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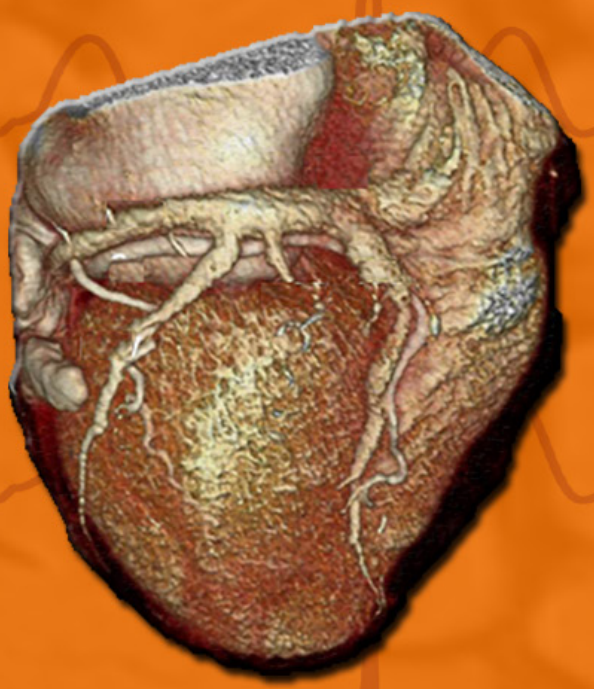

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Dear Colleagues

Welcome to the spring issue of JAFIB 2016. Hope everyone had a great spring break. From the editorial desk we have a few updates some of the national meetings and a short review of some exciting work that will be show cased in this issue.

The 4th edition of the International Symposium on Left Atrial Appendage (ISLAA 2016) successfully organized in New York City, NY. This premier and most comprehensive CME event on the Left Atrial Appendage has been gaining significant momentum and interest amongst health care professionals especially interventionalists and electrophysiologists. Increasing awareness of the contribution of the LAA in systemic thrombo-embolization and arrhythmia burden has brought renewed interest for preventive strategies. Suboptimal experience with 6 decades of Warfarin experience has recently been replaced by more effective Novel Oral Anticoagulants, but the bleeding complications still continue to be a major issue with the anticoagulation strategy. The concept of eliminating the left atrial appendage from the systemic circulation has evolved into an attractive strategy in place of long term OAC. With the Watchman device getting FDA clearance and evaluation from CMS, the need for skilled operators who can perform LAA exclusion procedures will continue to increase. ISLAA is a perfect medium of education for both experienced and novice operators alike. Experts from all over the world joined in this two day meeting sharing their experience, research on various technologies.

In the current issues Somberg etal have a good review of intravenous Sotalol compared against Amiodarone for cardiac arrhythmias. Over the last few years as the drug went out of production people almost forgot about this drug which used to be frequently used in the emergency room, critical care and EP lab settings. IV sotalol definitely shows some promise on its return and perhaps some creative ways of using it to minimize the duration oral loading would be an important area to study. A wide array of topics from wearable cardioverter defibrillators to contact force catheters are being covered. Wong etal presented a nice featured review on the current state of the contact force catheter ablation. Dellurgio and team presented a review on AF and risk of dementia/cognitive decline. Additionally Forleo and colleagues presented some fascinating data on asymptomatic cerebral infarcts in AF. Given the heightened risk of dementia in AF patients not undergoing ablation, the relationship between AF and SCI is an old issue but only larger volumes of cerebral lesions have been associated with cognitive decline. From a pathophysiological point of view, new ischemic lesions on MRI after AF ablation, should suggest worse neuropsychological outcome; however, the available data are discordant. Most silent MRI-detected lesions observed acutely after AF ablation procedures are small or medium-size events and the majority of acute lesions regress at medium- term follow-up suggesting the overall risk of not treating AF probably has worse implications than the SCI after AF ablation that mostly disappear on long term follow up.

Garcia-Bolao and team presented the rationale, feasibility, outcomes and technique of a combined procedure of AFCA and percutaneous LAAO, two percutaneous interventions that share some procedural issues and technical requirements, in patients with symptomatic drug-refractory AF, high risk of stroke, and contraindications to OACs. Anguera etal presented a review of AF ablation in adults with repaired congenital heart disease specifically those patients with atrial septal defects.

We are happy to announce that JAFIB is officially PubMED listed now. All the previous issues will be retrospectively published in the pubmed repository going forwards. This is a well-deserved recognition after 8 years of serving the need for quality education in the science of AF both for physicians and patients. We encourage you to continue to submit your quality work to the journal. We will see you at the Heart Rhythm Annual Sessions in San Francisco in May.

Best Wishes

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Sotalol versus Amiodarone in Treatment of Atrial Fibrillation

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Abstract

The availability of intravenous (IV) Sotalol has equalized the treatment options since both amiodarone and sotalol are available in both IV and oral formulations. A review of the efficacy of sotalol as compared to amiodarone both for conversion of atrial fibrillation (AF) and maintenance of normal sinus rhythm (NSR) following cardiac surgery was undertaken. Standard methods of meta-analysis were employed. Full text publications of clinical trials written in English that compared the efficacy of sotalol to amiodarone were included in the analysis. For the conversion of AF to NSR, five studies were found eligible for the analysis. Two studies clinically compared sotalol to amiodarone for the maintenance of NSR after cardiac surgery. The common relative success of sotalol was 0.947 (95Cl: 0.837 to 1.071, P = 0.385), revealing essentially no differences in efficacy for conversion between amiodarone and sotalol. The average conversion rate was 47% with sotalol and 52% with amiodarone. The conversion rates were lower for persistent AF (sotalol 22% and amiodarone 27%), while greatest for recent onset AF (88% sotalol and 77% for amiodarone). The risk of developing post-operative atrial fibrillation was practically the same in both regimes, relative risk = 1.214 (95% Cl: 0.815-1.808, p=0.339). In summary, sotalol and amiodarone are equally effective in AF conversion and maintenance of NSR post-cardiac surgery.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia with an estimated prevalence of between 2.7 million and 6.1 million patients in the United States.[1] Atrial fibrillation results in significant morbidity including thromboembolic events, stroke, heart failure and increased risk of mortality.[2] Currently there are two management strategies for AF, a "rate control" strategy which aims to control the rate of ventricular response, and a "rhythm control" strategy which aims to restore and maintain normal sinus rhythm.[2] The restoration of sinus rhythm either with electrical cardioversion or antiarrhythmic drugs and successful maintenance of sinus rhythm has been recently reported to yield improvements in symptoms and quality of life.[2,4] However, neither strategy offers a mortality benefit.[2,3] The role of sotalol is well established for maintenance of sinus rhythm after successful restoration of normal sinus rhythm (NSR).[2] With the introduction of intravenous (IV) Sotalol, we thought it useful to compare the efficacy of sotalol to amiodarone, both for maintenance of sinus rhythm and the conversion of AF. Sotalol's role in pharmacologic conversion of AF is controversial. Prior meta-analyses have reviewed the role of sotalol in maintenance of sinus rhythm and prevention of AF following cardiac surgery,[5,6] but its efficacy in AF conversion as compared to amiodarone has not been reviewed.

Methods

A systematic review of the published literature was undertaken and meta-analyses were performed to assess the efficacy and safety of sotalol in the pharmacologic conversion of AF and the maintenance of sinus rhythm following cardiac surgery.

Publications of clinical trials on pharmacologic conversion of AF that evaluated the efficacy of sotalol in comparison to amiodarone were collected for inclusion in this report. Studies could employ either IV or oral route of administration for sotalol or amiodarone. Publications were limited to full text papers written in English. Selected publications must have had sufficient information on patient selection, study methods, and primary outcome(s) to be included. Studies that used electrophysiologic drug testing during induced AF were not included.

The following databases were searched from the earliest date possible to June 30 2015: PubMed, SCOPUS, CINAHL, Cochran Database of Systematic Reviews. The strategy and the results of the search of PubMed are shown in Figure 1. The keywords "sotalol" and "amiodarone" resulted in 700 publications. Using the combination of "sotalol", "amiodarone" and "atrial fibrillation" reduced the number of the publications to 319. When the search was limited to publications written in English with human subjects, the number of publications was reduced to 245. Further limiting the search to reviews and clinical trials resulted in 160 publications, of these, 54 were original

Key Words:
Sotalol, Atrial Fibrillation, Treatment, Meta-Analysis.

Disclosures:
Dr. Somberg lead the team developing IV Sotalol and has since sold his proprietary interest. He also has investments in generic drug companies manufacturing amiodarone.

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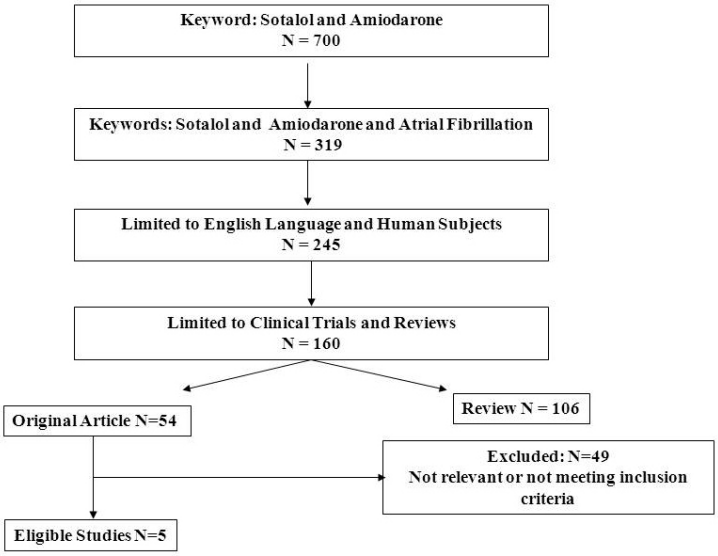

Figure 1: **Flow Chart of Study Selection**
This flow chart shows the search strategy for studies on the comparative efficacy of amiodarone and sotalol in AF conversion employed with PubMed . The systematic review resulted in 5 eligible studies

reports and 106 reviews. For the review on AF conversion, of the 54 original reports, 49 did not meet the inclusion criteria, either being not relevant (most often the topic was maintenance of sinus rhythm without data on pharmacologic AF conversion), or the studies were case series without a comparator. As a result, 5 publications met inclusion criteria and were analyzed for AF conversion in this study. The search of SCOPUS, CINAHL, and Cochran Database of Systematic Reviews did not result in additional eligible publications. A summary tabulation of the 5 published studies is enumerated in Table 1.

For maintenance of sinus rhythm following cardiac surgery, using the key word "sotalol" resulted in 2,683 publications, searching for "sotalol" and "Atrial Fibrillation" reduced the articles to 495, those in English and on human subjects were 370, 242 were original reports and only 2 publications directly compared sotalol to amiodarone.[6]

The studies were grouped according to the treatment employed, i.e. sotalol versus amiodarone, as well as the goal of therapy: AF conversion, or maintenance of sinus rhythm.

For each group, a meta-analysis was performed to obtain the common relative success of the primary endpoint (AF conversion). Additionally, data were extracted for adverse events. The statistical analysis was performed by using the Comprehensive Meta-Analysis software (BiostatTM, Englewood, NJ, USA). Heterogeneity of the studies was assessed for each outcome in each group by using Q_statistics and I2 statistics. Those studies that were homogeneous for an outcome were analyzed by the fixed effect model, while those studies that were heterogeneous for an outcome were analyzed by the random effect model to determine the common relative success (relative risk of successful AF conversion) and the relative risk of developing AF post cardiac surgery. The relative success is the ratio of the proportion of patients who had successful AF conversion in the sotalol versus the amiodarone group. The common relative success is the weighted estimate of the success ratios across the studies. The relative risk was computed by a similar approach resulting in the weighted estimate of the relative risks of developing AF. A two-sided alpha error of less than 0.05 was considered to be statistically significant ($p<0.05$). Existence of publication bias was evaluated by using a funnel plot and Egger's regression intercept.

Results

Sotalol vs. Amiodarone for AF Conversion

Five studies[7,8,9,10,11] evaluated the efficacy of amiodarone in comparison to sotalol for AF conversion (Figure 2). This comparison has the largest patient population, with 420 patients receiving sotalol and 544 receiving amiodarone. While the studies differed in the duration of AF before an attempt at cardioversion, the follow

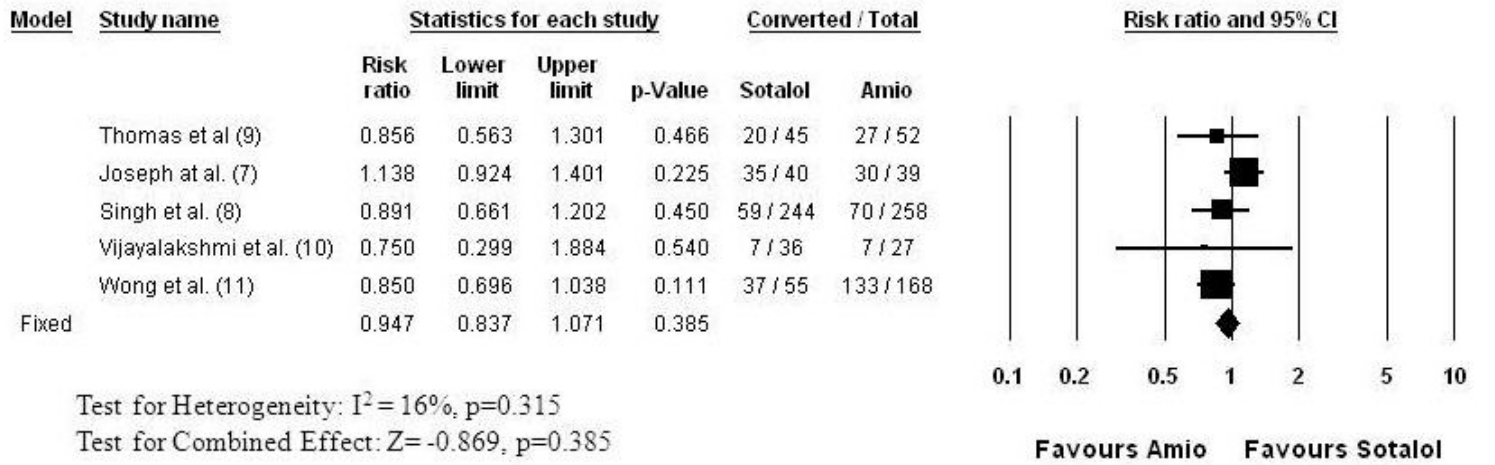

Figure 2: **Relative Success of AF Conversion to Normal Sinus Rhythm: Sotalol versus Amiodarone**
Each row shows the name of the first author of the publication followed by the reference number in parenthesis, the relative success (Risk ratio: "risk" of successful AF conversion) with 95% confidence interval (95% CI), and the significance (p) of the difference in success. The number of patients of whom AF converted and the total number of the patients (Event/Total) in the sotalol and the amiodarone arms are also shown for each study. The graphic presentations of the results are shown on the right (Forrest Plot). The boxes represent the relative success and the lines represent the 95% CI for individual studies. The size of boxes and the thickness of lines reflect the weight of a study in the analysis. The result of the meta-analysis is shown in the last row (bottom) numerically, as well as graphically (the diamond in the Forest Plot). Test for heterogeneity: I2 is the percentage of total variation in study estimates that is due to heterogeneity (16%.). The studies effect sizes were homogenous, thus the fixed effect model was employed for meta-analysis. The combined relative success is 0.947 (95% CI: 0.837 to 1.071, p=0.385), indicating no difference between the two drugs in pharmacologic conversion of AF

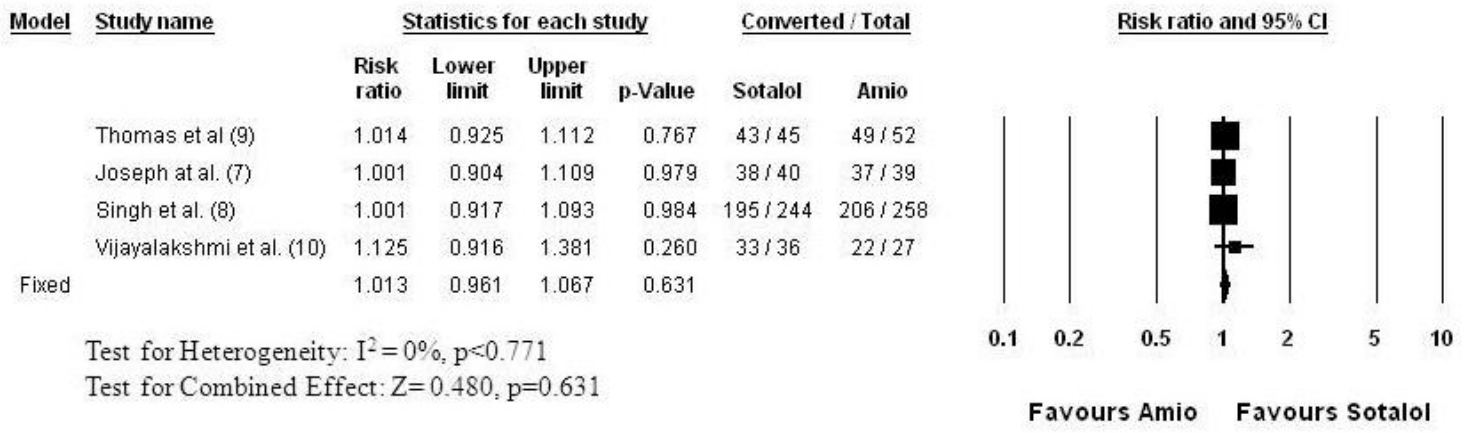

Figure 3: **Relative Success of AF Conversion to Normal Sinus Rhythm: Sotalol versus Amiodarone Followed by DC Shock in Non Converters**
Those patients, who did not convert by the drug they were randomized to receive (amiodarone or sotalol) underwent direct current (DC) electrical cardioversion. The figure shows the combined success of pharmacological and DC cardioversion. The studies and data elements are organized as in Figure 2. The studies were homogenous (I2 = 0%), thus the fixed effect model was employed for meta-analysis. None of the studies found a significant difference between the amiodarone and sotalol groups. The meta-analysis indicates practically identical efficacy with a common relative success of 1.013 (95% CI: 0.961 to 1.067, p=0.631)

up time to evaluate success, as well as in the dosing regimens, the studies were homogenous for the primary outcome, AF conversion. The common relative success of sotalol was 0.947 (95% CI: 0.837 to 1.071, p=0.387), indicating no difference compared to amiodarone in pharmacologic conversion of AF. The conversion rate ranged between 19 and 88% in the sotalol and between 26 and 79% in the amiodarone groups, with an average conversion rate of 49% with sotalol and 52% with amiodarone. The conversion rates were the lowest in persistent AF studies[8,10] ranging between 19 and 24% for sotalol and 26 and 27% for amiodarone, while in recent onset AF of less than 24 hour duration (paroxysmal AF) the success rate was 88% for sotalol and 77% for amiodarone. Four of these five studies[7,8,9,10] evaluated the combined success rate of pharmacologic and electrical AF conversion (Figure 3). Those patients, who did not convert by their assigned drug treatment received direct current (DC) cardioversion. None of the studies found significant difference in the success of pharmacologic and DC conversion between the amiodarone and sotalol groups (Figure 3). The meta-analysis indicates a practically identical efficacy with a common relative success of 1.013 (95% CI: 0.961 to 1.067, p=0.631). The success rate ranged between 80 and 96% in the sotalol groups and between 80 and 95% in the amiodarone groups.

