an increasing number of comorbidities. Buxton et [24] also reported a risk stratification and found that NYHA class, conduction disturbance, history of heart failure, LVEF, atrial fibrillation, and age were predictors of mortality. We did not find a difference in mortality in primary versus secondary as indication for implantation. However, the above mentioned comorbidities were associated significantly with mortality. In our study, 16.6 % and 22% of patients who had ICD implanted for secondary prophylaxis received appropriate therapy by 1 and 2 years respectively. This is much lower than what has been previously reported in the Antiarrhythmics Versus Implantable Defibrillator (AVID) trial. In that trial, at least one episode of therapy, either ATP or shock, was delivered in 51% of patients at 1 year, censoring patients who had died. [3] In our study 28% received appropriate therapy and 37% died without receiving any appropriate therapy. Patients who had ICD implanted for secondary prophylaxis were 57 times more likely to receive appropriate therapy compared to when primary prophylaxis was the indication for implantation. For reasons difficult to explain, hypertension was one of the predictors for appropriate therapies.

Table 3b: Multivariate Analysis for All cause mortality

	Hazard ratio	95% CI	p value
Age at implant	1.10	(1.05 , 1.15)	0.0000682
DM	1.62	(1.10 , 2.40)	0.01438
Hyperlipidemia	1.29	(0.80 , 2.08)	0.29114
Atrial Fibrillation	1.47	(0.99 , 2.17)	0.05559
CAD	2.26	(1.23 , 4.15)	0.00857
COPD	2.41	(1.60 , 3.61)	0.0000248

Table 4a: Univariate anlaysis for Appropriate therapy

Parameters	Hazard ratio	95% CI	p value
Primary or secondary	0.41	(0.25 , 0.68)	0.00045
Age at implant	0.97	(0.91 , 1.04)	0.43
Ischemic	0.99	(0.46 , 2.16)	0.98
DM	1.03	(0.62 , 1.70)	0.91
Hypertension	0.37	(0.16 , 0.83)	0.016
Smoking Status	1.10	(0.61 , 1.97)	0.75
	1.18	(0.63 , 2.20)	0.6
Hyperlipidemia	1.06	(0.59 , 1.93)	0.84
GFR time	1.00	(0.98 , 1.01)	0.54
Chronic Kidney Disease	1.44	(0.87 , 2.37)	0.15
Atrial Fibrillation	0.80	(0.46 , 1.41)	0.45
CAD	1.74	(0.82 , 3.71)	0.15
COPD	1.48	(0.88 , 2.50)	0.14
TIA	0.96	(0.38 , 2.41)	0.93
LVEF	1.00	(0.98 , 1.02)	0.85

DM: Diabetes Mellitus, GFR: Glomerular filtration rate, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, TIA: Transient ischemic attack, LVEF: Left ventricular ejection fraction.

The appropriate therapy rate of 6.5% for primary prophylaxis is similar to the rate reported in the literature [3], [2]. In our study, 7.62 % of patients received inappropriate therapy at 2 years, 11% at 45.5 months and 12.9% at 5 years of follow up respectively. This is less than what has been reported in MADIT-II [25] and SCD-HeFT trials [22]. In SCD-HeFT, [22] 17% of patients received inappropriate shocks over a median of 45.5 months of follow-up. Similarly in MADIT-II, 13% of patients had inappropriate shocks during 2 years of follow-up [25].

Table 4b: Multivariate Analysis for Appropriate Therapy

	Hazard ratio	95% CI	p value
Primary or secondary	0.43	(0.26 , 0.70)	0.00081
Hypertension	0.37	(0.15 , 0.95)	0.039

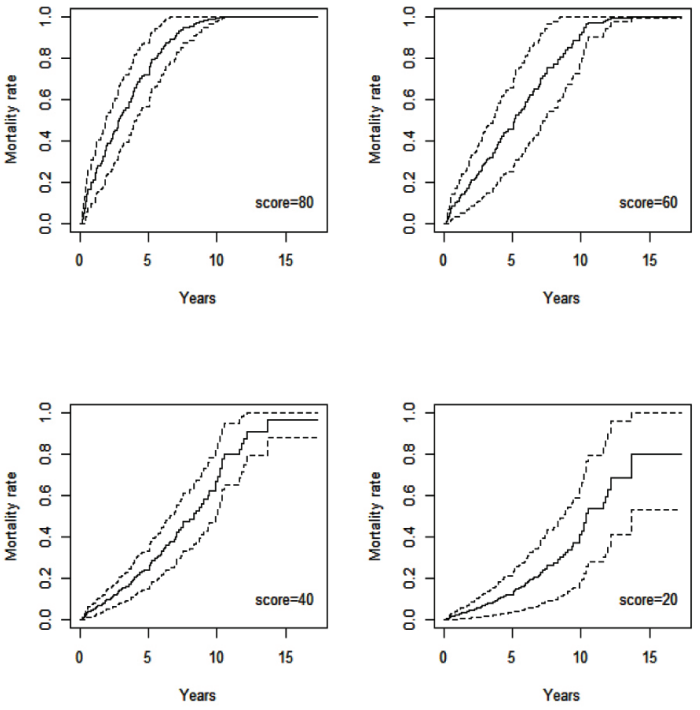


Figure 3a: Overall mortality for subjects with different risk scores

Table 3a.1: Multivariate Analysis for All cause mortality

	1 year Mortality rate and 95 % CI		5 year Mortality rate and 95 % CI	
Score=80	0.2122	(0.1026 , 0.3217)	0.7207	(0.5672 , 0.8742)
Score=60	0.1067	(0.0502 , 0.1631)	0.4530	(0.3230 , 0.5830)
Score=40	0.0505	(0.0210 , 0.0799)	0.2419	(0.1480 , 0.3357)
Score=20	0.0243	(0.0062 , 0.0424)	0.1234	(0.0501 , 0.1967)

In these studies, the most common cause of inappropriate shocks in decreasing order of frequency were atrial fibrillation; supraventricular tachycardia; and oversensing caused by lead fracture, T wave oversensing, and electromagnetic interference. In our study, age at the time of implant and presence of atrial fibrillation (AF) were predictors for inappropriate therapies. This is easily understandable. The prevalence of atrial fibrillation increases with age [26] with 2.3% at age 40 years and 5.9% at age 65 years. Approximately 70% of individuals with AF are between 65 and 85 years of age [27]. The finding that atrial fibrillation was a primary reason for inappropriate therapy, combined with the increased

Figure 3b: Incremental risk score with different variables.

Variables	Incremental Risk Score
Age at implant	2.4 per one year increase
DM	12.6
Hyperlipidemia	6.7
Atrial Fibrillation	10.0
Coronary artery disease	21.2
COPD	22.8

Table 5a: Univariate anlaysis for Inappropriate therapy

Parameters	Hazard ratio	95% CI	p value
Primary or secondary	0.97	(0.44 , 2.15)	0.95
Age at implant	0.87	(0.80 , 0.95)	0.0029
Ischemic Cardiomyopathy	0.76	(0.26 , 2.26)	0.62
DM	1.63	(0.76 , 3.51)	0.21
Hypertension	2.60	(0.95 , 7.15)	0.063
Smoking Status	0.62	(0.24 , 1.58)	0.31
	1.00	(0.41 , 2.43)	1
H/o Hyperlipidemia	0.62	(0.28 , 1.37)	0.23
GFR	1.01	(0.99 , 1.03)	0.26
Chronic Kidney Disease	0.67	(0.30 , 1.47)	0.32
Atrial Fibrillation	2.19	(1.05 , 4.56)	0.037
CAD	1.63	(0.48 , 5.55)	0.44
COPD	1.26	(0.56 , 2.78)	0.57
TIA	1.23	(0.39 , 3.86)	0.72
LVEF	1.01	(0.97 , 1.01)	0.42

DM: Diabetes Mellitus, GFR: Glomerular filtration rate, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, TIA: Transient ischemic attack, LVEF: Left ventricular ejection fraction.

prevalence of atrial fibrillation with age, likely explains why we found associations of age and atrial fibrillation with inappropriate therapy

Overall device related adverse events in our study population was 10.5% which is higher compared to NCDR registry data with complication rate of 5.8% in 2006 to 4.8% in 2010 in

Table 5b: Multivariate Analysis for Inappropriate Therapy

Parameters	95% CI	p value
Age at implant	(0.79 , 0.95)	0.0019
Atrial Fibrillation	(1.11 , 4.89)	0.025

patients >65 years of age [28]. However, NDCR doesn't include device recalls as complications. If device/lead recalls are excluded from adverse events in our study, the complication rate drops to 7.7%, which is still higher than 4.8% mentioned above. Possible reasons for this higher incidence of complications include: 1. Infection and hematoma could be secondary to a higher incidence of advanced comorbidities in this age group. 2. Immunosenescence has been used to describe loss of immune functions in elderly individuals (> 65 years old). Although the mechanisms leading to immunosenescence are not clear, it has been associated with increased susceptibility to disease, infections, and poor response to treatments and vaccination [29].

Limitations

There are several limitations of this study. First, it is a retrospective study with a relatively small sample size. A detailed review of the records was done which included review of outside records, which were scanned in the CPRS. However, there could have been some arrhythmia episodes (therapy), which might have been missed and not recorded in the system. The veteran population is special with a different set of comorbidities from the general population and therefore the results of this study might not be generalized to the overall population. We propose a newer scoring system to

Table 6: Device Related Complications in the Study Population

Patient	Indication	Age at Implantation (years)	Implant to Death (years)	Age at Death (years)	Time to Appropriate Therapy (days)	Time to Appropriate Therapy (days)	+/- 1 day of implant	< 30 Post Implant Complication	> 30 Day Post Implant Complication	Complication
209	Primary	73.2	0.8	74				Yes		Hematoma
133	Secondary	72.7	2.3	75					Yes	Infection
258	Primary	83.9	3.1	87					Yes	Lead fracture leading to multiple shocks
241	Primary	70.9	5.1	76	791				Yes	Recall
254	Primary	72.3	5.7	78					Yes	Vegetation on lead
131	Primary	77.3	6.7	84		63		Yes		Hematoma
194	Primary	79.1	6.9	86	497	1654			Yes	Recall
267	Primary	72.2	7.8	80		53	Yes			LV lead dislodgement
182	Primary	74.6	8.4	83			Yes			Device recall
193	Secondary	75.6	8.4	84		1440			Yes	Lead Fracture
66	Secondary	78.3	8.7	87				Yes		Recall-component failure
273	Secondary	70.6	9.4	80	191	2870			Yes	Lead fracture
260	Secondary	76.8	14.2	91	4473		Yes			Lead revision
41	Primary	77.4	0.85				Yes			Hematoma
54	Secondary	76.6							Yes	Battery recall
55	Primary	86.4			669				Yes	Battery recall
65	Primary	73.1						Yes		ICD pocket infection
101	Primary	75.7							Yes	LV lead noise
102	Primary	81.1							Yes	Infection
105	Primary	77.6					Yes			CS Dissection
106	Secondary	72.4			2424				Yes	Lead fracture
122	Secondary	73.2				Yes				RV perforation
129	Primary	72.2						Yes		Hematoma
141	Primary	75.9			306				Yes	Battery Recall
160	Primary	80.3						Yes		Hematoma

estimate overall mortality when the patient is first seen in the clinic for an ICD. This needs validation in prospective study.

However, this is an important step for futureprospective studies, which might lead to a new section in ICD guidelines, addressing this specific age group

Conclusion

To our knowledge, our study represents the first attempt to look into the natural history of ICDs when implanted at ≥70 years of age in veterans. This is a very special population with multiple different comorbidities. The findings from this study suggest that ICD implantation in the elderly should be given individualized consideration. We believe that current criteria for ICD implantation cannot be fully applied to this age group and prospective studies are needed for better define this age group.

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Inappropriate Dosing Of Direct Oral Anticoagulants In Patients With Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) is a common cardiovascular disease for which newer oral anticoagulants are available. The main objective of this study was to evaluate the appropriateness in prescriptions of direct oral anticoagulant (DOACs), more specifically apixaban, dabigatran and rivaroxaban. This was a single-centre, retrospective study conducted in the province of Quebec, Canada. Adult subjects hospitalized between October 2011 and October 2014, with a diagnosis of AF, and a DOAC prescription were included. Data were retrieved from the electronic medical records and prescriptions were evaluated according to appropriateness criteria. A total of 500 subjects were included (235 subjects on dabigatran, 222 on rivaroxaban and 43 on apixaban). Overall, 70.4% (95% confidence interval [CI] 66.4–74.1) of DOAC prescriptions were considered appropriate. About 24% of subjects received an inappropriate dose of apixaban, dabigatran or rivaroxaban. A reduced dose was prescribed in 56.8% of subjects with no clear indication, and 43.2% received a dose that was not reduced while indicated. DOACs were frequently prescribed at a dose that was considered inappropriate. There is a need to strengthen dosing recommendations of DOACs in clinical practice.

Introduction

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia. AF affects between 1% and 2% of the population and its prevalence increases with age [1, 2]. AF is associated with a three to five-fold increased risk of ischemic stroke, and anticoagulants are effective in preventing thromboembolic events [3, 4]. Vitamin k antagonists (warfarin) have mainly been used in AF management, but direct oral anticoagulants (DOACs) such as dabigatran, rivaroxaban and apixaban are increasingly used. DOACs have a rapid onset of action, few food drug interactions, and blood monitoring is required less frequently when compared with warfarin. However, DOACs are contraindicated in patients with severe renal failure (creatinine clearance [CrCl] <25-30 mL/min), and not all have antidotes to reverse their effect [5, 6]. Selecting the appropriate dosing of DOACs is important to prevent thromboembolic events and reduce the risk of bleeding. Warfarin has been used for several years and its efficacy and long-term safety are well known [5]. However, only a few real-world studies on DOACs have been published [7-14]. Short-term studies have confirmed the efficacy and safety of DOACs in AF [15-17], but it is essential to evaluate their appropriateness in use. Thus, the main objective of this study was to evaluate overall appropriateness in prescriptions of DOACs in adults with AF.

Key words

Atrial fibrillation, direct oral anticoagulants, apixaban, dabigatran, rivaroxaban

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Material and methods

Study design and study population

A retrospective cohort study was conducted in a single centre (Centre hospitalier universitaire de Sherbrooke, Quebec, Canada). The study population included subjects hospitalized between October 2011 and October 2014, with a diagnosis of AF documented on the discharge summary. Subjects were identified using ICD-10 codes (International Statistical Classification of Diseases and Related Health Problems - 10th revision) for the diagnosis of AF (I48X, I48.XN-001 and I48.XN-002). Medical records were reviewed to determine eligibility (inclusion and exclusion criteria are listed in Table 1). Only the first hospitalization following October 1th 2011, was selected.

Data Collection:

Electronic medical records were reviewed, more specifically the discharge summary, laboratory data (values that were closest to DOAC prescription), and discharge prescriptions. Data collected for each subject were sociodemographic characteristics (age, gender, weight, height and body mass index), serum creatinine (to estimate renal function using the Cockcroft-Gault equation), liver enzymes, comorbidities, length of stay, healthcare unit of admission, concomitant medications that are contraindicated with DOACs (ketoconazole, itraconazole, voriconazole, posoconazole and ritonavir) or known to increase bleeding risks (antiplatelets and nonsteroidal anti-inflammatory drugs (NSAIDS). Valvular AF was determined when the diagnosis was specified on the discharge summary or in the presence of mitral or tricuspid valve replacement or repair.

Appropriateness in Prescriptions:

The appropriateness criteria were developed and reviewed by the anticoagulotherapy committee of our institution. The criteria were mainly based on DOACs product monographs along with the 2012 update of Canadian Society of Cardiology (CSC) guidelines [18-22]. The appropriateness criteria used are presented in Table 2. A total of 8 appropriateness criteria were evaluated for each subject included in the study.

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• At least 18 years of age at the time of hospitalization	• AF associated with: congenital heart disease, uncontrolled hyperthyroidism, illicit drug or drug intoxication
• Diagnosis of AF documented on the discharge summary	• Another indication for anticoagulation such as deep vein thrombosis, pulmonary embolism, orthopedic surgery or hypercoagulable state
• DOAC prescribed during hospitalization and at discharge	• AF with a duration of less than 48 hours
• Availability of a discharge prescription and the list of usual medications	• Peri-operative AF

Table 2: Appropriateness criteria for DOACs prescriptions

Criteria
1. Type of AF DOACs are prescribed in patients with non-valvular AF (i.e. mitral or tricuspid valve replacement or repair) [18].
2. Mitral stenosis In the case of mitral stenosis, DOACS are prescribed in patients with mild to moderate mitral stenosis only (not moderate to severe) [18].
3. CHADS2 score When DOACs are prescribed, the CHADS2 score is ≥ 1. If the CHADS2 score = 0, the CHA2DS2-VASc score must be ≥ 2 or there has been a cardioversion [18].
4. Heart valves In the case of heart valves, DOACs are used in patients with a bioprosthetic valve (and not a mechanical valve) [19].
5. Concomitant medication DOACs are prescribed in patients that do not use ketoconazole, itraconazole, voriconazole, posaconazole or ritonavir [5, 20-22].
6. Renal function Dabigatran and rivaroxaban are prescribed when the estimated CrCl is ≥ 30 mL/min [5, 21, 22]. Apixaban is prescribed when CrCl is ≥ 25 mL/min [20].
7. Liver enzyme levels DOACs are prescribed if blood levels of AST and ALT are ≤ twice the upper limit of normal [5].
8. a. Dose of dabigatran Dabigatran is prescribed at a reduced dose of 110 mg twice daily if one of the following factors is present: • Weight < 50 kg • Age ≥ 80 years old • Haemorrhagic risk factors: HAS-BLED score ≥ 3 and/or CrCl is between 30 and 49 mL/min [5, 21].
8. b. Dose of rivaroxaban Rivaroxaban is prescribed at a reduced dose of 15 mg once daily if CrCl is between 30 and 49 mL/min [5, 22].
8. c. Dose of apixaban Apixaban is prescribed at a reduced dose of 2.5 mg twice daily when 2 of the 3 following criteria are present: Serum creatinine > 133 µmol/L • Age ≥ 80 years old • Weight ≤ 60kg [5, 20].

Legend: CrCl, creatinine clearance; CHADS2: Congestive Heart Failure, Hypertension, Age ≥ 75 years, Diabetes, Stroke; CHA2DS2-VASc: Congestive Heart Failure, Hypertension, Age ≥ 75 years old, Diabetes, Stroke history, Vascular disease, Age between 65 and 74 years, Sex Category; HAS-BLED: Hypertension, Abnormal renal and/or liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs.

Statistical Analyses

Baseline characteristics were described estimating means, medians, standard deviations, ranges and proportions with 95% confidence intervals (CI). The proportion (with 95% CI) of prescriptions that were in accordance with each of the 8 appropriateness criteria was initially calculated. Then, the proportion (with 95% CI) of prescriptions that were in accordance with all appropriateness criteria for a given DOAC was estimated. Statistical analyses were performed using the IBM SPSS Statistics software.

Ethical Considerations

This project was approved by the ethics committee of our institution. Data were kept confidential using a denominalized database.

Results

A total of 1051 subjects were initially screened for their eligibility, and 551 were excluded (Figure 1). Most of them had an exclusion criterion (n=417) and 134 were previously selected (more than one hospitalization). The main reasons for exclusion were the lack of a discharge prescription (80.3%), DOAC not prescribed at discharge (17.0%) and anticoagulation for an orthopedic surgery (7.4%). Thus, 500 subjects were included, 235 on dabigatran, 222 on rivaroxaban and 43 on apixaban. More patients were on dabigatran and rivaroxaban because they were introduced earlier (October 2011, and March 2013, respectively), than apixaban (January 2014) on the therapeutic formulary. Excluded and included subjects had similar baseline characteristics (Supplementary Table 1).

Table 3 presents sociodemographic characteristics, hospitalization data, laboratory values, comorbidities, and concomitant drugs. Data on compliance related to each appropriateness criteria are found in Table 4. Subjects were 74 years old on average, and about half were males (52.4%). Most subjects (71%) had a body mass index (BMI) greater than 25.0 kg/m2. Subjects were mainly hospitalized at the cardiology unit (41.0%), followed by internal medicine (21.4%), family medicine (17.0%), neurology (8.6%) and respiratory medicine units (3.4%). Moreover, 63.4% of subjects were previously anticoagulated.

Overall, 70.4% (95%CI 66.4–74.4) of subjects were prescribed a DOAC in accordance with all criteria. A high proportion of subjects (94.6%) had a thromboembolic score (CHADS2 score) equal to or greater than 1. In patients who had a CHADS2 score of 0 (n=27), 13 had a CHA2DS2-VA2Sc score of at least to 2 and/or a cardioversion, and 6 had a surgical ablation. About 3% of patients had valvular AF and 1.0%, moderate to severe mitral stenosis. No patients had a me-

Table 3: Baseline characteristics of included patients (n=500)

Characteristics		n (%) *
Age (years), mean ± SD		74.3 ± 11.5
Male gender		262 (52.4)
BMI (kg/m2)°	< 18.5	12 (2.4)
	18.5 – 24.9	132 (26.6)
	25.0 – 29.9	164 (33.0)
	≥ 30.0	189 (38.0)
Hospitalization data		5; 1 – 70
Length of stay, median; range (days)		
Health Care units	Cardiology	205 (41.0)
	Internal medicine	107 (21.4)
	Family medicine	85 (17.0)
	Neurology	43 (8.6)
	Surgery	22 (4.4)
	Respirology	17 (3.4)
	Others[1]	21 (4.2)
Laboratory data		
CrCl (CG), median; range (mL/min) °		63.9; 20.4 – 120.0
CrCl < 30 mL/min		11 (2.2)
Level of liver enzymes °	AST, median ; range (U/L)	21; 8-155
	ALT, median ; range (U/L)	17; 5-529
Clinical data		
Atrial flutter		79 (15.8)
Valvular AF		13 (2.6)
Mitral stenosis	Mild to moderate	25 (5.0)
	Moderate to severe	5 (1.0)
Biological heart valve		13 (2.6)
Congestive heart failure		183 (36.6)
Hypertension		397 (79.4)
Diabetes		157 (31.4)
Stroke		139 (27.8)
Atherosclerotic heart disease		212 (42.4)
Atherosclerotic vascular disease		84 (16.8)
Cirrhosis		5 (5.2)
CHADS2 ≥ 1		473 (94.6)
CHADS2-VA2Sc ≥ 2		455 (91.0)
Drugs		10 ; 2 – 8
Number of drugs at discharge, median ; range	Prevalent	82 (16.4)
	Incident	30 (6.0)
Antiplatelets	Switch	317 (63.4)
NSAIDs		148 (29.6)
DOACs user's type		35 (7.0)

Legend: BMI, body mass index; CrCl, creatinine clearance; CG, Cockroft-Gault; NSAIDs, nonsteroidal anti-inflammatory drugs.
* Data are presented as a proportion, unless otherwise noted.
° Presence of patients with missing data: 3 for BMI and 93 for liver enzymes.
[1] Other care units: gastroenterology, nephrology, geriatrics, hematology, ORL, orthopedics, urology, rheumatology, psychiatry and palliative care.

chanical heart valve, but 2.6%, a bioprosthetic heart valve. Similarly, no patients were prescribed a medication that is contraindicated with DOACs.

Most subjects on dabigatran or rivaroxaban had an estimated creatinine clearance (CrCl) greater than 30 mL/min (97.8%), and all patients on apixaban had an estimated CrCl greater than 25 mL/min. Liver enzymes values were available for 81.4% of patients, and 97.1% of them had values of AST (aspartate aminotransferase) and ALT (alanine aminotransferase) lower than twice the upper limit of normal.

About a quarter of subjects were prescribed a dosing of dabigatran that was considered inappropriate: 38.7% were prescribed 110 mg without having a characteristic justifying a reduced dose, while 61.3% were prescribed 150 mg when a lower dose was indicated.

For subjects on rivaroxaban, 19.4% were prescribed a dose that was considered inappropriate. About 70% were prescribed a dose of 15 mg while having an estimated CrCl greater than 49 mL/min and 30.2% had an estimated CrCl between 30-49mL/min and were prescribed 20mg. For patients on apixaban, 30.2% received a dose of 2.5 mg without having two characteristics justifying this reduced dose.

Discussion

DOACs were frequently prescribed at a reduced dose in adults

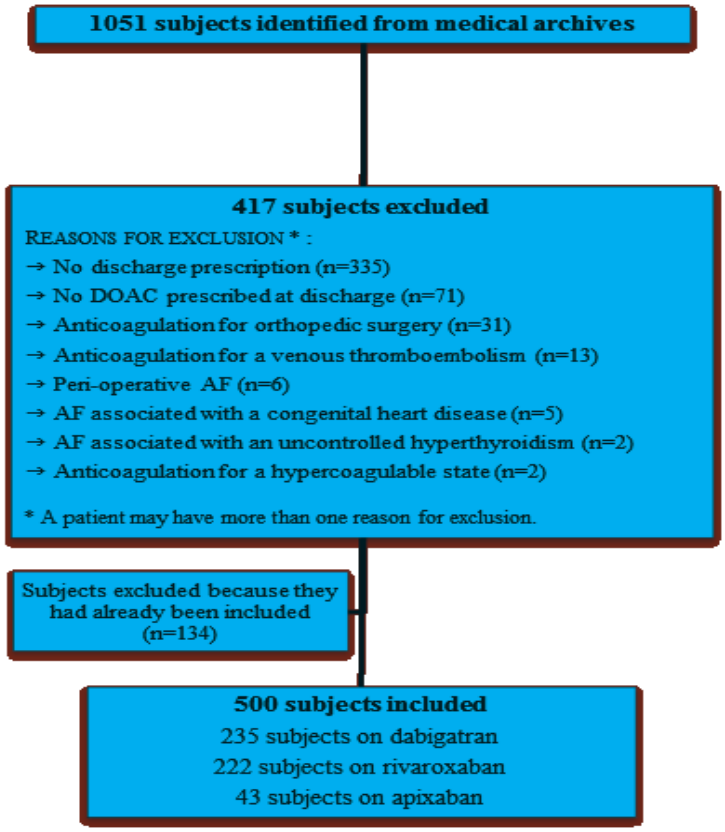

Figure 1: Flow chart for subjects selection

with AF. Up to a third of patients were prescribed a dose of dabigatran that was considered inappropriate. Proportions of inappropriate dosing (without specification for under or overdosing) of dabigatran (14.4%) and rivaroxaban (35.4%) has been reported [7] [13]. A Danish study reported that only 55.5% of subjects were prescribed 150 mg of dabigatran while indicated (a lower dose was used) [14]. Larock et al. reported that the dosage of dabigatran was reduced in 10.1% of subjects with no clear indication, while 4.3% of subjects had a regular dose when a reduction was indicated [12]. Finally, up to a third of subjects were prescribed a dose of apixaban that was considered inappropriate, but some clinicians might reduce the dose in the presence of only one justification factor.

We found a lower proportion of subjects with valvular disease (2.6%) than the ones reported by Larock et al. (7.2%) [12] and Carley et al. (10.9%) [8], but it was similar to the one found by Armbruster et al. (2.8%) [7]. DOACs were rarely prescribed in subjects with moderate to severe mitral stenosis (1.0%), which was also described by Tellor et al. (0.8% of patients with moderate to severe mitral stenosis received rivaroxaban) [13], and Armbruster et al. (0.2% of patients with moderate to severe mitral stenosis received a dose of dabigatran) [7].