Three studies reported data about the suppression of AF after successful conversion of AF.[8,9,10] One study with 12 hour follow up reported early recurrence,[9] one study reported AF recurrence during 6 weeks and 6 months follow up,[10] and one study reported long term AF suppression during 12 months follow up.[8] The results are shown in Figure 4. Figure 4 shows that with longer follow up time the risk of AF recurrence increases more in patients who received sotalol compared to those who received amiodarone. The relative risk of AF recurrence on sotalol became significant at 6 months (p=0.027) and became more significant during 1 year follow up (p<0.001). The meta-analysis (Figure 4) indicates a significantly higher common relative risk of AF recurrence for sotalol (relative risk: 1,462, 95% CI: 1.260 to 1.697, p<0.001). Overall, these results translate to less effective long term AF suppression with oral sotalol therapy than with amiodarone.

Two studies reported adverse events affecting the cardiovascular system.[7,9] Combining these 2 studies, there were 2 cases of symptomatic bradycardia and 2 cases of hypotension among patients who received sotalol. There were more cases of adverse events among

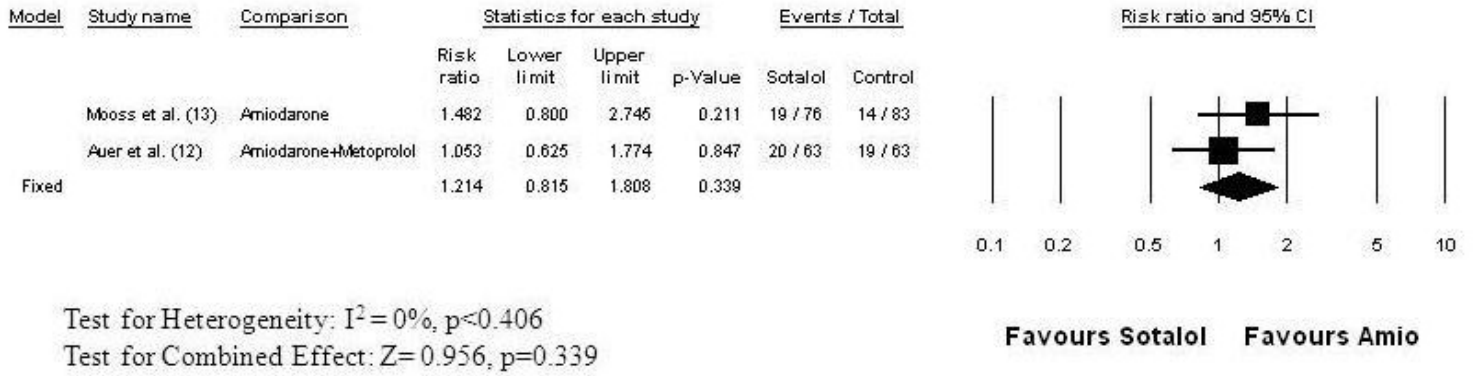

Figure 4: **Recurrence of AF among Patients with AF Conversion: Sotalol versus Amiodarone**
The studies and data elements are organized as in Figure 2. The studies were homogeneous (I2 = 2%), thus the fixed effect model was employed for meta-analysis. The combined (weighted mean) relative risk of AF recurrence is 1,462 (95% CI: 1.260 to 1.697, p<0.001) indicating a significantly higher common relative risk of AF recurrence for sotalol. The figure also indicates that with longer follow up time the risk of AF recurrence increases more in patients who received sotalol comped to those who received amiodarone. The relative risk of AF recurrence on sotalol became significant at 6 months follow up (p=0.027) and became more significant during 1 year follow up (p<0.001)

Table 1: Summary Tabulation of the Clinical Trials

Authors	Study Type	Drug Regimen	AF Duration Before Treatment	Follow up for Efficacy	Patient Conditions/ Characteristics
Joseph et al.[7]	Randomized	1. IV sotalol 1.5 mg/kg over 30 min	<24 h	48 h.	Emergency
	Open Label	then 3x80 mg oral/day for 2 days			admission for
		2. IV amiodarone 5 mg/kg over 30 min			symptomatic
		then 3x400 mg oral/day for 2 days			AF
Singh et al.[8]	Randomized	1. Oral sotalol 2x80 mg a day	>72 h.	28 days	Persistent AF
	Double blind	for 1 week, 2x160 mg thereafter	to years		eligible for
		2. Oral amiodarone 800 mg a day			cardioversion
		for 2 weeks then 600 mg/day for 2 weeks,			
Thomas et al.[9]	Randomized	1. IV sotalol 1.5 mg/kg over 10 min	<48 h.	12 h.	Emergency
	Open Label	then 2x80 mg oral a day	in 80%		admission for
		2. IV amiodarone 10 mg/kg over 30 min	of the patients		symptomatic
		Then 2x200 mg oral a day			recent onset
					AF

AF; Atrial Fibrillation, AFL; Atrial Flutter, h; hour, IV; intravenous, MI; myocardial infarction. Note: Wong et al.[15] did not provide dosing regimens

patients who received amiodarone including 2 cases of bradycardia, 5 cases of hypotension, and 4 cases of left ventricular failure. Discontinuation of therapy was similar for amiodarone and sotalol with a relative risk of 1.194 (95% CI: 0.311 to 4.587, p=0.796).

Sotalol vs. Amiodarone for Maintenance of NSR Post Cardiac Surgery

Two clinical trials directly compared the efficacy of sotalol with amiodarone for the prevention of atrial fibrillation after cardiac surgery.[12,13] Both were randomized double-blind trials (Figure 5). In the study of Mooss and colleagues,[13] atrial fibrillation occurred in 17% of the 83 patients taking amiodarone and in 25% of the 76 patients taking sotalol (RR=1.482, 95% CI: 0.80 to 2.745, p = 0.211), a nonsignificant difference. In the study of Auer and coworkers,[12] patients were randomized to receive placebo, sotalol, metoprolol, or amiodarone plus metoprolol. Atrial fibrillation occurred in 20 of the 63 patients (32%) randomized to sotalol and in 19 of the 63 patients (30%) randomized to amiodarone plus metoprolol. The risk of developing postoperative atrial fibrillation was practically the same with both regimens (RR = 1.05, 95% CI: 0.625 to 1.774, p = 0.847).[6] The combined relative risk of developing postoperative atrial fibrillation on sotalol therapy was 1.214 (95% CI: 0.815 to 1.808, p = 0.339) (Figure 5). Discontinuation of therapy due to adverse events (hypotension, bradycardia, AV block) were similar for amiodarone (8.9%) and sotalol (13.7%) in the post cardiac surgery setting with a relative risk of 1.554 (95% CI: 0.801 to 3.016, p=0.192).

Adverse Events and Drug Toxicity Following Acute and Chronic Administration of Amiodarone and Sotalol

The number of studies is limited in this meta-analysis and most of the studies had short duration. Therefore they do not provide a full picture about the incidence of adverse events that may be anticipated with these drugs. Therefore, we performed a thorough review of the literature to provide estimates of adverse events and toxicities with acute and long term administration of sotalol and amiodarone that should be considered when administering these drugs to patients for conversion of AF and to maintain NSR. The results are summarized in Table 2. Most of the adverse events are related to the pharmacologic effects of these drugs. Both sotalol and amiodarone are Vaughan-Williams Class III (action potential prolonging) agents with Class II (beta receptor blocking) properties. With acute, predominantly IV administration, hypotension, bradycardia, AV block and new onset CHF can be anticipated with both drugs. Both drugs prolongs the QTc interval, and Torsades de Pointes (TdP) ventricular tachycardia may occur with both, but to a much lesser extent for IV sotalol (<1%) than observed with chronic oral sotalol administration for the

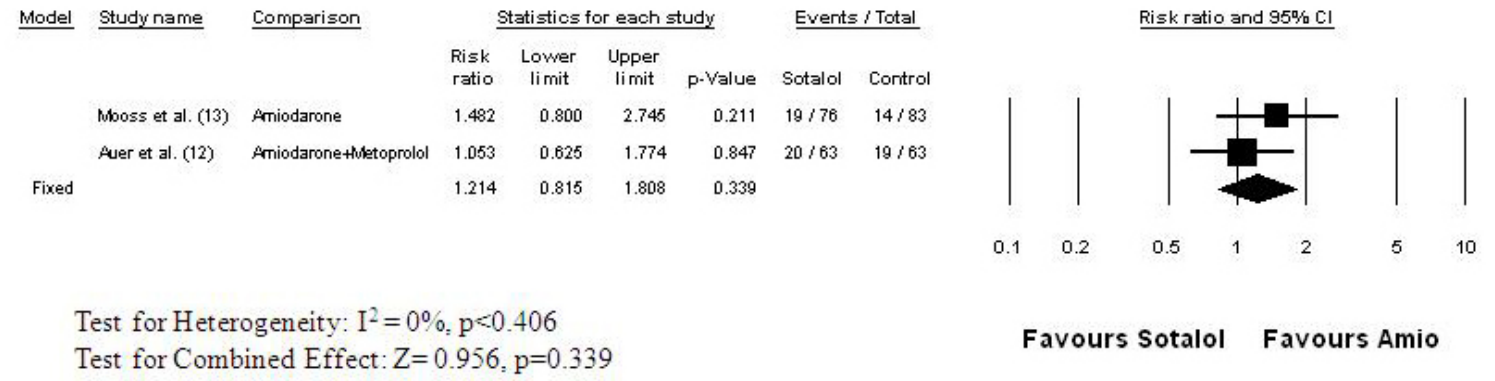

Figure 5: **Relative Risk of Developing Atrial Fibrillation after Cardiac Surgery: Sotalol versus Amiodarone**
The studies and data elements are organized as in Figure 2. The studies were homogeneous (I2 = 0%), thus the fixed effect model was employed for meta-analysis. The combined (weighted mean) relative risk is 1.214 (95% CI: 0.815 to 1.808) indicating no significant difference between sotalol and amiodarone in preventing atrial fibrillation following cardiac surgery (p<0.339)

Table 2: Adverse Events and Drug Toxicity Following Acute and Chronic Administration of Amiodarone and Sotalol

Administration	Amiodarone	Sotalol
Acute (Predominantly IV)		
*Hypotension	12-20%[14]	6.3%[15]
*TdP	<2%[14]	<1% (0.1%)[15]
Bradycardia/AV block	4.9%[14]	12-13%[16]
*Cardiac Arrest	3%[14]	0.1%[15]
Heart Failure	2%[14]	1.2%[16]
*ARDS	214-11%[17]	0%
*Optic neuropathy/neuritis	infrequent[14]	0%
Peripheral neuropathy	infrequent[14]	extremely rare[16]
*Thyrotoxicosis	infrequent[14]	0%
Hepatic injury	2.8-4.2%[14]	extremely rare[16]
Chronic (Oral)		
*Proarrhythmia (TdP)	<1%[18]	0.3-3.2%[16]
CHF (new onset)	2-2.2%[14]	1.2-3.3%[16]
*Pulmonary toxicity	1-17%[19]	0%
Non-Allergic Bronchospasm	0%	1.8-2.4%[16]
*Optic neuropathy/neuritis	<1-2%[20]	0%
Photophobia, corneal microdeposits	>90%[14,20]	0%
Gastrointestinal Complaints	30%[18]	20.5-20.7%[16]
Elevated Liver Enzyme Levels	15-30%[14]	extremely rare[16]
*Hepatitis and Cirrhosis	<3%[14]	0%
*Hypothyroidism	4-22%[14]	0%
*Hyperthyroidism	2-12%[14]	0%
Neurologic Events (i.e. Dizziness, Headache, Insomnia, Malaise, etc.)	3-30%[18]	22-29%[16]
Fatigue	4-9%[21]	10-11%[16]
Tremor, ataxia	3-35%[20]	0%
Peripheral neuropathy	0.3%[20]	extremely rare[16]
Photosensitivity	25-75%[14,20]	extremely rare[16]
Skin discoloration	4-9%[20]	0%
*Aplastic anemia	rare[14]	0%

* indicates major adverse event/toxicity. Superscript numbers indicate the reference numbers of the data source. 0% indicates that no report of that adverse event has been found. "infrequent" and "extremely rare" indicate that events were occasionally reported as part of either the post marketing experience or foreign experience and the actual incidence have not been or cannot be estimated. ARDS; Adult Respiratory Distress Syndrome, CHF; congestive heart failure, IV; intravenous. TdP; Torsades de Pointes ventricular tachycardia

suppression of AF (0.3-3.2%) or ventricular tachycardia (2-4%).[15,16] Adult Respiratory Distress Syndrome (ARDS) is a potentially lethal complication which is due to amiodarone toxicity. It is especially frequent with IV administration following pulmonary surgery (11%),[17] but the lower end of the estimate is still considerable with a 2% incidence of ARDS.[14] Other serious amiodarone toxicities like optic neuropathy, optic neuritis and thyrotoxicosis are realitve rare with acute IV administration, hepatic injury may occur in 2.8-4.2% of the patients.[14] With chronic oral administration for maintenance of NSR after AF conversion, Tdp is the most serious adverse event that occurs between 0.3 to 3.2% of the patients with sotalol, and extremely rare with amiodarone.[16,18] Non allergic bronchospasm occurs only with sotalol administration.[16] Less serious adverse events show a similar incidence between sotalol and amiodarone therapy including gastrointestinal complains (sotalol ≈20%, amiodarone≈ 30%), dizziness, headache, insomnia malaise may occur as high as ≈ 30%, as well as fatigue ≈10% of the patients by both drugs. On the other hand, pulmonary toxicity, hypo- and hyperthyroidism, hepatitis and cirrhosis, may occur frequently with amiodarone therapy and not at all with sotalol. Aplastic anemia is relatively rare with amiodarone but can be fatal and does not occur with sotalol.[14,19] Other frequent, but potentially non fatal amiodarone toxicities manifested as photophobia, corneal microdeposits, photosensitivity and skin discoloration (See Table 2). Optic neuropathy or optic neuritis (estimated incidence <1% to 2%) caused by amiodarone may lead to blindness.[20] In summary, both drugs may cause serious adverse events, but amiodarone therapy may result in a number of potentially fatal non cardiovascular organ toxicities, while sotalol therapy has not been associated with potentially fatal organ toxicity.

Discussion

With the availability of IV, as well as oral sotalol and amiodarone, both agents can be employed in a number of different situations with flexibility in the route of delivery. We thus undertook a systematic literature review and meta-analysis to evaluate the efficacy of sotalol for the pharmacologic conversion of AF, and reviewed meta-analysis of the maintenance of sinus rhythm after cardiac surgery.[6] The efficacy of sotalol IV and oral was similar to amiodarone in AF conversion and sotalol and amiodarone were equally effective in the maintenance of normal sinus rhythm after cardiac surgery.

While the focus of this study was AF conversion and prevention of AF following cardiac surgery, we also hade limited data on the efficacy of both drugs in the long term maintenance of NSR with oral administration following cardioversion of AF. We found a better long term suppression of AF with oral amiodarone compared to oral sotalol treatment. Our findings are in agreement with a recent meta-analysis, which evaluated the long term efficacy of both drugs in the maintenance of NSR following cardioversion.[22]

An important consideration is that amiodarone has numerous none cardiovascular adverse events, some of them can be fatal such as amiodarone-induced pulmonary toxicity. Our review of the adverse events and toxicity of the two drugs indicates that sotalol has much less serious non cardiovascular adverse effects. This is confirmed in a study on the reassessment of clinical outcomes by initial antiarrhythmic drug therapy in the AFFIRM Trial, which concluded that death, intensive care unit hospitalization and non-cardiovascular death were more frequent with amiodarone.[23]

The estimates of the incidence of adverse events and toxicities can have a wide range (see Table 2). This can be explained by the underlining disease status of a patient group, as well as the wide range of doses employed of the two agents. For example, the incidence of TdP was less when it used for maintenance of NSR after AF conversion (0.3-3.2%) than in the treatment of ventricular tachycardia (2-4%).[15,16] Furthermore, sotalol has a linear pahramacokinetic profile and the QT prolongation caused by sotalol is dose related. Consequently, with high sotalol doses the risk of developing TdP is higher than with lower daily doses of sotalol. Similarly, pulmonary toxicity of amiodarone has been reported more frequently when high maintenance doses are employed and declined when the daily dose was reduced to 400 mg or below. Still, pulmonary toxicity may happen at any dose at any time with amiodarone therapy. Given the long elimination half life of amiodarone, toxicities may occur after discontinuation of amiodarone for up to one year.

Side effects contribute an important dimension in the decision

to employ sotalol, or amiodarone. The cardiac side effects of Sotalol are bradycardia, hypotension and QT prolongation with a 1-3% incidence of TdP tachycardia, more frequently seen in low EF patients. Amiodarone also causes bradycardia, as well as hypotension, but proarrhythmia and TdP is much more infrequent. The non-cardiac side effects are significantly different between sotalol and amiodarone. Amiodarone is well known to cause a long list of side effects from photosensitivity and skin discoloration to blood dyscrasias (neutropenia and agranulocytosis), to hypo or hyperthyroidism , hepatic toxicity and pulmonary toxicity (ARDS like picture or pulmonary fibrosis). Neuropathies, including optic and peripheral are also reported. Often the non-cardiac side effects of amiodarone are such as to influence the choice of which agent to employ.