Most of our patients had a CHADS2 score greater than or equal to one. At the time of the study, we considered the prescription of DOACs in patients who were 65 years and over with a CHADS2 score of 0 inappropriate (this represents 8 patients),

Supplements:
Supplementary Table 1:

Characteristics		Patients included (n=500) n (%) *	Patients excluded (n=417) n (%) *
Age (years), mean ± SD		74.3 ± 11.5	70.5 ± 13.5
Male gender		262 (52.4)	258 (61.9)
Hospitalization data			
Length of stay, median; range (days)		5 ; 1 – 70	4 ; 1 – 85
Care units	Cardiology	205 (41.0)	205 (49.2)
	Internal medicine	107 (21.4)	35 (8.4)
	Family medicine	85 (17.0)	16 (3.8)
	Neurology	43 (8.6)	31 (7.4)
	Surgery	22 (4.4)	37 (8.9)
	Respirology	17 (3.4)	5 (3.6)
	Orthopedics	1(0.2)	47 (11.3)
	Others	20 (4.0) [1]	31 (7.4) [2]
Drugs			
DOACs user's type	Prevalent	317 (63.4)	254 (60.9)
	Incident	148 (29.6)	138 (33.1)
	Switch	35 (7.0)	25 (6.0)

Legend:
Data are presented as a proportion, unless otherwise noted.
Other care units: gastroenterology, nephrology, geriatrics, hematology, ORL, urology, rheumatology, psychiatry and palliative care.
Other care units: geriatrics, gastroenterology, ORL, urology, hematology, neurosurgery, plastic surgery, endocrinology, gynecology, psychiatry, rheumatology and palliative care.

while it is no longer the case [23].

In our study, no subjects with a mechanical heart valve were prescribed a DOAC. In fact, dabigatran was found to increase the risks of thromboembolic and bleeding events in such patients [24].

No subjects received a concomitant medication that is contraindicated with DOACs. In a study conducted in Denmark, one patient (0.02%) was taking ketoconazole or itraconazole at the beginning of treatment with dabigatran, and six patients (0.1%) were prescribed itraconazole while on dabigatran [9].

A low proportion of subjects (2.2%) received a DOAC while having an estimated CrCl lower than 30 mL/min. Previous studies have also reported minimal use of dabigatran in patients with this level of renal function, with proportions varying between 0.4% and 2.9% [7, 10-13].

About 20% of subjects were prescribed a DOAC with no recent values of liver enzymes available . This is of concern since DOACs are not recommended in the presence of severe hepatic impairment.

Our study is limited by several factors; a few numbers of patients on apixaban were included, several subjects were excluded because of incomplete discharge prescriptions (but their baseline characteristics were similar to the ones of included subjects), it was conducted in a single centre, and data were collected retrospectively. Also, the appropriateness criteria are based on limited evidence. Furthermore, factors influencing dose selection may not have been documented in the medical chart. DOACs are increasingly prescribed and physicians are now more familiar with their use, which could influence results from future studies on this subject.

Table 4: Appropriateness criteria for DOACs prescriptions

Criteria		Appropriateness, n (%)	95% CI
1. Type of AF	Appropriate use	487/500 (97.4)	96.0 – 98.8
2. Mitral stenosis	Appropriate use	495/500 (99.0)	98.1 – 99.9
3. CHADS2 score		473/473 (100.0)	
• CHADS2 ≥ 1	Appropriate use		
• CHADS2 = 0	Appropriate use	13/27 (48.1)	
	Total number of appropriate use	486/500 (97.2)	95.8 – 98.7
4. Heart valves	Appropriate use	500/500 (100.0)	
5. Concomitant medication	Appropriate use	500/500 (100.0)	
6. Renal function			
• Dabigatran and rivaroxaban	Appropriate use	446/457 (97.6)	96.5 – 99.0
	Appropriate use	43/43 (100.0)	
• Apixaban	Total number of appropriate use	489/500 (97.8)	
7. Liver enzymes levels	Appropriate use	395/407 (97.1)	95.4 – 98.7
8. a. Dose of dabigatran			
• Dabigatran 110 mg BID	Appropriate use	106/130 (81.5)	
	Appropriate use	67/105 (63.8)	67.9 – 79.3
• Dabigatran 150 mg BID	Total number of appropriate use	173/235 (73.6)	
8. b. Dose of rivaroxaban			
• Rivaroxaban 15 mg DIE	Appropriate use	31/61 (50.8)	75.4 – 85.9
	Appropriate use	148/161 (91.9)	
• Rivaroxaban 20 mg DIE	Total number of appropriate use	179/222 (80.6)	
8. c. Dose of apixaban			
• Apixaban 2,5 mg BID	Appropriate use	7/20 (35.0)	55.5 – 84.1
	Appropriate use	23/23 (100.0)	
• Apixaban 5 mg BID	Total number of appropriate use	30/43 (69.8)	
Overall appropriateness	Appropriate use	352/500 (70.4)	66.4 – 74.4

Legend: C-Gault, Cockcroft-Gault; GFR, glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PO, per os; BID, twice a day; QD, once a day

Conclusion

Dabigatran, rivaroxaban and apixaban were commonly prescribed with a dose that was considered inappropriate. Our results support the need to implement measures to promote appropriate dosing of DAOCs. Further studies should investigate underdosing of DOACs in a larger setting.

Disclosures

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Esophageal Temperature Monitoring During Radiofrequency Ablation of Atrial Fibrillation A Meta-Analysis

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Abstract

Atrio-esophageal fistula is an infrequent but devastating complication of catheter-based ablation of atrial fibrillation (AF). Thermal esophageal injury may be the precursor of atrio-esophageal fistula. Here, we evaluated the role of esophageal temperature monitoring in preventing thermal esophageal injury during pulmonary vein isolation for AF with radiofrequency energy. In this meta-analysis, we searched the PubMed, Cochrane, Scopus, Embase, and Refworks databases for all published studies from January 2004 to June 2016 to evaluate the role of esophageal temperature monitoring. We searched for terms esophageal temperature monitoring, AF, radiofrequency ablation, atrio-esophageal fistula, and thermal esophageal injury. We included studies comparing luminal esophageal temperature (LET) monitoring with no LET monitoring during radiofrequency ablation of AF. We excluded studies in which post-ablation esophagogastroduodenoscopy (EGD) was not performed to identify esophageal thermal injuries. To perform the meta-analysis, we used Review Manager statistical software and a fixed-effects modeling to derive the outcomes. Given significant heterogeneity between the studies, we used meta-regression analysis to adjust for age and sex. We identified 4 non-randomized controlled trials that met our search criteria and included a total of 411 patients (n=235 in the LET monitoring group; n=176 in the no LET monitoring group) in the analysis. There were 21 (8.9%) patients with thermal esophageal injury in the LET monitoring group and 12 (6.8%) in the no LET monitoring group. The pooled odds ratio was 0.66 (0.23-1.89), indicating no statistically significant differences between the 2 groups with regard to esophageal injury. Because of the small sample size and the non-randomized nature of the trials, we observed significant heterogeneity in outcomes among the trials. The role of esophageal temperature monitoring in reducing the risk of esophageal thermal lesions during pulmonary vein isolation for AF has not been established, and more studies including randomized controlled trials are needed to assess its true impact.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting millions of people around the world. In addition, AF has a significant health, economic, and social impact. Because of technological advances and improved operator experience, radiofrequency ablation for rhythm control of AF has become increasingly common. The efficacy of pulmonary vein isolation using radiofrequency ablation has been well established, but major complications have been reported in 4.5% of patients.[1] Although its incidence is low (0.03-0.1%), atrio-esophageal (AE) fistula is a devastating complication with a high mortality.[2-4] The precursor for AE fistula formation is thought to be thermal esophageal injury during radiofrequency ablation, given the proximity of the anterior esophageal wall to the posterior left atrial wall. Most AE fistulas manifest [2-6] weeks after an ablation procedure, suggesting that direct mechanical trauma during the procedure is not likely the sole mechanism underlying this complication.[5,6]

The incidence of esophageal lesions during radiofrequency ablation has been reported as 2-47%.[7-11] Various techniques have been examined to reduce the risk of esophageal injury during radiofrequency ablation. These include imaging the esophagus during ablation, limiting energy delivery on the posterior left atrial wall, using mechanical deflection of the esophagus during catheter ablation, insulating the esophagus from thermal injury, and monitoring luminal esophageal temperature (LET) during the procedure.[6,9,12-17] All reports on esophageal temperature monitoring during AF ablation are from single-center studies with small sample sizes. The aim of this meta-analysis is therefore to evaluate the role of luminal esophageal temperature monitoring in preventing thermal esophageal injury on the basis of pooled data available in the literature.

Methods

We searched the PubMed, Scopus, Cochrane, Embase, and Refworks databases for studies published from January 2004 to June 2016 that compared radiofrequency ablation for AF with and without LET monitoring. We searched the title field for terms esophageal temperature monitoring, AF, radiofrequency ablation, AE fistula, and thermal esophageal injury. We included only studies in which

Key Words:
Atrio-esophageal fistula,esophageal temperature monitoring,atrial fibrillation,atrial fibrillation ablation

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esophagogastroduodenoscopy (EGD) was performed within 72 hours after the ablation procedures with thermal esophageal injury as the primary endpoint. Meta-analysis was performed by using Review Manager (RevMan) [Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014]. Fixed-effects modeling was primarily used to conduct the outcomes meta-analysis from the included studies. The pooled incidence rates of thermal esophageal injury for patients in the esophageal temperature monitoring arm and in the no esophageal temperature monitoring arm were derived from the studies that we identified as meeting our criteria. The pooled odds ratios were then calculated for the comparisons. Because of the significant heterogeneity among the studies, we conducted a meta-regression analysis to determine the differences in the incidence of esophageal lesions using 2 different strategies after adjusting for age and sex. The meta-analysis has been reported in accordance with the Observational Studies in Epidemiology Guidelines.[18]

Results

Our search resulted in the identification of 4 non-randomized controlled trials that met our search criteria (Table 1).[10,19-21] In the first study published in 2008, Singh et al[21] retrospectively analyzed 81 consecutive patients who had undergone AF ablation followed by EGD and compared the LET vs no LET groups. They noted a significantly higher frequency of esophageal injury in patients who had not undergone LET monitoring during ablation. Subsequently in 2011, Deneke et al[19] reported a higher incidence of esophageal injury in patients who underwent LET monitoring than in those who did not undergo LET monitoring during AF ablation. This study included 90 patients. These results were consistent with those reported by Muller et al[20] in 2015 who evaluated 80 patients who underwent AF ablation. They noted a significantly higher incidence of esophageal injury in the analyzed 160 patients who underwent AF ablation with or without LET monitoring. They reported a significantly lower incidence of esophageal injury in the LET monitoring group. We have reported the ablation parameters and the esophageal temperature probes used in these four studies in Table 2.

The total number of patients included in our analysis was 411. Of these, 235 patients underwent LET monitoring and 176 did not undergo LET monitoring during radiofrequency ablation of AF. All patients underwent EGD to determine the presence of post-ablation esophageal thermal injury, which was defined as the primary endpoint. Thermal esophageal injury was seen in a total of 21 (9%) patients in the LET monitoring group and 12 (7%) patients in the no LET monitoring group. In a meta-analysis of these 4 studies, a fixed-effects model showed that the pooled odds ratio was 0.66(confidence interval, 0.23-1.89) (Figure 1). The Z score was 0.77 (P value = 0.44) that failed to reach statistically significant difference between the two groups with regard to thermal esophageal injury. We observed significant heterogeneity because of the small sample size and non-randomized nature of the studies. In the meta-regression analysis in which the data were adjusted for age and sex, there was no significant difference in outcomes of esophageal thermal injury between the two groups.

Discussion

LET monitoring during left atrial radiofrequency ablation for AF is frequently used to try to minimize excessive esophageal thermal injury, thereby reducing the risk of developing AE fistula. Here, we present the first meta-analysis of studies evaluating LET monitoring during AF ablation. Our findings indicate that there is no conclusive evidence at this point supporting the use of esophageal temperature monitoring in prevention of esophageal mucosal injury during radiofrequency ablation of AF.

The close proximity of the esophagus to the posterior left atrial wall is one of the most important factors contributing to esophageal mucosal injury during AF ablation.[22-24] Thermal injury is thought to affect the microvasculature of esophageal tissue leading to ischemic necrosis of the mucosal layers.[6]Multiple studies have reported esophageal thermal injury after AF ablation. Redfearn et al[25] and Perzanowski et al[26] reported that real-time monitoring of esophageal luminal temperature during AF ablation was feasible and could be used to detect esophageal heating. They also suggested luminal esophageal temperature monitoring as a means of reducing esophageal injury. Maximal LET of 40˚C-41˚C has been shown to be directly associated with an increase in the incidence of esophageal lesions.[8,16] Halm et al8 have demonstrated significantly increased odds of esophageal injury for every 1˚C rise in LET. Singh et al[21] were the first to report a reduction in the incidence of esophageal injury with the use of esophageal temperature monitoring during AF ablation. However, various limitations of LET monitoring have been recognized. Deneke et al[19] and Muller et al[20] have suggested that esophageal temperature monitoring may increase the risk of esophageal mucosal injury. The proposed underlyingmechanism is that the esophageal temperature probe itself may act as a conductor for the transfer of heat energy to the esophagus, thereby increasing the thermal injury risk. However, in a simulation study, Perez et al[27] showed that the temperature increase in the esophagus is due primarily to thermal conduction only and that electrical conduction between the ablation catheter and the esophageal probe does not play a significant role.

One of the major limitations of LET monitoring is the underestimation of temperature of esophageal intramural tissue.[28] Because the direct monitoring of esophageal intramural tissue temperature is not currently feasible, luminal temperature monitoring is the best strategy available. The major drawback of LET monitoring is that it does not accurately reflect the esophageal intramural tissue temperature because of the variable and unpredictable distance between the temperature probe and the anterior wall of the esophagus. In addition, the physical composition and dimensions of the tissue between the posterior left atrium and the esophagus vary significantly among individual patients. Furthermore, the safe maximal LET and critical temperature rise from the standpoint of esophageal injury remain to be established. Another major limitation to the monitoring of esophageal temperature is the variability among different thermistor probes. Recently, investigators reported a significant difference in thermodynamics with the use of two different esophageal probes in both experimental and clinical settings.[29] All of these factors may limit the ability of LET monitoring to accurately predict esophageal damage during ablation. In addition, given the extremely low incidence of AE fistula, esophageal thermal injury has been used as a surrogate marker to predict the risk of fistula formation in all major studies. Our understanding of the evolution of AE fistula from esophageal thermal injury remains incomplete.

Our study has limitations. The non-randomized nature of the studies in our meta-analysis as well as the small number of studies/patients available limit our findings and indicate the

Table 1: Esophageal thermal injury during radiofrequency ablation of AF with and without LET monitoring.

Study	LET monitoring		No LET monitoring		Weight	Odds ratio	95% CI
	Injury	Total	Injury	Total			
Singh 2008[21]	n=4	67	n=5	14	36.60%	0.11	(0.03, 0.51)
Deneke 2011[19]	n=5	48	n=0	42	9.50%	10.75	(0.58, 200.42)
Muller 2015[20]	n=12	40	n=1	40	18.40%	16.71	2.05,136.08)
Kiuchi 2016[10]	n=0	80	n=6	80	13.1%	0.07	(0.00,1.29)
Total events	n=21		n=12				
Total (95% CI)	235		176		100%	0.66	(0.23, 1.89)

LET: Luminal esophageal temperature. CI: confidence interval.
Test for overall effect: Z=0.77 (P=0.44).
Heterogeneity: Chi^2 = 20.22, df = 3 (P<0.0002), I^2=85%.

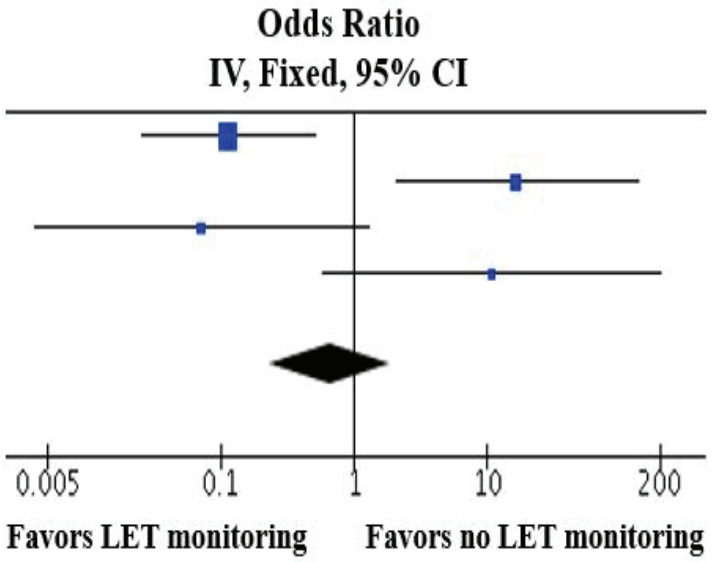

Figure 1: Pooled odds ratio after meta-analysis using a fixed-effects model. There is no significant difference between the incidence of esophageal injury between LET monitoring and no LET monitoring groups. Odds Ratio – 0.66, 95% CI (0.23, 1.89).

need for a large-scale, randomized multicenter trial. Another limitation of our analysis was the significant heterogeneity. noted among the studies. The ablation parameters and the esophageal temperature probes used in the four studies varied (Table 2). In addition, we examined only the use of esophageal temperature monitoring in preventing esophageal mucosal injury. Other approaches such as limiting the power and duration of the delivery of radiofrequency energy at the posterior left atrial wall, using a deflectable esophageal probe or previous esophageal imaging, and insulating the esophagus were not evaluated in this meta-analysis, which could have affected the incidence of thermal esophageal injury in these studies.

Table 2: Ablation parameters used in the four studies included in our meta-analysis

Study	Ablation catheter	Ablation parameters (power and temperature)	Esophageal probe	Maximal LET
Singh et al21	3.5 mm external or 4 mm internal irrigated catheter	35W and 40°C	n/a	38.5°C
Muller et al20	Irrigated catheter (Size not specified)	35W (25W at posterior wall), 43°C	Sensitherm, 5 electrodes	39.5°C
Deneke et al19	Multi-channel RF system	10W, 60°C	Esotherm, 3 electrodes	40°C
Kiuchi et al10	Irrigated catheter	30W (20W for post), 43°C	Sensitherm, 5 electrodes	39°C

LET: Luminal esophageal temperature. RF: radiofrequency. W: watts.

Use of esophageal temperature monitoring during cryoballoon ablation for atrial fibrillation.

When approved initially by FDA, the risk of esophageal injury with cryoballoon (Medtronic, Inc.) ablation of atrial fibrillation was perceived to be minimal. However, atrio-esophageal fistulas have been reported with both firstgeneration and second generation cryoballoons[32-33]. Risk of thermal esophageal injury during cryoballoon ablation has been reported to be 2% to 19% depending on the lower esophageal temperature cut-offs used [34-36]. While the risk of esophageal injury increases at temperatures below 30 C, an esophageal cut-off temperature of 10-120 C has been suggested, given the progressive decline in temperature after cessation of ablation[35-36]. Furkranz et al demonstrated a reduction in esophageal injury from 18.8% to 3.2% by use of LET guided cryoballoon ablation[34]. Based on current evidence available, it seems vital to use LET monitoring for assessing esophageal cooling than relying primarily on cryoballoon temperatures.

Future Directions

Accurate esophageal wall temperature monitoring probes are currently being studied and will aid in the real-time identification of early esophageal heating, which will help reduce the risk of esophageal thermal injury. Safe retraction of the esophagus away from the ablation plane by using mechanical probes such as EsoSure (Northeast Scientific Inc., Boynton Beach, Florida) is also under evaluation. Capsule endoscopy is a reliable tool for detecting esophageal injury after AF ablation without the risk of insufflation with EGD.[7] Recent data also suggests that esophageal injury from radiofrequency ablation is not limited to mechanical damage but also involves esophageal dysmotility.[30] Incorporation of improved tools such as capsule endoscopy and assessment of both mechanical and functional esophageal injury will help design better

trials, thereby lowering the overall risk of esophageal injury.

Conclusion

In this first meta-analysis of studies evaluating LET monitoring during AF ablation, we found that the evidence from non-randomized clinical trials supporting its role in preventing esophageal mucosal lesions is far from conclusive. Randomized controlled trials are necessary to evaluate the true impact of LET monitoring. Furthermore, advances in the technology for temperature monitoring and diverting the esophagus further away from the ablation site may improve our strategies for avoiding esophageal thermal injury.

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Apixaban-Induced Resolution Of A Massive Left Atrial And Appendage Thrombosis In A Very Elderly Patient

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Abstract

A 86-year-old woman with first diagnosed atrial fibrillation (AF) underwent mitral valve annuloplasty 10 years before was admitted to our Unit due to congestive heart failure. Trans-thoracic echocardiogram (TTE) revealed a large fluctuant echogenic mass in the posterior wall of the left atrium. Trans-esophageal echo (TEE) showed the origin of the mass within the left atrial appendage. An adjusted dose of the novel oral anticoagulant (NOAC) apixaban, was prescribed. A complete disappearance was appreciated by examination at 12 weeks after the first drug administration. Although apixaban, resulted superior to warfarin in preventing stroke and thrombo-embolic events in patients with non valvular AF, while causing less bleeding, few data are actually available regarding the efficacy and safety of this drug in left atrium and appendage thrombosis management. Our report shows that this NOAC could be a simple and useful option to manage huge atrial thrombosis in very elderly patients.

Introduction

Oral anticoagulant therapy (OAC) is used to prevent thrombo-embolic complications in atrial fibrillation (AF) patients and to resolve left atrial appendage (LAA) thrombosis[1]. OAC is potentially associated with major bleedings[2],requires regular monitoring of the INR and it is not easy to be controlled due to its narrow therapeutic range, food and drug interactions, and varying inter-individual response. At present, novel oral anticoagulants (NOACs) are indicated to prevent thrombo-embolic complications associated with non-valvular AF[3] but few data are actually available regarding the efficacy and safety of these novel drugs in left atrium and appendage thrombosis management, in particular in fragile patients with biological heart valves or prior valve repair.[4]

Case Report

A 86-year-old fragile (height 155 cm, weigh 54 Kg, BMI 22.48) woman with first diagnosed AF, underwent mitral valve annuloplasty 10 years before, admitted to our hospital because of peripheral oedema, and pulmonary congestion with pleural effusion at X-ray evaluation. EKG showed atrial fibrillation with ventricular heart rate of 150 bpm. Blood tests revealed a creatinine (Cr) level of 0.82 mg/mL (eGFR, 41.98 mL/min) and a D-dimer level of 6 µg/mL. Transthoracic echocardiography (TTE) demonstrated a mobile large echogenic mass (1.9x2.3 cm) in the posterior wall of the left atrium ([Figure 1]) and moderate left ventricular dysfunction (ejection fraction 40%). No significant valve heart disease was observed. Trans-esophageal echocardiography (TEE) confirmed the presence of a large homogenous mobile mass in a dilated left atrium coming from the left atrial appendage: diagnosis of thrombus was made ([Figure 2]). No hypercoagulability conditions (hematologic diseases, infections, cancer) were reported. Intravenous furosemide was administered to treat the congestive symptoms while bisoprolol (10 mg daily) plus digoxin (0.125 mg daily) were given orally to achieve a lower ventricular response rate. Because of the very old age and the potential associated difficulties to manage a conventional oral anticoagulant therapy (i.e. warfarin, dicumarol etc.), we decided to treat the massive left atrial thrombosis with the novel oral anticoagulant (NOAC) apixaban (CHA_2DS_2VASC score: 5, HAS-BLED score: 3). According to the current guidelines, an adjusted (age ≥80 years, weight ≤60 kg) dose of 2.5 mg twice daily was given[5]. A progressive reduction in thrombus size was appreciated by TTE examination 30 days ([Figure 3]) after the first apixaban administration. The NOAC therapy was continued for 12 weeks more without any serious bleeding or thrombo-embolic complications, while TTE and TEE finally confirmed the complete thrombus resolution. ([Figure 4] and [Figure 5])Oral anticoagulant therapy (OAC) is used to prevent thrombo-embolic complications in AF patients and to resolve LAA thrombosis[1].

Although OAC is of paramount importance to reduce the stroke rate in AF patients, however it is potentially associated with major bleedings.[2] Furthermore, it requires regular monitoring of the INR and it is not easy to be controlled due to its narrow therapeutic range, food and drug interactions, and varying inter-individual response.

At present, novel oral anticoagulants (NOACs) are indicated to prevent thrombo-embolic complications associated with non-

Key Words:
Apixaban ,Atrial fibrillation,Left Atrial Thrombosis

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valvular AF (that occurs in case of the absence of mechanical prosthetic heart valves and the absence of moderate to severe mitral stenosis) in patients at high risk of thrombo-embolic and bleeding events[3]. Apixaban is a rapidly absorbed novel oral anticoagulant

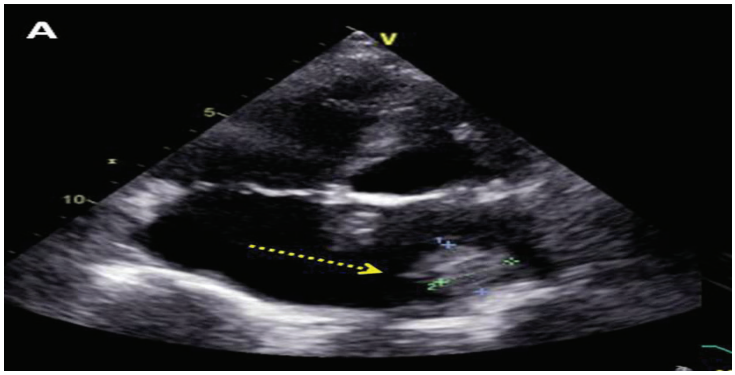

Figure 1: Transthoracic echocardiography (TTE) shows a mobile large echogenic mass (1.9x2.3 cm) in the posterior wall of the left atrium.

that inhibits the direct factor Xa (FXa), while has a lower half-life and percentages of renal excretion compared to other NOACs. This novel drug has been shown to be associated in non-valvular AF patients with lower stroke, thrombo-embolic events, bleedings and mortality rates compared to warfarin.[6] However, few data are actually available regarding the efficacy and safety of these novel drugs in left atrium and appendage thrombosis management, in particular in fragile patients with biological heart valves or prior valve repair.[4] Atrial fibrillation in patients with biological valves or after valve repair (conditions that by itself do not require oral

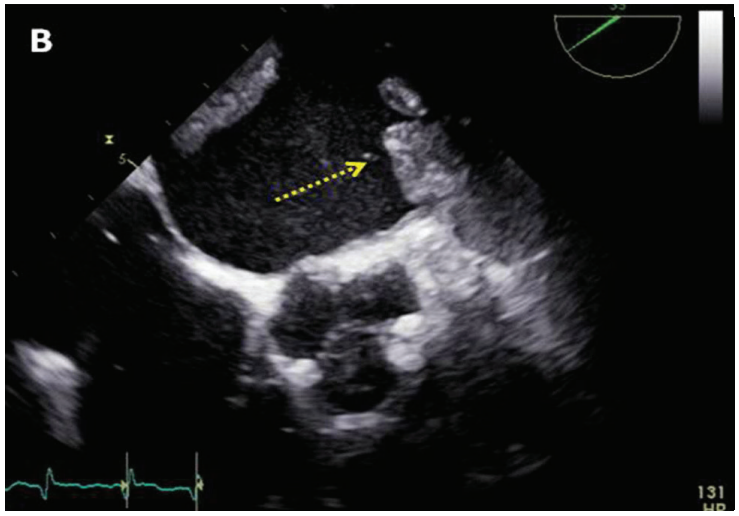

Figure 2: Trans-oesophageal echocardiography (TOE) confirms the presence of a large homogenous mobile mass in a dilatated left atrium coming from the left atrial appendage.

anticoagulation) constitute a grey area, and were included in some trials on 'non-valvular AF' but no prospective data are available except for the few hundred patients in ARISTOTLE (both types, but without information on how many patients with bioprosthesis) [8] and ROCKET-AF (only valvuloplasty) [9]. Current American Heart Association (AHA) guidelines do not recommend NOAC administration in patients with biological heart valves or prior valve repair. [9] In the case we described, apixaban was chosen as a first line therapy because the surgical intervention was performed 10 years before hospital admission with full preservation of the native mitral

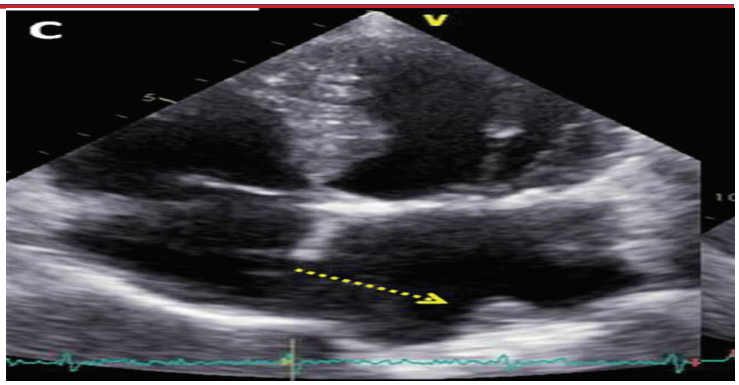

Figure 3: Transthoracic echocardiography (TTE) shows reduction in thrombus size at 30 days.

valve leaflets while an adjusted dose was preferred because of the patient's features (old age and low body weight). Recent report has demonstrated that dose reduction to 2.5 mg bd may resolve left atrial thrombi. [10]

The present case shows how apixaban could be an useful drug to resolve left atrial and appendage thrombi within a manageable time period and without major complications in very old patients with limited therapeutic options, late after valve repair. Further, larger data are needed to confirm our anecdotal finding.

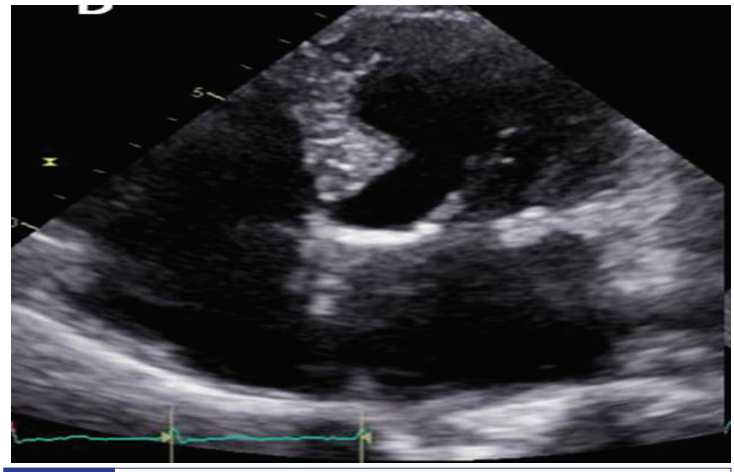

Figure 4: Transthoracic echocardiography (TTE) shows complete thrombus resolution in let atrium.

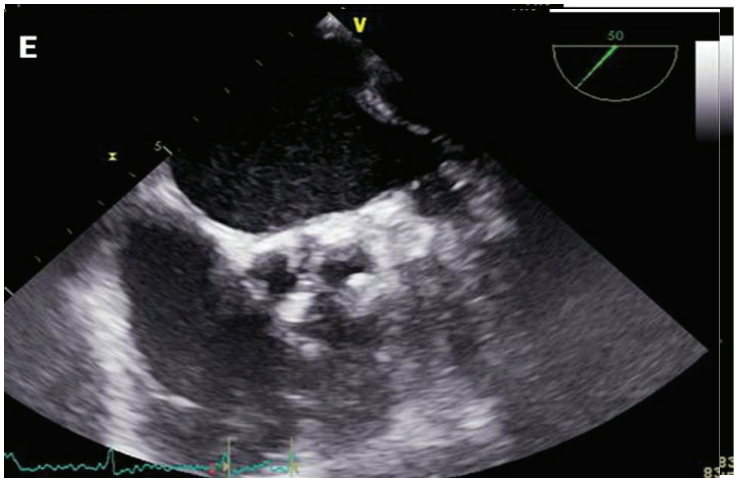

Figure 5: Trans-oesophageal echocardiography (TOE) shows complete thrombus resolution in left atrial appendage.

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Dilated Cardiomyopathy With Severe Arrhythmias In Emery- Dreifuss Muscular Dystrophy From Ablation To Heart Transplantation.

Olga Blagova, Alexander Nedostup, Dmitry Shumakov, Vitaly Poptsov, Anna Shestak, Elena Zaklyasminskaya

Abstract:

We present a 38-years male patient. He has suffered from muscle weakness since 5 years. Arrhythmias appeared at the age of 32. In 37 years he had sick sinus syndrome, transient AV block II degree, paroxysmal atrial fibrillation, atrial flutter, and ventricular arrhythmias. At this time, dilated cardiomyopathy was also detected. The evaluation revealed knees and elbows contractures, increased level of creatine kinase. The genetic testing revealed a frame shift deletion c.del619C in the emerin (EMD) gene and c.IVS4-13T> A in the lamin (LMNA) gene, and c.del619C deletion in the heterozygous state in a patient`s mother. Radiofrequency ablation of cavotricuspid isthmus, implantable cardioverter-defibrillator (ICD) implantation were performed. Heart transplantation was performed nine months later, due to severe heart failure and electrical storm. A morphological evaluation revealed sclerosis, atrophy and hypertrophy of cardiomyocytes. He underwent an induction therapy with (basiliximab) methylprednisolone, tacrolimus, mycophenolate after heart transplantation. During 40 months after transplantation, patient`s condition is satisfactory.

Conclusion: Heart failure in Emery-Dreifuss muscular dystrophy can progress quickly unless the previously stable condition. The use of correct regimens of immunosuppression therapy provides good long-term results of the heart transplantation.

Introduction

If we detect arrhythmias and dilated cardiomyopathy (DCM) in young patients with symptoms of myopathy and / or increased levels of total creatine kinase, we should always exclude a hereditary neuromuscular disease. Genetic testing in DCM with the neuromuscular disease gives positive answers more frequently (62%) than in family cases (25%) and sporadic (8%) forms of DCM [1]. There are large varieties of clinical forms of progressive myopathy with heart failure.

Case report

A male patient of thirty-eight years age came to our clinic in May 2012 with moderate weakness in the proximal muscles of the limbs, presyncope episodes not associated with physical activity, proximal muscular weakness, dyspnea at moderate physical activity and episodes of palpitation.

Patient`s mother was implanted pacemaker at the age of fifty-four (Fig. 1), his sixty-six years old father had a stroke. Two patient`s sons 3 and 11 years were clinically healthy. The patient has smoked since a young age. Otherwise he had a healthy lifestyle.

Key Words

X-linked Emery-Dreifuss muscular dystrophy,implantable cardioverter defibrillator,radiofrequency ablation,heart transplantation

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Proband is indicated by a blue square. His mother was implanted with a pacemaker in 54 years. The nature of her disease was unknown. Two patient`s children are clinically healthy.

A. Detail of direct Sanger sequencing of exon 6 EDM gene. The arrow indicates place of the lost nucleotide C. B. Compare fragments of the nucleotide sequence of exon 6 of the gene patient EDM («Query») with the reference sequence of exon 6 of the gene EDM patient NG_008677.1 («Sbjct"). Red line underlined the place of deletion.

The patient has suffered from low progressive skeletal myopathy since childhood. Since 5 years he have has progressive muscular weakness, frequent episodes of falling. In the age of six he was diagnosed muscular dystrophy. He has had arrhythmias and minimal ejection fraction (EF) reduction since the age of 32. Palpitatons and presyncope appeared and increased in 2012. Echocardiography and Holter monitoring showed signs of DCM, sick sinus syndrome, transient AV block II degree type 1, paroxysmal atrial flutter and fibrillation, more than 4000 premature ventricular beats (PVBs) and non-sustained ventricular tachycardia. However he had normal coronary angiograms.

He was undergone radiofrequency ablation of cavotricuspid isthmus in Bakoulev Center. The dual-chamber ICD implantation was also performed. Amiodarone showed good clinical effect. Left ventricular (LV) EF was forty-three percent. However, he got worse four months later. The patient had palpitations, progressive dyspnea and edema. Atrial flutter, low LV EF (less than twenty percent) and severe mitral and tricuspid regurgitation were detected at this time.

Emery-Dreifuss muscular dystrophy diagnosis have been already genetically confirmed by that time. They found two genetic variants (Fig. 2): 1) frame-shift deletion c.del619C in emerin (EMD) gene

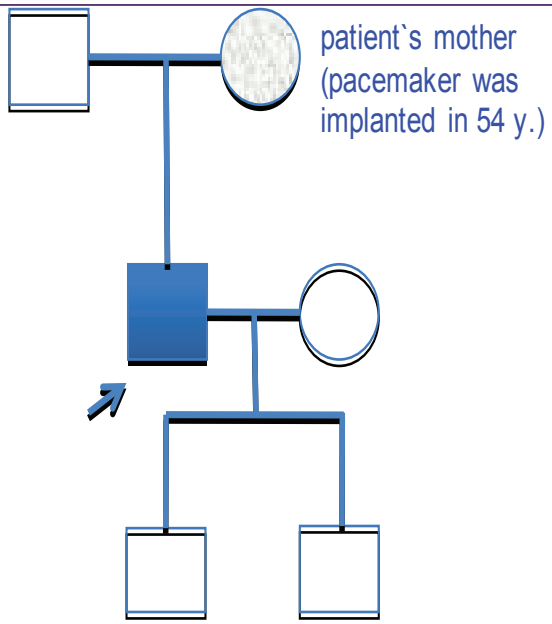

Figure 1: The pedigree of patient.

Proband is indicated by a blue square. His mother was implanted pacemaker in 54 years. The nature of her disease was unknown. Two patient`s children are clinically healthy.

causing premature stop-codon appearance and protein shortening (p.236X); 2) intron replacement c.IVS4-13T>A in lamin (LMNA) gene with unknown clinical significance. Both variants were not found in control group of 100 healthy volunteers.

The patient was in our clinic in February 2013. He had tachycardia 120 beats per minute, irregular pulse, deficits 10-15 beats per minute and severe congestive heart failure symptoms with signs of hepatomegaly and cholestasis. The level of creatine kinase remained high (458 U/l). His thyroid status showed euthyroid hyperthyroxinemia.

We had to exclude myocarditis because of heart failure dramatic progression in previously stable patient. Real-time polymerase chain

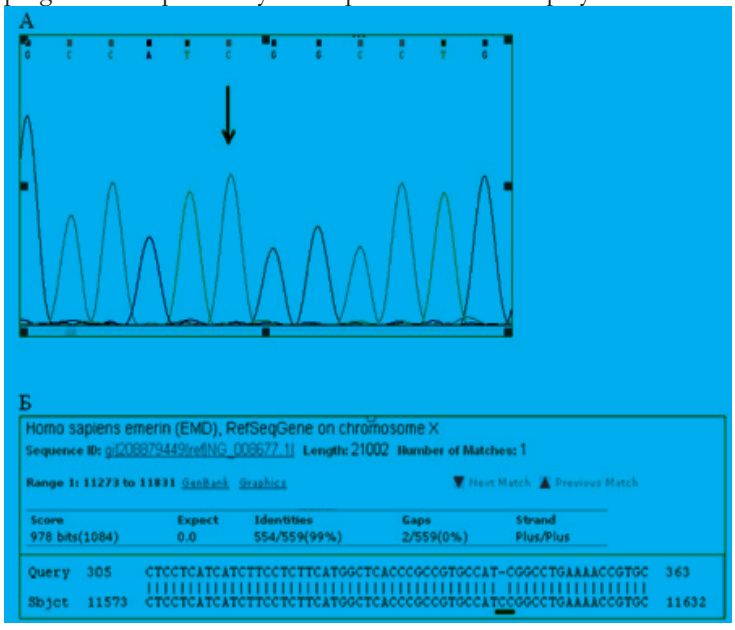

Figure 2: Results of DNA diagnostics.

A. Detail of direct Sanger sequencing of exon 6 EDM gene. The arrow indicates place of the lost nucleotide C. B. Compare fragments of the nucleotide sequence of exon 6 of the gene patient EDM («Query») with the reference sequence of exon 6 of the gene EDM patient NG_008677.1 («Sbjct"). Red line underlined the place of deletion.

reaction found no viral genome in blood. The level of anti-heart antibodies moderately increased (1:160 toward endothelial antigens and antigens of conductive system). By the way, it could be secondary immune reaction of cardiomyocytes' damage.

ECG showed (Fig 3A) atypical atrial flutter with FF waves period 0.20 s., heart rate was 90/min, right bundle branch block (QRS duration 0.16 s.), both ventricles hypertrophy signs. Holter monitoring revealed sustained atrial flutter with moderate tachycardia, atrial flutter (2:1, 3:1, 4:1), ICD VVI pacing (20% of QRS) 75 beats

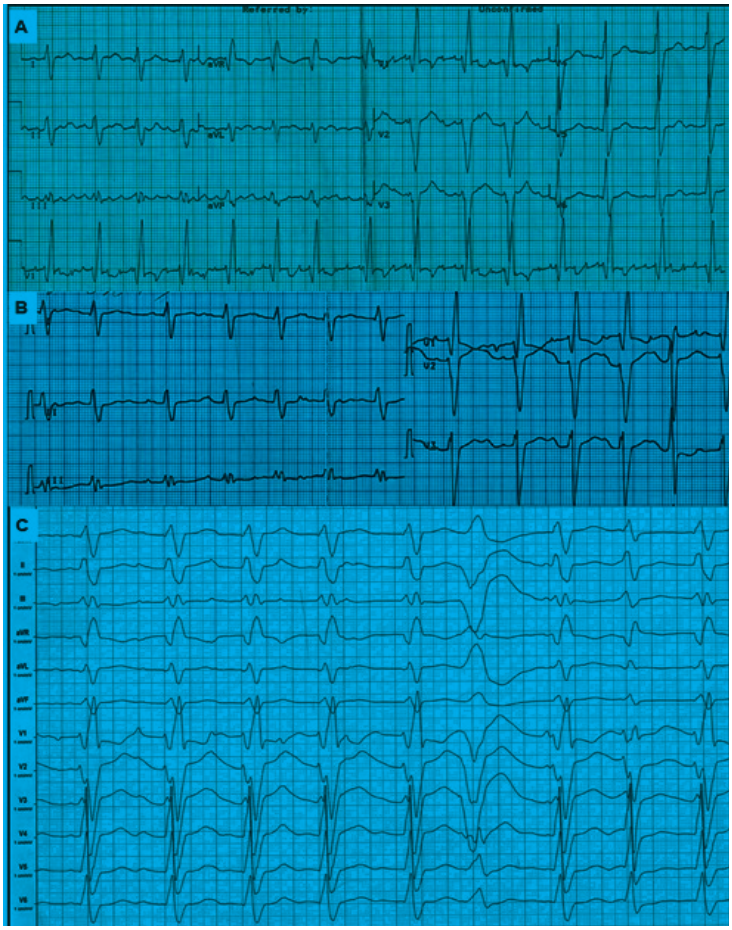

Figure 3: Electrocardiogram.

Speed 25 mm/s (A, B), and 50 mm/s (C). A - ECG in February 2013, B - ECG after electrical cardioversion. C - ECG after repeated ICD shocks.

per minute, average heart rate was 85/minute daytime and 76/minute nighttime, 787 PVBs, 18 couplets, 1 triplet. Left ventricular ejection fraction was about thirty percent, though left ventricular end-diastolic diameter (7.0 cm) and volume (305 ml) and left and right atria volume (187 ml and 148 ml) were significantly dilated. The patient also had moderate pulmonary hypertension (46 mm Hg) and tricuspid regurgitation (II degree). Multi-slice computed tomography showed no evidence of coronary atherosclerosis and cardiac thrombosis.

There were several possible causes of deterioration in the condition. It could have been the increasing of tricuspid regurgitation and ICD implantation asynchrony, relapse of sustained tachyarrhythmia and the development of disease. Thus, we discussed CRTD reimplantation and heart transplantation. Electrical cardioversion was successful (Fig. 3B). It was complicated by sustained ventricular tachycardia and did not significantly improve the condition. He was treated with

perindopril 2.5 mg, amiodarone 400 mg, warfarin 2.5-3.75 mg and furosemide 40-60 mg per day. Despite of the amiodarone treatment he had an electrical storm (ventricular tachycardia and fibrillation) with multiple ICD shocks. ECG after shocks is He was urgent hospitalized to Shumakov Federal Research Center of transplantology and artificial organs. He was implanted extracorporeal membrane oxygenation (ECMO) system. He was undergone successful orthotopic heart transplantation. ECMO system was removed the next day after heart transplantation. Basiliximab induction therapy, prednisone, tacrolimus and mycophenolate were assigned later. Temporary pacing 90-100 per minute have been supported for 4 weeks. There were no signs of rejection in the control myocardium biopsy (0-I degree). Morphology of the explanted heart showed 470 g weight, 11x9x4.5 cm size and normal coronary arteries. The myocardium was flabby, homogeneous, pink-brown. Histology of the explanted heart showed diffuse myocardial fibrosis, cardiomyocytes polymorphism (atrophy and hypertrophy), perinuclear edema, decaying nuclei (apoptosis) (Fig. 4.). There were no signs of associated myocarditis.

Forty-month follow-up showed significant health improvement. There were no signs of rejection and other specific complications, muscle weakness did not progress. Patient took up to work and he had a great physical activity.

We also found the heterozygous state deletion c.del619C in gene of emerin in the 63-years-old patient`s mother. She has been diagnosed coronary heart disease (without signs of atherosclerosis) and arterial hypertension for a long time. She had satisfactory functional status. She was implanted pacemaker because of sick sinus syndrome, AV block with syncope. Manifestation of X-linked Emery-Dreifuss muscular dystrophy included moderate DCM (LV end-diastolic diameter 6.4 cm, EF about 50%). We did not need any genetic testing of patient's sons because of X-linked recessive type of disease.

Discussion. As we know, there are three major forms of muscular dystrophy, which involve heart: Duchenne, Becker and Emery-Dreifuss. Degrees of the involving are variable. [2]. We suspected EDMD in our patient because he had a combination of gait disorders, moderate knees and elbows contractures, high levels of creatine kinase, normal intellect, DCM-form heart involvement and AV block. Genetic test confirmed the diagnosis.

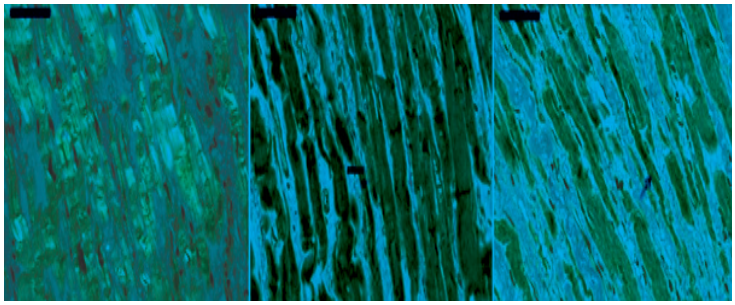

Figure 4: **Morphology of explanted heart (left ventricle).**

Microscope 40x magnification. Left picture (polarized light) shows thin fibers, interstitial sclerosis. The central and the right picture (Masson's Trichrome stain) showed thin cardiomyocytes in the longitudinal sections; interstitial sclerosis, thin fibers, nuclear decay).

Genetic nature of Emery-Dreifuss muscular dystrophy (EDMD) was described in 1994, when mutations were identified in the gene emerin [3]. There are at least five other genes which are responsible for the development of the disease (LMNA, SYNE1, SYNE2, TMEM43 and FHL1). The combinations of mutations in two genes could be reason for quick progression of cardiomyopathy [4]. Other reason could be production of anti-heart antibodies, for example to troponin I [5]. In addition, intervention (radiofrequency ablation and ICD implantation) could disrupt compensatory mechanisms.

There are no guidelines for the treatment of EDMD patients. The optimal treatment strategy, especially surgical, should be individual. There are just a few reports of radiofrequency ablation in patients with myopathies[6]. The reduction of arrhythmia does not improve the disease in case of severe cardiomyopathy. The use of an ICD could be considered in EDMD patients if there are indication for pacing and evidence of ventricular arrhythmias (class IIb, level B), [7]. We believe that implantation of ICDs was useful to our patient and gave him a chance to survive up to heart transplantation.

However, ICD implantation could have been one of the causes of arrhythmias and heart failure progression. Artificial interventricular dyssynchrony could be the reason of deterioration. Our patient did not have a high right ventricle stimulation (20%). The restoration of sinus rhythm did not improve the condition. Development of electric storm determined the further tactic. It is not typical for patients with MDMD. Heart failure is more common reason for heart transplantation. Italian registry of LMNA-associated myopathies includes 78 patients, 17 (22%) have EDMD2, ICD or pacemaker was implanted in 41 (53%) and heart transplantation was performed in 8 (10.3%) myopathic patients [8]. There were two percent of patients with muscular dystrophies through all cases of heart transplantation [9].

Surgeons usually face some problems in transplantation connected with myopathy. There are higher perioperative risk in general, difficulty of anesthesia due to respiratory and neck muscles damage, higher risk of aspiration, rhabdomyolysis, malignant hyperthermia metabolism, worsening of peripheral myopathy due to steroids. Total IV anesthesia and non-depolarizing muscle relaxants are the optimal for use. The same was used in our patient.

The immunosuppression therapy was effective and relative safety in our patient. He got basiliximab (monoclonal antibodies to interleukin-2 receptor, CD25), tacrolimus and mycophenolate. The recent study estimated 10 years' experience this scheme compared with cyclosporine: at equally high survival rate (66.7% and 80.0%), tacrolimus provided a lower incidence of acute rejection and vasculopathy transplanted heart [10].

Conclusion

Cardiomyopathy in patients with primary myopathy (Emery-Dreifuss muscular dystrophy, EDMD) could develop quickly despite of early stable course. These patients should be regular evaluated by cardiologist. Two genes mutation could explain severe cardiomyopathy in our patient with EDMD. Myocarditis should be excluded in all cases of «unexplained» decompensation in EDMD patients. Verification of genetic myopathy variant with cardiac involvement is useful to decide the way of treatment, including surgery. Indications for radiofrequency ablation and ICD implantation in EDMD patients should be choose in case of immediate and long-term prognosis. Although patients with EDMD have peripheral myopathy and limitations of anesthetics use, heart transplantation could be successful done if we use correct regimens of immunosuppression therapy. Women with X-linked EDMD have a mild form of disease. It could looks like more frequent heart diseases so it could not be diagnosed for a long time.

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Management Of Atrial Fibrillation Post Bypass Surgery With Intravenous Sotalol A Case Study

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Abstract

Intravenous sotalol has been available for many years outside of the United States, but has only recently become available in the US. The safety and feasibility of intravenous sotalol for the prevention of recurrent atrial fibrillation following bypass surgery has not been described. The present case study is of a patient with several other co-morbidities undergoing coronary artery bypass graft surgery, who post-operatively developed atrial fibrillation. The patient received intravenous sotalol and was then transitioned to oral sotalol. The patient remained hemodynamically stable, with normal QTc and without further atrial fibrillation or tachyarrhythmias in the post-operative period until discharge. Intravenous sotalol is a reasonable alternative to intravenous amiodarone in the post bypass surgery patient with better tolerability and safety profile.

Introduction

Atrial fibrillation is commonly encountered following open heart surgery, with an incidence of approximately 20 – 40% in this patient population [1, 2]. Although many of these episodes are short lived and self-terminating, at times it may result in significant hemodynamic compromise as well as further complications. Studies have shown that patients developing atrial fibrillation following cardiac surgery have a significant increased risk of thromboembolic phenomenon, stroke, congestive heart failure, myocardial infarction and mortality compared to patients who maintained sinus rhythm [1, 3]. In addition, the cost of managing atrial fibrillation following open heart surgery is also significantly higher due to the prolonged ICU stay as well as use of other resources. The choice of anti-arrhythmic drug therapy is quite limited. Until recently the only intravenous antiarrhythmic medication available in the United States was amiodarone. The acute hemodynamic effects as well as the long-term side effect profile of the oral form of this medication makes this a less than desirable option for the management of these post open heart surgical patients. We present a case in which intravenous sotalol was utilized in this scenario with a positive patient outcome.

Case study

The patient is a 73-year-old male with a history of coronary artery disease (CAD) status post anteroseptal myocardial infarction in 1993, for which he underwent TPA administration. In August, 2000, the patient also underwent stent placement to the left anterior descending artery and the right coronary artery. The patient recently presented with complaints of unstable angina and underwent stress testing which demonstrated a large reversible defect involving the anteroseptal wall. Coronary angiography demonstrated an 80% left main stenosis as well as restenosis involving the right coronary artery. His left ventricular systolic function was approximately 40%.

His past medical history is notable for CAD, as mentioned above, as well as a history of chronic obstructive pulmonary disease (COPD), hypertension, hyperlipidemia, and hypothyroidism. The patient also has a history of an underlying chronic left bundle branch block.

The patient subsequently underwent coronary artery bypass graft surgery with a left internal mammary artery to the left anterior descending artery and the obtuse marginal as well as a saphenous vein graft to the right coronary artery. On his third post-operative day, the patient developed a sustained episode of atrial fibrillation with ventricular rates of 180 – 200 bpm (Figure 1). The patient was symptomatic with these episodes of atrial fibrillation associated with chest pain, palpitations and dyspnea, as well as becoming somewhat hypotensive with a systolic blood pressure of 90 – 100 mm Hg. These episodes of atrial fibrillation would self-terminate and then re-initiate abruptly. Per ICU protocol the patient was initially started on amiodarone at a rate of 1 mg/min without a bolus.