Clinical Implications

Given the similar efficacy of sotalol and amiodarone and the short and long term toxicity of amiodarone, consideration should be given to employing IV and oral sotalol in the treatment of AF in patients with adequate left ventricular function.

Perhaps the greatest utility of IV sotalol is in the treatment of AF is in preventing AF post coronary artery bypass surgery and valve surgery where AF remains a problem.[6] Currently, IV amiodarone is often employed, though even brief periods of amiodarone use can lead to optic and peripheral neuropathies,[24,25] as well as rarely an acute respiratory distress syndrome like picture.[26,27] The efficacy of oral sotalol has been demonstrated in patients post CABGS[28] and it is possible that with IV loading a pharmacoeconomic advantage may be found with IV sotalol over oral sotalol.

Limitations

One of the limitations of this systematic review is the relatively small number of studies in our meta-analyses. However, the studies were homogenous for all outcomes and publication bias was not found, which support the creditability of our findings. Another limitation is that most of the studies in our meta-analysis had short follow up time. Given the limited number of studies and the short follow up times, we had limited data on the adverse event profile of amiodarone and sotalol in AF conversion and during long term administration.

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Efficacy, High Procedural Safety And Rapid Optimization Of Cryoballoon Atrial Fibrillation Ablation In The Hands Of A New Operator

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Abstract

Background: Cryoballoon (CB) ablation is successful in eliminating atrial fibrillation (AF).

Purpose: The purpose of this study was to assess procedural efficacy and safety of CB ablation performed by a newly trained operator.

Methods: Forty patients with documented paroxysmal AF (58 ± 11 years, 26 male) undergoing CB catheter ablation were prospectively enrolled.

Results: Electrical pulmonary vein (PV) isolation was achieved in all patients (156 PVs). The primary end point (PV isolation using CB only) was reached in 31 patients (92% PV isolation, 144/156 PVs). In the remaining 9 patients (12 PVs), additional single point cryofocal ablations were required to achieve isolation of all veins (LSPV, n = 5; LIPV, n = 3; LCPV, n = 2; RSPV, n = 1; RIPV, n = 1). There was no vascular access complication, pericardial effusion/tamponade, stroke/transient ischemic attack, phrenic nerve palsy, acute PV stenosis, or atrioesophageal fistula. The procedure duration decreased with experience by 30% from 155 min during the first 10 procedures to 108 min (final 10 treatments). Similar effects were observed with fluoroscopy time (-57%; from 28 min to 12 min), dose area product (-66%; from 22 Gy x cm2 to 8 Gy x cm2), CB time in the left atrium (-24%; from 99 min to 75 min), and cryoenergy delivery time (-19%; from 83 min to 67 min), when comparing cases #1-10 to cases #30-40.

Conclusions: CB ablation of AF is effective and safe in the hands of a new operator. Procedure and fluoroscopy times decrease with user experience.

Introduction

Catheter ablation is effective in eliminating symptomatic atrial fibrillation (AF).[1] Ablation strategies include pulmonary vein (PV) isolation, the creation of linear lesions, and ablation of complex fractionated atrial electrograms, autonomic ganglia, or electrical rotors.[2-7] Advanced technologies such as remote robotic navigation (RRN), visually-guided endoscopic balloon ablation, and cryoballoon (CB) ablation have evolved to improve catheter manipulation, ablation efficacy, and procedural safety while reducing procedure times, fluoroscopy exposure and physical demands (including manual dexterity).[8-14] In particular, CB ablation represents a simplified and commonly used technique that achieves anatomical PV isolation without the need for a three-dimensional mapping and navigational system. Additional advantages of the CB approach include the introduction of a dedicated inner-lumen circular mapping catheter (Achieve; Medtronic, Minneapolis, MN, USA) that serves as supporting guidewire and allows for real-time assessment of electrical PV isolation during ablation.[15-19] Conversely, CB ablation is associated with a considerable prevalence of phrenic nerve palsy (PNP) that requires caution during cryoenergy application.[8,14,20] Given the growing number of centers offering catheter ablation of AF and considering the increasing clinical use of CB technology for AF ablation, we sought to assess CB ablation in the hands of a newly training operator within an experienced high-volume electrophysiology environment. To this end, 40 patients presenting with symptomatic paroxysmal and drug refractory AF were prospectively enrolled, and acute ablation efficacy, procedural characteristics, and safety were evaluated.

Key Words:

Atrial Fibrillation, Catheter Ablation, Cryoballoon, Fluoroscopy, Learning curve.

Disclosures:
E. Scholz received speaker's honoraria from St. Jude Medical and travel compensation from Boston Scientific. P. A. Schweizer received travel grants from Medtronic and from St. Jude Medical. E. Zitron received speaker's honoraria from Medtronic and from St. Jude Medical. D. Thomas received research support, speaker's honoraria and travel compensation from Medtronic as well as speaker's honoraria and travel compensation from St. Jude Medical.

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Table 1: Patient Characteristics

	Study population (n = 40)
Age (years; mean ± SD)	58 ± 11
Male (n; %)	26 (65)
Body mass index (kg / m2; mean ± SD)	29 ± 5.6
Paroxysmal AF (n; %)	40 (100)
Time since AF diagnosis (months; mean ± SD)	61 ± 63
Failed class I through IV AAD (mean ± SD)	1.3 ± 0.8
Failed class I and III AAD (mean ± SD)	0.6 ± 0.7
EHRA score (mean ± SD)	2.5 ± 0.6
CHA2DS2-VASc score (mean ± SD)	1.4 ± 1.1
Prior stroke or TIA (n; %)	0
Left atrial diameter (mm; mean ± SD)	40 ± 3.9
Mildly reduced LVEF (n; %)	4 (10)
Hypertension (n; %)	21 (53)
Concomitant heart disease (n; %)	9 (23)
Coronary artery disease (n; %)	6 (15)
Dilated cardiomyopathy (n; %)	2 (5.0)
Hypertrophic cardiomyopathy (n; %)	1 (2.5)
Diabetes mellitus (n; %)	1 (2.5)
Chronic obstructive pulmonary disease (n; %)	3 (7.5)

AAD, antiarrhythmic drug; AF, atrial fibrillation; EHRA, European Heart Rhythm Association; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack

Material and Methods

Ethics Statement

The study protocol was approved by the ethics committee of Heidelberg University (Heidelberg, Germany), and the study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all study patients. This study was registered at www.clinicaltrials.gov (NCT01448265). The procedural methods used in this investigation were standard-of-care during the operation of this study.

Patients

The study population consisted of 40 consecutive patients between 18 and 75 years referred for catheter ablation of symptomatic paroxysmal AF despite treatment with ≥1 antiarrhythmic drug at the Medical University Hospital of Heidelberg (Germany). Patients with prior AF ablation procedures, left atrial size ≥ 50 mm, left atrial thrombus, irregular PV anatomy as assessed by pre-procedural transesophageal echocardiography, left ventricular ejection fraction < 40%, moderate to severe valvular heart disease or previous heart valve replacement, or contraindication for anticoagulation medication were excluded from this study.

Operator

The primary operator (E.S.) had no previous experience in CB AF ablation, allowing for an unbiased learning curve assessment and review. Of note, the operator did exhibit expertise in the employment of focal catheter ablation, including radiofrequency ablation of patients with AF and other cardiac arrhythmias.

Electrophysiology Study Procedures

Oral anticoagulation (OAC) was discontinued prior to ablation until an international normalized ratio (INR) < 2 was reached. Bridging of OAC was performed using low-molecular weight heparin, and transesophageal echocardiography (TEE) was conducted within 24 h to assess PV anatomy and to exclude left atrial thrombus. TEE studies were performed using multiplane 5-MHz TEE probes. For visualisation of the PV anatomy a transducer angle of 0° was generally employed. When necessary, manipulation of the probe and use of Doppler color ultrasound were applied. No additional preprocedural cardiac imaging was done. Procedures were performed in the postabsorptive state under conscious sedation and analgesia with appropriate doses of midazolam, fentanyl, and/or propofol. Vital parameters such as blood pressure and oxygen saturation were monitored throughout procedure. Catheter entries were accessed via right and left femoral veins, respectively. A steerable diagnostic quadripolar catheter (Xtrem, ELA Medical, Sorin Group, Munich, Germany) was positioned in the coronary sinus. A fluoroscopy-guided, double transseptal approach using a Brockenbrough needle was then followed in all procedures. The surface ECG and bipolar endocardial electrograms were monitored continuously and stored using a digital amplification and recording system (LabSystem, Bard Electrophysiology Division C. R. Bard, Lowell, MA, USA). During the intervention, a continuous titrated infusion of heparin was maintained to achieve an activated clotting time (ACT) between 300 and 400 s.

Cryoballoon Ablation of AF

For CB ablation a steerable transseptal sheath (12 F, FlexCath™, Medtronic, Minneapolis, MN, USA) was introduced into the left atrium (LA) over a guidewire to steer the Arctic Front™ CB (28 mm diameter; Medtronic). The circular mapping catheter (20 mm diameter, Achieve™, Medtronic) was inserted through the lumen of the CB. An additional SL1 sheath (St. Jude Medical, St. Paul, MN, USA) was placed as part of the study protocol to allow for cross-over to regular CB guidewire and simultaneous placement of a circular mapping catheter if stable balloon positions could not be obtained. Transseptal sheaths were constantly perfused with heparinized 0.9% saline. After transseptal puncture, a patient weight-adjusted unfractionated heparin bolus was given. The CB was manoeuvred to all PV ostia. Balloon position and the degree of PV occlusion were evaluated by injection of radiopaque contrast agent diluted in 1:1 ratio with 0.9% saline. As a standard, two deliveries of cryoenergy were applied for 5 min per application to each PV, which was a commonly used dosage for the first generation CB. Before targeting the right-sided PVs, the steerable quadripolar catheter (Xtrem, ELA Medical, Sorin Group) was positioned in the superior vena cava for continuous phrenic nerve stimulation (10 V, 2.9 ms; ~50 mA) during cryoenergy application. Delivery of cryoenergy was terminated immediately upon loss of capture during phrenic stimulation. LA-PV and PV-LA conduction blockade (entrance and exit block) was confirmed by complete elimination of PV potentials or by dissociated electrical PV activity and by using pacing manoeuvres aiming for capture within the PV, respectively. If electrical PV isolation could not be achieved using the CB alone, additional single point cryofocal ablations were

Table 2: Complications

	Number of patients
Vascular access complications	0/40 (0%)
Pericardial effusion / tamponade	0/40 (0%)
Stroke / transient ischemic attack	0/40 (0%)
Phrenic nerve palsy	0/40 (0%)
Acute pulmonary vein stenosis	0/40 (0%)
Atrio-oesophageal fistula	0/40 (0%)

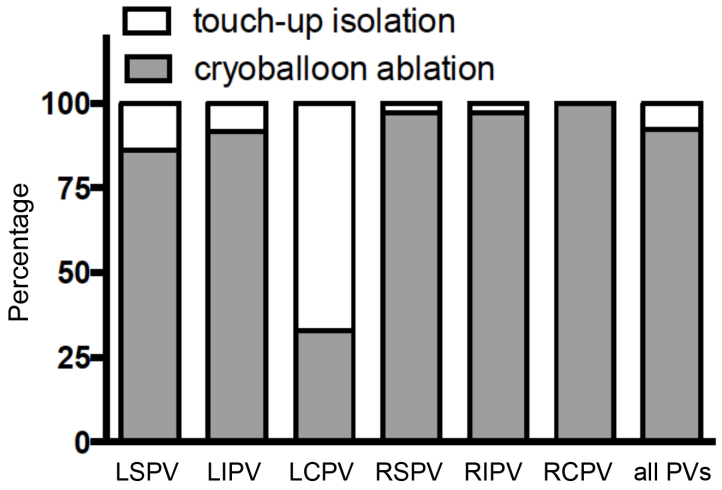

Figure 1: **Successful Pulmonary Vein (PV) Isolation Using the Cryoballoon (CB) Technique**
The percentages of veins isolated using solely the cryoballoon and of veins requiring touch-up ablations are indicated for each PV. In 40 patients (156 PVs), a total of 12 PVs could not be isolated using the CB alone. Abbreviations: LSPV, left superior PV; LIPV, left inferior PV; LCPV, left common PV; RSPV, right superior PV; RIPV, right inferior PV; RCPV, right common PV

applied using a focal cryocatheter (Freezor Max®, Medtronic) until the respective PV was isolated.

Postablation Management

Transthoracic echocardiography was performed immediately after the procedure and on the next day to exclude pericardial effusion. Following removal of sheaths and pressure taping, patients received unfractionated heparin targeting a partial thromboplastin time of 40 to 60 seconds until an INR of 2 to 3 was achieved by oral anticoagulation that was resumed 24 to 48 hours after the procedure. OAC was maintained for at least three months after the procedure and according to current guidelines thereafter. Prior to discharge, 12-lead ECG and 24-hour Holter ECG recordings were performed.

Statistics

Continuous variables are expressed as mean ± standard deviation (SD). Procedural data are provided as median with 25th and 75th percentiles. For between-group comparisons, the unpaired Student's t-test (two-tailed test) was used. Categorical variables are described as count and percentage. A P value <0.05 was considered statistically significant.

Results

Patient Characteristics

Between December 2011 and July 2013 a total of 40 patients (26 male, 14 female) suffering from paroxysmal atrial fibrillation (mean EHRA score, 2.5 ± 0.6) were prospectively included (Table 1). The mean time from AF diagnosis to catheter ablation was 61 ± 63 months. Prior to ablation, antiarrhythmic drug therapy had remained ineffective with 1.3 ± 0.8 antiarrhythmic drugs applied per patient. The mean left atrial diameter was 40 ± 3.9 mm, and structural heart disease was present only in a minority of the patients (Table 1).

Feasibility and Procedural Safety

Within these 40 patients, 156 PVs were identified by angiography and successfully isolated during the ablation procedure (left superior (LS)PV, n = 37; left inferior (LI)PV, n = 37; right superior (RS) PV, n = 39; right inferior (RI)PV, n = 39; left common (LC)PV, n

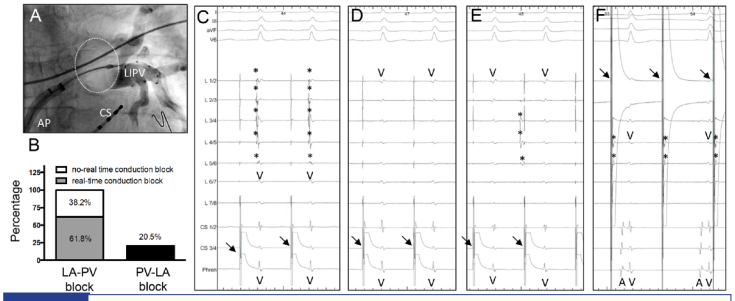

Figure 2: **Procedural Findings Obtained During Cryoballoon (CB) Ablation of Atrial Fibrillation (AF)**
(A) Angiogram of a left inferior pulmonary vein (LIPV) in anterior-posterior projection, revealing proper occlusion of the vein by the CB
(B) Percentage of real-time conduction block verified using the circular mapping catheter. Left atrium (LA)-pulmonary vein (PV) conduction block (either in real-time or post ablation) could be documented in all cases, whereas PV-LA conduction block was obtained in 20.5% of the PVs only. (C-F) Typical electrogram recordings before and after isolation of a PV using the CB
(C) Prior to ablation during electrical stimulation in the coronary sinus (indicated by arrows), PV spikes (indicated by asterisks) are clearly visualized by the circular mapping catheter right before a ventricular far-field signal (V)
(D) After successful isolation, PV spikes are eliminated unmasking the ventricular far-field signal (V) in all poles of the circular mapping catheter
(E) A dissociated PV signal (indicated by asterisks) was observed occasionally, indicating complete conduction block between the PV and the LA
(F) Electrical stimulation between the first and second electrode of the circular mapping catheter (indicated by arrows) results in PV capture reflected by a small PV signal following the stimulation artefact (indicated by asterisks). Successful PV stimulation not exerting atrial electrical activity demonstrated PV-LA conduction block. A, atrium; AP, anterior-posterior projection; CS, coronary sinus catheter; V, ventricle

= 3; right common (RC)PV, n = 1). 144 (92%) of the veins could be isolated using the cryoballoon and circular mapping catheter setup (Figure 1). For the isolation of the remaining 12 (8%) veins (9 patients), touch-up isolation using an additional cryofocal catheter was necessary. LSPV, LIPV, LCPV, RSPV and RIPV required 5, 3, 2, 1 and 1 touch-up cryoenergy deliveries, respectively (Figure 1). A mean number of 11.6 additional energy applications/patient with a mean energy delivery time of 12.1 minutes were applied to achieve PV isolation. Among the group of 40 patients there were no reported complications with respect to vascular access site, pericardial effusion/tamponade, stroke, transient ischemic attack, phrenic nerve palsy, PV stenosis, and atrio-oesophageal fistula (Table 2).

Performance of the Circular Mapping Catheter

PV isolation using the cryoballoon with the achieve mapping catheter has been performed similar to the technique described previously by Chun et al.[17] The additional use of a regular guidewire for CB positioning was not required during the course of the study. Cryoenergy was delivered as soon as appropriate occlusion of the PV had been confirmed by angiography (Figure 2A). The circular mapping catheter was retracted towards the ostium of each PV prior to cryoablation to visualize PV spikes. Real-time LA-PV conduction block during energy delivery could be observed in 61.8% of isolated veins (Figure 2B). In all other veins (38.2%), no PV spikes could be visualized prior to energy delivery, probably due to the distance between the mapping catheter and the PV ostium. In these cases, LA-PV conduction block was verified after ablation by withdrawing

the mapping catheter to more proximal positions inside the PV ostium. An exemplary case before and after successful ablation is displayed in Figures 2C - 2F). In addition to LA-PV blockade, PV-LA conduction block was analysed by stimulating each vein close to the PV ostium using a rectangular voltage step (5 V, 1.9 ms; ~25 mA). PV capture was assumed when the stimulus was followed by a small sharp near field signal in the circular mapping catheter (Figure 2F). Despite careful repositioning, PV capture and hence PV-LA conduction block could only be observed in the minority of cases (20.5%; Figure 2B).