At the time of our assessment the patient had received approximately 2 hours of amiodarone therapy. It was decided that, due to the patient's history of CAD as well as underlying COPD, that he would be better suited with sotalol rather than amiodarone therapy. We were quite concerned about the long-term effects on his lung function as well as the potential hypotension associated with IV amiodarone. His creatinine clearance measured 129.41 mL/min. Potassium and magnesium levels were within normal range. Amiodarone was discontinued, and after approximately 6 hours, the patient received sotalol 75 mg IV infusion over 5 hours. The patient was monitored in the ICU. His QTc remained stable throughout the entire infusion.

Key Words
Intravenous Sotalol,Atrial Fibrillation,Post Bypass Surgery

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On the following day, he was switched to oral sotalol 80 mg twice daily. He remained in sinus rhythm throughout the remainder of his hospital stay without any further arrhythmias. QTc remained within normal range corrected for his left bundle branch block.

Discussion

The present case demonstrates a situation in which we were able to administer intravenous sotalol for the management of post-operative atrial fibrillation following coronary artery bypass graft surgery. The patient had initially received amiodarone as part of the hospital protocol. Although the side effects of amiodarone are usually experienced when given in high doses for a prolonged period of time, we were concerned about the long-term use of amiodarone in this patient with underlying lung disease. Obviously the administration of sotalol could potentially have had increased effects on the patient's QTc interval after having received amiodarone. By administering sotalol as an infusion over 5 hours we were able to monitor the QTc carefully during the entire infusion, and if necessary, modify or discontinue its infusion if a QTc prolongation was observed or if Torsades de Pointes were to occur. The QTc was able to be corrected despite his underlying chronic left bundle branch block. The patient was already in the intensive care unit following his bypass surgery and thus provided the best environment for the use and monitoring of this medication. Since we were able to quickly transition the patient to its oral counterpart, the use of IV sotalol did not prolong the patient's ICU stay.

The management of atrial fibrillation in the post open heart patient can be somewhat difficult. Class I-C antiarrhythmic agents are contraindicated in the setting of coronary artery disease, thus Class III agents, including amiodarone, sotalol or dofetilide are the medications currently utilized in this scenario. Until the introduction of intravenous sotalol, the only one of these agents available in the acute conversion as well as maintenance of sinus rhythm. an intravenous formulation was amiodarone. Intravenous amiodarone has been shown to cause hypotension, thus making it difficult to control the hemodynamics in these very tenuous patients. Further, upon transitioning to oral form, the side effect profile of long-term amiodarone use can have serious long-term consequences. The SAFE-T trial compared the use of sotalol and amiodarone for the

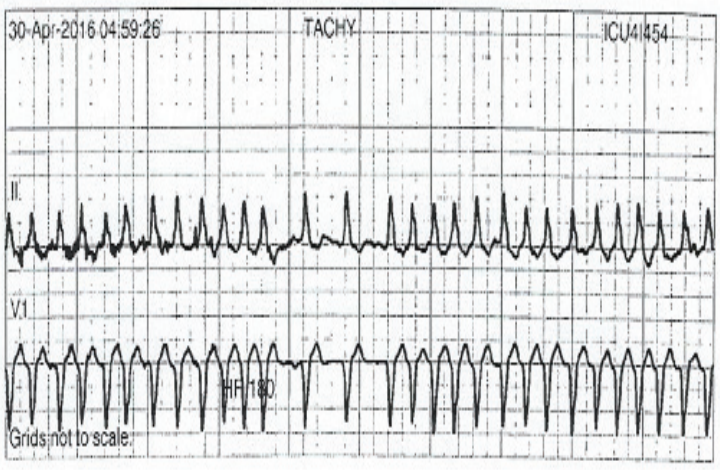

Figure 1: Figure illustrates an episode of atrial fibrillation with a rapid ventricular response rate (180 – 200 bpm) in this patient. Underlying intraventricular conduction defect consistent with a left bundle branch block is noted.

acute conversion as well as maintenance of sinus rhythm.

The investigators found similar rates of efficacy between the two agents, especially with respect to the median time in recurrence of atrial fibrillation in patients with ischemic heart disease [4]. Two further studies evaluated amiodarone vs. oral sotalol in the post bypass population and found similar efficacy and discontinuation rates [5, 6]. Piccini and colleagues recently reported the safety in the long term use of sotalol vs. amiodarone in patients with ischemic heart disease. Although sotalol was associated with an increased mortality compared to no antiarrhythmic drug therapy, the mortality rate was less compared to the use of amiodarone [7]. A recent meta-analysis by Somberg et al comparing amiodarone vs. sotalol for the management of atrial fibrillation demonstrated similar rates of acute conversion (risk ratio = 0.947, 95% CI: 0.837 – 1.071, p = 0.387) [8]. Similarly, the maintenance of sinus rhythm was not statistically different between amiodarone and sotalol (RR = 1.05, 95% CI: 0.625 – 1.774, p = 0.847) [8]. In another recent meta-analysis, the use of sotalol, both IV as well as oral, was found to be similar to Class I-A and Class I-C antiarrhythmic agents in the acute conversion of atrial fibrillation [9]. These studies demonstrated the efficacy of long-term oral sotalol in comparison to amiodarone, however it is important to also evaluate their safety. Intravenous amiodarone has been described to cause hypotension, bradycardia, heart block as well as Adult Respiratory Distress Syndrome (ARDS). Acute hepatic injury has been described in 2.8-4.2% of patients receiving IV amiodarone. The long term side effect profile of oral amiodarone can include pulmonary fibrosis, hypothyroidism, hyperthyroidism, optic neuritis, hepatitis and peripheral neuropathy. Other less concerning side effects include corneal deposits and skin discoloration [10]. Somberg et al described in their meta-analysis the adverse events related to both acute and chronic amiodarone and sotalol therapy [8]. Compared to amiodarone, sotalol had significantly lower incidence of the aforementioned adverse events with the exception of bradycardia and AV block (12-13% vs. 4.9% for amiodarone) and fatigue (10–11% vs. 4 -9% for amiodarone). The incidence of Torsades de Pointes with both the acute intravenous form as well as the chronic oral route of amiodarone is quite rare (<2%). Torsades de Pointes, on the other hand, has been demonstrated to be quite common in patients receiving chronic oral sotalol (2-4%) [11-13]. This is primarily due to its effect on QTc prolongation. Conversely, in a meta-analysis studying 962 patients receiving IV sotalol, the risk of Torsades de Pointes with IV sotalol was 0.1%, significantly lower than with oral sotalol [14]. Piccini et al did discuss that although the all-cause mortality of patients receiving sotalol was greater compared to patients receiving no antiarrhythmic drug therapy, there was a significantly decreased mortality compared to amiodarone (hazard ratio 0.72, 95% CI: 0.55 – 0.91, p = 0.0141) [7]. Although dofetilide is also a potential option in this patient population as well, it is only available
in oral form and one also has to weigh the potential risks of QTc prolongation as well as the risk of Torsades de Pointes [15].

In conclusion, intravenous sotalol provides a much safer and efficacious option in the management of post-operative atrial fibrillation in comparison to intravenous amiodarone. The ability to then transition these patients to oral sotalol provides a better long-term side effect profile compared to oral amiodarone. The infusion of sotalol over a period of five hours also gives the flexibility of halting the drip if any ventricular arrhythmias are observed. This would obviously not be possible after a patient consumed an oral dose

of sotalol. The success in the ability for IV sotalol to convert post-operative atrial fibrillation provides another tool for the management of these patients compared to the standard amiodarone therapy. The clinician prescribing these antiarrhythmic agents should be aware of all potential effects of these drugs and be familiar with their dosing.

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SVT Therapy – Yesterday, Today and Tomorrow

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Abstract

This essay is a brief review of advances in treatment of patients with supraventricular tachycardia (SVT) over the past 55 years. We review the knowledge base available in terms of arrhythmia diagnosis and the limited availability of drug therapy. Significant advances resulted in the introduction of direct-current defibrillators as well as introduction of ambulatory ECG recordings. We also witnessed a tremendous increase in an understanding of the mechanisms of SVT which in turn led to the development of first surgical and subsequently catheter based techniques for localization and ablation of foci or pathways responsible for arrhythmias. More recently, surgical and catheter techniques have been introduced in an attempt to cure atrial fibrillation. These techniques have proven especially effective for those with paroxysmal atrial fibrillation and less effective for those with long standing persistent fibrillation. The future brings hope for more extensive use of non-invasive techniques both to diagnose arrhythmia mechanisms together with techniques to ablate cardiac foci without patient instrumentation and finally in the use of gene therapy for patients with cardiac arrhythmia.

Treatment of Supraventricular tachycardia (SVT) – then and now

For this essay, I decided to restrict myself from the time I entered medical school (1956) to the present. It must be said at the onset that in this short essay one could not possibly list all the individuals who have made major contributions, therefore, I offer apologies for any omissions.

Our characterization of supraventricular arrhythmias was actually fairly well developed by the 1950s ([Fig1]). Uses of the electrocardiogram to diagnose rhythm disorders were well established and clinicians interested in cardiology routinely used an ECG machine. The anatomy of the specialized conduction system pioneered by the work of Tawara and His [1] were widely appreciated. Furthermore, due to the efforts of the past masters (i.e. Sir Thomas Lewis, Wenkebach, Scherf, Mines, Pck, and Langerdoff), we were taught to recognize the ECG pattern of atrial fibrillation, atrial flutter as well as, paroxysmal supraventricular tachycardia.

The Wolff-Parkinson-White (WPW) Syndrome

In 1930, Drs. Wolff, Parkinson, and White described a clinical syndrome characterized by a short PR interval and SVT. [2] Prior to this report, isolated case reports were described by others [3],[4] but the report by Drs. Wolff, Parkinson, and White was the largest and most complete description of the syndrome which is now recognized as an important cause of SVT.

Key Words:

Supraventricular tachycardia ,Atrial Fibrillation,Wolff-Parkinson-White

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The mechanism of the tachycardia is now well established and is due to differences in the conduction and refractoriness between the AV node – His axis and the accessory pathway. The WPW pattern is recognized as a fusion complex due to simultaneous activation of the AV node – His axis and ventricular myocardium via the accessory pathway ([Fig2])

Special attention is focused on the masterful work of Pick and Langendorf [5],[6] where by painstaking analyses, discovered so many of the concepts that underlie our present understanding of supraventricular tachycardia. For example, their contribution to our understanding of the genesis of SVT as it relates the Wolf Parkinson's White syndrome is illustrated in [Fig3]. They also recognized the relationship of atrial fibrillation to the WPW syndrome.

While diagnostic criteria separating SVT from other arrhythmias, as well as, the various types of SVT were well appreciated, available treatment options were rather limited [Fig4]. For example, digitalis preparations were the prime drugs used for either acute or chronic management of SVT. We used very rapid acting preparations (i.e. acetyl strophanthidin) for acute rhythm control of SVT or Atrial fibrillation and oral digoxin for chronic treatment. We were taught to administer these drugs to the onset of side effects and then to back off for chronic administration. It is a small wonder that we have so many instances of arrhythmias attributed to digitalis toxicity, an entity which is seldom seen in contemporary cardiology practice. Oral Quinidine was used for attempted conversion of atrial fibrillation to sinus rhythm as well as for attempted rhythm control in those with paroxysmal or permanent atrial fibrillation. As with the digitalis medications, untoward side effects (especially diarrhea) were fairly common with chronic Quinidine use. The rest of the therapeutic arsenal contained intra venous procainamide for ventricular tachycardia as well as atropine or isoproterenol for bradycardia.

The early 1960s were especially noteworthy with the introduction of the direct-current defibrillation [7]. This device had a truly remarkable

effect in terms of prompt reversion of SVT or VT to sinus rhythm and truly revolutionized care of seriously ill cardiac patients. This innovation rivaled the introduction of permanent pacemakers for treatment of bradycardia. Another revolutionary contribution in the early 1960s was the introduction of ambulatory ECG monitoring by Holter which led to the concept of prolonged monitoring in specialized units championed by Dr. Lown. The late 60s were noteworthy for the introduction of electrical stimulation of the heart first introduced by Wellens and Durrer [8],[9] whose work actually laid the foundation for our current understanding of the mechanisms of SVT. This was well established even before our potential ability to record the His bundle electrogram [10].

In addition, we must give homage to the impressive contributions of our surgical colleagues [fig5]. In the 1960s, patients with SVT refractory to drug therapy were treated with cardiotomy and direct ligation or cryoablation of the AV junction which, of course, required permanent pacing. Durrer and Roos were the first to perform intraoperative mapping and cooling to locate a free wall accessory pathway at the time of cardiotomy [11] subsequently Burchell used intra-operative mapping to locate a right-sided accessory pathway whose function was temporarily abolished by local injection of procainamide. It was left for Dr. Sealy to be accorded the honor of being the first surgeon to successfully and permanently ablate an accessory pathway [12].

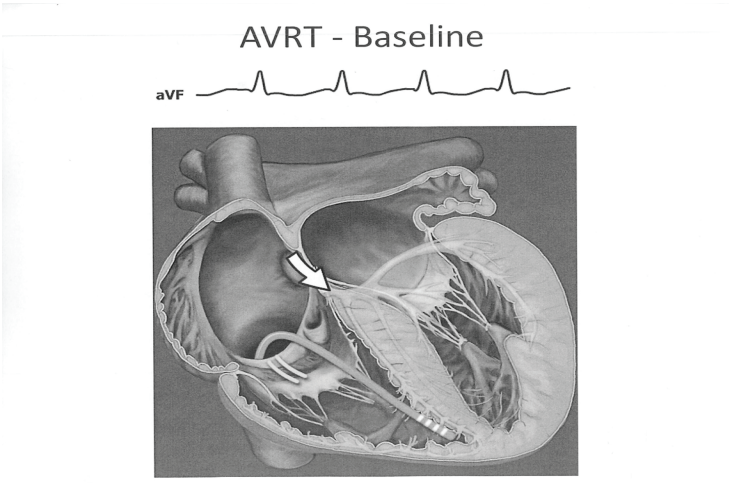
The surgeons in the ensuing decade showed that accessory pathways in any location were amendable to ablation. They defined the anatomic regions in which pathways were located [fig 7] and served as the bases for the development of catheter ablative techniques.

AV nodal reentry

AV nodal reentry is the most common mechanism of SVT. Evidence for duality of nodal conduction was initially described by Mendez and Moe in 1966. [13] A schema often used to describe this mechanism is shown in [fig6]. In the typical form an atrial premature beat is blocked in the normal (or fast pathway) and conducts slowly over the slow pathway and returns to the fast pathway when it is no longer refractory and give rise to an echo beat or to sustained tachycardia.

The earliest description of a non-pharmalogic approach for cure of AVNRT was described by Ross et al in 1985 [14]. Catheter techniques targeting the fast pathway was introduced in 1989 [15] and the current approach targeting the slow pathway was introduced by Jackman et al in 1993 [16]. This technique was associated with a very high incidence of arrhythmia cure and a low incidence of AV block. This technique is still the preferred method for ablative cure of AVNRT.

The early 80s witnessed the birth of catheter techniques for ablation of either the AV junction or accessory pathways [fig6]. The initial catheter technique involved use of high energy direct-current discharges in the region of the compact node [17]. Subsequently, a similar technique was used for successful ablation of posteroseptal accessory pathways [18]. In the late 1980s, high energy direct-current discharge was replaced by radio frequency energy which proved to be much safer and more applicable to ablation of a wide variety of SVTs. Use of radiofrequency energy was introduced by Borgreffe and Breithardt in Europe [19] and by Huang and Marcus in the United States. This technique avoided the intense barotrauma associated with high energy direct current shocks and served as a vital catalyst to external ablative procedures to a wide variety of SVTs. These included ablation of the slow pathway for AV nodal reentry [16] as well as ablative procedures for atrial tachycardia as well as atrial flutter.



In the 1990s, we witnessed the introduction of mapping techniques [fig8] which allowed for better elucidation of tachycardia pathways and allowed for expansion of ablative techniques to complex atrial (or ventricular) tachycardia circuits. Prior to the three-dimensional mapping, even the clinician was obliged to remember the sequence of activation points which was quite cumbersome for complicated

Knowledge of arrhythmias 1950- 1960

1. Electrocardiography well developed
2. Anatomy of specialized conduction system defined
3. Diagnoses of types of cardiac arrhythmias well-established:
   (a) atrial fibrillation/flutter
   (b) paroxysmal supraventricular tachycardia
   (c) ventricular tachycardia
   (d) sinus node disease, atrioventricular (AV) block
4. Diagnostics Masters 2 step exercise stress test

KATZ-PICK-LANGENDORF (1952-1956)

(a) variation in conduction/refractoriness between node/pathway

(b) link between WPW and orthodromic PSVT and atrial fibrillation

(c) concealed conduction into pathway

(d) extranodal vs. nodo fascicular pathways

tachycardia circuits.

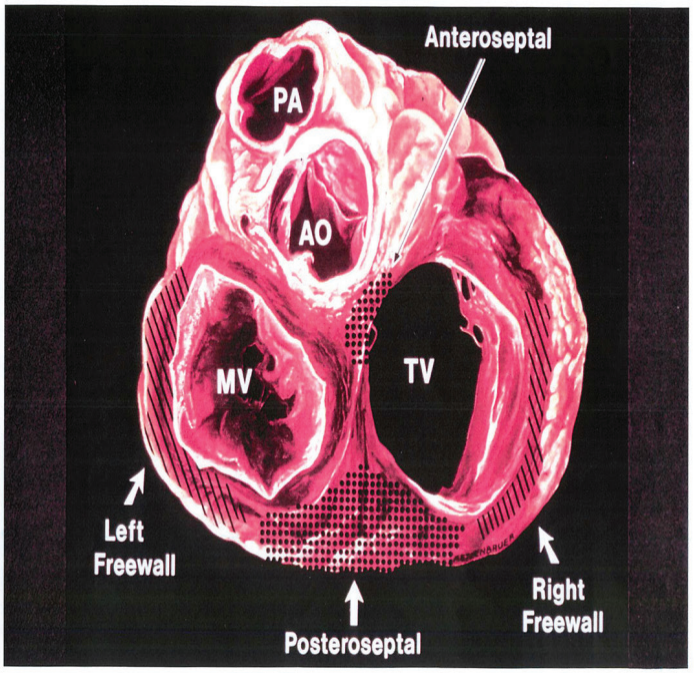
The 1990s also witnessed the introduction of the Cox maze procedure for cure of atrial fibrillation [20]. The original maze procedure involved a cut and sew approach for isolation of wide areas of the posterior left atrium, removal of the left atrial appendage as well as construction of a variety of surgical lines connecting the left atrial room as well as the mitral isthmus [Fig9]. The original procedure also involved creation of surgical lines in the right atrium (i.e. intercaval and CTI lines). This procedure was associated with an astonishingly high success rate but had to be modified because of the high incidence of sinus node dysfunction and because of the length of the procedure. The original Cox procedure has been modified and is still in use today primarily for these patients with atrial fibrillation who require cardiac surgical procedures for other reasons (i.e. valvular or coronary artery disease).

Available therapy 1950-1960

1. Digitalis - supraventricular arrhythmias
2. Quinidine - oral therapy for both supraventricular and ventricular arrhythmias
3. I.V. procainamide for ventricular tachycardia
4. Isoproterenol or Atropine for bradycardia
5. External chest shocks for AV block

The 21st century has witnessed a veritable explosion of newer techniques for ablative cure of atrial fibrillation. We now appreciate the importance of rapid electrical discharge from the left atrial muscles that coat the pulmonary veins [21]. Initial attempts involved localization of the vein(s) that harbored the discharging impulses but we have subsequently learned the importance of total isolation of both the pulmonary veins as well as the surrounding left atrium [22]. A number of ancillary techniques have been introduced to improve the results of catheter ablation for cure atrial fibrillation. These include construction of ablation lesions to connect the left atrial roof as well as the mitral isthmus as adjunctive therapy in difficult cases [23] The incremental effectiveness of these lines are still a matter of debate.

In addition, we have learned a great deal about the pathophysiology of atrial fibrillation. There, however, is still debate about the importance of rotor activity as well as techniques introduced to identify and ablate rotor activity [24]. In addition, the value of ablation of complex fractionated potentials [25] has not been established. A host of other factors appear to play important roles in the genesis and maintenance of atrial fibrillation including the role of the intrinsic cardiac anatomic ganglionic plexi (Scherleg, Jackman) as well as the role of inflammation. In some families, genetic mutations involving the cardiac sodium or potassium channels appear to play an important role in the geneses of atrial fibrillation.



As opposed to the rapid development of catheter ablative techniques for treatment of Atrial Fibrillation, development of newer drug

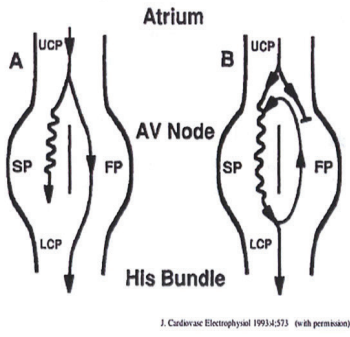
SURGICAL CONTRIBUTION

(1) Surgical ligation or cryoablation of the AV junction for refractory SVT Driefus(1968)

(2) Durrer and Roos - first to perform intraoperative mapping and cooling to locate a right free-wall accessory pathway

(3) Burchell - intraoperative mapping located a right free wall AP, and preexcitation was abolished by injection of procainamide (1967)

(4) Sealy - successful ablation of a right free-wall A.P. (1968)



J. Cardiovasc Electrophysiol 1993;4:573 (with permission)

Fig 7

therapy has been disappointing. For example, attempts to develop drugs that specifically target K+ channels that are seen in atrial tissue alone (i.e. iKur) have not proved helpful. Early in vitro and animal studies show that specific blockers of the late sodium current may prove of value in controlling Atrial Fibrillation.

A Glimpse into the Future

As pointed out, the last six decades have brought incredible advances in the management of patients with complex cardiac rhythm disturbances. Looking into the crystal ball, I think the future portends a greater emphasis on non-invasive techniques for better diagnosis and treatment of rhythm disturbances. Among these advances are the development of external recordings from the chest wall to accurately map complex tachycardia circuits such as the ECGI technique developed by Dr. Ruddy [26]. This technique promises to give clinicians important insights into tachycardia mechanisms prior to taking the patient to the catheter laboratory. Moreover, we are witnessing the development external beam radiation to target specific areas involved in maintain or initiation of tachycardia. Early uses of these procedures clinically have already been reported [27]. Finally, a variety of techniques have been used in animal models to introduce genes that modify channel or protein functions to cure disease. Some of the outstanding developments include the work of Kevin Donohue involving the introduction of a mutation responsible for prolongation of the atrial action potential and showing that treated animals become resistant to pacing induced atrial fibrillation. [28] In addition, Priori has developed a mutation that results in gain of function of the $CASQ_2$ gene which both prevents development of CPVT as well is effective in reversal of signs of CPVT (i.e. bidirectional VT) in mice. [29]

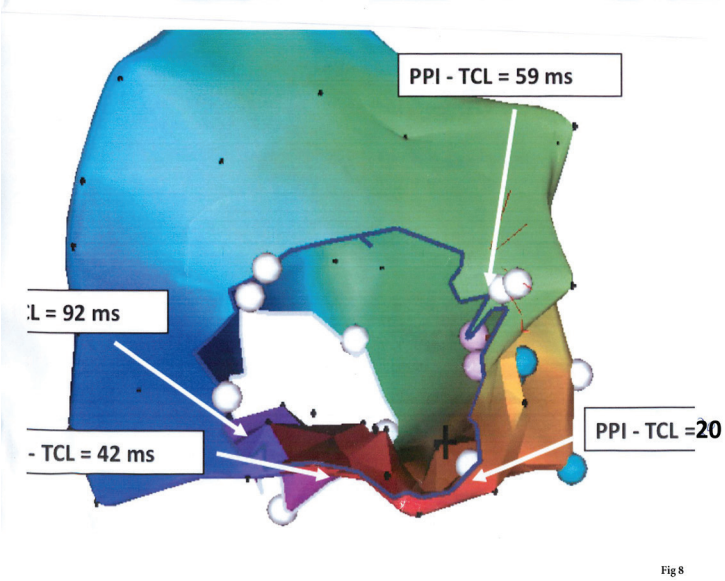
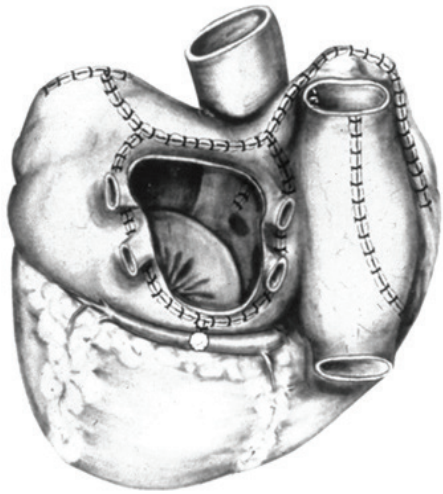


Fig 8



Three-dimensional representation of the original Maze I procedure. A "window" has been drawn in the posterior left atrium to allow visualization of the location of the mitral valve, atrial septum, and AV node.

Figure 9: Cox JL. The first Maze procedure. J Thorac Cardiovasc Surg. 2011 May;141(5):1093-7.

It is clear that brilliant pioneers as well as technological developments have achieved a great deal. In addition, the future including more use of non-invasive techniques as well as development of gene therapy adds great potential to our goal of curing cardiac rhythm disturbances.

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Neuro-Atriomyodegenerative Origin of Atrial Fibrillation and Superimposed Conventional Risk Factors: Continued Search To Configure The Genuine Etiology of "Eternal Arrhythmia"

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Abstract

Atrial fibrillation (AF) is the most challenging rhythm disturbance worldwide. Arrhythmia and its behavior represent complex pathogenesis highly opposing to contemporary curative modalities. Increasing age of patients carries a certain level of risk for AF. Some underlying diseases in concordance with aging actually accelerate the occurrence of AF. Underestimated superimposed risk factors – aging plus any known risk factor or condition (hypertension, diabetes etc.) – elicit great interest and concern. In light of these concerns we offer an elaborated universal hypothesis in attempt to elucidate the genuine origin of AF substrate. Putative chronic toxicity - toxins and/or involution related pseudo-toxins potentially generate micro- and macro-structural changes in atrial myocardium thus inciting both intracellular damage (degeneration of myocites, apoptosis) and extracellular fibrotic proliferation (interstitial fibrosis, formation of matrices, degeneration of cells with fibrotic replacement). The co-products of related underlying diseases in cooperation with cellular senescence, endogenous overproduction of specific lipids/lipoproteins and other pro-atherosclerotic and/or inflammatory components generate a total atrial response - vascular/microvascular damage, intracellular and extracellular injuries. These organizational arrangements covering the entire atrial myocardium and perhaps ganglionated plexi/autonomic branches of the nervous system eventually cause clinical havoc - atrial overstretch, atrial adaptation/maladaptation, electromechanical dysfunction, arrhythmias, heart failure, etc. In essence, valvular heart disease potentially evokes similar changes "violating" thin atrial walls to obey the same scenario. Depicted atriomyodegenerative processes most likely represent the true nature of AF substrate development. Available clinical and morphological evidence potentially designates the atriomyodegenerative or plausible neuro-atriomyodegenerative origin of AF. Deductively fusion of reasons rather than purely heterogeneity is responsible for AF induction. Thus, the uniform approach and synoptic vision of clinical and pathohistological entity may offer an alternative or refreshed viewpoint in AF substrate formation.

Introduction

Atrial fibrillation (AF) is originally known as a disease of the aging population [1], [2], [3]. Considerable ongoing efforts have been undertaken to identify potential substrates for AF [4]. There has been an explosion in the understanding of the pathophysiology of AF in the last 20 years in particular [5]. Such a traditional introduction of the reports associated with AF becomes encouraging platitude. Unfortunately, our understanding of mechanisms and etiology of AF remains incomplete [5], [6], [7], [8].

In general, it may be postulated that atrial myocardium represents vulnerable tissue, however the primary cause/true nature of nonvalvular AF is still unclear. Van Gelder and colleagues [9] state, that AF is not a benign disease. This disorder apparently is non-autonomous. Mysteries associated with AF are the most pervasive and challenging that remain [10].

Modern AF treatments e.g. ablative procedure, usually do not provide desirable and well-established clinical results; transient effects, high AF recurrence rate or negative side effects are reported [3]. An increasing volume of patients is returning for re-ablation despite years of AF freedom after the procedure [11]. In real life-practice even ultra-radical destructive approach fails to eliminate arrhythmia. Persistent AF recurrences are observed after biatrial surgical ablation procedures with complete isolation of all 4 pulmonary veins under the visual control [12]. Consequently, ablation procedure per se is far from the causal AF treatment.

Despite huge explorative efforts the arrhythmia demonstrates high resistance to contemporary treatment modalities and their notable reluctance to submit to the "domestication". Progressive atriomyodegenerative processes and fibrotic proliferation likelihood opposes to revive still viable atrial myocites and to restore their previous condition. This paper focuses on some aspects associated with arrhythmogenic substrate formation in order to conceptualize the suggested hypothetical scenario. The framework of the new vision is based on brief review of current status of histopathological findings of atrial myocardium and adjacent structures, preferably ganglionated plexi.

Key Words

Atrial fibrillation, arrhythmogenic substrate, autonomous nervous system, ganglionated plexi, aging, superimposed risk factors, fusion reasons, neuro-atriomyodegenerative origin, toxins, pseudo-toxins, involution, cellular senescence.

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Compact review of histopathological changes in atrial myocardium

Numerous studies have comprehensively analyzed all aspects associated with AF. Therefore we offer just a minimum of the well-known information to present a context for the reader as it relates to the novel hypothetic/speculative postulations.

The progression of AF is caused by the accumulation of damage in cardiomyocites which makes the atria more vulnerable for AF. [3]. Increased fibrosis and inflammatory infiltrates are found in the atria and pulmonary veins-left atrium junctions [8]. Allessie and colleagues [13] have revealed the presence of diffuse biatrial disease in animal models.

Marked histological abnormalities in aging atria were found by Xu and colleagues in their excellent experimental and human studies [4]. They demonstrated abnormal pathohistological and ultrastructural changes - accelerated fibrosis, apoptosis, matrix degeneration and collagen synthesis; the myolysis was documented in aged dogs. Atrial remodeling was characterized by the researchers as "adaptive responses with maladaptive consequences". Degradation of the myofibril structure (myolysis) is found in patients with persistent AF [14], [15] especially during the end-stage of atrial remodeling [16]. Degeneration of myocites with exhibited abundant interstitial fibrosis was also reported by Lee, Kostin, Everett and co-authors [7], [17], [18] it was indicated that structural remodeling may be an adaptive process (dedifferentiation of cardiomyocites) aimed at protecting the atrial myocites or a maladaptive process (degeneration of cells with fibrotic replacement). Ultrastructural changes - loss of sarcomeres, mitochondrial atrophy, etc. - were documented by electron microscopy [15].

Importantly, cardiac apoptosis results from "mild" but repetitive or prolonged episodes of stress – ischemia, stretch or overload with aging and/or AF [4] chronic hemodynamic overload may be an important factor in triggering a programmed cell death pathway and atrial fibrosis. Due to hemodynamic overload thin atrial walls undergo substantial overstretching [4]. It suggests, that valvular heart disease produces similar atrial effects. According to Zado [19] both AF and heart failure are common conditions and each promotes the other.

Atrial fibrosis in humans may be visualized by newer MRI techniques [20]. Goldberger and co-authors [20] have indicated four stages of atrial fibrosis: no disease, early disease that is not detectable, detectable substrate without AF (ie, preclinical substrate), and manifest AF. The first three stages likely represent an atrial adaptation period while the last one represents – disadaptation. Noteworthy to stress, that in animal models reversal or prevention of fibrosis prevents AF [21], [22].

Superimposed risk factors - a set of circumstances initiating AF

Various reports have highlighted the role of common risk/proarrhythmic factors and predisposing conditions which contribute to the development of AF: old age, ischemic heart disease, rheumatic, valvular, thyroid disease, pre-existent pulmonary disease, hypertension, heart failure, renal failure, chronic hemodynamic overload, obesity, cardiac lipid everload, dyslipidemia, diabetes, metabolic syndrome, high body mass index, obstructive sleep apnea, hypoxia, cardiomyopathy, sick sinus syndrome, significant alcohol/tobacco use or abuse, inflammation, interstitial fibrosis, atrial overstretch, atrial volumetric changes, oxidative stress and prolonged PR interval [6], [23]-[27]. Some of them are attributed to powerful category. Recently underweight was indicated as a risk factor as well [28]. Atriomyopathy or fibrotic atrial cardiomyopathy is also a favorable milieu for AF [20], [29]. Interactions between these risk factors or their cumulative effects may not be excluded.

AF is strongly age-dependent with approximately 70% of the AF patients between 65 and 85 years [30]. The incidence increases markedly with advancing age [31]. As the population ages, AF will become more and more prevalent [32]. Let's assume that aging is the most important and the most prevalent risk factor for AF. The other well-known proarrhythmic factors however may act in solidarity with the age-dependent one or in self-independent manner as alone contributor. In AF patients the hypertension and high body mass index are likely to increase left ventricular stiffness by elevating vascular resistance, thereby leading to increased left atrial enlargement [7]. Herein two overlapping risk factors for AF are mentioned, i.e., hypertension and high body mass index. Individual advanced age as the 3rd factor is to be kept in mind. Due to the convergence of several risks the atrial myocardium becomes much more vulnerable. The preferred aging risk factor in some cases (e.g., in valvular heart disease) may play a less important role, however not of a zero value.

Notably, left atrium size is increased in elderly patients [37] not just in patients suffering from valvular heart disease. Consequently clear relationship may be tracked: an obvious link exists between nonvalvular AF, valvular AF, heart failure, atrial overstretch, atrial volumetric overload, e.g. due to mitral regurgitation and/or due to atrial overload on aging or on congestive heart failure basis. It means that sensitive atrial myocites and the entire atrial myocardium are easily vulnerable. Obviously, atrial enlargement per se is a favorable pro-arrhythmic parameter.

In the natural course of heart failure progression, the viable myocardium is gradually replaced by collagen-rich tissue [33]. It is noteworthy that the progression of heart failure or any other underlying disorder takes time; concordantly the patients are growing older thereby complicating the course of the corresponding chronic disease. Ischemic heart disease, diabetes, obesity, metabolic disorders, chronic obstructive pulmonary disease, inflammation and much more negative ingredients solitary or by coalescence favor AF induction. Co-existence of superimposed factors is to be considered as synoptic heterogeneity of causes which serve for the formation of arrhythmogenic substrate.

Age-related involution processes taking part in the entire human body and atrial wall are actually accelerated by underlying diseases or by appropriate comorbidity. Reportedly, abnormal lipid accumulation is observed in the cardiomyocites of obese and diabetic patients and is thought to contribute to an increased risk of arrhythmia [27]. Overall acceleration of activity of factors mentioned results in the transition of paroxysmal to long-standing AF and finally to atrial functional abnormality.

It seems unbelievable that the underlying heart/non-heart disease may form circumscribed region(s) as a substrate for AF and that these limited pathological areas might be abolished by ablative or other destructive intervention [34]; alternative pathophysiology of AF may be depicted as an appearance of focal area (e.g. inflammation) which expands centrifugally to the reminder of the atria. A similar mechanism is described of focal atrial tachycardia after surgery [34].

Hypothetic, near-realistic considerations

It is most likely that the AF occurrence is time-dependant and it correlates with the coincident phase of advanced underlying disease which in turn produces unfavorable "environmental" pro-atrial toxins.

Two hypothetic constituent components participating in the primary substrate formation may be suggested: 1) toxic and 2) pseudo-toxic containing pro-degenerative and pro-arrhythmic ingredients. The first one is represented by the underlying etiology which does not directly pertain to atria. It may be renal failure, rheumatic disease along with its inflammation ingredient and corresponding consequences which in turn leads to valvular incompetence, atrial overload, overstretch, enlargement and evolving rough structural changes. The same can be said about the adverse synergistic effects on atrial myocardium that appear on the basis of above mentioned wide spectrum of various underlying diseases. The nature of these toxic products is to be proven yet however they demonstrate "natural" affinity for atrial myocites.

Pseudo-toxic initiating mechanism may occur due to the complex involution/regressive alterations in the entire human body associated with aging processes. Cellular senescence, endogenous overproduction of specific lipids/lipoproteins [35], [36] and other pro-atherosclerotic components sooner or later do evoke vascular/microvascular damage resulting in intracellular and extracellular injury. In this regard the coronary artery disease may play the crucial role. Hypertension and diabetes may also be included into the list of pro-pseudo-toxic activities. Most likely atria are affected negatively by both factors – toxic and pseudo-toxic which finally are responsible for the release of extraordinarily complex atriomyodegenerative or neuro-atriomyodegenerative pathology. These putative key factors likely determine the creation of genuine pathophysiological substrate for arrhythmia. Thus, atrial myocardium is compromised as a target organ for the activity of co-products of underlying disease(s)/conditions. In this regard the underlying diseases apparently trigger the whole clinical entity associated with AF. Atrial propensity to atract the provocative factors delegated by underlying or comorbid illnesses might be the target of future investigation.

Individual peculiarities (atrial vulnerability, susceptibility, comorbidity, immunological state etc.) negatively contribute to AF substrate formation and exacerbation of AF attacks. Elderly patients being free from AF probably are immune to provocative risks; some of them, especially those with the genetic robustness are refractory to arrhythmias throughout the life span.

Some authors indicate that AF manifests itself as a result of multiple heterogeneous groups of disorders [6]. According to Takemoto et al. [38] AF starts as paroxysmal but can evolve relentlessly to the persistent and permanent forms; the mechanisms governing such a transition are unknown. It is considered that the AF itself is not causal. However, it has been demonstrated that AF itself may result in changes in electrophysiology that promote further AF – so-called "AF begets AF" [39].

The role of ganglionated plexi

It is well known that the autonomic nervous system (ANS) is involved in the onset of AF [40]. Cardiac ANS system consists of extrinsic and intrinsic components, which play significant role in the modulation of the cardiac function [40]. This system has great plasticity in the initiation and maintenance of AF [41]-[43]. Intrinsic cardiac neurons are found in the atria and are innervated with both sympathetic and parasympathetic neurons that are connected to both the spinal cord and medullary neurons [44]. According to Kondo et al. [45] ganglionated plexi are highly associated with AF and are key targets for a maze procedure. Some reports show that intrinsic nerve activity could influence the occurrence of atrial triggers that would increase atrial vulnerability to AF [46]. Shen and colleagues [47] have stressed that activity of ANS is crucial in triggering paroxysmal AF. Interestingly, atrial neural network was described recently [48], [49].

Heightened atrial sympathetic innervation has been demonstrated in patients with persistent AF [50]. Relative curative influence on AF by generalized denervation of atria is reported [46], [51]. While targeting autonomic cardiac ganglia alone does not prevent long-term AF recurrences [52]. Some observations show that ganglionated plexi ablation without pulmonary veins' isolation may be proarrhythmic with decreased atrial sympathetic and parasympathetic innervations [53].

Apparently the ANS contribute to the electrophysiological creation of substrate for AF. Direct autonomic nerve recordings demonstrate that simultaneous sympathovagal discharges and intrinsic cardiac nerve activities are common triggers of AF [47]. We are still unaware as to which risk factor(s) predispose the activation of ganglionated plexi to initiate and/or to mainatain AF. These factors are perhaps already known risks, i.e. the common conditions that were enumerated above (aging, hypertension, diabetes and so forth). Noteworthy, ganglionated plexi could self-activate the influence of extrinsic cardiac ANS [54]. Xi and Cheng [55] have postulated that namely dysfunction of ANS impacts the pathogenesis of AF. Again, the dysfunction or imbalance of ANS perhaps stems from the hierarchic centers residing in spinal cord or in medulla. Such an uncertainty generates the idea of degenerative origin of ANS preferably its parasympathetic branch, thus allowing to be outweighed by sympathetic one. The question is: when and why the activity of ANS is accelerated and why this activity is depressed before the onset of AF? Asymmetry in activities of sympathetic and parasympathetic branches of ANS may explain the dominance of sympathetic component. Recently experimental studies have shown neural remodeling with atrial nerve sprouting and sympathetic hyperinnervation in metabolic syndrome [56]. Ablation impacts favorably the overall success by neutralizing the activity of both branches of ANS. In such a manner the discordance of ANS activity is annihilated presumably.

The degenerative predilection of ganglionated plexi is to be validated. Unfortunately conclusive data of microscopic changes of ganglionated plexi pertaining to AF are lacking. The epicardial fat pad most likely undergoes mechanical over tension, dilation and expansion which are associated with volumetric changes of atria. According to the report of Maesen and co-authors [57] left atrial epicardial adipose tissue (peri-atrial fat) increase with left atrial volume. Thus, secondary changes might be inspired and conspired, at least theoretically, with the involvement of peri/epicardial autonomous neural network.

The role of putative abnormal sympathetic and/or parasympathetic contribution to support the AF substrate formation is to be established yet. Nevertheless, the term of "neuro-degenerative" was incorporated prematurely into the title of this article. The neuro-degenerative component is probably activated due to atrial enlargement especially when it reaches critical parameters. At least theoretically the neuro-degenerative ingredient may play specific role in terms of maintaining rather than initiating of AF.

Unlearned but helpful definitions

In general, some nosological diseases do not demonstrate a complete set of classical symptoms. The term "forme fruste" represents an atypical or attenuated manifestation of a disease with the implications of incompleteness, partial presence or aborted state. There is a suspicion that overall ischemic heart disease, rheumatic disease, hypertension, diabetes, obesity etc., are not full-blown while lacking of AF. Arrhythmia potentially emerges as a natural course with constituted components of chronic diseases mentioned at least at their end-stage. The increasing age of the patient favorably accelerates the formation of AF substrate. In other words, aging as a "confident" ally strongly supports the release of AF. All together, a pro-arrhythmic underlying disease, AF per se, along with the patient's disposing age leads gradually to the "forme pleine" condition, i.e., to accomplished form of the disease. Myocardial devastation as a fait accompli reflects the presence of continuous pathognomonic sign of the provocative diseases. Such predisposing conditions or etiological heterogeneity most likely beget AF, not "AF begets AF". The onset of AF actually depends on the degree of atrial involvement into the developing processes.

Conclusion

We would like to conjoin multifactorial/multisource etiology into a unique monoetiologic concept of arrhythmogenesis. The proposed hypothesis is focused on conceptualization of the neuro-atriomyodegenerative processes which likely occur due to various launching/predegenerative factors of underlying diseases that initiate not only AF, but anatrial remodeling phenomenon as well. Single action or coaction of several prodegenerative ingredients potentially leads to a myodegenerative endpoint at the atrial level. A fusion of reasons rather than purely heterogeneity is most likely responsible for AF induction.

Atrial myocardium might be treated as an exclusive/specific milieu accumulating provocative troublemakers delegated from extracardiac or intracardiac sources along with the favorable proactivity of aging component. Thus, cooperative reasons – toxins and/or pseudo-toxins potentially affect the atrial myocardium and are responsible for AF. The possibility of interaction between these factors cannot be ruled out. Deductively, it may be postulated that AF is not an autonomous disease. In fact, atrial myocardium represents the "true victim" of superimposed invaders – toxic and pseudo-toxic products stemming from various chronic diseases or conditions. Hence, atrial myocardium undergoes violation by harmful co-products finally resulting in atrial remodeling. This abnormality is highly resistant to traditional AF therapies. Any well-known progressive degenerative disorder (e.g., idiopathic, arrhythmogenic, dilatative cardiomyopathy, degenerative valve, joint disease, neurodegenerative diseases etc.), are hardly reversible and usually are refractory to medical control. In other words, intramural deconstruction or reverse of already precipitated excessive fibrotic changes is hardly feasible. Such an image of arrhythmogenesis fundamentally reveals our failing efforts to restore the previous viability of affected myocites especially when degenerative processes continue their activity.

Some uncertainty emerges as far as whether the targeted ablation of viable myocites is helpful or not to regain the previous atrial functional status. To revive and to maintain the inherent viability of myocites, not to destroy them (e.g., by ablation) potentially would be the best choice of cure. Theoretically the annihilation of unfavorable intracellular changes or extracellular matrices might be more beneficial rather than execution of cardiac cells. Huge efforts are to be invested into the novel and more effective treatment modalities precluding and eliminating odds for AF. If neuro-atriomyodegenertive origin of AF is recognized the new treatment strategies should be established.

Thus, the prevention of underlying diseases, effective neuro-myoprotective therapy and hampering measures against aging might be the best strategy for AF prevention. Interestingly, weight loss results in regress of AF from persistent to paroxysmal [58]. Widely declared upstream AF control [59], [60] might be interpreted as a preventive "golden approach" not allowing the pathology to descent into the preclinical and/or clinical phases. Thus, underlying disease must be carefully identified and proeperly managed. All the remaining treatment options (pharmacological, non-pharmacological, cardioversion, ablation therapy etc.) actually represent palliation rather than eradication of „eternal arrhythmia". Aging protection and involution mitigation measures are to be invented as well.

Finally, the synthesis of well-known risk factors by unifying their features potentially enables to state/hypothesize that atrial myocardium demonstrantes high affinity and sensitive effects for specific toxins (unidentified yet) or pseudo-toxins in a „suicide manner" . The value of synoptic toxicity-induced model of AF development remains to be debated.

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His Bundle Pacing Or Biventricular Pacing For Cardiac Resynchronization Therapy In Heart Failure: Discovering New Methods For An Old Problem

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Abstract

Heart failure (HF) is one of the biggest epidemics of modern cardiovascular medicine. Cardiac resynchronization therapy (CRT) with biventricular (BiV) pacing has proven to have an integral role in the management of patients with reduced left ventricular (LV) function and left bundle branch blocks (LBBB). However, CRT with BiV pacing is not always feasible and even when it is, the percentage of non-responders remains high. Limitations in LV lead implantation due to anatomical or other constraints; non response to BiV pacing due to lead position or patient related factors and lack of benefit in patients with RBBB and patients with AV block and low normal LV function limit the use of BiV pacing. Permanent His Bundle pacing (HBP) is now a feasible alternative to BiV pacing for CRT therapy. This allows for recruitment of BBB disease and ventricular activation in a more physiological fashion. In this paper we review the physiology of HBP, available data on HBP for CRT and highlight how HBP can be a potential alternative in patients in whom BiV pacing did not provide clinical response or was unsuccessful.

Introduction

Heart failure (HF) has become one of the biggest epidemics of modern cardiovascular medicine. HF affects approximately 5.7 million patients in the United States and it is predicted that by the year 2030 an additional 3 million Americans will have HF, representing an astounding 25% increase from 2010[(1)]. As a consequence, the management of HF accounts for one of the biggest burdens on health care expenditure. In 2007, the American Heart Association estimated that $33 billion was spent on heart failure alone and the annual direct cost of HF treatment in the Unites states is expected to increase from $24.7 billion in 2010 to $77.7 billion in 2030[(2)].

Conventional cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT) has emerged as an integral part of the therapy for patients with HF with severely reduced ejection fraction and bundle branch block (representing inter-ventricular conduction delays). Conventional CRT achieves the synchronization of ventricular contraction through biventricular (BiV) pacing using an endocardial right ventricular (RV) lead and an epicardial left ventricular (LV) lead via the coronary sinus. The patients that benefit the most from BiV pacing are patients with severely reduced LV systolic function with a poor NYHA class and a wide left bundle branch block (LBBB) >= 150ms[3]. Multiple prospective randomized studies have shown that conventional CRT pacing yields improved quality of life, increased exercise capacity, reduced heart failure hospitalization and decreased all-cause mortality[4]-[9].

The indication for BiV pacing in patients with narrow QRS complexes has been limited to patients with a low LVEF undergoing implantation of a new or replacement pacemaker or implantable cardioverter defibrillator (ICD) with an anticipated requirement for a significant percentage (>40 %) of ventricular pacing[10].

Limitations of BiV pacing (Conventional CRT)

However, despite a significant benefit and evolving indications, there are still limitations to biventricular pacing. Firstly, up to a third of patients treated with conventional CRT do not derive a detectable clinical or echocardiographic benefit, and indeed, some worsen after resynchronization[4]; [6]; [11]. Secondly, procedural factors such as the location of the LV lead may also affect longer term outcome. An analysis from the MADIT-CRT trial by Singh et al[11] and other studies showed that a lead placed in the LV apical region is associated with a worse clinical outcomes. Anatomical limitations including lack of suitable coronary sinus venous branches and unavoidable phrenic nerve stimulation at ideal anatomic LV lead positions can limit the success of LV lead placement as well.

Conventional CRT has also shown a lack of benefit in patients with a normal QRS duration and among patients with RBBB[3]. It is also well known that long-term RV pacing can worsen LV function and HF. Recent trials have evaluated the utility of BiV pacing in the setting of heart block with contradicting results. The biventricular

Key Words

Right Atrial Septal Pacing, Paced PQ Interval, Atrial Fibrillation, The Percentage Of Atrial Pacing.

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pacing for atrio-ventricular block and systolic dysfunction (BLOCK-HF) trial randomized patients with atrioventricular block, NYHA symptom class I to III heart failure, and left ventricular ejection fraction ≤50% to BiV versus RV pacing and demonstrated an improved quality of life and NYHA class with BiV pacing, mostly driven by change in left ventricular (LV) systolic volumes[12]. On the other hand, results from the BiV pacing for atrio-ventricular block to prevent cardiac de-synchronization (BioPace) trial that randomized patients who needed ventricular pacing at least two-third of the time, failed to show a significant clinical benefit of BiV pacing over RV pacing[13].

His Bundle Pacing (HBP) for CRT

Over the past few years, permanent HBP has become more feasible with the availability of better delivery systems. More recently, it has become a more attractive alternative to BiV pacing for CRT with the demonstration of resynchronizing ventricular activation by various groups[14]-[18]. The physiologic benefit of permanent His bundle pacing (HBP) is the ability to stimulate the ventricles through the intrinsic His-purkinje system, which results in synchronous and a more physiologic electrical and mechanical activation. HBP can also be used as a bail-out strategy in cases where coronary venous anatomy limits the ability to place an LV lead. Other advantages include the lack of potential complications from LV lead placement that include coronary sinus dissection, venous perforation, cardiac tamponade and the potential for proarrhythmia.

Available data on HBP for CRT

The available data on HBP as an alternative to BiV pacing for CRT is limited. Only few studies with small number of participants and limited experience have been reported. [Table 1] summarizes these data.

Barba-Pichardo et al. described their experience with HBP in failed CRT cases[16]. They attempted HBP in 16 patients with cardiomyopathy and failed CRT (Ischemic cardiomyopathy in 7, Idiopathic in 9). This represented 14% of the total number of patients derived for CRT during the inclusion period. Of those, temporary HBP corrected LBBB in 13 patients (81%) who were considered suitable candidates for Hisian cardiac resynchronization. Successful CRT by permanent HBP was then obtained in 9 patients, corresponding to 69% of the selected patients (Ischemic 4, Idiopathic 5). Mean QRSd decreased from 166±8 ms to 97±9 ms. HBP threshold at implant 3.09±0.44V @ 1ms. NYHA functional class improved from class III to class II and there was an improvement in left ventricular ejection fraction (LVEF) and LV dimensions.

Lustgarten et al compared HBP versus biventricular pacing in a crossover design among patients with indications for CRT defibrillator implants[19]. They enrolled 29 patients and were successful in demonstrating electrical resynchronization in 21 (72%) cases. All patients received both a coronary sinus LV lead and a HBP lead connected to the LV port via a Y-adapter. Patients were randomized in single patient-blinded fashion to either HBP or BiV pacing. After 6 months,patients were crossed over and followed for another 6 months. 12 patients completed the crossover analysis at 1 year. Both groups of patients demonstrated significant improvements in ejection fraction, functional status, and 6-minute walk distance. They concluded that HBP was noted to have an equivalent CRT response to conventional BiV pacing.

Su et al evaluated various pacing configurations in 16 patients undergoing successful CRT-D with HBP lead in the LV port and 13 dual chamber ICD implants (patients with permanent AF)with the HBP lead in atrial port[20]. They demonstrated that incorporation of HBP into a CRTD/ICD system is feasible, and capture thresholds and R-wave sensing can be optimized using an integrated bipolar configuration with the RV lead.

Ajijola et al evaluated thirteen patients with indication for CRT

Table 1: Available data on HBP for CRT

Study Name	Design	Study population	Total attempted cases	Success rates (recruitment of BBB) using HBP	Outcomes
Barba-Pichardo et al 2013(16)	Prospective	HBP attempted in pts with failed LV lead placement	16	9	Improvement in NYHA class; Improvement in LVEF and LV dimensions
Lustgarten et al 2015(19)	Crossover	HBP and LV leads in all patients undergoing CRT	29	21	Significant improvements in ejection fraction, functional status, 6-minute walk distance with both HBP and BiV in 12 pts who completed the crossover.
Su et al 2016(20)	Prospective	HBP in pts with indication for CRT	N/A	29	Tested various pacing configurations and demonstrated lower pacing thresholds using a bipolar HB lead and RV lead configuration.
Ajijola et al 2015(21)	Prospective	HBP attempted in pts with failed LV lead placement	13	12	Improvement in LVEF and dimensions; Improvement in longitudinal strain.
Vijayaraman et al(22)	Prospective	Failed LV lead placement; HBP with LV leads; HBP alone in pts with indication for CRT	32	39	Improvement in NYHA functional class; Improvement in LVEF

BBB: bundle branch block; BiV: biventricular; HBP: His bundle pacing; LV: left ventricular; LVEF: left ventricular ejection fraction.

implant with failed coronary sinus LV lead placement[21]. The HBP lead was successfully placed in 12 of 13 patients (92%), with significant narrowing of the QRS duration to 120±23ms (p<0.0001). At 6-month follow up,they demonstrated an average increase in LVEF by 18.7%, and decrease in left ventricular end diastolic internal dimension (LVIDd) by 0.9cm. Echocardiographic global longitudinal strain improved from -9.1 to -10.5%.