New Operator's Learning Curve

As a main goal of the present study, procedural data including procedure time, balloon time and fluoroscopy time were determined to assess the learning curve of a newly trained operator. When comparing median procedure times of the first ten to the last ten patients of the series, a reduction by 30.3% from 155 to 108 minutes ($P < 0.01$) could be observed (Figure 3A). For the balloon time a reduction by 24.2% was apparent (Figure 3B). However, this reduction was not statistically significant ($P = 0.09$). With median values of 28 minutes for the first ten and 12 minutes for the last ten procedures, fluoroscopy time could be significantly reduced by 57.1% ($P < 0.01$; Figure 3C). Similar effects were observed for fluoroscopy dose area product (65.6% reduction; from 22.4 Gy x cm2 to 7.7 Gy x cm2) and cryoenergy delivery time (-19.4%; from 82.5 min to 66.5 min), albeit without statistical significance ($P > 0.05$). Interestingly, conversion to touch-up isolation did not negatively correlate with increasing experience. With in the first, second, third and fourth group of ten patients, 3, 1, 7 and 1 touch-up isolations were necessary, respectively.

Discussion

Main Findings

We demonstrate high acute efficacy and safety of CB AF ablation when performed by a newly trained CB operator. Furthermore, rapid technical optimization was illustrated by improvement of procedure duration (-30%), ablation time (-21%), and fluoroscopy time (-57%) when the first 10 procedures where compared with the final 10 patients in the present cohort of 40 study subjects. This work provides incremental information regarding efficacy and safety of CB ablation over previous studies that were mostly carried out by electrophysiologists with significant prior CB technology experience. Here, feasibility of CB ablation was apparent early during application of the technology by a first-time user in a real-world setting.

Comparison of a New Operator's CB Ablation Procedures with Previous Clinical Experience

During the first 40 cases, acute success (i.e., electrical PV isolation) was reached in 100% of cases, which is in line with first-generation CB data provided by a meta-analysis (98%).[21] The CB and circular mapping catheter alone were sufficient to achieve isolation in 92% of the veins in the present work, compared with 93% in the combined literature.[21] These findings highlight that effective isolation was feasible already during early use of the CB. Currently, PV isolation rates using only the CB are as high as 99-100% when the second generation balloon is used.[22-27]

The circular mapping catheter reliably served as guidewire for CB positioning in all cases. Real-time visualization of PV signals during ablation was possible in 62% of veins, which is similar to ongoing experience with the second generation CB (53-76%)[22,23,28] and exceeds earlier results with the first generation balloon (47-55%).[15-17,19,22,23]

Median procedure times decreased from 155 to 108 minutes, which appears acceptably short when compared with 108 to 371 minutes duration in other reports using the first generation CB.[21] By contrast, the ablation procedure is even quicker when the second generation CB (Arctic Front AdvanceTM, Medtronic) is used (93-135 min).[22,23,25] Similar to procedure duration, fluoroscopy times improved from 28 min to 12 min during the learning curve. The first-generation CB previously required a mean fluoroscopy time of 46 min (range, 20 to 95 min), indicating efficient application of the technology in the present study.[21] The operator in the present study achieved fluoroscopy times equivalent to those currently observed with procedure-optimized use of the improved second generation CB (12-25 min).[22,23,25,27]

We observed an exceptionally low 0% complication rate despite first-time CB ablation by the operator in the present study setting. Importantly, this experience included no reported cases of phrenic nerve damage. This result suggests that within an experienced environment CB ablation may be not only rapidly but also safely integrated into an operator's clinical ablation routine. In prior studies, the first generation CB has been associated with moderate complication rates that were mainly carried by PNP (6.4%; although only 3.5% PNP was reported with the 28 mm balloon used here), vascular access complications (1.8%), pericardial effusion or tamponade (1.5%), and embolic events (myocardial infarction, stroke, TIA; 0.6%). [21] Of note, the second generation CB is linked to PNP in 2-20% of cases and to 2.4% vascular access complications.[22,24,25,29]

Study Limitations

The primary goal of the study was to assess early characteristics and a learning curve associated with CB ablation of AF. Therefore, the number of patients was limited to.[40] In addition, analyses were confined to procedure-related parameters, and postprocedural outcome data were not acquired. The strict focus on acute safety and efficacy provides immediate support for decision making with respect to strategic planning of AF ablation programs. It is important to recognize that the operator had significant previous expertise in radiofrequency ablation of AF and was therefore skilled in obtaining transseptal access and in left atrial catheter manipulation. These prerequisites may have facilitated rapid implementation of CB ablation into the electrophysiologist's clinical routine. Thus, results of first-time CB use may vary among other operators depending on their individual experience with AF ablation.

Since the conduction of this study technical and procedural

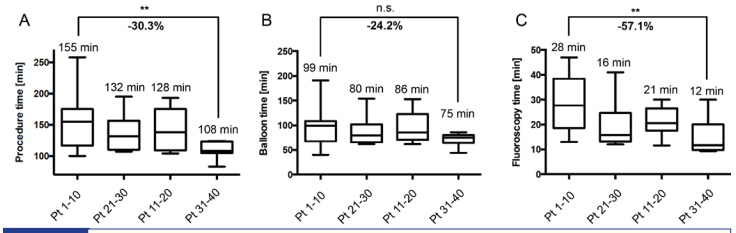

Figure 3: **Procedural Data, Analysed in Four Subgroups of Ten Consecutive Patients Among the Study Cohort of 40 Patients**
(A) Median procedure times decreased by 30.3% between the first and the last ten patients. (B) Similarly, balloon time revealed a reduction from 99 to 75 minutes (-24.2%). (C) Median fluoroscopy time showed a marked decrease from 28 to 12 minutes (57.1% decrease). Median, minimal and maximal as well as the 25th and 75th percentiles are displayed for the first, second, third, and forth subgroup of patients, respectively. Pt, patient; ***P < 0.01; n.s., not significant (P > 0.05)

standards have evolved further. Currently, single transseptal access and the second generation CB are routinely used, and periablation anticoagulation management has been modified. Furthermore, a strategy employing single energy applications per vein is increasingly embraced, and individual ablations times have been shortened to include 3 min applications/vein.[27,30] Considering these procedural simplifications that are now widely accepted, it is reasonable to assume that CB ablation procedure times and learning curve may be shorter in current practice compared to the present study.

Conclusion

CB ablation of AF is feasible and effective when performed by an operator without prior experience with this technology. Extremely low complication rates suggest safety of the procedure. Procedure duration as well as fluoroscopy and energy delivery times decrease rapidly during the first 40 procedures. Thus, the CB in combination with a circular mapping catheter appears to be an appropriate tool for AF ablation in the hands of a newly trained operator, provided that backup expertise is ensured.

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Cryoablation for the Treatment of Drug Refractory Symptomatic Atrial Fibrillation: A Regional Medical Center Experience

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Abstract

Introduction: PVI is an effective, guideline-based treatment for drug refractory symptomatic AF. Balloon cryoablation has been shown to be a safe and effective method for PVI. In the STOP-AF trial, data was produced from practitioners performing PVI with significant experience at high volume centers. This study evaluates the effectiveness and safety of treating symptomatic, drug refractory AF with PVI via cryoablation after implementation in a regional medical center.

Method: This represents a retrospective analysis of outcomes after cryoablation treatment for AF in 71 patients over 354.7 +/- 164.4 days. Reported and recorded episodes of AF were categorized into a representative percent of AF "burden" for each 90 day period. Primary effectiveness and safety end points paralleled those of the STOP-AF trial.

Results: Patients undergoing cryoablation had a 91% reduction of AF burden at 6 months following the procedure with an event-free survival rate of 45.5 % at a mean follow up of 12 months. The mean burden reduction was 3.21% per quarter. Anti-arrhythmic and anticoagulant medication use was reduced by 14.3% and 26.8% respectively. Significant complications included one report of pulmonary vein stenosis, one report of pseudoaneurysm and 5.5% of patients had transient pericarditis or pericardial effusion following the procedure.

Conclusion: The results of this study were comparable to those of the high volume multi-center STOP-AF trial. PVI via cryoablation is a safe and effective alternative treatment of drug refractory symptomatic AF in the setting of a regional medical center.

Introduction

Atrial fibrillation is a significant and growing health issue affecting more than an estimated 3.4 million people.[1,2] Atrial fibrillation often has a negative impact on quality of life, is the leading cause of stroke, and increases the risk of kidney disease and heart failure.[3,4,5,6] In addition, the cost to the United States healthcare system to treat atrial fibrillation is estimated at a staggering $12 billion.[7]

Pulmonary vein isolation via cryoballoon ablation was shown to be an effective treatment of drug refractory symptomatic atrial fibrillation in the STOP-AF trial.[8,9] Cryoablation demonstrated up to 70% effectiveness rate among patients with drug refractory atrial fibrillation compared to only 7% among those treated with anti-arrhythmic therapy alone. The safety and effectiveness of balloon cryoablation demonstrated in, and following, the STOP-AF trial helped pave the way for cryoablation to become a widely accepted FDA approved treatment option for the treatment of symptomatic, drug refractory atrial fibrillation.[9,10]

The primary operators and centers which were included in the STOP-AF trial were referral centers with developed AF treatment programs, and large high-volume academic medical centers. There is limited data available regarding the effectiveness and safety of PVI cryoablation in the setting of mid-sized regional medical centers, since its implementation. The purpose of this study is to review the outcomes of the first series of patients undergoing balloon cryoablation following adoption of the technique at a regional medical center.

Methods

This study is an IRB approved retrospective analysis of 71 patients that underwent cryoablation between March 2012 and November 2013 at New Hanover Regional Medical Center in Wilmington, NC. These represent the first 71 patients to receive cryoablation at this institution. Procedures were collectively performed by four Electrophysiology Board Certified physicians, experienced at performing ablation, but none of whom had performed any cryoablation procedures prior to this study. Pulmonary vein isolation via radio frequency ablation was only rarely performed at this institution prior to the availability of the cryoablation technique. All physicians were trained at Medtronic, Inc. The cryoablation procedure was a single transeptal technique using an Achieve catheter. The length of the lesions with the initial "Arctic Front" balloon were goal

Key Words:
Cryoablation, Atrial Fibrillation, Pulmonary Vein Isolation, Ablation , Arrhythmia.

Disclosures:
None.

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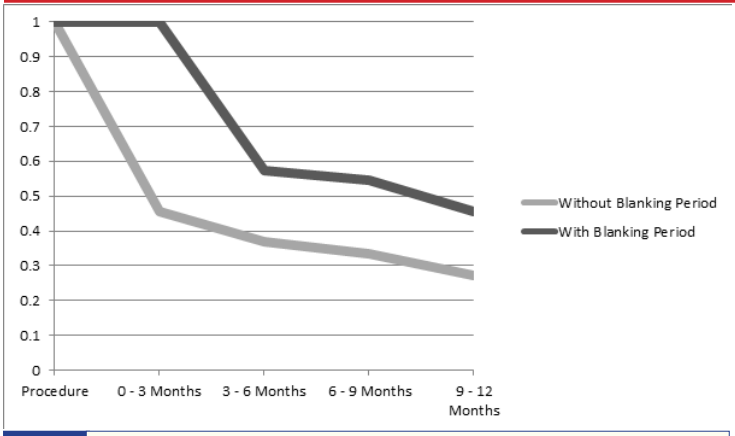

Figure:1 **Kaplan-Meier Survival Curve. Survival free from recurrent atrial fibrillation following cryoablation. Graphs shown represent the absolute event free survival of the population (grey) and the survival following a 90 day blanking period following ablation (black)**

two, 4 minute lesions performed at each site and minimum tolerated temperature of -60 degrees Celsius. With the newer generation "Arctic Front Advance" balloon, the lesions were goal two, 3 minute lesions performed at each site and minimum tolerated temperature of -55 degrees Celsius. Generally, no provocative testing was performed following demonstration of block, and additional lesions were only applied if an entrance/exit block was not demonstrated.

Patients were Caucasian (100%), predominately male (67.6%) with an average age of 65.4 years [SD 10.5] (Table 1). The vast majority of patients had paroxysmal atrial fibrillation (78.9%) and the rest were recently determined to be early persistent atrial fibrillation. Atrial fibrillation events were recorded most often with a wearable device (53.5%), and most patients had a normal ejection fraction (84.5%), a CHADS2 score less than 2 (59.2%) and a NYHA class of 0 (80.3%, Table 1). A history of atrial flutter was recorded in 36.6% of patients (26.8% had a history of atrial flutter ablation), and an enlarged left atrial diameter was noted in 49.3% patients (Table 1).

Atrial fibrillation burden was collected by patient reported symptomatic atrial fibrillation, through evaluation of external monitors and from interrogation of implanted devices. Symptomatic atrial fibrillation was extrapolated from patient reports in days per week, through emergency department visits for atrial fibrillation and through cardiology clinic appointments for symptomatic atrial fibrillation. These data were collected from two sources due to the

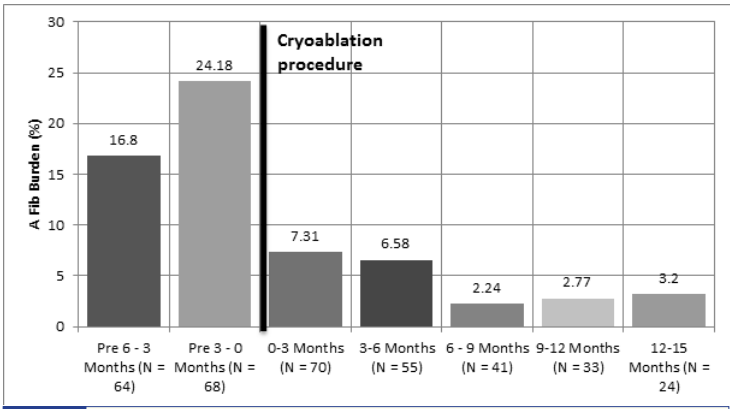

Figure:2 **Atrial Fibrillation Burden Over Time. There is a significant reduction in AFib burden from the pre-procedure time frames to the post-procedure time frames. Mean burden reduction of 3.21% per quarter. Generalized Linear Model, p<0.0001**

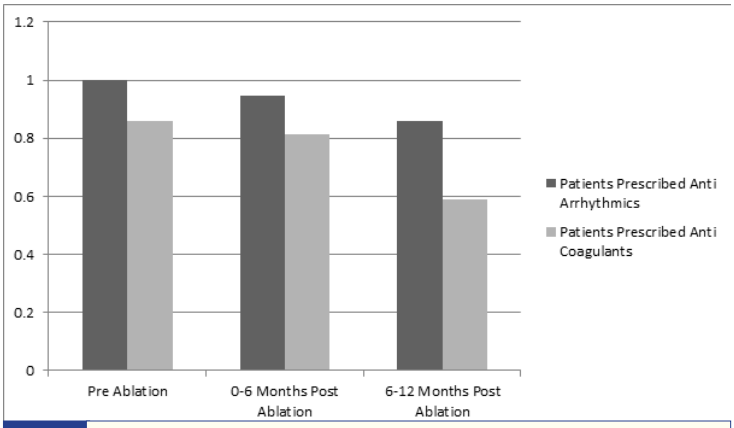

Figure:3 **Patients Prescribed Antiarrhythmics and Anticoagulants Pre- and Post- Procedure. Patients were prescribed significantly fewer anti-arrhythmic medications (shown in dark grey, p = 0.0033) and anti-coagulants (shown in light grey, p = 0.0006) in the months following cryoablation**

hospital converting from paper charts to electronic medical record during the time frame of this retrospective study. However, all of the data was extracted from available medical records. The reported and recorded atrial fibrillation event days were divided by the number of days reviewed since the prior follow up to estimate the burden of self-reported atrial fibrillation. Over each period, the representative percent burden of atrial fibrillation that the patient experienced was recorded. Follow up data after cryoablation was also recorded in the same manner for reported and recorded data for the correlating time periods of the study.

Overall treatment success was determined similarly to that in STOP-AF. Acute procedure success was achieved through demonstration of electrical isolation in at least three of four pulmonary veins following the cryoablation procedure. All patients received pre-procedure CT or MRI vein assessment. If common ostium were discovered, they were ablated with cryo balloon ablation and if successfully isolated then each of the branches of the common ostia were considered as an acute procedure success. Freedom from recurrent atrial fibrillation after a post procedure 90 day blanking period was also assessed, as noted. Additional measures included the proportion of patients with subsequent elimination of anti-arrhythmic drug requirements as well as anticoagulation following the 90 day blanking period. Safety of the procedure was assessed by measuring rates of cryoablation related adverse events including pericarditis or pericardial effusion, pulmonary vein stenosis, phrenic nerve palsy, pseudoaneurysm, atrial esophageal fistulas, tamponade, stroke and death.

Statistical Analysis

Categorical data were reported in counts and frequencies, and analyzed, as appropriate, using X^2 test of independence or Fisher's exact, as contingency tests used when evaluating two categorical variables. Numerical data were reported in means and standard deviations or least square means. Multi-factorial data was analyzed using one or two factor analysis of variance using a bonferroni adjustment to guard against error of bias due to overestimated p values caused by repeated testing effects, by using p values divisible by the number of factors being evaluated. Analysis was performed with SAS 9.0 (SAS Institute, Cary NC). P-values less than 0.05 were considered significant.

Results

The acute procedure success was 98.6% and the absolute atrial fibrillation-free survival rate was 45.5% at 12 months after cryoablation. Figure 1 shows the event-free survival rate following pulmonary vein cryoablation at New Hanover Regional Medical Center. Two survival curves are shown. One which represents the event free survival rate without the blanking period, and the other following the 90 day post procedure blanking period, as was performed in the STOP-AF trial. This blanking period is used to reduce the apparent skewing of the results due to a mild increase in arrhythmias which commonly follows ablation procedures.