Our experience with HBP for CRT

Our experience comprises of 29 patients with successful HBP for CRT (of 32 attempted cases)[22]. Fourteen of these were for failed coronary sinus LV leads, nine with primary HBP (AV nodal block), seven patients with HBP and LV leads and 2 patients with HBP leads due to conventional CRT non-response. QRSd improved from 165 +- 31 ms to 115 +- 19ms (p< 0.001).Over a mean follow-up of 17 +- 16 months, LVEF improved from a mean value of 30 +- 10 to 47 +- 11 percent (p< 0.05); and NYHA functional status improved by one class.

Possible mechanisms of Recruitment of LBBB with HBP

Various mechanisms for this recruitment of bundle branches in patients with bundle branch block/delay have been postulated. These include: (1) longitudinal dissociation in the HB with pacing distal to the site of delay/block and/or (2) differential source-sink relationships during pacing vs intrinsic impulse propagation and/or (3) virtual electrode polarization (VEP) effect[23].

The strongest postulated theory is that longitudinal dissociation exists within the HB and intrahisian disease is often responsible for BBB or delay. This concept was first elegantly studied by Narula et al back in 1977[24]. They postulated that delay within fibers in the HB could result in BBB or delay and demonstrated that pacing distal to the site of conduction delay could recruit fibers predestined to be the bundle branches and thereby narrow the QRS duration. Even if some of the disease is proximal within the intra-hisian region, it can be associated with a decrease in the number of conducting cells available to produce a sufficient upstream voltage gradient (source) to successfully depolarize through the diseased distal left bundle branch and increasing this number by pacing at a higher output might be sufficient to improve conduction[25].

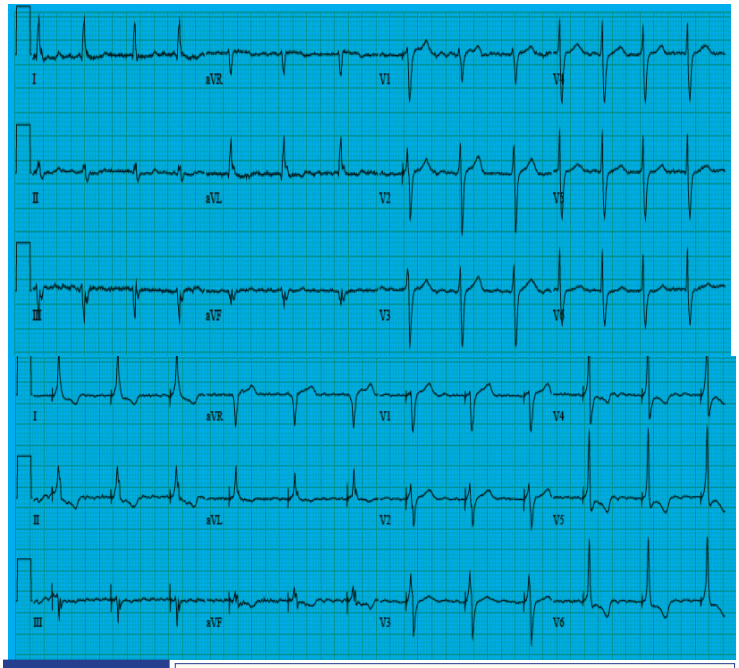

Figure 1: A. Twelve lead ECG of a patient with nonischemic cardiomyopathy and chronic atrial fibrillation at baseline is shown. B. Following AV node ablation, nonselective His bundle pacing with minimal RV fusion and paced QRS duration of 130 ms is shown.

Case Examples

Case 1: A 65-year-old man with nonischemic cardiomyopathy, LVEF of 20-24%, NYHA class III functional status and chronic atrial fibrillation was referred for ICD implantation for primary prevention of sudden cardiac death. His medical therapy included carvedilol 25 mg twice daily, digoxin 0.25 mg daily, lisinopril 40 mg daily and spironolactone 25 mg daily. Holter monitoring showed average HR of 70 bpm with periods of rapid ventricular rate and nocturnal bradycardia. He underwent dual chamber ICD with HBP lead connected to the atrial port in anticipation of need for ventricular pacing. The device was programmed to DDIR mode at 50 bpm. During 3-month follow-up he was noted to have 60% HBP (atrial) and 99.5% RV sensed events. Despite adequate AV nodal blockade, he presented several months later with episodes of near syncope and two ICD shocks while carrying groceries. ICD interrogation revealed multiple episodes of FVT due to AF with RVR but therapy withheld due to recognition as supraventricular arrhythmias and the 2 episodes required ICD shocks due to organization into atrial flutter with 1:1 conduction at 230 bpm. Subsequently AV node ablation was performed allowing >99% HBP with paced QRS duration of 130 ms with minimal fusion (figure 1 and 2). At 6 months his LV function improved to 38% and NYHA functional class to II. This case illustrates the value of HBP in patients with normal QRS in whom high percentage of ventricular pacing is anticipated. By preserving native His-Purkinje conduction through HBP, the adverse effects of right ventricular pacing can be prevented.

Case 2: A 70-year-old man with nonischemic cardiomyopathy and severely reduced LV function, LBBB and class III CHF on optimal medical therapy was referred for biventricular ICD. LV lead placement was unsuccessful due to lack of suitable lateral vein branches and diaphragmatic stimulation in the posterolateral vein branch with high LV capture thresholds. At this point, His bundle pacing was successfully performed and the lead connected to the LV port of biventricular ICD. During HBP, QRS duration significantly shortened from 210 ms at baseline to 130 ms (figure 3). LV ejection fraction improved from 25% to 40% and NYHA functional status changed from class III to II during follow-up. This case highlights the utility of permanent HBP as an option for cardiac resynchronization therapy in patients in whom LV lead placement is unsuccessful.

Conclusions and Future Directions

Cardiac resynchronization therapy with biventricular pacing has definitely made a significant impact in cardiovascular morbidity and mortality in patients with LV systolic dysfunction and heart failure. However, challenges remain due to high non-responder rates. While patients with LBBB, non-ischemic dilated cardiomyopathy, no or limited scar at MRI evaluation and female gender have high probability to be responders, permanent HBP may provide a real alternative to biventricular pacing in patients with low response rate. In our opinion HBP should be attempted in patients who fail LV lead placement prior to considering alternative options such as surgical epicardial or endocardial LV lead placement. HBP may be the more physiological primary option in patients with normal His-Purkinje conduction but requiring ventricular pacing in the setting of LV dysfunction and in patients undergoing AV node ablation.

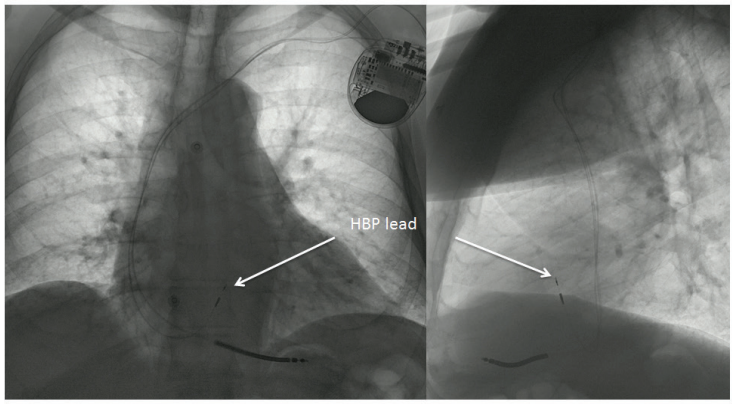

Figure 2: PA and lateral chest X-rays of patient in figure 1 is shown.

HBP may also be considered in patients with cardiomyopathy and underlying RBBB with or without prolonged PR intervals as an option for cardiac resynchronization therapy. [26]

Several questions remain regarding HBP as a viable option for cardiac resynchronization therapy. How effective is HBP compared to biventricular pacing in patients with LBBB? While preliminary data from a small, randomized, cross-over study suggest equivalent response, we do not have large, long-term outcome data. What percentage of patients with LBBB can be corrected by HBP? How much correction of LBBB is necessary to achieve electrical and mechanical resynchronization and clinical response? Can HBP correct BBB in similar fashion in both ischemic vs non-ischemic cardiomyopathy patients? Will HBP maintain electrical resynchronization during long-term follow-up? Can we improve

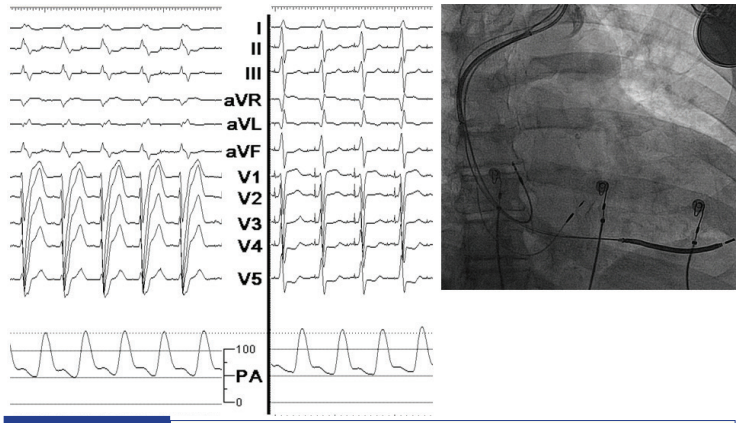

Figure 3: Twelve lead ECG of a patient with nonischemic cardiomyopathy and LBBB with QRS duration of 210 ms is shown. B. During selective HBP, QRS duration decreases to 130 ms with improvement in systolic BP by 6-10 mm of Hg. C. Fluoroscopic image of CRT-D with HBP lead is shown.

on capture thresholds required to correct BBB? In order to answer all these questions, additional clinical research and investment to improve clinical tools to achieve optimal HBP is necessary. Last but not the least,large, multicenter, randomized study comparing HBP to biventricular pacing needs to be performed to evaluate the clinical efficacy of HBP and to define its role in achieving cardiac resynchronization therapy.

Disclosure

Dr Sharma: no relevant disclosures

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How To Manage Oral Anticoagulation Periprocedurally During Ablations And Device Implantations

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Abstract

More than 150, 000 patients undergo ablation for atrial fibrillation (AF) each year. Current guidelines recommend oral anticoagulation in all patients undergoing AF ablation. A large number of patients undergoing cardiac implantable electronic devices (CIEDs) are on long-term oral anticoagulation. These patients are at increased risk for thromboembolism with interruption of oral anticoagulation. Due to the increased risk for bleeding complications during the procedure combined with the need to prevent thromboembolism, periprocedural management of anticoagulation in these patients can be challenging. In this article we review the current evidence for periprocedural management of oral anticoagulation in patients undergoing ablation and CIED implantation

Introduction

More than 150, 000 patients undergo ablation for atrial fibrillation (AF) each year.Current guidelines recommend oral anticoagulation in all patients undergoing AF ablation. A large number of patients undergoing cardiac implantable electronic devices (CIEDs) are on long-term oral anticoagulation. These patients are at increased risk for thromboembolism with interruption of oral anticoagulation. Due to the increased risk for bleeding complications during the procedure combined with the need to prevent thromboembolism, periprocedural management of anticoagulation in these patients can be challenging. In this article we review the current evidence for periprocedural management of oral anticoagulation in patients undergoing ablation and CIED implantation.

Methods And Materials

Presently, there are 6 million patients in the United States on long-term anticoagulation to both prevent and treat thromboembolism (TE). [1] These patients account for up to 35% of all patients undergoing cardiac implantable electronic devices (CIEDs) and nearly all patients undergoing ablation for atrial fibrillation (AF). [2] Periprocedural management of oral anticoagulation (OAC) for these patients can be challenging given the need to balance bleeding risk with thromboembolic risk, both of which can adversely affect morbidity and mortality. The reported bleeding risk associated with device implantation and atrial fibrillation ablation is 4.9% [3] and 2.7% [4] respectively. Conversely, even a brief interruption of anticoagulation has been associated with an up to 3-fold increase in systemic thromboembolic events. [5],[6]

Current guidelines recommend discontinuation of OAC and bridging patients at moderate to high risk for TE with intravenous unfractionated heparin (UFH) or subcutaneous low molecular weight heparin (LMWH) in the perioperative period. [7] Although clearly effective in preventing thromboembolic events, bridging has actually shown to increase bleeding complications by up to 25%. [8]. Furthermore, bridging can pose increased health care costs due to need for longer hospital stays for patients requiring UFH. [9] Due to these concerns, several centers now routinely perform CIED implant and AF ablation with brief or no discontinuation of OAC. In this article, we aim to provide a systematic review of the current data available regarding optimal management of anticoagulation in the periprocedural setting for patients undergoing CIED implantation or AF ablation.

Cardiac Implantable Electronic Devices

One third of patients undergoing CIED implantation are receiving oral anticoagulation. The most common complication post CIED implantation is pocket hematoma, which occurs more often in patients on OAC. [9] Hematoma increases risk for infection, potential need for reoperation and prolonged hospital stay in addition to patient discomfort. Given this risk, perioperative anticoagulation management continues to be challenging particularly in patients with moderate to high risk (>5%) for thromboembolic events. [2]

New data demonstrates a lower risk of bleeding without increasing the risk for a TE event in patients who do not interrupt OAC for CIED implantation. BRUISE CONTROL (Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial) was a multi-centered, single blinded, randomized control trial which evaluated patients with a greater than 5% yearly risk of TE undergoing CIED implantation. This study enrolled 668 patients when the data

Key Words

Right Atrial Septal Pacing, Paced PQ Interval, Atrial Fibrillation, The Percentage Of Atrial Pacing.

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and safety monitoring board recommended termination of the study based on the evidence favoring continuation of OAC. Warfarin was uninterrupted in 334 patients with an international normalized ratio (INR) of 2.0-3.0 and 325 patients stopped warfarin 5 days before scheduled procedure and started LWMH bridge. LMWH was discontinued after the morning dose the day before surgery and resumed 24 hours post procedure. Primary outcome (documentation of a clinically significant hematoma), was seen in 16% of patients on LWMH as compared to 3.5% of patients who continued warfarin. Prolonged hospital stays secondary to hematoma, occurred more in patients on LMWH (94.7% versus 1.2%). Patients on LMWH required cessation of anticoagulation secondary to hematoma (14.2% versus 3.2%) and surgical evacuation more frequently than patients who continued OAC (2.7% versus 0.6%). There was a 7-fold increase in infection risk in patients who had a clinically significant hematoma (11% vs. 1.5%). Patient satisfaction was significantly higher in those patients who continued warfarin without bridging. [10]

A meta-analysis of nearly 11,000 patients from 1400 studies compared uninterrupted anticoagulation (warfarin / antiplatelet therapy) with heparin bridging at the time of device implant. [9] Endpoints included hemorrhagic complications, mainly pocket hematoma (greater than 2 cm) +/- need for reoperation and thromboembolic events, including myocardial infarction (MI), transient ischemic attack (TIA), cerebrovascular attack (CVA), deep vein thrombosis (DVT) and pulmonary embolism (PE). Pooled data demonstrated that continued OAC had a lower incidence of pocket hematoma as compared to those patients who underwent UFH or LMWH bridging. There was no significant difference in thromboembolic events or bleeding complications between the two groups. Those patients who continued anticoagulation also had shorter hospital stays and improved quality of life. [9]

In 2012, Cano et al evaluated 129 patients with moderate to high-risk for TE (mechanical valve prosthesis, AF with $CHADS_2$ score of ≥2, mitral stenosis, previous stroke, active neoplasm or deep vein thrombosis within the past 3 months) in whom warfarin was continued without interruption (INR of 2-4) and 82 low risk patients in whom warfarin was interrupted for 72 hours prior to surgery. They also included a retrospective review of patients managed with a standard heparin bridging strategy serving as a control group.Patients classified by this standardized protocol had significantly lower rates of pocket hematoma (2.3% OAC vs 17.7% bridging). The low risk arm had no pocket hematomas for interrupted OAC versus 13% for bridging controls. Patients who were not bridged were discharged 3.34 days earlier as compared to those who underwent bridging. [11]

While there are numerous studies supporting the safety of continuing warfarin during device implantation, there are no randomized, controlled trials evaluating novel oral anticoagulants (NOACs). These drugs include dabigatran (direct thrombin inhibitor),rivaroxaban, apixaban and edoxaban (direct factor Xa inhibitors). NOACs have become increasingly popular due to their short onset of action, reliability, lack of routine monitoring and convenience. One concern is the lack of antidotes for the direct factor Xa inhibitors, which are currently under development.

Jennings et al evaluated the strategy of uninterrupted dabigatran (D) in 48 patients, holding on the morning of the procedure in 14 patients versus uninterrupted warfarin in 195 patients. Bleeding complications occurred in 1 of 48 patients (2.1%) with uninterrupted dabigatran, 0 of 14 with interrupted D, and 9 of 195 patients (4.6%) on warfarin (9 pocket hematomas), P = 0.69. [12] In 2014, Kosiuk et al studied 176 patients on either dabigatran or rivaroxaban undergoing CIED implant. Postoperative bleeding complications and thromboembolic events occurring within 30 days of procedure were included. 2% of patients on dabigatran had clinically significant pocket hematomas. 5% of patients on rivaroxaban had clinically significant pocket hematomas and one pericardial effusion. Three of the bleeding complications in the rivaroxaban group required surgical intervention. One patient on dabigatran had a TIA. [13]

BRUISE CONTROL 2 is an ongoing randomized controlled trial evaluating whether continued versus interrupted NOAC at the time of device surgery in patients with moderate to high risk of TE events reduces the incidence of clinically significant hematoma. Secondary endpoints include hemothorax, tamponade, TE events and quality of life. Completion for primary outcome measure is expected December 2016. [14]

Based on current literature, low risk patients (less than 5% risk for TE) on warfarin with an INR of less than 3.0 may hold warfarin 3-4 days preoperatively without UFH or LMWH bridging ([Table 1]). For those patients with an INR greater than 3.0, warfarin should be discontinued at least 5 days prior to planned procedure. Updated INR should be measured the morning of the procedure. For those patients who have a greater than 5% annual risk for TE, warfarin may be continued with an INR for 2.0-3.0. Updated INR should be measured on the morning of the procedure. Due to slow onset of therapeutic levels, warfarin may be resumed the evening of the procedure if no significant bleeding complications occurred. [9],[10]

For low risk patients on NOACs, anticoagulation may be discontinued prior to planned procedure. The timing and duration of this cessation depends on both the type of anticoagulant (direct thrombin inhibitor versus direct factor Xa inhibitor) and the patient's renal function. For those patients with normal renal function, NOAC should be discontinued at least 24 hours preoperatively. For those with renal dysfunction,anticoagulation should be held up to 48-72 hours prior to procedure[13], [15], [16]. Resumption of NOAC is typically recommended within 24-48 hours. (see [table 2])

High-risk patients on NOACs pose a more difficult decision.

Table 1: Classification of Thromboembolic Risk

Risk group	clinical characteristics
High	• Mechanical Mitral Valve • Mechanical Aortic Valve • CVA/TIA within 3 months • $CHADS_2$ score greater than 5 • Rheumatic heart disease • Clotting Disorder • VTE or PE within 3 months
Moderate	• Bileaflet Aortic Valve • $CHADS_2$ greater than 3 • VTE within 6-12 months • Active Cancer
Low	• $CHADS_2$ score less than 2 with no prior history of TIA/CVA • VTE > 12 months without prior risk factors

CVA = cerebrovascular accident; TIA = transient ischemic attack; VTE = venous thromboembolism; PE = pulmonary embolism. Adapted from the standardized protocol for the perioperative management of chronically anticoagulated patients receiving implantable cardiac arrhythmia devices. [11]

Transitioning them to warfarin around the time of procedure versus continuing NOACs may have to be individualized based on risks versus benefits. The results of ongoing BRUISE CONTROL 2 trial will help to better answer this question. [14]

Ablation of Atrial Fibrillation

In the United States alone, more than 150,000 patients undergo radiofrequency catheter ablation (RFCA) for AF each year. [17] A worldwide survey on methods, efficacy and safety of AF ablation demonstrated that 4.5% of patients undergoing ablation experienced a major complication. Major bleeding accounted for 2.8% of complications where as thromboembolic events accounted for 0.94%. [18],[19] The management of anticoagulation during the perioperative period can have a significant effect on these events [20]. Current guidelines recommend that warfarin be discontinued and patients be bridged with LWMH or UFH during the ablation setting.

Recent randomized trials however show that RFCA can be safely performed without interruption of anticoagulation. The COMPARE trial (Role of Coumadin in Preventing TE in Atrial Fibrillation Patients Undergoing Catheter Ablation) was a prospective, randomized multicenter study assessing the safety of continuous warfarin therapy in preventing thromboembolic events around the time of RFCA. A total of 1584 patients were included in the three-year study. In group 1, warfarin was discontinued 5 days prior to ablation and then bridged with LWMH until the evening before procedure.Transesophageal echocardiogram was performed prior to procedure. UFH was administered prior to transseptal puncture to maintain an activated clotting time (ACT)>350 seconds. A single dose of 325 mg of aspirin was given post procedure. LWMH at 0.5 mg/kg was resumed 3 hours post procedure and was continued until INR was greater than 2.0. In group 2, patients were on warfarin with 3 to 4 weeks of therapeutic INR.

Transesophageal echocardiogram was only performed on patients with a subtherapeutic INR on the day of the procedure. If INR was 3.0-3.5, patients received fresh frozen plasma. If INR was > 3.5, patients were excluded. All patients received UFH to maintain ACT >300 seconds. Protamine was given after the procedure and sheaths were removed once ACT was less than 200 seconds. Warfarin was resumed the night of the procedure in both groups. Ablation was performed in the standard fashion for patients with paroxysmal or persistent atrial fibrillation.

Thromboembolic events occurred in 4.9% of patients in group 1 and 0.25% of patients in group 2 (p<0.001). The majority of the patients who had a thromboembolic event had long standing persistent atrial fibrillation. Major bleeding complications (pericardial effusion, groin hematoma and pseudoaneurysm) occurred in 0.76% of patients in group 1 and 0.38% of patients in group 2 (p=0.31). This clearly demonstrated that uninterrupted warfarin around the time of RFCA significantly reduced the risk for thromboembolic events without increasing the bleeding risk. Warfarin discontinuation was associated with a 10 fold higher risk for cerebral TE without significant reduction in hemorrhagic events.[20]

A meta-analysis published in 2012 reviewed 9 studies on RFCA of AF comparing patients on uninterrupted warfarin versus discontinued warfarin. 6 studies reported prospective design. The target INR for all studies was 2.0-3.5. Intracardiac echocardiography (ICE) was used in 5 studies. Irrigated catheters were used in 7 studies.The review included a total of 27,402 patients. Of these, 6400 continued warfarin. The majority of the continued warfarin patients (89%) were from large prospective or comparative studies. 21,002 patients discontinued warfarin and followed LMWH bridging. Uninterrupted warfarin therapy was associated with significant reduction in thromboembolic events (0.06% versus 0.94% in interrupted warfarin, p<0.001, OR 0.1) and minor bleeding complications (4.5% vs 18.6%, p=0.002, OR 0.38). Major bleeding complications, mainly cardiac tamponade, were seen in 0.55% of patients who continued warfarin and 1.25% who discontinued warfarin (p=0.30, OR 0.67). [21],[22]

Although the majority of studies evaluating anticoagulation and RFCA for AF have only included warfarin, there are increasing reports regarding NOACs. This review will focus on the larger sample size studies involving dabigatran, rivaroxaban and apixaban.

Dabigatran

Data from the The Randomized Evaluation of Long-term Anticoagulant Therapy (RELY) trial provided some reassurance on periprocedural safety of dabigatran. In this trial more than 4500 patients underwent >7500 procedures during a 2 year follow-up. The rate of major bleeding complications for patients who underwent procedures within 24 hours of discontinuing dabigatran was significantly less than those taking warfarin.Additionally, patients who held dabigatran were able to undergo procedure sooner as compared to patients holding warfarin due to the shorter half-life of

Table 2: Last Dosing of NOAC Prior to Surgical Procedure

	Dabigatran	Dabigatran	Rivaroxaban	Rivaroxaban	Apixaban	Apixaban	Edoxaban	Edoxaban
	LR	HR	LR	HR	LR	HR	LR	HR
CrCl > 80 ml/min	>=24 hours	> =48 hours	>= 24 hours	>= 48 hours	>= 24 hours	> =48 hours	> =24 hours	> =48 hours
CrCl 50-80 ml/min	> =36 hours	> =72 hours	>= 24 hours	> =48 hours	> =24 hours	> =48 hours	> =24 hours	> =48 hours
CrCl 30-50 ml/min	>=48 hours	> =96 hours	> =24 hours	> =48 hours	> =24 hours	>=48 hours	> =24 hours	>= 48 hours
CrCl 15-30 ml/min	Not indicated	Not indicated	> =36 hours	> =48 hours	> =36 hours	>= 48 hours	> =36 hours	>= 48 hours
CrCl < 15 ml/min	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated

CrCl = creatinine clearance; LR = low risk; HR = high risk . Adapted from the EHRA Guidelines on use of NOACs [14]

dabigatran. [5],[17]

Bassiouny et al in a single center, cohort study of 999 patients undergoing AF ablation,compared continuous warfarin versus holding 1 to 2 doses of dabigatran preprocedure and resuming immediately post procedure. [23] Arshad et al compared the strategy of continuous warfarin vs interrupted warfarin plus bridging vs holding 1 dose of dabigatran preprocedure and restarting that evening. [24] There was no significant difference in bleeding or TE risks between the groups.

In 2012, Dr Lakireddy et al published their findings from a multicenter prospective registry including 290 patients from 8 high volume centers comparing the safety and efficacy of dabigatran with continuous warfarin in the peri-ablation period. Patients were matched equally in each group. Patients in the dabigatran group held one dose the morning of procedure and resumed 3 hours post procedure. Warfarin was continued throughout the procedure with therapeutic INR 2.0-3.5 for at least 30 days prior to procedure. As compared to the prior mentioned studies, this prospective registry yielded significantly higher rates of bleeding in patients on dabigatran compared to continuous warfarin ((6% vs 1% major bleeding, p=0.019 and 14% vs 6% total bleeding rates,p=0.031). Three thromboembolic complications (2.1%) occurred in the dabigatran group compared with none in the warfarin group (p=0.25). The increased bleeding risk in this study as compared to other studies may be due to the short discontinuation period of dabigatran prior to the procedure. Dabigatran taken the night before, with an average half-life of 12-14 hours, may have still been in effect at the time of procedure start. It was also resumed 3 hours post procedure and given rapid onset of action, patients were therapeutic at a much faster interval. This, in addition to the overlapping of UFH during transseptal puncture, could account for the increased bleeding reports. As compared to other studies above where dabigatran was held for 24-48 hours prior to procedure, there was a much lower risk of bleeding. Dosing prior to procedure in combination with UFH seems to be a higher predictor of bleeding complications as compared to resumption time.

Rivaroxaban

The VENTURE – AF trial (ActiVe-controlled multi-cENTer stUdy with blindadjudication designed to evaluate the safety of uninterrupted Rivaroxaban and uninterrupted vitamin K antagonists in subjects undergoing cathEter ablation for nonvalvular Atrial Fibrillation), published in 2014, was a prospective, randomized,controlled, multicenter trial looking at 250 patients undergoing ablation for AF. Patients were started on rivaroxaban daily or warfarin with INR of 2.0-3.0 for minimum of 3weeks pre-ablation. Primary endpoint was incidence of major bleeding within 30 days.