Although the absolute event-free survival rate was lower in our series, compared with that seen in the STOP-AF trial, there was a significant reduction in atrial fibrillation burden over time following PVI by cryoablation. Figure 2 shows the burden of atrial fibrillation among the pooled population at baseline (24% in the 3 months prior to ablation) and for each three-month interval following PVI cryoablation. As shown in the figure, there was a decrease in mean atrial fibrillation burden from a baseline of 24% prior to cryoablation, to approximately 3% twelve months after cryoablation ($p<0.0001$). This represents an eight fold reduction in the overall burden of AF in the population. In addition, the modeled reduction of 3.2% per quarter was also a highly significant trend ($p <0.0001$).

Analyses were performed to assess for variables which may have contributed to procedural success rates. Ejection fraction, left atrial diameter, moderate to severe valve disease, sick sinus syndrome and prior atrial flutter ablation played no significant role in determining the change in AF burden. The only variable which was significantly related to procedural success rates in our series was the CHADS2 score. For each unit increase in CHADS2 score, the patient experienced an average increase in atrial fibrillation burden of 2.5% ($p = 0.0085$). This may have led to lower post procedure event free rates in patients with higher CHADS2 scores as only 12.5% of patients with scores of 2 or less had at least one episode of AF by six months following cryoablation compared to 73% of patients with a score of 3 or greater.

Two patients required repeat ablation procedures, both of which occurred during the earlier portion of patients that had cryoablation in this series. Significant complications include one report of pulmonary vein stenosis, one report of pseudoaneurysm and 5.5% of patients had transient pericarditis or pericardial effusion following the procedure. In each case the symptoms resolved and there were no lasting side effects.

The use of anti-arrhythmic drug therapy and anticoagulation was also decreased following cryoablation procedure. At 12 months after receiving a cryoablation procedure in our medical center, approximately 15% of patients being treated with anti-arrhythmic therapy ($p = 0.0033$) and roughly 30% of the patients being treated with anti-coagulants ($p = 0.0006$), no longer required therapy as shown in figure 3.

Table 1: Patient Demographics and Medical History Characteristics

Characteristic		Patients N = 71
Age		65.4 ± 10.5
Gender	Male	48 (67.6)
	Female	23 (32.4)
Race	Caucasian	71 (100%)
Atrial Fibrillation Burden Reporting Method	Internal Device	13 (18.3)
	External Device	38 (53. 5)
	Patient Reported	20 (28.2)
Left Ventricle Ejection Fraction	Normal (≥ 55 %)	60 (84.5)
	Abnormal (< 55 %)	10 (14.1%)
CHADS2	0	13 (18.3)
	1	29 (40.9)
	2	14 (19.7)
	3	14 (19.7)
	4	1 (1.4)
NYHA	0	57 (80.3)
	1	5 (7.0)
	2	4 (5.6)
	3	5 (7.0)
History of Artrial Flutter		26 (36.6)
History of Artrial Flutter Ablation		19 (26.8)
Left Atrial Diameter	Normal	33 (46.5)
Comorbidities	Abnormal	35 (49.3)
	Missing	3 (4.2)
	Hyperlipidemia	53 (74.7)
	Hypertension	52(73.2)
	Tobacco Use	37 (52.1)
	Coronary Artery Disease	28(39.4)
	LVH	24(33.8)
	Diabetes	19 (26.8)
	Thyroid Disorder	19 (26.8)
	OSA	18 (25.5)
	Moderate to Severe Valve Disease	17 (24.0)
	Congestive Heart Failure	14 (19.7)
	Sick Sinus Syndrome	13 (18.3)
	Low Testosterone	5 (7.0)

Data reported in N(%),Mean ± Std, or Median [Q1-Q3]

Discussion

The procedure success rate, as measured by event free survival without atrial fibrillation at 12 months, was lower in this series (45.5%) than in the STOP-AF trial (69.9%).[9] The reasons for this discrepancy are likely multifactorial. As with any new technology or technique, there is a learning curve upon implementation. Procedural effectiveness for cryoablation has been correlated to the number of procedures which an operator has performed.[11] All four physicians at New Hanover Regional Medical Center being represented in this series were performing their first cryoablation procedures. The patients in this series therefore represent a cohort when the operators were relatively inexperienced. It is possible that higher overall treatment success rates could be achieved as the operators and institution become more experienced at performing the technique, which echoes the importance of reviews such as this following implementation of a new technique.

There was also a change in the cryoballoon technology after approximately the first one third of the data was recorded during the collection period. The Medtronic Arctic Front "Advance" Cryoballoon replaced the first-generation balloon in the later cases. The second generation "Advance" balloon has more cooling jets resulting in a more expansive and homogenous cryoablation surface area spanning the entire front hemisphere. This improvement in

balloon technology, larger treatment surface area compared to the equatorial cryoablation surface of the first generation cryoballoon and potentially more complete ablation lesions may have led to more effective ablation outcomes later in the study.[12] Unfortunately, the exact timing of the change in balloon technology was not recorded.

As our series and the STOP-AF population were not from the same cohort, patient selection or patient characteristics may have contributed to different outcomes. In our series, a higher CHADS2 score correlated with lower rates of treatment success following cryoablation. This likely reflects the greater comorbidity burden in patients with higher CHADS2 scores. Those with more complex medical histories, such as CHF and hypertension, may be less optimal candidates for the procedure. Different baseline patient characteristics could have contributed to some of the difference between our series and the STOP-AF patients, but due to the small sample size of this series it is difficult to comment on this with any certainty.

Despite a lower absolute event-free survival procedural success rate, there remained a large reduction in the overall burden of atrial fibrillation. This is perhaps more important to the patient than the absolute event reduction rate. Though about half of the patients had recurrence of atrial fibrillation, their burden was dramatically reduced.

Limitations of this study include a change in the cryoablation procedure technology during the data collection period and the use of two different forms of medical records as previously described. Data abstraction was carried out with the same measures in each system, to maximize consistency. One of the major challenges in our series was to translate patient-reported and external monitor recorded information regarding the presence and amount of atrial fibrillation into a quantifiable "burden". This required extrapolation and some estimation of reported burden into a quantifiable burden, as only a minority of patients had an implanted device to record a true burden.

Conclusion

In the setting of a regional medical center, pulmonary vein isolation via cryoablation for the treatment of drug refractory, symptomatic atrial fibrillation compares favorably to prior reports from larger hospital centers in the STOP-AF trial. Although a smaller event-free survival was seen, there was a dramatic reduction in the overall atrial fibrillation burden with minimal adverse events, and a reduction in antiarrhythmic and anticoagulation requirements.

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Misleading Advertising by Attorneys Concerning NOACs is Adversely Costly to Our Patients and Our Society

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Abstract

Over the past five years, "ambulance-chasing" attorneys have aggressively advertised for patients who have bled on a new oral anticoagulant (NOAC) or their family members. It is an infrequent day when American consumers do not see a TV advertisement saying something like: "Have you or a loved-one had a serious bleeding event while taking [fill in the NOAC]? If so, you may be entitled to monetary compensation. Call XXX, attorneys at law, and we will get you the money you deserve."

Introduction

Unlike medical presentations, whether CME or "promotional", such ads are apparently not subject to fair balance requirements. Consequent to such advertisements, many patients have discontinued NOAC therapy or have refused to start it. I have encountered such a patient on more than one occasion, mostly atrial fibrillation (AF) patients with an increased risk profile for stroke and systemic embolism (CHA_2DS_2-VASc score of 2 or higher).[1] It takes considerable effort to make them understand both the benefits and the risks of NOAC therapy and in particular, the overall antithrombotic and mortality benefits to them of being on NOAC therapy despite the risks of a bleed.

Part of such discussions with patients should involve the concepts of fair balance and of net clinical benefit. Using data from the 4 major NOAC vs warfarin pivotal AF trials[2-5] and historical data from AF warfarin vs placebo trials,[6] several calculations can be made to help them understand both what they are not being told in the advertisements they see and the consequences that may arise based upon the non-use of the NOAC.

Based upon the pivotal NOAC versus warfarin trials,[2-5] assuming increased risk AF patients changed from NOAC to warfarin therapy: embolic events would increase by 1.1 to 2.1 %/yr; major bleeds would increase by 2.1 to 3.4 %/yr, total mortality would increase by 3.5 to 4.9 %/yr, but fatal bleeds would increase by only 0.06 to 0.5 %/yr. In other words, with a change from a NOAC to warfarin, their risk of a stroke or mortality would be much greater than would any change in fatal bleeding risk. Moreover, since warfarin reduces stroke by almost 70% and mortality by about 30% versus placebo,[6] if patients changed from NOAC to no therapy or refused to start any anticoagulant, stroke rates and mortality would be correspondingly higher than the rates cited above. Given the estimate of over 8 million AF patients in the U.S. now, and the current anticoagulation paradigm using CHA2DS2-VASc, such changes have substantial adverse implications for both population health and costs. Our governmental representatives, the FDA, and the media need to recognize the consequences of such unbalanced and inadequately controlled advertising and, in my opinion, initiate appropriate regulations.

Key Words:
Atrial Fibrillation, NOACs, Anticoagulation, Stroke, Mortality

Disclosures:
None.

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Supraventricular Tachycardia with Irregular Ventricular-Atrial Intervals and Ventriculo-Atrial Block

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Abstract

The patient was a 68-year-old female with recurrent paroxysmal, regular narrow QRS complex tachycardia. We observed complete VA conduction block, during tachycardia in our patient. A characteristic feature of our patient is the noticeable irregular atrial and ventricular rates. We considered that possible mechanism of this tachycardia was atrioventricular nodal reentrant tachycardia (AVNRT) with retrograde complete type block in the upper common pathway.

Case

The patient was a 68-year-old female with recurrent paroxysmal, regular narrow QRS complex tachycardia despite treatment with metoprolol. Baseline surface electrocardiogram was normal, intracardiac intervals revealed an HV interval of 44 ms. The tachycardia cycle length was 380 ms, and earliest retrograde atrial activation at the His bundle catheter. We observed complete ventriculo-atrial (V-A) conduction block, during tachycardia in our patient (Figure 1). A characteristic feature of our patient is the noticeable irregular atrial and ventricular rates. We considered that possible mechanism of this tachycardia was atrioventricular nodal reentrant tachycardia (AVNRT) with retrograde complete type block in the upper common pathway (Figure 2). We observed slow accelerated junctional rhythm arise during radiofrequency energy delivery. The narrow complex tachycardia was not inducible after the radiofrequency ablation. The possible mechanisms for supraventricular tachycardia with VA dissociation include automatic junctional tachycardia, tachycardia with concealed nodoventricular, or nodofascicular pathway as the retrograde limb and atrioventricular nodal reentrant tachycardia.[2] Sarrias-Merce et al. described the narrow QRS complex tachycardia with faster ventricular rate than atrial rate (V-A block) which is a rare variant of AVNRT with retrograde block in the upper common pathway.[3] The electrophysiological characteristics of the upper common pathway defined in patients with various types of V-A block in AVNRT. An upper common pathways were reported

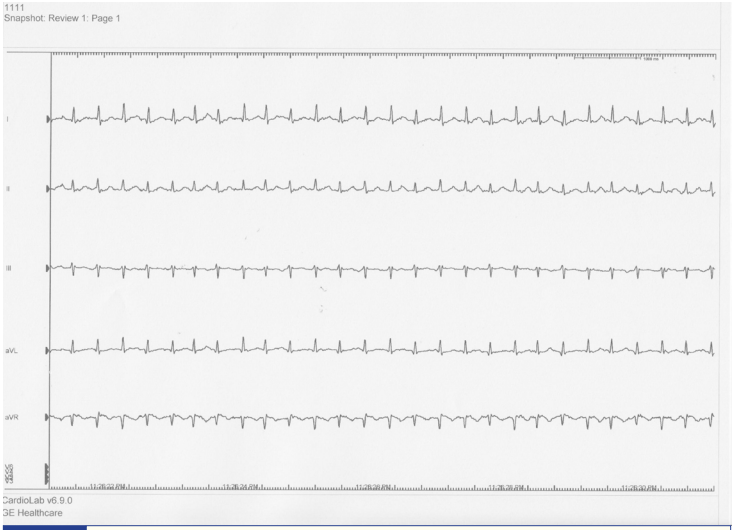

Figure 1: Ventriculo-atrial conduction block, during tachycardia on ECG

of patients with complete VA conduction block during AVNRT.[4] Successful elimination of tachycardia by radiofrequency ablation in the inferoseptal right atrium at the level of the coronary sinus ostium, where no His bundle potential was recorded, provides strong evidence that the tachycardia was AVNRT as opposed to intra-hisian reentry. Distinct features of our case are the markedly irregular atrial and ventricular rates, without an apparently relationship at first view.

In summary, markedly irregular atrial and ventricular rates, without an obvious relationship at first glance should bring to mind retrograde V-A block of upper common pathway.

Key Words:
AVNRT, Upper Common Pathway, Ablation.

Disclosures:
None.

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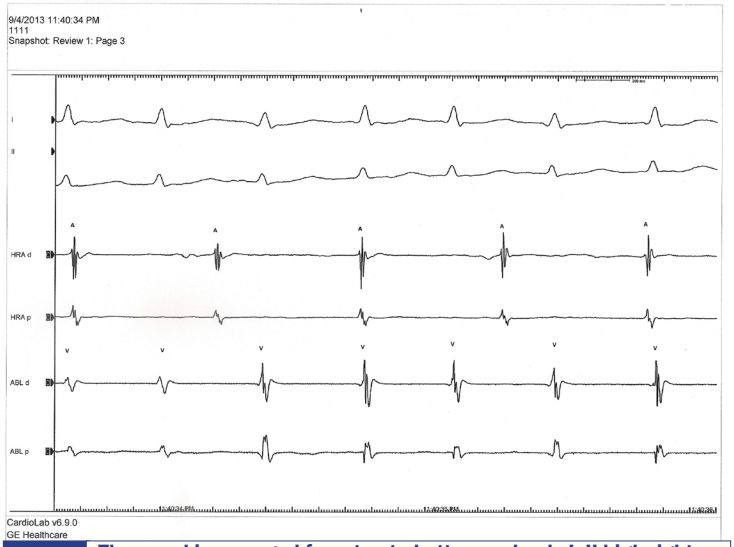

Figure 2: **The panel is arranged from top to bottom as leads I, II high right atrium (HRA) catheter in the right atrial appendex, and ablation catheter (Abl) in the right ventricle. Other abbreviations as in A: atrial electrogram, V: ventricular electrogram**

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Lyme Arrhythmia in an Avid Golfer: A Diagnostic Challenge and a Therapeutic Dilemma

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Abstract

Lyme disease is a multisystem disorder affecting dermatologic, cardiac, nervous and musculoskeletal systems. Cardiac manifestations occur in about 5% of Lyme infections and stem from the involvement of the cardiac conduction system, resulting in varying degrees of sino-atrioventricular block. Occasionally, Lyme infection may also present with myopericarditis. Unlike isolated conduction node disease, myocardial involvement presents a great diagnostic and therapeutic dilemma for the physician. We report the case of a 68 year-old male cardiologist who presented with new onset exertional dyspnea and palpitations.

Electrocardiograms revealed intermittent Wenckebach with markedly prolonged PR interval varying between 290-350ms. During his hospitalization, he also had a transient episode of atrial fibrillation/flutter with AV block. The patient was promptly treated with intravenous Ceftriaxone. He remained hemodynamically stable, and within 48 hours of antibiotic treatment, the patient's arrhythmias began to resolve, and the PR interval had shortened to 230ms. He was discharged on oral Doxycyline for three weeks.

Case Report

A 68-year-old male Cardiologist, with history of Prediabetes and Benign Prostatic Hyperplasia, presented with new onset exertional dyspnea and palpitations. He reported these symptoms for one day; however, mild fatigue and general malaise had been present for approximately 6 weeks. Of note, he remained fairly active with excellent exercise tolerance until the day of presentation. The patient was an avid golfer and ran on the treadmill 5 days a week. He did not recall any tick bites, rashes or fever. Review of systems was otherwise negative. Physical examination revealed a well-nourished male who appeared his stated age.

Cardiac exam revealed irregularly irregular rhythm and a variable intensity of S1 and the remainder of the physical examination was unremarkable.

Electrocardiograms revealed intermittent Wenckebach with markedly prolonged PR interval varying between 290-350ms (figure 1) and a transient episode of atrial fibrillation/flutter with AV block (figure 2, 3). His labs were as follows: Lyme antibodies titers IgM (3/3 bands) and IgG (5/10 bands) were positive: WBC 6.8 x 109/L, RBC 13.1 g/dL, HCT 38.9%, platelet 203 x 109/L, serum glucose 109 mg/dL, BUN 18 mg/dL, creatinine 1.03 mg/dL, Sodium 140 meq/L, Potassium 4.3 meq/L, chloride 103 meq/L, bicarbonate 28 meq/L, Calcium 9.3 mg/dL, Albumin 4.0 g/dL, T. Bilirubin 0.3 mg/dL, AST 72 units/L, ALT 150 units/L, ALP 115 units/L. On admission, his vitals were blood pressure 136/67, pulse 75, 98% oxygen saturation on room air, temperature 98.0 F. The patient was promptly treated with intravenous Ceftriaxone. Within 36 hours of antibiotics the patients arrhythmias began to resolve. By 48 hours the patients PR interval had shortened to 230ms (figure 4). The patient remained hemodynamically stable throughout admission, and was discharged on three weeks course of oral Doxycycline.

Discussion

Lyme borreliosis is the most prevalent tick-borne disease in the United State[1] Lyme disease exists throughout much of the world, including USA, Canada, Europe and Asia. In Europe and USA, Lyme carditis occur in approximately four percent of untreated Lyme disease patients[2,3]

The degree of myopericardial involvement will largely dictate the broad array of clinical manifestations. While AV nodal disease is by far the most common manifestation, Lyme carditis may also present with SA node dysfunction, pericarditis, endocarditis, myocarditis, pericardial effusion, myocardial infarction, coronary artery aneurysm, QT interval prolongation, tachyarrhythmia's, and congestive heart failure[4]

Lyme infection should be suspected in any patient who engages in high-risk activities or lives in endemic areas. Our patient, an avid

Key Words:
Arrhythmia, Therapeutic Dilemma, Electrocardiograms,Cardiologist.

Disclosures:
None.

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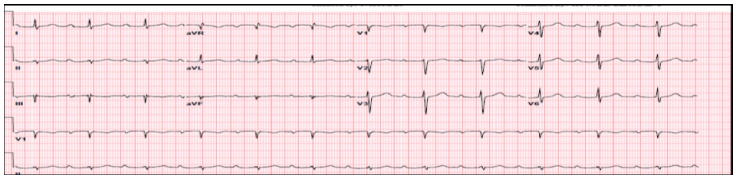

Figure 1

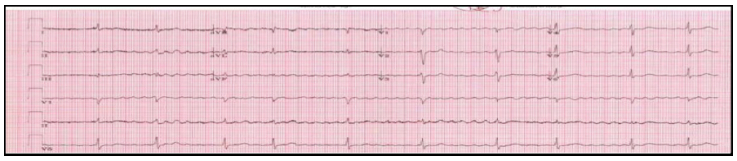

Figure 2

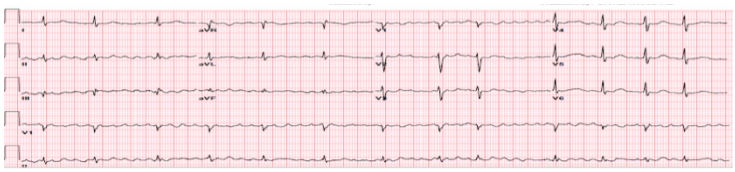

Figure 3

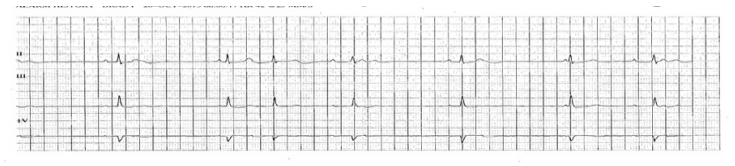

Figure 4

golfer living in a Lyme endemic area, presented with atrial fibrillation, and complete AV block with no prior cardiac disease or risk factors.

The association of Lyme carditis with Atrial Fibrillation is infrequently reported.[5]

The etiology may be related to either SA disease or myocarditis. Management of Atrial fibrillation in the setting of Lyme carditis poses many challenges, as many of our traditional algorithms used to treat arrhythmias would be deemed unsafe. Electrical Cardioversion in the setting of an inflamed myocardium could be proarrhythmogenic and fatal. Pharmacological cardioversion may uncover underlying AV nodal disease caused by Lyme and induce complete heart block. For the same reasons, Class I, II, III, and IV antiarrhythmic drugs traditionally used for rate control, cannot be used in this setting. Finally anticoagulation traditionally used for stroke prevention, would be contraindicated if concomitant pericardial involvement is present for the fear of causing hemopericardium.

Antibiotics remain the mainstay of therapy.[6] There have been no trials to compare one antibiotic from another; the data on appropriate treatment regimen comes mainly from case reports and case series. Intravenous ceftriaxone is the drug of choice in symptomatic patients (e.g. syncope, dyspnea, or chest pain) and asymptomatic patients with marked PR prolongation (PR>300ms);[7] as the degree of block may fluctuate and rapidly worsen in such patients. Patient allergic to penicillin and its derivatives should be desensitized. IV antibiotic should be continued till the PR interval is <300ms.[6] Asymptomatic patient should be treated with oral doxycycline, except in children <8 years old and pregnant women, where amoxicillin can be used.

Only one third of patients remember a tick bite or present with a rash,[8] neither the serodiagnosis is positive in the initial weeks of the illness. This case is a timely reminder for all resident physicians that Lyme disease should be high on differential in a patient with atypical presentation of Atrial fibrillation and conduction defect. If untreated the natural history of Lyme carditis will often result in congestive heart failure and/or sudden cardiac death.[9] Misdiagnosis of AV dysfunction could lead to unnecessary implantation of a permanent pacemaker. Thus the treatment algorithm in Lyme induced Atrial fibrillation is different, and largely depend upon prompt diagnosis and antibiotics.

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A Case of Wide Complex Tachycardia in a Patient with a Biventricular Assist Device

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Abstract

This case report highlights the variety of wide complex tachycardias, and the need for their prompt management, in the growing population of patients with circulatory support devices. We present a case that demonstrates how a wide complex supraventricular tachycardia in a patient with a biventricular assist device can be safely and effectively targeted for treatment using percutaneous radiofrequency catheter ablation, allowing for clinical improvement, weaning of RVAD treatment, and discharge home with LVAD alone.

Introduction

With the increasing use of ventricular assist devices (VAD) as a bridge to transplant or as destination therapy, there have been more reports of the presence and implications of arrhythmias associated with such devices. This case report illustrates that although patients with underlying heart failure requiring VADs may have a high pretest probability of having ventricular tachycardia and ventricular fibrillation, one must also consider other etiologies for wide complex tachycardias, including supraventricular arrthythmias in the presence of baseline bundle branch block or rate-related aberration.

Case Report

A 54 year old man with a remote history of Hodgkin's lymphoma, treated with splenectomy and radiation in 1986, was transferred from an outside hospital for further management of acute cardiogenic shock. He initially presented to his primary doctor with chest pain and had an electrocardiogram (ECG) with anterior ST elevations concerning for acute myocardial infarction. He underwent coronary catheterization at the outside hospital, which showed a complete occlusion of the proximal left anterior descending artery as well as an unspecified circumflex artery lesion. During balloon angioplasty, the patient became hemodynamically unstable. The procedure was aborted and an intra-aortic balloon pump (IABP) was placed. At this time, he was transferred to our medical center's cardiac intensive care unit for further management.

Because of the severely reduced biventricular function and refractory cardiogenic shock despite the presence of an IABP, a biventricular assist device (BiVAD) was implanted. His post-operative course was complicated by acute renal failure requiring continuous veno-venous hemodialysis. He was also noted to have several episodes of wide complex tachycardias in the setting of a baseline non-specific intraventricular conduction delay. Several arrhythmias were identified, including ventricular tachycardia (VT) and ventricular fibrillation (VF) (see Figure 1), as well as atrial flutter with varying amounts of AV block (Figure 2). The patient was treated with esmolol, amiodarone, procainamide, and lidocaine for these arrthythmia. However, the patient continued to manifest one predominant wide complex tachycardia that complicated attempts to wean the patient from a BiVAD to a left ventricular assist device (LVAD) alone (Figure 3, left panel). Therefore, an electrophysiology study (EPS) and radiofrequency ablation was performed with the goal of stabilizing rhythm control and optimizing hemodynamic management.

Despite more pronounced AV block during previous episodes of atrial flutter (Figure 2), at EPS the arrhythmia was diagnosed as cavotricuspid isthmus-dependent atrial flutter with 2:1 conduction to the ventricle (Figure 3). During radiofrequency ablation to the cavotricuspid isthmus (CTI), the arrhythmia terminated to sinus rhythm. Moreover, further programmed ventricular stimulation did not result in inducible VT. After the atrial flutter ablation, the patient was maintained on oral amiodarone and metoprolol and did not have recurrence of any significant tachycardia through hospital discharge three weeks post-ablation. After sustained restoration of sinus rhythm and improvement in right-sided hemodynamics, the

Key Words:
Vad, Arrhythmia, Ablation, Tachycardia, Atrial Flutter, Atrial Fibrillation.

Disclosures:
None.

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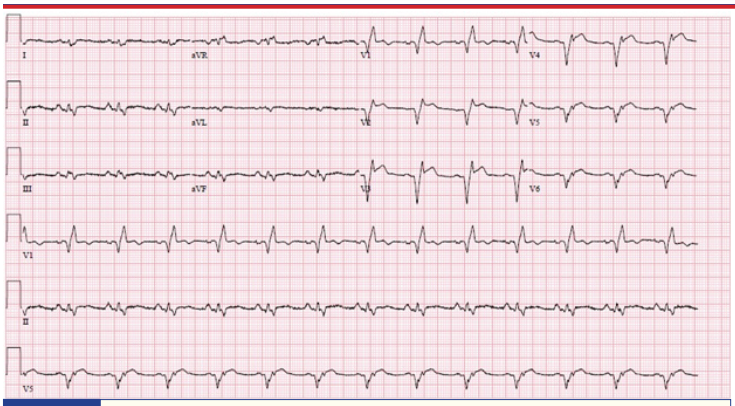

Figure 1A: **Baseline ECG**
Baseline 12-lead ECG showing normal sinus rhythm, right bundle branch block, and evidence of an extensive anterior myocardial infarction

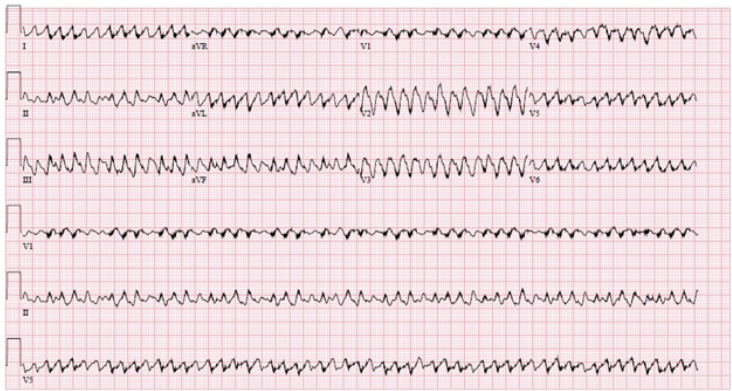

Figure 1B: **Ventricular Fibrillation. 12-lead ECG showing a polymorphic wide complex tachycardia consistent with coarse ventricular fibrillation. The artifact present is secondary to electrical interference from a normally functioning VAD**

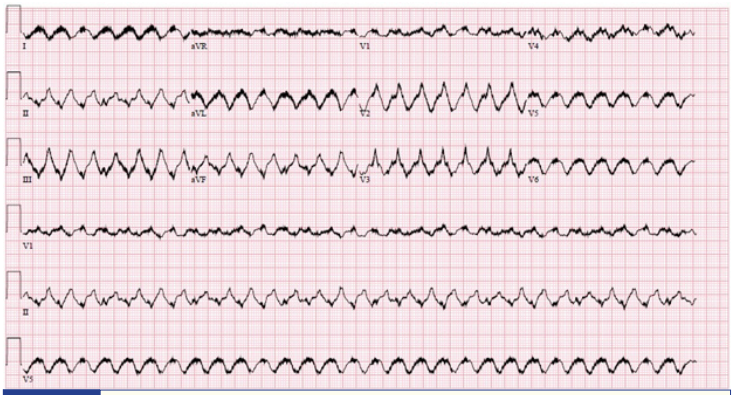

Figure 1C: **Ventricular Tachycardia. 12-lead ECG noting a wide complex tachycardia with rapid ventricular conduction and a profound axis shift from baseline, most consistent with ventricular tachycardia. The artifact present is secondary to electrical interference from a normally functioning VAD**

patient's right ventricular level of support was weaned, allowing for the right ventricular assist device (RVAD) circuit to be explanted and the patient to be discharged home with destination LVAD therapy.

Discussion

This case report highlights that even in patients with a high pretest probability of having VT/VF, it is important to consider other known causes of wide complex tachycardias that can contribute toward hemodynamic compromise. Studies have shown that patients with severe heart failure requiring VADs were more likely to have ventricular

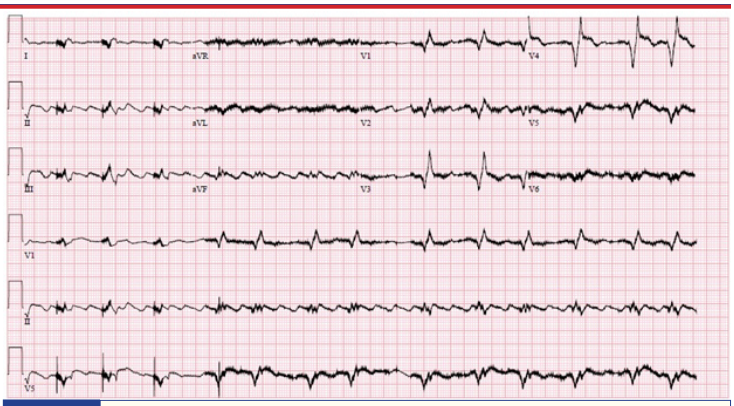

Figure 2: **12-lead ECG noting a wide complex tachycardia with variable AV block and intermittent ventricular pacing allowing for visualization of atrial flutter waves. The QRS complexes are similar to that of baseline, including RBBB and Q-waves in anterior leads. The artifact present is secondary to electrical interference from a normally functioning VAD**

arrhythmias that negatively impacted survival and other outcomes.[1] Nevertheless, it has also been demonstrated that atrial arrhythmias are fairly common in patients with VADs and have affected outcomes including mortality by a variety of proposed mechanisms.[2, 3] This case illustrated that in patients with VADs, the treatment not only of ventricular arrhythmias but also of supraventricular arrhythmias is important for longer term management, as ablation of the atrial flutter allowed for RVAD explantation and discharge home with destination LVAD.

The main etiologies of a wide complex tachycardia may include ventricular arrhythmias, supraventricular arrhythmias in the setting of underlying bundle branch block/intraventricular conduction defect or with rate-related aberrancy, or supraventricular arrhythmias with ventricular pre-excitation. While certain non-invasive diagnostic algorithms for distinguishing between ventricular or supraventricular sources of the arrhythmia have been suggested historically and reviewed more recently, there is still much inter-user variability among the algorithms, making them somewhat unreliable especially in the context of regular wide complex tachycardias.[4, 5] Furthermore, their utility in LVAD patients has not been established. The use of EPS to diagnose the arrhythmia is more invasive, but also provides definitive information as well as the potential for immediate and

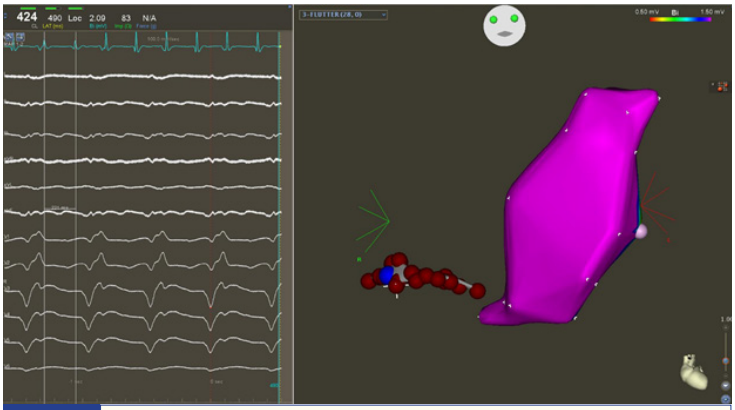

Figure 3: **CTI and Right Ventricular Mapping. The left panel shows electrograms demonstrating 2:1 atrial flutter with a cycle length of 424 msec. The artifact present is secondary to electrical interference from a normally functioning VAD. The right panel is a left anterior oblique (LAO) projection of the ablation lesions along the CTI line as well as the right ventricle map, which is free of scar**

effective treatment with ablation. Since EPS has been demonstrated to be safe in patients with VADs and can produce excellent results regardless of the etiology of the arrhythmia, it should be considered a safe adjunct or alternative to oral and parenteral antiarrhythmic treatments.

Patients with VADs can tolerate wide complex tachycardias including ventricular tachyarrhythmias more effectively from a hemodynamic standpoint. However, a known common presentation of ventricular arrhythmias is not sudden death, but rather acutely worsening right heart failure.[6] Catheter ablation of ventricular arrhythmias has been shown to be safe in patients with VADs and can result in decreased symptoms and burden of antiarrhythmic medications.[7,8] Nevertheless, atrial arrhythmias have previously been shown to be prevalent in patients with VADs with resultant increased signs and symptoms of right heart failure.[2] We show in this case that effective control of atrial arrhythmias helped permit recovery of this patient's right ventricular function and ultimately allowed for explantation of the RVAD and discharge from the hospital.

Conclusion

As the use of mechanical assist devices for heart failure continues to expand, there remains much to be studied about the impact these devices have on arrhythmia prevalence and patient outcomes, and vice versa. This case demonstrates that: (i) VAD patients can sustain multiple wide complex tachycardias of different etiologies, including ventricular tachycardia, ventricular fibrillation, and supraventricular tachycardias such as atrial flutter with baseline intraventricular conduction defect or rate-related aberration; (ii) electrophysiology study and radiofrequency ablation of clinically deleterious wide complex tachycardias in VAD patients, including supraventricular tachycardias with rapid ventricular response, are possible and effective for rhythm control and can facilitate recovery and overall clinical outcome. In summary, consideration of supraventricular tachycardias in VAD patients with medically refractory wide complex tachycardias allows for relatively straightforward diagnosis and management with ablation, resulting in a significantly positive impact upon a patient's clinical course.

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From Incidental, Mechanically-Induced Arrhythmias to Reflex-Defined Arrhythmogenicity: On The Track of The Ternary Reflex System Resemblance to The "Infancy" of New Era or Rediscovery

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Abstract

The underlying pathophysiology of supraventricular and ventricular arrhythmias remains a matter of intense investigation. Though evolving, the contemporary explanations do not encompass all aspects of arrhythmogenicity. An improved understanding of arrhythmia substrate is needed to augment therapeutic capabilities. Our observation and literature sources demonstrate relatively high incidence of transitory arrhythmias which are non-intentionally generated by the endocardial lead/catheter manipulation. These findings are interesting and potentially may crystallize the reflex-dependent proarrhythmic cardiac activity. Herein we suggest the "reflexogenic arrhythmogenicity" concept extending an overall spectrum of known hypotheses. Cardiovascular reflex action can be categorized into three-tiered levels – intra-cellular, inter-cellular and inter-organic. The first two levels of the triplicate system reside within the cardiac anatomical landmarks (in fact intramurally, intra-organically), however the third one implicates central (cerebral) activity which boomerangs back via centripetal and centrifugal connections. These levels likely compose synoptic ternary reflex set system which may be validated in future studies. To hypothesize, coordinated mutual reciprocity of reflex activity results in stabilization of heart rhythm in robust heart. Any stressful cardiac event may lead to the shift of the rhythm toward unfavorable clinical entity probably via the loss of the influence of dominant reflex. Overall, an interaction and likely intrinsic inter-tiered competition along with possible interplay between physiological and pathological reflexes may be treated as contributing factors for the inception and maintaining of arrhythmias and cardiac performance as well. These assumptions await further documentation. If such a tenet were recognized, the changes in the clinical approach to arrhythmia management might be anticipated, preferably by selective reflex suppression or activation strategy.