Secondary endpoints were post procedure thromboembolic events, minor bleeding and medication adherence. Both rivaroxaban and warfarin were continued throughout the procedure. UFH was administered with goal ACT of 300-400 seconds. Post procedure warfarin was continued per protocol. Rivaroxaban was resumed 6 hours post procedure if hemostasis was achieved. Bleeding events occurred in 21 patients on rivaroxaban as compared to 18 patients on uninterrupted warfarin. There was 1 ischemic stroke and 1 vascular death in the warfarin group, none in the rivaroxaban group. This study reassures that in patients undergoing RFCA for AF, the use of uninterrupted oral rivaroxaban was feasible and event rates were similar to those for uninterrupted VKA therapy. [26]

In 2015, Vamos et al completed a systematic review and meta-analysis of the efficacy and safety of rivaroxaban compared with warfarin in patients undergoing RFCA. 16 studies involving 7400 patients were reviewed. Of those patients, 1994 received rivaroxaban periprocedurally. Only one study was a randomized controlled clinical trial.The remaining 15 studies were either observational retrospective or prospective studies.Rivaroxaban was administered daily and discontinued 24-48 hours prior to procedure although 6 studies used uninterrupted rivaroxaban. In general, rivaroxaban was resumed within 12 hours of the procedure. Warfarin was uninterrupted. Target activated clotting time was 300-400 seconds. There were fewer thromboembolic events in the rivaroxaban group compared to the warfarin group (0.2% vs 0.3%, p=0.52). Major bleeding events occurred in 1.15% of patients on rivaroxaban and 1.66% of patients on warfarin (p=0.23).Minor bleeding events were similar (4.96% vs 4.12%, p=0.22). One fatality was reported in each group, a ruptured cerebral aneurysm on rivaroxaban and one vascular death on warfarin. Overall, rivaroxaban was deemed a safe alternative to warfarin with no increased risk for bleeding. [19]

Apixaban

In 2016, Kuwahara et al conducted an open label, randomized multicenter study evaluating the efficacy of either uninterrupted apixaban or warfarin in preventing cerebral TE during AF ablation. 200 patients were evaluated and assigned to take either apixaban or warfarin for at least one month prior to ablation. Neither drug was interrupted throughout the procedural period. All patients underwent brainmagnetic resonance imaging (MRI) post ablation to screen for silent cerebral infarctions (SCIs). It was noted that during the ablation, the apixaban group required more heparin to maintain an ACT of greater than 300 seconds (14,000 ± 4,000 units vs. warfarin 9,000 ± 3,000 units). The apixaban group had two SCIs, one major bleed and 3 minor bleeds where as the warfarin group had three SCIs and four minor bleeds (p=1.0), concluding similar safety and efficacy profiles for both drugs during the periprocedural period. [27] Information regarding periprocedural use of edoxaban is currently limited.

When approaching a patient prior to AF ablation, risk for TE and risk for serious bleeding events need to be considered. There is enough evidence to recommend that warfarin be continued without interruption during the peri-ablation period. It is recommended that INR be checked weekly for one month preprocedure including the morning of procedure.TEE should be performed on all patients with labile INR. Patients with INR> 3.5, on the day of the procedure should be reevaluated prior to proceeding given increased bleeding risks. It is essential to be prepared for any major bleeding complications including readily available reversal agents (protamine, vitamin K) and blood products.

For patients on NOACs, data suggests continuing until the day before the procedure, if renal function is normal (see [table 2]). Due to the short half life, cessation of drug for 24hours prior to start of procedure has proven safe and effective. Resumption of the drug post procedure varies amongst studies, but on average is within 6-10 hours once hemostasis is achieved. It is known that patients on long term NOACs require higher amounts of UFH to achieve and maintain safe ACT throughout AF ablation. [17] A major impediment regarding the use of uninterrupted NOAC strategy for ablation had been the lack of reversal agents. Idarucizumab (PraxbindTm) is a

humanized monoclonal antibody fragment that acts immediately after administration to completely reverse the effects of dabigatran and is currently available for use in the United States. [28] Several agents(Andexanet alfa and Ciraparantag) are currently under evaluation for reversal of factor Xa inhibitors and are likely to be available soon. [29]

Conclusion

Despite the current guidelines recommending cessation of OAC and bridging with either UFH or LWMH for patients at moderate to high risk for thromboembolic event undergoing CIED placement or AF ablation, there has been strong accumulation of evidence supporting the continuation of OAC during the periprocedural period. Warfarin has the most data supporting this, however evidence for minimally interrupted or uninterrupted NOAC strategy is growing. Patients who have continued OAC during the time of CIED implant or AF ablation with adequate precautions have not significantly increased bleeding or thromboembolic risks. Continuation of OAC has also been associated with shorter hospital stays, less health care costs and increased patient satisfaction.

Disclosure

SSAW – none; PV (Medtronic-Speaker, Consultant; Boston Scientific-Advisory board).

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Adjunctive Therapies for Catheter Ablation of Non-Paroxysmal Atrial Fibrillation

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Abstract

The success rate of pulmonary vein antral isolation (PVAI) for paroxysmal atrial fibrillation (AF) has not been realized for persistent or long-standing AF, collectively termed nonparoxysmal AF. Many investigators have described adjunctive ablation strategies to improve outcomes for catheter ablation in patients with non-paroxysmal AF. In this focused review we aim to describe these therapies and current evidence pertaining to their utilization. At present, left atrial posterior wall (LAPW) ablation, non-pulmonary vein (non-PV) trigger ablation and rotor ablation appear to improve outcomes for patients with non-paroxysmal AF when performed in conjunction with PVAI. Randomized controlled trials are necessary to further elucidate such claims.

Introduction

Atrial Fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice, and is associated with significant morbidity and mortality. In 2010 it was estimated that AF afflicted 5.2 million patients, with 1.2 incident cases diagnosed yearly. These numbers are expected to more than double by the year 2030 to 12.1 million and 2.6 million respectively [1] .

Clinically, AF is classified by the duration of time in the arrhythmia and can be categorized as paroxysmal (self-terminating usually within 48 hours but must last <7 days including spontaneous or electrical cardioversion), persistent (episodes lasting >7 days including pharmacologic or electrical cardioversion after that time), and long standing (continuous AF lasting >1 year at which time a rhythm-control strategy is adopted). These distinctions have been adapted in clinical trials and other forms of research as such classifications have prognostic and therapeutic implications when considering catheter ablation [2] .

Catheter Ablation of Atrial Fibrillation

Although approximately 20-40% of patients with AF are asymptomatic, the vast majority of patients present with symptoms [3]. In general, the approach to asymptomatic patients usually involves a rate-control strategy, whereas symptomatic patients tend to prefer rhythm-control. Radiofrequency (RF) catheter ablation is a successful therapy for eliminating AF and reducing the symptomatic burden in patients with this arrhythmia. Pulmonary Vein Antral Isolation (PVAI) has become the primary ablation strategy for catheter ablation of AF [4]. Success rates vary based on patient characteristics, comorbidities and operator experience, but in general those patients with paroxysmal AF undergoing pulmonary vein isolation have success rates with freedom from atrial arrhythmias approaching 80-85% [5],[6]. Unfortunately, these outcomes have not been realized when PVAI alone is carried out in patients with non-paroxysmal AF where freedom from atrial arrhythmias is closer to 50-60% [7].

Current indications for catheter ablation as proposed by three societal guidelines are outlined in [table 1] [2],[4],[8].These indications continue to evolve over time as catheter ablation has been shown to be more effective in maintaining sinus rhythm as compared to antiarrhythmic drugs (AADs) and the rate of adverse pre, peri and post-procedural events, though not trivial, is comparable to that associated with AADs [2],[9]. Given the disparity in outcomes surrounding paroxysmal and non-paroxysmal AF after PVAI, multiple adjunctive ablation strategies have been described with varying rates of success; the subject of which is discussed below.

Adjunctive Modalities for Non-Paroxysmal Atrial Fibrillation

Adjunctive therapies have been developed and studied in an attempt to increase success rates after PVAI in patients with non-paroxysmal AF. These methods, described below, include left atrial posterior wall (LAPW) ablation, non-pulmonary vein trigger ablation of the superior vena cava (SVC), inferior vena cava (IVC), left atrial appendage (LAA), coronary sinus (CS), and vein of marshall (VOM), complex fractionated atrial electrogram (CFAE) ablation, and rotor ablation. It is important to note that these therapies occur in conjunction with PVAI or on repeat catheter ablation.

Left Atrial Posterior Wall Ablation/Isolation

The LAPW has been documented as a potential contributor to the initiation and maintenance of AF [10]. In addition, the structure shares an embryologic cell lineage with the pulmonary veins and thus logically may play a role in the initiation of atrial arrhythmias.

Isolation of the posterior left atrial wall. (A) Electroanatomical

Key Words:
Catheter Ablation,Atrial Fibrillation,PVAI

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map of the posterior wall of the left atrium during sinus rhythm following an initial set of ablations. A multispline catheter positioned in the posterior wall showing the site of breakthrough (arrow). (B) Recording from the multispline catheter during ablation showing isolation of the posterior wall during the third beat.

Catheter ablation of the LAPW is accomplished via linear lesions connecting circumferential PV ablation sites, or spot ablations to the entire structure ([Figure 2]). Ablation and proven isolation of the LAPW in conjunction with extended PVAI resulted in superior outcomes (freedom from any atrial arrhythmia) throughout follow up at 1, 2, and 3 years and more than tripled the median time to recurrence in patients with persistent AF [12]. It has also been shown that isolation of the LAPW as compared to PVAI + Linear lesions (Roof and Anterior LA) was associated with a significant (>50%) reduction in the rate of recurrence over the course of 12 month follow up [11]. LAPW ablation/isolation can be accomplished without compromising the pump function of the LA, with few complications and no significant difference in fluoroscopy and procedural times [11],[12].

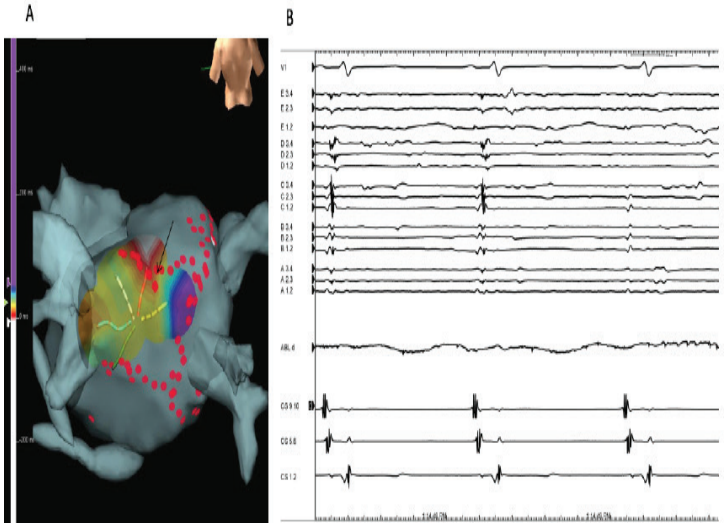

Figure 1: LAPW ablation.
Isolation of the posterior left atrial wall. (A) Electroanatomical map of the posterior wall of the left atrium during sinus rhythm following an initial set of ablations. A multispline catheter positioned in the posterior wall showing the site of breakthrough (arrow). (B) Recording from the multispline catheter during ablation showing isolation of the posterior wall during the third beat.

(A) Circular mapping catheter in the SVC and ablation catheter at the site of ablation at the ostium of the SVC. (B) Superior Vena Cava Isolation. Intracardiac recording showing isolation of the SVC which continues to be in atrial fibrillation while the atrium was in sinus as demonstrated by the recording of the coronary sinus catheter

Superior Vena Cava (SVC)

The SVC shares an embryologic cell lineage with that of the sinus node and thus can represent an arrhythmogenic focus in patients with AF [13]. It also represents the greatest non- PV trigger with an incidence reported anywhere from 6-12% [14]. Although it represents the dominant site of non-PV triggers, early data supporting systematic SVC isolation has not been reproduced for patients with non-paroxysmal AF [15]. The potential benefits of this adjunctive therapy require further examination in larger randomized trials. Phrenic nerve paralysis and injury also poses a limitation on this procedure and precludes up to 15-18% of patients from successful

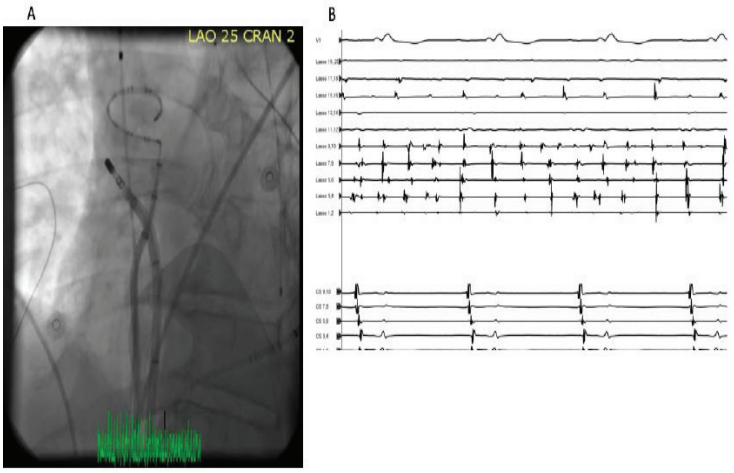

Figure : Superior Vena Cava Isolation.
Figure 2: (A) Circular mapping catheter in the SVC and ablation catheter at the site of ablation at the ostium of the SVC. (B) Superior Vena Cava Isolation. Intracardiac recording showing isolation of the SVC which continues to be in atrial fibrillation while the atrium was in sinus as demonstrated by the recording of the coronary sinus catheter

ablation of the SVC [14].

Inferior Vena Cava (IVC)

The IVC has been documented in case-reports as a focal source of ectopic beats resulting in atrial fibrillation. While this trigger is very rare, it does exist and could account for a small proportion of AF recurrences following PVAI. Routine focal ablation of the IVC is not recommended unless triggers are identified [17],[18].

Left Atrial Appendage (LAA)

The LAA is a known trigger of AF and has been reported in as many as 27% of patients undergoing repeat catheter ablation. In the same patient population, the LAA was found to be the only source of arrhythmia in 8.7%. With complete isolation of the LAA, patients with nonparoxysmal atrial fibrillation had a significant reduction in rate of AF recurrence, while those with focal LAA ablation or no ablation did not [19].

While catheter ablation leading to isolation of LAA has been shown to be effective during repeat ablation, endocardial isolation can be difficult to achieve due to significant anatomic variation in LAA anatomy, and inability to maintain catheter stability. As such epicardial methods to exclude and/or isolate the LAA have been studied. Devices such as the LARIAT© device [SentreHEART, Redwood, CA] and AtriClip® [AtriCure, West Chester, OH ([figure 4]) have been shown to not only mechanically exclude the LAA but also provide complete electrical isolation. Recently, epicardial LAA exclusion and isolation with the LARIAT© device was found to provide a significant reduction in AF burden at both 3 and 12 month follow up for patients with non-paroxysmal AF [20]. In addition, the strongest predictor of response was known LAA triggers in which the reduction of AF burden was even more pronounced. Complete electrical isolation of the LAA either by catheter ablation or thoracoscopic epicardial exclusion as an adjunct to current ablative therapies seems reasonable, especially in patients with known LAA triggers. A randomized clinical trial (AMAZE AF) is currently being conducted and aims to demonstrate the role of adjunctive exclusion of the LAA

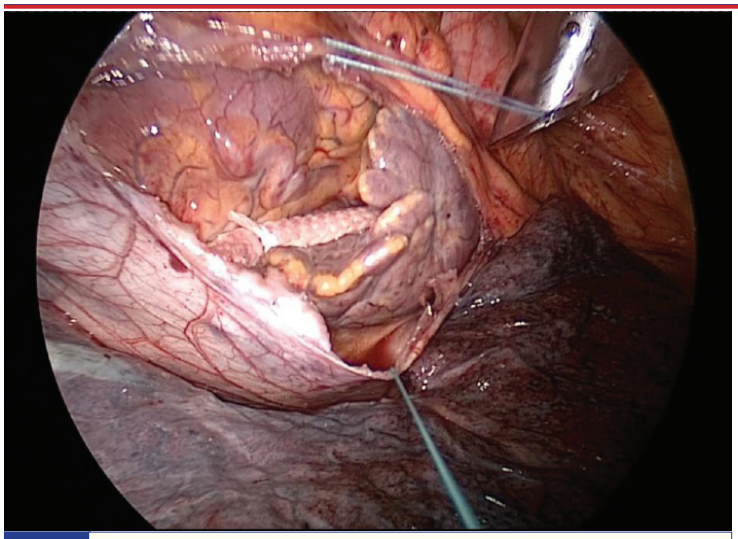

Figure :3 **Epicardial Left Atrial Appendage Ligation. Intraoperative epicardial left atrial appendage ligation using AtriClip® [AtriCure, West Chester, OH]. Credit: Roger G. Carrillo MD MBA, University of Miami Miller School of Medicine**

Coronary Sinus (CS)

The CS has been implicated as a source of triggers contributing to the initiation and maintenance of AF after catheter ablation. In small samples and preliminary data both epicardial and endocardial catheter ablation (complete isolation) in comparison to focal ablation of the coronary sinus resulted in intraprocedural termination of AF in 30% of patients with nonparoxysmal AF [21], [22]. While data regarding CS ablation is less robust than other trigger ablation targets, experts in the field support both epicardial and endocardial ablation of the CS in conjunction with PVAI and other non-PV trigger ablations if spontaneously observed or induced [6].

Vein of Marshall (VOM)

The VOM is the embryologic remnant of the left common and anterior cardinal veins, and has been associated with intrinsic autonomic activity and trigger activity. The VOM was also found to play a role in PV reconnection and recurrence of AF after PVAI [23]. Ethanol infusion into the VOM was effective in disconnecting some of the previously reconnected PVs. In addition, the use of the VOM as a vascular route to the intrinsic cardiac nerves (ICNs) in an effort to modulate autonomic input to the AV node has been investigated [23], [24]. The above mentioned studies are small and larger trials are needed to confirm the role of VOM ablation as an adjunctive therapy for the treatment of AF.

Rotor Ablation

Rotor ablation is founded on the localized source theory in which spiral waves (rotors) and/or focal sources of re-entrant electrical activity can become disorganized and sustain AF. This is in contrast to the multiple wavelet theory in which multiple wandering waves of electrical activity lead to AF. Such rotors and focal sources were found in 97% of cases presenting for ablation in the CONFIRM trial in which focal impulse and rotor modulation (FIRM) was found to successfully slow or terminate AF in 86% of patients (paroxysmal and non-paroxysmal) prior to conventional ablation [25]. In addition, there was a significant reduction in early and late recurrence (median follow up 271 days and 890 day post procedure) in patients undergoing FIRM and conventional ablation as compared to those undergoing only conventional ablation.

Guideline	Indication	AF Type	Recommendation Class	Level of Evidence
HRS 2012	Failure or Refractory to at least 1 Class I/III AAD	Persistent	IIa	B
		Longstanding	IIb	B
	First line therapy	Persistent	IIb	C
		Longstanding	IIb	C
ACC/AHA 2014	Failure or Refractory to at least 1 Class I/III AAD	Persistent	IIa	A
		Longstanding	IIb	B
	First line therapy	Persistent	IIb	C
ESC 2016	Failure or Refractory to at least 1 Class I/III AAD	Persistent/Long-standing	IIa	C

Table 1: **Indications for catheter ablation for symptomatic non-paroxysmal AF as defined by different societal guidelines.**

There was no difference in procedural time or complications [26]. Patient specific mapping and FIRM ablation is a promising adjunctive therapy and remains to be further validated in randomized controlled trials.

Complex Fractionated Atrial Electrograms (CFAE)

CFAEs are fractionated electrograms that are thought to result from the collision of wavelets and electrical signals traveling in different directions as atrial remodeling occurs. These fractionated electrograms are thought to maintain AF and can be targeted during catheter ablation along with conventional PVAI in an attempt to reduce AF burden. The literature regarding CFAE ablation is conflicting as one meta-analysis reports a significant increase in freedom from all atrial tachyarrhythmias (ATs) in patients with non-paroxysmal but not paroxysmal AF with reported follow up between 10-19 months post procedure depending on the study. Upon repeat analysis in which non-randomized clinical trials were taken out, this effect was no longer statistically significant [27].

In a larger randomized clinical trial with 589 patients, no significant difference in freedom from AF was observed at rigorous 18 month total follow up when comparing PVAI with PVAI + CFAE and PVAI + Linear ablations for patients with non-paroxysmal AF. CFAE ablation also increases procedural time as well as time under fluoroscopy [7]. As a result, it is important to recognize that improved outcomes with CFAE ablation in patients with nonparoxysmal AF have not been uniformly reported and that the rationale of CFAE ablation is not universally accepted.

Conclusion

Isolation of the pulmonary veins is a successful therapy for those patients with paroxysmal but not persistent or long standing (non-paroxysmal) AF. As such, adjunctive ablation strategies to combat recurrence rates in non-paroxysmal AF are the subject of significant research. Although many adjunctive strategies described above lack data from large randomized controlled trials, current evidence seems to support the use of LAPW ablation, rotor ablation, and non-PV trigger ablation of the LAA (from an endocardial or epicardial approach) and to a lesser degree the CS, SVC, IVC and VOM. These therapies are reasonable adjuncts to PVAI in patients with nonparoxysmal atrial fibrillation aimed at long-term freedom from AF recurrence while balancing the risks associated with more technically

complex and lengthy procedures. It is important to remember that these procedures are highly dependent on experienced operators in specialized centers.

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Basic Properties And Clinical Applications Of The Intracardiac

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Abstract

The electric signals detected by intracardiac electrodes provide information on the occurrence and timing of myocardial depolarization, but are not generally helpful to characterize the nature and origin of the sensed event. A novel recording technique referred to as intracardiac ECG (iECG) has overcome this limitation. The iECG is a multipolar signal, which combines the input from both atrial and ventricular electrodes of a dual-chamber pacing system in order to assess the global electric activity of the heart. The tracing resembles a surface ECG lead, featuring P, QRS and T waves. The time-course of the waveform representing ventricular depolarization (iQRS) does correspond to the time-course of the surface QRS with any ventricular activation modality. Morphological variants of the iQRS waveform are specifically associated with each activity pattern, which can therefore be diagnosed by evaluation of the iECG tracing. In the event of tachycardia, SVTs with narrow QRS can be distinguished from other arrhythmia forms based upon the preservation of the same iQRS waveform recorded in sinus rhythm. In ventricular capture surveillance, real pacing failure can be reliably discriminated from fusion beats by the analysis of the area delimited by the iQRS signal. Assessing the iQRS waveform correspondence with a reference template could be a way to check the effectiveness of biventricular pacing, and to discriminate myocardial capture alone from additional His bundle recruitment in para-Hisian stimulation.

The iECG is not intended as an alternative to conventional intracavitary sensing, which remains the only tool suitable to drive the sensing function of a pacing device. Nevertheless, this new electric signal can add the benefits of morphological data processing, which might have important implications on the quality of the pacing therapy.

Introduction

The intracardiac electrograms recorded in right atrium and ventricle (AEGM, VEGM) play a pivotal role in permanent cardiac pacing and defibrillation, as pacing inhibition or shock administration fully rely on the detection of myocardial intrinsic depolarization. To maximize sensing specificity, bipolar lead technology has been developed and suitable band-pass filtering is applied. As a result, conventional AEGM and VEGM are mostly sensitive to local activity, restricted to the area surrounding the tip electrode, and the provided information is limited to the occurrence and timing of a sensing event [1]. With this approach, indeed, any activation pattern gives rise to similar signals and no discrimination is possible between AV conduction and ectopic generation of the sensed beat.

Although the electric therapy regulation still remains the most important task, electrogram recording has become, in addition, a source of diagnostic information on the incidence and nature of cardiac arrhythmias. In dual-chamber devices, supraventricular and ventricular tachycardias (SVTs, VTs) can be distinguished from the presence or absence of a relationship between atrial and ventricular signals.[2-4] However, the morphological evaluation of ventricular waveforms can add further insight, and is feasible even with a single-chamber stimulator. To this purpose, the electrogram filter bandwidth must be enlarged and the sensitivity to remote phenomena increased, at the expense of specificity. Normally, the electrograms used by the sensing algorithms are high-pass filtered, while those recorded for diagnostic applications include lower frequency components. Some ICDs offer in addition the possibility to record "far-field electrograms" between the defibrillation coil and the stimulator can, besides the standard "near-field signals" derived by the pacing electrodes, in the aim to better recognize wide and narrow QRS complexes, which in turn would orient the diagnosis toward a VT or SVT, respectively [5,6].

An alternative approach to far-field sensing, which can be accomplished in pacemakers and. ICDs as well, has recently been developed and referred to as intracardiac ECG (iECG) [7-10]. The iECG tracing closely resembles a surface ECG lead, featuring striking different waveforms in case of physiological AV conduction along the His-Purkinje pathway, left or right bundle branch block (LBBB, RBBB), idioventricular rhythm or ectopic ventricular beats (PVC). If the ventricle is paced, the ventricular component of the iECG depends on the stimulation target, which can therefore be identified. In the event of a tachycardia, the iECG allows reliable discrimination of VTs and SVTs, providing in addition detailed information on pre-excitation and retrograde AV conduction [7,8].
The main properties of the iECG and its actual and potential applications in the clinical setting are reviewed in the present paper.