Introduction

Some conceptual mechanisms of arrhythmogenesis and differences between automatic and triggered rhythms remain moot.[1] According to current knowledge cardiac arrhythmias as well as atrial fibrillation (AF) most often stem from the ischemic or cardiomyopathic areas or on genetically determined basis, but overall underlying pathogenetic mechanisms are not completely understood yet. The mechanisms responsible for cardiac arrhythmias are generally divided into 2 major categories:

(a) enhanced or abnormal impulse formation and

(b) conduction disturbances.[2] Basic derivatives of existing hypothetic explanations – focal, triggered activity, micro- and macro re-entry, circus movement, spiral waves, meandering waves, rotors, multiple wavelets, delayed afterdepolarizations, double layer hypothesis, bifurcated theory, etc.[3-9] do not cover all aspects of vulnerable substrate of supraventricular and ventricular arrhythmias.

Invasive intracardiac procedures are often accompanied by rhythm eccentricities. Premature contractions are typically induced by mechanical touch - pressure or trauma - to the endocardium. Dysrhythmia being interventional in nature usually resolves when irritation discontinues. Both atrial and ventricular arrhythmias may occur and disappear under similar circumstances. These observations are interesting and may herald new conceptual insights into the arrhythmogenicity.

The musculature like any muscle cell, including myocardial ones, is implicated in motor effects in response to many inputs or stimuli - electrical, mechanical, thermal, neurohumoral, metabolic, pharmacological, toxic, ischemic - hypoxic, hyponutritional, etc.[10-16] Specific sensitive receptors are involved in activating the reflex circuit.

Knee jerk – a kick reflex is produced by sharply tapping the patellar ligament.[17] Similarly, cardiac motor effects – premature cardiac contractions – are posed by endocardial lead impingement on atrial or ventricular wall.

The primary goal of the article is to sketch out a universal theory

Key Words:
Cardiovascular Reflexes, Ternary Reflex System, Reflex Control, Mechanically-Induced Arrhythmias, Automaticity, Autonomic Control.

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None.

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which potentially might explain, at least in part, the pathophysiology of arrhythmologic substrate. To stress the reflex-dependent arrhythmogenicity and to facilitate its descriptive explication we start with the leveling of several semantic definitions which are close to identical:

(1) cardiac/cardiovascular autonomic control,

(2) cardiac/cardiovascular reflex regulation, and

(3) automaticity. In normal cardiologic state these definitions can be interchangeable and might be interpreted as a natural reflexogenic or reflex-dependent cardiac activity. Hypothetically, cellular automaticity, cardiovascular reflex activity and autonomic nervous system functions are uniquely condensed for precise tuning of heart rhythm. Any pathological cardiac event (ischemic, cardiomyopathic, structural, inflammatory, etc.) likely interferes with functionally well-organized harmony, thus paving the way for rhythm disturbances.

New insights into arrhythmogenic milieu presumably could contribute to better comprehension of complex nature of arrhythmogenesis. This analysis is intended to contribute to our evolving understanding of the arrhythmia mechanism and enrichment of existing hypotheses. Prior to accepting the proposed hypothetic approach an assessment by independent studies is needed to validate the postulations that are construed on a deductive basis.

Background and General Reflections

Any accidental insertion of the pacing lead into the pulmonary artery or ventricular outflow tract often results in firing of chaotic premature ventricular beats leading occasionally to critical destabilization of heart rhythm. Supraventricular extrasystoles or premature atrial contractions are incited less often by an atrial lead compared to a ventricular one. Risky manipulation of the lead resulting in provocative cardiac response is thought to be relatively benign. Immediate release of the lead usually solves the problem. Lingering maneuvering however, may result in severe problems. The character of evoked dysrhythmia may vary considerably from patient to patient. Non-intentional induction of cardiac activation prematurity in general is highly reproducible and may serve as endocardial or intramural activation pattern during mechanically induced stress. Most likely the arrhythmia is elicited by the whip or abutting the cardiac wall by the lead. This statement comes from personal experience and perception that this type of mechanical triggering of the areas mentioned may be associated with arrhythmia manifestation on purely reflexogenic basis.

We are not alone when it comes to empirical observations of premature contractions evoked by lead maneuvers. Mechanically-induced cardiac arrhythmias and mechanoelectrical feedback are well described.[18-20] Ventricular arrhythmias during catheterization of right heart chambers or pulmonary artery are extremely common.[21-23] Catheter-induced atrial or ventricular arrhythmias are potential but poorly understood complications.[22,24] According to Jie et al.[20] regional ischemia is responsible for the genesis of mechanically-induced ventricular ectopy and the mechanisms by which it degrades into spontaneous arrhythmia. Perceptible mechanistic pressure or even a gentle touch by lead on endocardium or intima of pulmonary artery actually evokes myocardial deformation and local micro-ischemic subtlety. It is still unclear which stimulus plays the dominant role - whether mechanical or ischemic impact, or both. Hypothetically, immediate cardiac response to the mechanical impact refers to as potential affliction of sensitive mechanoreceptors along with reflex or reflexes, rather than ischemic ingredients. Despite the ischemic factor providing a strong incentive for cardiac events, not every ischemic attack produces extrasystole or more serious rhythm disturbances. Though uncommon, there are well-known silent ischemia manifestations with angina-free course and arrhythmia-free one as well.[25,26]

According to our observations the intracardial manipulation by lead does not evokes dysrhythmia in every patient. It depends perhaps on allocation and high distribution variability of sensitive receptors. Absence of anatomic, ischemic, electrolytic and genetic substrate suggests the presence of other arrhythmia causes, one of which might be reflexogenic. Dube and colleagues[27] have observed premature ventricular contractions (ventricular bigeminy) immediately after application of the Valsalva maneuver. Again, it suggests that arrhythmias, at least some of them, may originate on reflexogenic basis.

Key Characteristics of Reflexes

It is well established that any muscular activity, be it skeletal, cardiac or smooth one is actually influenced by reflex control.[10, 11, 17, 28] In general, it is improbable that the human heart as a key muscular organ might be out of reflex regulation: it may be considered as an obvious, time-tested axiomatic truth. There is a long list of reflexes with 336 positions attributable to humans.[29] First of all let's look at skeletal muscles and their behavior under the influence/participation of reflexes.

The classical knee jerk (knee reflex) represents the group of so called physiological reflexes.[17] There are also pathological reflexes, e.g. Babinski's sign[17, 30] reflecting the presence of corresponding illness. Aberrant reflexes indicate spinal cord injury.[31] Clinicians often observe symptoms and signs entitled hyperreflexia, hyporeflexia and areflexia.[32] Hypothetically, assumptions associated with reflexes relevant to skeletal muscles may be extrapolated to the cardiovascular system and specifically to the myocardium.

The cardiovascular system nevertheless is "equipped" with the physiological reflexes, e.g. Bainbridge, Bezold-Jarisch, etc.[10, 17, 33] Clinicians are familiar with "reverse" Bainbridge reflex.[33] The mechanoreceptors that elicit this reflex are located at the junction of the right atrium and caval veins or at the junctions of the pulmonary veins and the left atrium;[34] this reflex is controversial, however, because its existence cannot always be demonstrated. The Bezold reflex effects are implemented through complex transformers, transducers and encoders being incorporated into the central feedback mechanism and affecting sensory input at receptor level.[10, 35]

Pathological and aberrant reflexes which might be attributed to the cardiovascular system are still unknown, just "pathological reflex effects" are mentioned.[36] To cover all aspects of cardiovascular regulatory system the pathological reflexes as such hopefully will be discovered. Cardiac contractile tissues like skeletal muscles may potentially demonstrate the presence of pathological reflexes especially in critical cardiac situations or at least on a virtual basis. Thus, coexistence of several kinds of reflexes, including hyper-, hypo- and areflexia, may lead to functional cardiac confusion, hence, to unpredictable consequences.

Fundamental Reflex Physiology

Reflex is an automatic, boomerang back response to a stimulus or changes within or outside the human body. Reflex is typically fast and involuntary, because most reflexes do not require much brain activity.

The reflex circuit or reflex arc compose a feedback loop and has two general components: one is for sensory purpose, and the other is for the motor/response one. In general, reflexes and autonomic nervous system are helpful in any cardiorespiratory and somatic adaptation which is stated in textbook manuals analyzing reflex regulation of various organ systems including muscular or cardiovascular one.[17,37,38]

The cardiovascular system is subject to precise regulation so that an appropriate supply of oxygenated blood can be reliably provided to different body tissues under a wide range of circumstances.[28] The afferent information from changes in arterial pressure and blood gas levels reflexively modulates the activity of the relevant visceral motor pathways and, ultimately, of target smooth and cardiac muscles and other more specialized structures.[28] Cardiac autonomic nervous system consists of two branches – the sympathetic and parasympathetic systems – that work primarily through actions on cardiac pacemaker tissue in a delicately tuned, yet opposing fashion in the heart.[16, 37] Hence, the concept of accentuated antagonism has emerged to define the functional relationship between these systems.[39, 40] Hasan[16] has stressed that the crosstalk between both limbs of the autonomic nervous system is critical for maintenance of normal cardiac rhythm and function. The author has concluded that: examination of the mechanisms involved in the development of these intimate connections will potentially allow therapeutic approaches to be harnessed for reversing breakdown in these communications in diseased states. The work by Vaseghi and Shivkumar.[37] showed that both sympathetic and parasympathetic nervous systems are intricately involved in the modulation of cardiac excitability and arrhythmias; neural remodeling creates the electrophysiological substrate necessary to initiate and maintain arrhythmias. It is well-known that imbalance in the autonomic regulation of heart rate is characterized by enhancements and decrements in sympathetic and parasympathetic activity, respectively.[41, 42] In other words, sympathetic and parasympathetic impulses drive the heart rate pursuant to sinus node functional demand and, as mentioned above, do participate in modulation of myocardial excitability and arrhythmias.

Circulatory reflexes are integrated at various levels of the central nervous system or "central command";[38, 42] important role play mechanoreceptors located in the atria and ventricles being sensitive to mechanical stretch. Thus, it may be postulated that whenever muscles are involved we deal with reflexes irrespective of whether the muscles represent voluntary or involuntary pattern. Undoubtedly, the reflex participation in the regulation of any muscle activity including cardiac one is very important, even if still underestimated.

More discussions is needed to elucidate proper cardiovascular regulation via autonomic nervous system. According to contemporary knowledge, intracardiac and/or intravscular signals are transferred centripetally through neurohumoral, baro- and mechanoreceptors. In skeletal muscle fibers the refractory period is about 1 ms to 2 ms in duration; the total refractoriness – absolute+relative – of about 2 ms to 100 ms, whereas the cardiac muscle refractory period reaches 150 ms to 300 ms.[43] Interposition of the refractoriness (also anisotropy being common in damaged myocardium) in the complex chain - myocardium, afferent and efferent limbs – makes the reflex action less pliable and less adaptive. Nevertheless, the refractoriness represents an indispensable component to secure the stability of heart rhythm, otherwise malignant tachyarrhythmias may develop. Typical interference of refractory window actually allows the myocardium to regain its contractility power. Reportedly, the changes in duration of the refractory period may affect cardiac performance significantly.[6, 14, 44] Micro- and macro- structural heterogeneity, anisotropy as well as the shift of the refractoriness are observed in diseased myocardium.[6, 45, 46] That is why, due to anisotropic architecture of most myocardial regions,[47] the "reflexogenic arrhythmogenicity" remains to be explored more precisely.

Novel Debatable Insights

While arrhythmias vary widely in their clinical presentations, they possess shared electrophysiologic properties at the cellular level.[6] Talking about reflex activity in general, first of all we consider automatic reflex mediated mechanic cardiac response to any selective stimulus. If we were to accept the theory by which the reflexes contribute to cardiac arrhythmogenicity, consequently the synoptic concept of three-tiered/ternary reflex system might be suggested. This concept defines different levels of autonomic components - reflexes with different length of their limbs participating in healthy and diseased cardiac/cardiovascular regulation. According to the reflex arc's span the limbs may be categorized as ultra-short, medium and long. Thus, the first level is represented by intracellular reflexes ("eponymously" known as cellular automaticity, triggered, focal, ectopic activity). Hypothetically the receptors along with the afferent and efferent reflex limbs reside inside the pacemaker cell(s). The second level might be referred to as inter-cellular (intraorganic, intracardiac, intramural) reflexes demonstrating their activity via cell-to-cell communication (per intercalated discs, genuine conduction pathways, also accessory pathways). Therapy may be implemented by the disruption of conduction system elements or anomalous accessory pathways. The presence of pathological inter-cellular reflexes may partially be explained by the appearance of arrhythmias' in denervated transplanted hearts. Finally, the 3rd tier might be characterized as inter-organic reflexes integrated into hegemonic centers. The latter one has close hierarchic interrelationship between the heart and central (cerebral) command centers[42] via centripetal and centrifugal connections. It can be assumed that triple protection entity (as the life protective unconditional reflex activity) may serve for survival reasons; presumably it is the result of natural human ontogenetic evolution.

Collation of Reflexes

Trilateral components – automaticity, autonomic regulatory function and reflex action/reaction operating "in corpore" potentially create a unique physiological and clinical entity.

The fundamental function defined as automaticity of pacemaker and non-pacemaker cells[6, 48] seems to be the most important feature of cardiac motor activity. Automaticity is the property of cardiac cells to generate spontaneous action potentials;[2] abnormal automaticity includes both reduced and enhanced automaticity. It appears that cardiac automaticity at the organ level is a very complex phenomenon and that, beside cellular mechanisms, integrative factors are involved in cardiac pacemaking.[49] According to Podrid and colleagues[50] the underlying ischemic heart disease evokes enhanced and/or triggered automaticity.[50] Automatism and reflexes are potentially interrelated and functionally intermingled. In other words, the functional activity of every involved tiered reflex chain(s) may be realized via automaticity. The disbalance of reflex-dependent capabilities potentially leads to proarrhythmic occurrences. Putative mechanism of overall reflex activity covers their multiple effects including crosstalk, unconditional joint action, competition or collision. Unconditional response to any

suprathreshold stimuli (incorporating "proper respect" to cardiac refractoriness) creates a specific cardioarrhythmologic scenario – normalization or degradation of heart rhythm.

The cardiovascular system is influenced by both intrinsic cardiac factors and extrinsic noncardiac ones. Chief among these is the autonomic nervous system, which mediates signals from physiological "sensors" in the heart and great vessels, such as baroreceptors, stress receptors, and various chemoreceptors.[51] Shusterman and colleagues in early 1998[52] have demonstrated that atrial arrhythmias, such as atrial fibrillation, have a long-established relationship with the autonomic nervous system, including associations with both sympathetic and parasympathetic signaling. This association has been extended to primary ventricular arrhythmias.[51]

Physiological reflexes largely orchestrate and control the heart rhythm normalcy. Arrhythmias conceivably are initiated by the substrate vitalizing pathological reflexes. The triggers residing in cardiomyopathic/ischemic areas are responsible for arrhythmic outbreaks most likely via corresponding micro- or macro-reflex arcs. It may happen by solitary pacemaker cell micro-reflex activity or by interference of upper level reflexes finally resulting in "mixed, bifunctional or trifunctional confusion". The arrhythmogenic scenario presumably may be "enriched" by hyper-, hypo-, or areflexia making corresponding myocites more or less excitable. Complex interactions between physiological and pathological reflexes actually may lead to unpredictable consequences including exhibition of pro-arrhythmic chaos. Any stressful cardiac event can alter myocardial excitability and eventually predispose to arrhythmia. Regarding the degree of myocardial damage and the amount of deactivated/destroyed sensitive receptors the cardiac responses may be mild, exaggerated or stormy, also acute or chronic. Such a viewpoint actually necessitates a new term – reflex activation threshold or reflex sensitivity parameter. The "game" of reflex capture thresholds which belongs to different dimensions, i.e. to physiological and pathological reflexes, in fact essentially creates a new milieu and new effects. Mutual/multilateral interactions and potential competition between these reflexes as well as the inter-tiered rivalry may generate both advantages and disadvantages - life saving or life-threatening outcomes. It means that we enter a virtual battlefield – "occult phenomenon" which is not explored yet and where "decision makers of arrhythmogenicity" do reside.

As mentioned above, we face well-organized and disorganized composition regarding the presence or absence of myocardial pathology. If so, the advanced myocardial pathology may exacerbate rhythm disturbances and vice versa – cardiac recovery may lead to arrhythmia regression. Furthermore, affliction of the refractoriness in general results in unpredictable functional collision of reflexes. Their integrated action does orchestrates fluently prior to occurrence of the cardiac event, however, it may result in an impairment or complete disintegration of cooperative activities with the development of an unexpected and unique electrophysiological scenario. In other words, inter-reflex turmoil after stressful cardiac crisis may emerge. Thus, reflex co-activities being harmonic in healthy myocardium and disharmonic in diseased one, presumably influence cardiac motor behavior.

Last but not least severe comorbidity in the elderly patient group may contribute secondary to arrhythmic whimsy, again via cardiovascular reflexes.

Conclusions

Cardiac premature contractions may be reproducibly incited by lead/catheter mechanical irritation of the right heart chambers. These findings are interesting and potentially crystallize the reflex-dependent proarrhythmic cardiac activity. The suggested concept of "reflexogenic arrhythmogenicity" incorporates the synoptic three-tiered or ternary cardiovascular reflex system. Cardiac motor effects like the prompt response of skeletal muscles may be reflex-determined, at least hypothetically. Complex interactions between reflex activities may provide the normal heart rhythm in healthy cardiac state, though abnormal one in ischemic or in structural heart disease. Changes in the clinical approach to arrhythmia management in light of reflex control might be anticipated preferably in terms of selective reflex suppression or activation strategy. Thorough investigation, however, is needed to assess the true value and controversies of hypothetical postulations.

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The Cost Effectiveness of LAA Exclusion

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Abstract

Left atrial appendage (LAA) exclusion strategies are increasingly utilized for stroke prevention in lieu of oral anticoagulants. Reductions in bleeding risk and long-term compliance issues bundled with comparable stroke prevention benefits have made these interventions increasingly attractive. Unfortunately, healthcare funding remains limited. Comparative cost economic analyses are therefore critical in optimizing resource allocation. In this review we seek to discourse the cost economics analysis of LAA exclusion over available therapeutic alternatives (warfarin and the new oral anticoagulants (NOACs)).