Key Words

Cardiac electrograms,Fusion detection,Hisian pacing,CRT

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The intrinsic intracardiac ECG

The iECG is a multipolar electric signal derived by the set of electrodes used in bipolar dual-chamber pacing. It is available in the most recent DDD, single-lead VDD, and CRT-P devices by Medico (Padova, Italy). The voltage detected by each electrode is weighted by an impedance network in order to balance the near and far field

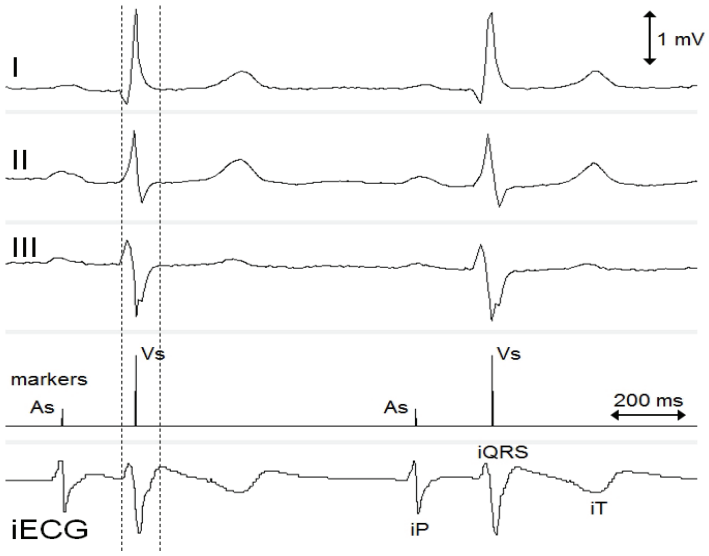

Figure 1: From top to bottom: surface ECG leads I, II, III, pacemaker event markers (As: atrial sensing; Vs: right ventricular sensing), intracardiac ECG (iECG, scaled in arbitrary units). The same tracings are displayed in the next figures. Sinus rhythm with intrinsic AV conduction and narrow QRS. Surface QRS and iQRS feature a similar time-course (iQRS onset and trailing edge are marked by dashed vertical lines). Full description in the main text.

components and summed to provide a waveform which reflects the global electric activity of the heart. The information reported in the literature so far, as well as our Center experience, refer to pacing systems where the atrial lead was positioned in right appendage and the right ventricular lead was either in the apex, mid to high septum, or para-Hisian region [9,10]. In addition, the iECG was recorded in the presence of different tachycardias during EP studies, by means of temporary leads positioned in ventricular apex and high right atrium, connected with an external device. [7,8]

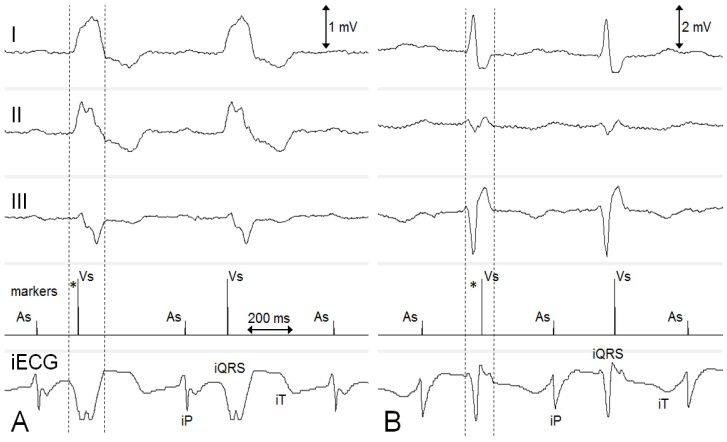

Figure 2: Sinus rhythm and intrinsic AV conduction with (A) LBBB and (B) RBBB. The iQRS onset and trailing edge are marked by dashed vertical lines. Note the prolonged latency between the iQRS onset and the ventricular sensing marker (*) in the presence of RBBB.

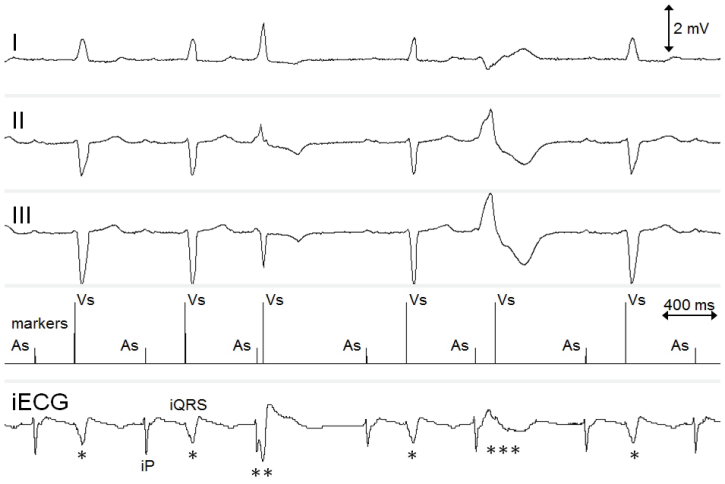

Figure 3: First degree AVB (PQ = 304 ± 2 ms). The iQRS features different specific morphology in case of AV conduction (*) or each of two PVC types (**, ***). Note the overlapping of PVCs and previous iP waveforms

In all tested conditions, the iECG signal typically comprises the 3 components of a surface ECG lead, i.e.: atrial depolarization (iP) and ventricular depolarization (iQRS) and repolarization (iT). Figures 1 and 2 compare the iECG with the corresponding surface ECG in different patients with RV apical (Fig. 1 and 2B)

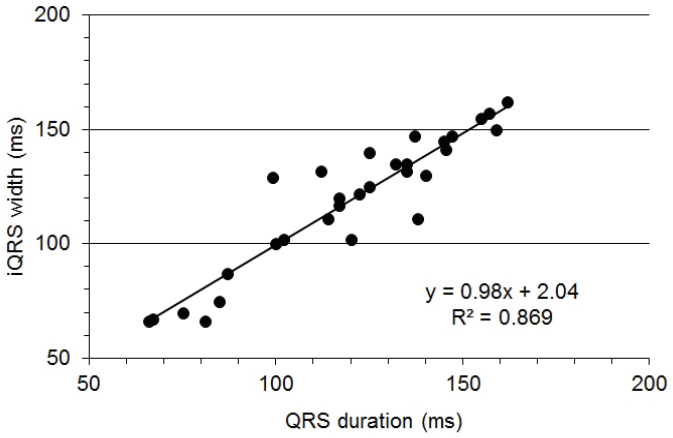

Figure 4: Linear relationship between surface QRS and iQRS duration in 13 patients. Ventricular pacing and different kinds of intrinsic activity (AV conduction with narrow QRS, LBBB, RBBB, PVCs) are pooled in the same plot, for a total of 30 paired determinations. The global least square line demonstrates a high correlation, with slope and intercept close to 1 and 0, respectively, indicating that the two variables are equivalent.

or septal implantation (Fig. 2A). All recordings refer to intrinsic AV conduction in sinus rhythm. In such conditions, discrimination of iP and iQRS is easy, as iP is the first deflection and generally corresponds to a biphasic or negative waveform. With cardiac rate increase and especially in case of a re-entry tachycardia, the iP-iQRS temporal sequence might result no more apparent and the iP shape can change. In such instances, cross-matching with the near-field event markers is advisable for prompt iP and iQRS recognition. Combining iECG and event markers evaluation is also helpful in bundle branch diagnosis. Fig. 1 shows a case with narrow QRS (98 ± 5 ms; mean ± SD in five consecutive beats) and iQRS (97 ± 5 ms), where the iQRS onset precedes the ventricular sensing marker by 45 ± 3 ms. The iQRS peak occurs close to the marker, which indicates

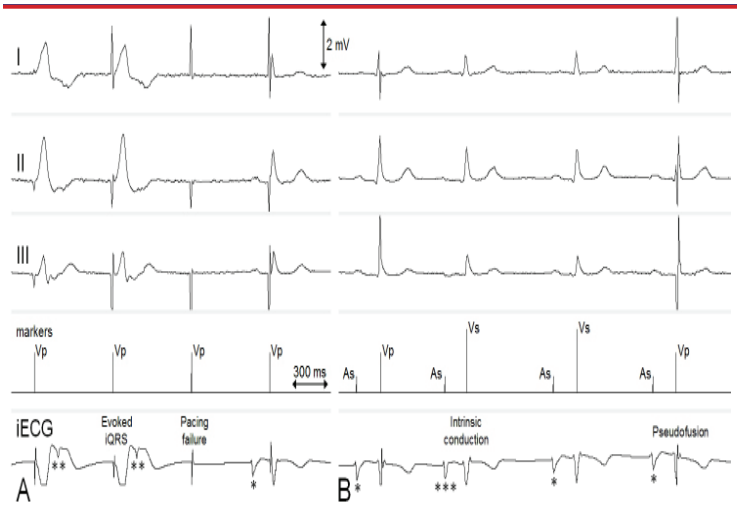

Figure 5: **Para-Hisian pacing with myocardial capture only. The emission of a pacing pulse is marked as Vp. A: threshold test in VVI (90 bpm). The third spike is ineffective and no electric signal but the stimulation artifact is detected on the iECG tracing. The fourth spike is ineffective as well, though it falls right at the onset of a QRS complex, as both the surface ECG and the iECG feature their intrinsic conduction pattern and the ventricular activity is preceded by a sinus P-wave (*). The iECG ventricular signal is different in the presence of capture (1st and 2nd cycles; note the iQRS peak saturation with the applied gain) and in this patient it shows a fast deflection at the beginning of the iT-wave, indicating pacing-induced retroconduction (**). B: VDD pacing with 200 ms AV delay. This interval is quite similar to the intrinsic PR detected by the pacemaker, so that pacing inhibition takes place in the 2nd and 3rd cycle. In contrast, a pacing pulse is released in the 1st and 4th cycles, resulting in pseudofusion. The intrinsic iQRS is detected in all instances. In addition, it is noteworthy that the P-wave recorded in the 2nd cycle (***) is different from the sinus P-waves (*) both on the iECG and the surface ECG leads.**

the time of RV apex activation. Conduction with LBBB (Fig. 2A) is characterized by a wide iQRS (150 ± 7 ms) featuring a short latency (35 ± 5 ms) from its onset to the sensing marker (representing septal activation in this case). The opposite is observed with RBBB (Fig. 2B), where both the onset and main peak of a wide iQRS (130 ± 2 ms) precede the sensing marker (70 ± 4 and 30 ± 3 ms latency, respectively, in the reported example).

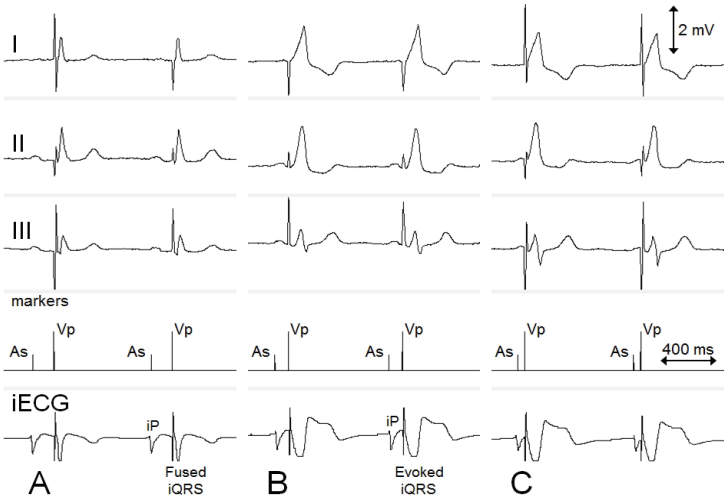

Figure 6: **Same case as in Fig. 5. VDD pacing with AV delay of 150 ms (A), 100 ms (B) and 50 ms (C), with correspondingly lower degree of fusion. Sequential atrium-driven pacing removed the fast deflection following the paced iQRS in VVI (Fig. 5), confirming that it actually was a retrograde P-wave.**

The iQRS waveform is highly sensitive to the pattern of ventricular activity. The signal shape, amplitude and duration are substantially modified when the intrinsic AV conduction is interrupted by ectopic ventricular beats. In the presence of PVCs originating from more than one site, correspondingly different iQRS subtypes are noticed (Fig. 3). With any ventricular activation modality (AV conduction with or without bundle branch block, idioventricular rhythm, or PVCs), the iQRS width closely reflects the duration of the surface QRS (Fig. 4). Relying on these properties, the iECG has been proposed as a tool to discriminate SVTs with narrow QRS from other tachyarrhythmias (VTs or wide complex SVTs). During EP studies, all SVT episodes with narrow QRS exhibited a iQRS waveform similar to the signal recorded in sinus rhythm, while all VTs were characterized by a widened iQRS, morphologically different from the sinus rhythm reference.[7] The information gained from the analysis of either the iECG or the surface ECG tracings had a comparable diagnostic value.

The paced intracardiac ECG

Myocardial ventricular pacing entails electromechanical desynchronization, which can lead to detrimental effects on ventricular function.[11-14] Though careful selection of the best stimulation site in each patient can reduce these adverse effects, QRS axis and duration are unavoidably affected by ventricular pacing, unless a substantial fusion of paced and intrinsic conduction occurs.[15-19] Since the iECG is sensitive to any change in the electric activity of the heart, the signal can be applied as a surrogate of the surface ECG to distinguish fully evoked beats from fusions or capture failure in implanted devices.

Single-site myocardial pacing

A comparison of the iECG waveform recorded with ventricular pacing or intrinsic AV conduction is provided in Fig. 5, which refers to a case of para-Hisian implantation where only septal-myocardial stimulation was achieved. Panel A shows a ventricular threshold test with two paced beats, followed by two ineffective spikes. Capture or pacing failure are promptly recognized, either in absence or presence of spontaneous activity. In the former case, no electric activity but the pacing artifact is recorded (3rd pulse); in the latter, the spike is associated with a different iQRS waveform, featuring the typical intrinsic conduction pattern.

If a threshold assessment routine is in progress, the capture loss can be diagnosed with the same morphological approach usually applied to the surface ECG. Panel B shows VDD pacing in the same patient, with the AV delay set very close to the intrinsic PR interval (200 ms). Ventricular stimulation was inhibited in some cycles and not in others, where the spike was delivered in the late portion of the intrinsic QRS, just preceding the expected sensing. A condition of this type would easily produce false alarms of pacing failure in most capture surveillance systems relying on the detection of intracavitary evoked potentials, as the residual signal after the end of the stimulation artifact is very small. The iQRS, in contrast, is detected since the beginning of the QRS complex, even before the spike release.

The effect of progressive AV delay shortening, with corresponding reduction in fusion degree, is shown in Fig. 6. Morphological modifications in the iQRS were described as changes in the area under the waveform, measured by off-line data processing in the attempt to simulate a potential pacemaker algorithm. The iQRS area was assessed in the interval from 30 ms before to 70 ms after

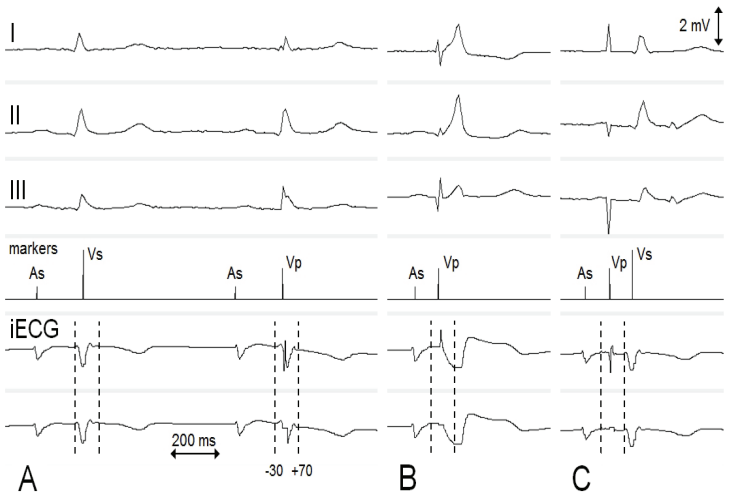

Figure 7: Same case as in Fig. 5. VDD pacing with AV delay set at 200 ms (A) and 100 ms (B, C). In panel A, ventricular sensing (Vs) and pseudofusion (Vp) alternates in two consecutive cycles. Panel B and C show, respectively, effective stimulation with fully evoked QRS and capture loss, followed by intrinsic conduction. The area delimited by the iQRS waveform was measured in the interval from 30 ms before to 70 ms after the ventricular marker (dashed lines), considering the absolute value of the voltage and removing the stimulation artifact by a 20 ms blanking triggered by the spike (lowest tracing). Note that the iQRS area is much smaller in C than in any other condition, pseudofusion included.

a sensing or pacing marker, blanking the signal to 0 in the 20 ms following a spike to exclude the stimulation artifact (Fig. 7). The results were finally expressed as the ratio between the average areas of paced and intrinsic waveforms, at various AV delays (Fig. 8). The paced waveform area exceeded that measured with intrinsic AV conduction (ratio > 1) in case of fusion (150 ms AV delay) or fully evoked QRS (100 ms AV delay). In the presence of pseudofusion (200 ms AV delay ending with spike emission), the area was lower with pacing than with intrinsic conduction (ratio < 1), since the 20

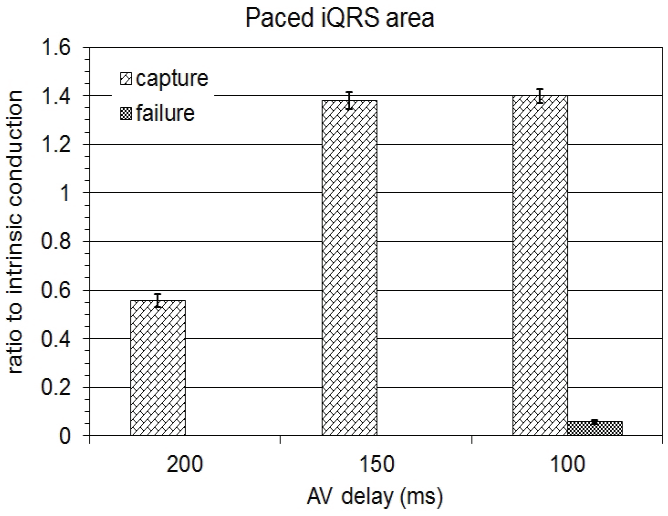

Figure 8: The histogram represents the area under the iQRS signal measured with different AV delays in VDD pacing mode. Data derived from the tracings shown in Fig. 5 and 6 are expressed as the ratio between the average area of the paced and sensed waveforms, ± the standard error of the quotient according to the error propagation theory. Both effective and ineffective stimulation (with pulse amplitude set just below the threshold) were performed at 100 ms AV delay.

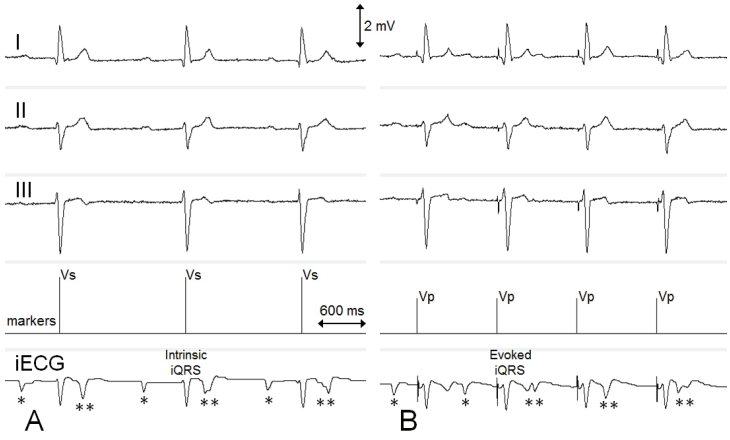

Figure 9: Pacing lead in the Hisian region in a patient with 2:1 AV block. A: VVI mode with basic rate of 30 bpm (A), resulting in pacing inhibition. Though ventricular markers only are displayed, iP-waves are easily recognized on the iECG (*). In addition, hidden iP-signals are likely fused with the iT waveform, which shows remarkable beat-to-beat variability (**). B: VVI pacing at 60 bpm, with capture of the His bundle. Both the iECG and the surface ECG feature the same ventricular complex as in panel A, demonstrating that the physiological conduction pattern was maintained.

ms blanking triggered by the spike removed part of the ventricular signal. Nevertheless, the iQRS area was about 10-times higher in case of pseudofusion than with real pacing failure independent of tissue refractoriness (to assess the effects of capture loss in the absence of intrinsic activity, the AV delay was set at 100 ms and the ventricular pulse amplitude was temporarily reprogrammed just below the threshold). As all types of ventricular activity, including fusion and pseudofusion, entail a iQRS signal featuring a wide safety margin

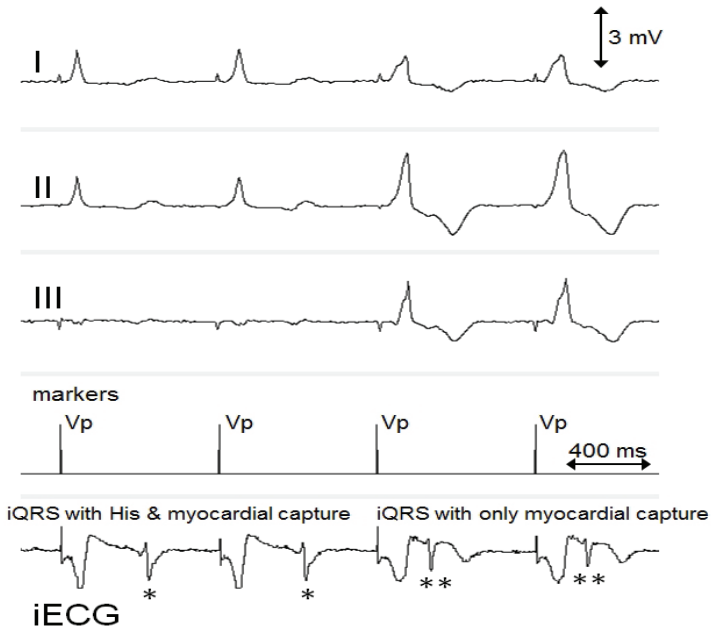

Figure 10: Pacing lead in the para-Hisian region. Ventricular threshold test in VVI: all the spikes are effective, but the QRS complex suddenly changes during the energy scan, when Hisian capture is lost and fusion is replaced by pure myocardial stimulation. The iQRS waveform is consistently modified (duration 95 ± 3 ms and 110 ± 5 ms, respectively, in presence or absence of Hisian recruitment). At the same time, the sinus P-waves (*) are replaced by retroconduction (**).

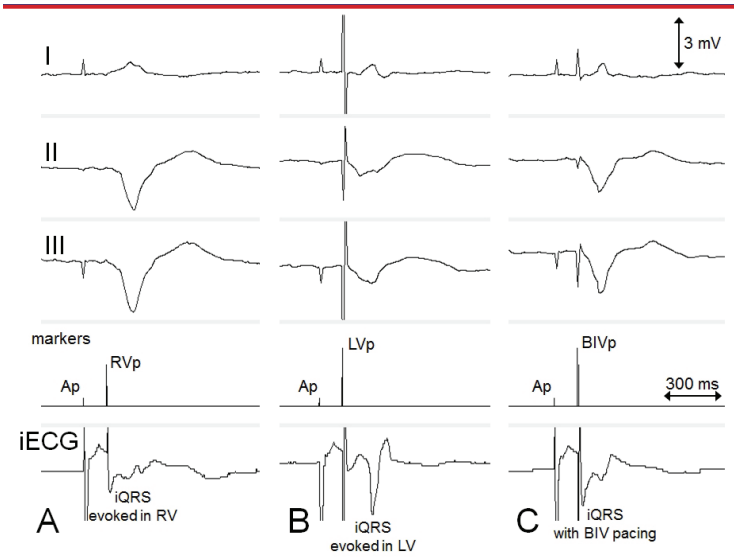

Figure 11: **DDD pacing with (A): bipolar right ventricular stimulation; (B): unipolar left ventricular stimulation; (C): biventricular stimulation; in a chronic biventricular implant. The iQRS waveform is different in each ventricular activation modality, featuring a duration of 248, 256, and 170 ms in panel A, B and C, respectively.**

versus the "no response" condition, the iECG can be proposed as an alternative tool in capture monitoring, preventing the undue increase in pacing energy caused by fusion-related false alarms [20-23].

His bundle pacing

The only pacing technique which can preserve the physiological ventricular activation pattern is the stimulation of the His bundle [24,25]. When this approach is fully successful and direct His bundle pacing is achieved, the paced QRS complex is unaltered with respect to intrinsic conduction in every surface ECG lead. This principle applies to the iECG as well (Fig. 9), which can provide therefore valuable insight on the actual effects of a stimulation performed in the Hisian region. Indeed, in case of para-Hisian capture, only the myocardium is paced at low energy and both the QRS and iQRS complexes are wide, with no latency between the spike and the Q-wave. At increased output, the additional recruitment of the His bundle is achieved, with corresponding QRS and iQRS narrowing and more physiological axis orientation [26,27]. In this case, the issue is not the presence or absence of an electric response, but its nature and quality. Standard capture recognition methods are useless, as they are designed to detect any signal representing active myocardial depolarization, independent of the paced substrate. The iQRS waveform, in contrast, changes in shape, amplitude and duration according to the kind of ventricular activity, and is therefore much better suited to the discrimination of myocardial stimulation from the fusion of myocardial and Hisian responses (Fig. 10). This might have a relevant impact in the clinical setting, as the safety margin applied to ensure myocardial capture could be too small for reliable Hisian pacing. On the other hand, permanent high energy stimulation would strongly reduce the stimulator expected life. The analysis of the iECG represents an intriguing alternative, allowing His-bundle capture monitoring either beat by beat or at proper time interval, in the aim of keeping the pulse amplitude just above the Hisian threshold.

Biventricular pacing and CRT

Similar considerations apply to biventricular pacing, where reliable dual-side capture should be achieved with the lowest possible energy expense. As quite different iQRS waveforms are recorded in the presence of right-, left-, or bi-ventricular stimulation (Fig. 11), a device could regulate the pacing parameters in both ventricles in order to maintain the electric evoked response close to the reference template, representing actual and properly timed biventricular activity. This strategy would allow checking the stimulation effectiveness in both right and left ventricle, as well as managing the AV and VV delays according to the intrinsic conduction timing. If fully evoked biventricular activity is the clinical goal, the iECG-based information could be useful to prevent fusions, which might alter the interventricular relationship and reduce the therapy effect in non-responding patients .[28] Conversely, in other instances fusion is the aim, as for single-side left ventricular stimulation synchronized to right ventricular intrinsic conduction in LBBB patients. [29-32] Significant synchronization impairment would modify the iQRS waveform, thereby prompting the necessary AV delay adjustment.

Clinical Implications

The iECG properties make it suitable to morphological characterization, similarly to a surface ECG lead. At present, the tracing interpretation requires the evaluation of an observer, who must compare the recorded signal with the reference stored in the pacemaker memory. In the event of tachycardia, the iECG is automatically acquired and can help exclude a VT, provided that the iQRS waveforms are similar in sinus rhythm and tachycardia as well. The reliability of this approach has been confirmed by previous studies, which suggested in addition a possible application in the automatic control of shock delivery by an ICD. [7,8]

The iECG has proved a valuable diagnostic tool in the analysis of the patient's rhythm, which can complement the surface ECG by emphasizing the relationship between atrial and ventricular events, with special regard to retroconduction.[9,10] The potential applications in capture surveillance (with fine discrimination of fusion beats from real failure), in para-Hisian pacing (to recognize true Hisian capture from myocardial stimulation), and in biventricular pacing (to check the suitability of stimulation energy and timing) still require the development of dedicated algorithms of waveform processing, which should be run by the device during independent routine operation. This is a realistic goal, since clear-cut waveform changes are expected on the basis of the available preliminary evidence. Such autoregulation mechanisms would have a great impact in the clinical setting, ensuring the stimulation of the appropriate target and reducing the incidence of false alarms of capture loss, which still affect the performance of most capture monitoring systems by inducing a useless increase in energy consumption.[21-23] As the care for the quality of the pacing therapy is progressively rising, the strategic relevance of advanced control tools like the iECG correspondingly grows.

Conclusion

The iECG is a method of multipolar recording of the electric cardiac activity, which provides a tracing with properties similar to a surface ECG lead by means of the implanted electrodes used in dual-chamber pacing. The waveform changes according to the ventricular activation pattern, allowing to distinguish intrinsic AV conduction from ectopic beats, as well as evoked responses induced by different pacing modalities. This new cardiac signal can discriminate VT from SVT episodes and could drive the automatic recognition of ventricular pacing failure with special sensitivity to fusion and pseudofusion. It

might be applied, in addition, to the autoregulation of Hisian/para-Hisian and biventricularstimulation, substantially contributing to the progress of the pacing technology.

Disclosures

None.

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