Introduction

Atrial fibrillation (AF) is an abnormal heart rhythm characterized by rapid, disorganized activation (fibrillation) of the left and right atria of the heart. It is solely responsible for 15% of 700 000 strokes occurring in the United States each year.[1] Multiple pharmacologic therapies are employed for stroke prevention in AF, including vitamin K antagonists (VKA) such as warfarin, newer agents such as dabigatran, rivaroxaban and apixaban and antiplatelet agents including aspirin and clopidogrel.

In recent years, nonpharmacologic therapies have been gaining acceptance as alternative stroke prevention strategies. They encompass exclusion of the left atrial appendage (LAA) from systemic circulation by surgical ligation or excision, percutaneous ligation and endovascular implantation of a left atrial occlusion device. Reductions in bleeding risk and long-term compliance issues bundled with comparable stroke prevention benefits have made these interventions increasingly attractive.[2]

While physicians are faced with a constantly expanding list of suitable treatment algorithms, healthcare funding remains limited. Comparative cost economic analyses of these interventions are therefore critical in optimizing resource allocation. They serve as an indispensable tool in the identification of neglected opportunities and redirection of resources to more efficient treatment strategies. It is predicted that the total number of life years saved by healthcare intervention could be doubled if proper reallocation of resources were to take effect.

In this review we seek to discourse the cost economics analysis of LAA exclusion over available therapeutic alternatives (warfarin and the new oral anticoagulants (NOACs)).

Key Words:
Left Atrial Appendage Exclusion,Cost Effectiveness,Watchman,Lariat

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None.

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Worldwide Epidemiology of AF: A Cost Perspective

Awareness of the magnitude of the AF problem is warranted in understanding its cost economics analyses. AF constitutes a significant public health impediment, with an estimated share of 1% of the National Health Service budget in the United Kingdom[3] and 16 to 26 billion dollars in annual United States expenses.[3, 4] Several regional studies suggest a rising prevalence and incidence of AF.[2, 5-8] In the United States, it is estimated that the number of adults with AF will more than double by the year 2050.[9] Because the frequency of AF increases with advancing age, these secular trends may be explained in part by the demographic transition to an inverted age pyramid.[10] Alternatively, an increase in AF incidence after age adjustment has been demonstrated, likely a reflection of fluctuating comorbidities and cardiovascular risk factors, in addition to miscellaneous contributors such as lifestyle changes.[11]

Chung et al[10] conducted a comparative assessment of the burden of AF from 1980 to 2010 based on available epidemiological data from the 21 Global Burden of Disease (GBD) regions. The estimated global prevalence of AF in 2010 was 33.5 million. Burden associated with AF, measured as disability-adjusted life-years, increased by 18.8% (95% UI, 15.8–19.3) in men and 18.9% (95% UI, 15.8–23.5) in women from 1990 to 2010. Mortality associated with AF was higher in women and increased by 2-fold (95% UI, 2.0–2.2) in men and

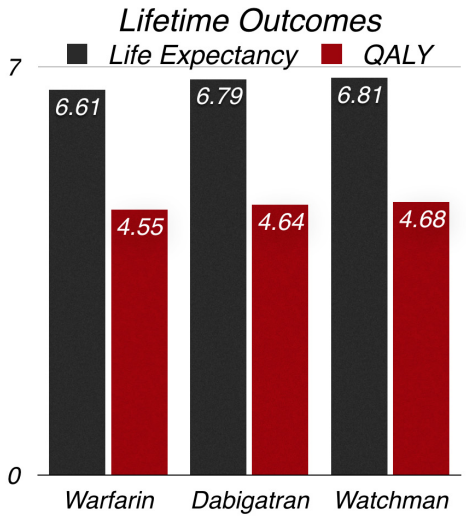

Figure 1: Relative impact of available stroke prevention interventions on life expectancy and quality adjusted life years in patients with NVAF as derived from Singh et al, 2013

1.9-fold (95% UI, 1.8–2.0) in women during the same time period. Overall, the data depicted strong evidence of progressive increases in overall burden, incidence, prevalence, and AF-associated mortality with significant public health implications.

Though the specific impact of stroke on mortality and disability was not scrutinized in this study, it remains a well-established contributor that influences outcomes of patients with AF.[12] A substantial proportion of the mortality in AF patients is attributable to ischemic strokes, which account for 10% of early deaths and 7% of late deaths following AF diagnosis.[11] The risk of ischemic stroke occurrence is increased 4-5 fold in patients with atrial fibrillation.[11,12] Furthermore, AF is a known risk factor for stroke severity, recurrence and mortality.[13] Roger et al approximated the annual cost of stroke care to be $40.9 billion.[14]

Cost Economic Evaluations: Cost-Effectiveness and Cost–Benefit Analysis

Cost-effectiveness analysis (CEA) is often employed in the evaluation of healthcare services. Typically cost effectiveness is quantified as the relationship between the cost associated with health gain given a certain measure (years of life, premature births averted, sight-years gained, etc.) divided by the health gain measure itself. Of course, healthcare benefit is not a black or white phenomenon. Aversion of death is no longer the only goal of healthcare providers. Alternate measures have been proposed to differentiate between a year of life in perfect health and a year of life with some degree of health impairment. One of the most commonly utilized outcome measures for this purpose is the quality-adjusted life year (QALY.[15] This may be reported as discounted or undiscounted QALY, the former representing an adjustment that factors in the devaluation of a given outcome with time. The logic behind it is that any benefit is considered to be at its peak value to the patient in the immediate setting, with a predictable depreciation over time as adverse events result in declining quality of life. CEA uses a numerical indicator named "Incremental cost-effectiveness ratio" (ICER) which translates as the additional cost of extending a particular intervention divided by the additional health gain that would result1. Costs are usually described in monetary units while benefits/effects in health status are measured in terms of QALYs gained or lost. Though the numerical value may fluctuate from one nation to another, in the US, it is accepted that spending $50,000 per QALY is considered cost-effective expenditure. Conversely, a therapy that leads to an increase in cost with a decrease in QALY is deemed counterproductive.

Another commonly employed mean of investigation is Cost Benefit Analysis (CBA). It is a systematic process that serves to calculate and contrast the benefits and costs of an intervention. It involves comparing the total expected cost of each option against the total expected benefit, to see whether the benefits outweigh the costs, and by how much. In CBA, benefits and costs are expressed in monetary terms, and are adjusted for the time value of money, so that all flows of benefits and flows of project costs over time are expressed on a common basis in terms of their "net present value".

Several decision-analytical models are utilized in economic evaluations, the Markov model most commonly chosen to address sophisticated health problems. This type of modelling permits presentation and analysis of probabilistic processes over time. It is usually used to simulate disease progression, and is particularly suitable for diseases that are chronic and recursive in nature, such as AF.

Cost-Effectiveness Analyses of NOAC for Stroke Prevention in AF

NOACs have pharmacological advantages over conventional anticoagulants that generally result in clinical benefit, as evidenced by various trials in a range of clinical settings.[16-19,18-22] Unfortunately, these new drugs remain more expensive than VKA, thereby imposing a greater cost burden on health systems. Despite this, studies[20-22] have consistently shown that the NOAC are cost-effective for stroke prevention in AF patients as compared to the more widely utilized conventional anticoagulants, particularly warfarin. For instance, Limone et al in a systematic review of economic models of NOACs vs Warfarin reported that ICERs vs Warfarin range between $3,547-$86000 for Dabigatran 150mg, $20,713 -$150,000 for Dabigatran 110mg, $23,065- $57,470 in Rivaroxaban and $11,400- $25,059 in Apixaban, concluding that all agents are ultimately cost effective. Of the available NOACs, apixaban has been shown to be the most cost-effective followed by dabigatran and rivaroxaban.[23] All three agents exhibit a negative incremental cost and therefore produce savings.[24]

In brief, these new agents represent a paradigm shift in

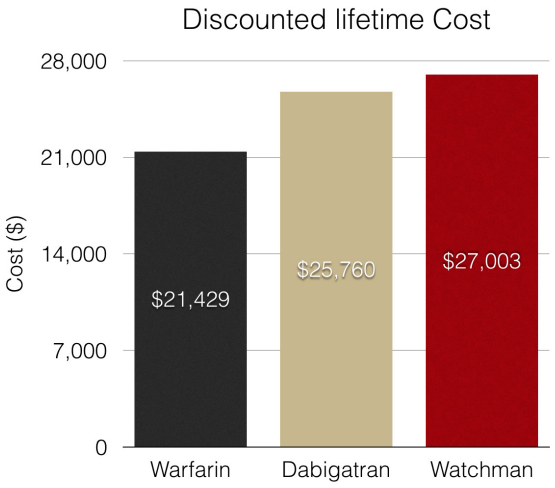

Figure 2: Relative discounted lifetime costs associated with various stroke prevention interventions in patients with NVAF as derived from Singh et al, 2013

anticoagulant therapy for stroke prevention in AF. This will have to be taken into account when pharmacologic therapies are compared to non-pharmacologic alternatives.

Cost-Effectiveness Analyses of Left Atrial Catheter Ablation (LACA) for Stroke Prevention in AF

LACA is more and more commonly employed in the treatment of AF. Solid evidence supports LACA as an effective tool for AF symptom suppression, but only observational data support stroke prevention.[25, 26] A large multicentre randomized clinical trial (CABANA) is under way, specifically designed to address the impact of LACA in stroke and other outcomes. Therefore, though not specifically aiming for stroke prevention, this treatment modality could theoretically decrease stroke incidence by virtue of rhythm control. A decision-analytic model was designed to assess the cost effectiveness of LACA in low and moderate stroke risk patients.[27] Costs and outcome measures were derived from the literature and Medicare data. The study concluded that LACA could be cost-effective in AF patients at moderate risk for stroke, but remains ineffective in low-risk patients.

A CBA is warranted in further analysing the advantages of LACA as compared to LAA exclusion and pharmacotherapeutic stroke prevention modalities. Such a model would take into account the broader benefit spectrum of LACA as pertains to heart failure progression, symptomatic relief and more.

Evaluation of Net Clinical Benefit of Left Atrial Appendage Closure for Stroke Prevention in AF

Current international guidelines propose the consideration of LAA closure in patients at high risk of stroke, who have contraindications to anticoagulation, are at high bleeding risk or prefer an alternative means of prevention.[28-32] In a clinical setting, 61.8% of patients implanted with a Watchman device were considered ineligible for anticoagulation therapy based on their comorbidities, bleeding history/risk, and compliance issues.[28] Of these, 38.7% had prior major bleeding or predisposition to bleeding (HASBLED score >2). Unfortunately, available cost-effectiveness data derives from large trials, such as PROTECT AF, which sought to compare LAAC outcomes to Warfarin therapy, and included only patients eligible to Warfarin.[33] As such, conclusions from these analyses cannot be applied directly and reliably to LAAC in clinical practice.

Gangireddy et al[34] conducted a post-hoc analysis utilizing patients who underwent Watchman device closure as compared to those maintained on anticoagulation. A total of 707 patients in the PROTECT AF trial and 566 patients from the Continued Access PROTECT AF (CAP) registry were included. Net clinical benefit (NCB) of LAA closure was estimated based on incidence of ischemic stroke, intracranial haemorrhage, major bleed, pericardial effusion and death. Each adverse outcome was weighted according to its relative impact in disability and death. NCB was 1.74%/year in the PROTECT AF trial and 4.97%/year in the CAP registry, both in favour of LAAC over anticoagulation. Furthermore, greater benefit was documented in patients with CHADS2 score of 2 as compared to those with a CHADS2 score of 1. A temporal analysis showed a linear benefit curve for anticoagulation with time, as opposed to a bimodal curve for LAAC. Early procedure related strokes and pericardial effusions adversely influenced the early benefit subsequent to LAAC. However, a later decline of these complications bundled with decreasing incidence of intracranial haemorrhage and death lead

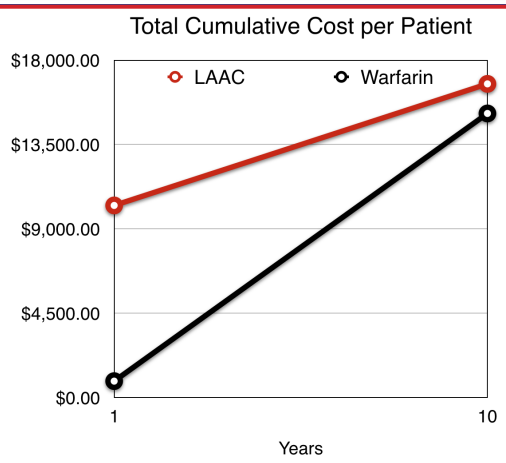

Figure 3: Total cumulative cost of LAA occlusion vs Warfarin at year 1 and year 10. Cost of LAA occlusion is significantly higher initially, but costs level off at 10 years post-intervention

to an improvement in NCB as compared to Warfarin in the long run.

Economic Evaluation of Percutaneous Left Atrial Appendage Occlusion, NOAC and Warfarin for Stroke Prevention in Patients with Nonvalvular AF

To date, there are no trials that directly compare NOAC with LAA exclusion devices from an economic perspective. Therefore, we will have to derive this endpoint from broader warfarin-controlled trials as it remains the established standard.

Singh et al[35] evaluated the quality-adjusted survival and costs associated with warfarin, dabigatran, or LAA occlusion strategies in patients with non-valvular AF at risk of stroke. A Markov model was developed that simulated 10,000 individual patient iterations in order to assess the projected costs and outcomes, estimating probabilities of different potential outcomes based on published data. Three primary treatment modalities were incorporated: (1) Dose-adjusted warfarin with a target international normalized ratio (INR) of 2.0 to 3.0, (2) Dabigatran, and (3) LAA occlusion. Outcomes of interest were life expectancy (measured in years), QALYs, costs and the ICER. For each therapeutic approach, 5 health states were possible: (1) No significant events, (2) myocardial infarction (MI), (3) stroke, (4) bleed, or (5) death.

At 4.55 years, warfarin therapy exhibited the lowest discounted quality-adjusted life years, followed by dabigatran at 4.64 and LAA occlusion at 4.68 (Figure 1). The average discounted lifetime cost was $21,429 for patients on warfarin therapy, $25,760 in the dabigatran arm, and $27,003 for LAA occlusion patients (Figure 2). Compared with warfarin, the ICER for LAA occlusion was $41,565 while that of dabigatran was $46,560. This meant that dabigatran imposed a higher financial weight per added unit of effectiveness as compared to LAA occlusion.

Subsequently, the study concluded that LAA occlusion and dabigatran are both cost-effective as compared to warfarin therapy. More importantly, it affirmed that based on current evidence, a strategy of LAA occlusion is more cost effective than dabigatran therapy.

The same group more recently published a similarly designed Markov model (Micieli et al), this time to assess interventions in new onset NVAF.[36] In addition to the previously studied interventions, it incorporated Rivaroxaban and Apixaban. The present study adopted a base case consisting of patients with new onset NVAF presenting

to the ED. In contrast, the group's previous base case[35] (Singh et al, 2013) consisted of NVAF patients presenting to outpatient care with stroke risk factors similar to those in the RE-LY and PROTECT AF trials. The new study again looked at QALY's and discounted lifetime cost. Warfarin again had the lowest QALY (5.13), followed by Dabigatran (5.18), Rivaroxaban (5.21), LAAO (5.21) and Apixaban (5.25). Similarly, Warfarin again had the lowest discounted lifetime cost ($15,776) followed by Rivaroxaban ($18,280), Dabigatran ($20,794), LAAO ($21,789) and Apixaban ($28,167). Overall, the study related that Apixaban is the most cost effective intervention for new onset NVAF.

Unresolved Pitfalls

The study by Singh et al is the first comparison of these novel therapies for stroke prevention in NVAF. Although a direct comparison of LAA exclusion and dabigatran would be ideal, such a study would require a large patient population with long-term follow-up to demonstrate noninferiority[35] and is therefore unlikely to be available to us in the foreseeable future.

Singh et al employed a population aged at 76 years, a factor that sheds controversy on the applicability of these results to younger patient populations. Moreover, it also remains to be seen whether these calculation may be applicable to other jurisdictions with different models of healthcare delivery and funding.

The LAA exclusion leg in this study is modelled closely after, and derives data from the PROTECT AF trial.[37] Follow-up data from the trial published recently also showed non-inferiority for the composite endpoint but affirmed more primary safety events in the LAA occlusion group than in the warfarin group.[38] Furthermore, the recently published PREVAIL trial reported significantly improved procedural safety parameters compared to PROTECT AF. Pericardial effusions requiring surgical repair decreased from 1.6% to 0.4% (p=0.027), and those requiring pericardiocentesis decreased from 2.9% to 1.5% (p=0.36). Therefore, it seems plausible to infer that ICERs derived from this trial could demonstrate an even larger cost-effectiveness in the LAA occlusion arm.

Most relevantly, Singh et al assumed the price of the Watchman to be ~$8500 in both studies described above. Current prices of the Watchman device in the US are $12500 - $18000. These differences would significantly alter all cost-effectiveness analyses.

A CBA of LAA Closure versus Warfarin for Stroke Prevention in AF

Reddy et al[39] constructed a cost benefit model, established using clinical data from the PROTECT AF trial. Adverse outcomes for LAA closure were estimated from PROTECT-AF data and warfarin outcomes were derived from the literature. Costs encompassed the cost of treatment and procedural complications. Benefits were defined as the savings accrued through reduction in stroke and mortality. The model showed an initial disadvantage to LAA closure, with the first 5-year cumulative cost benefit of -$2,300 when each additional life year is valued at $10,000. At year 6 however, the tables were turned as a positive cost benefit of $750 was evident, with further benefits accumulating each life year thereafter. The following year, the group constructed a Markov model comparing clinical outcomes, quality of life and total costs of LAAC vs Warfarin, once again derived from PROTECT AF data.[40] They reaffirmed that LAAC is cost effective at 6 years and dominant at 10 years, at which time it becomes less expensive and more effective than Warfarin (Table 1).

Table 1: Results of a cost utility analysis of LAAC vs Warfarin conducted by Reddy et al[40]

Time (Years)	6	10	Lifetime
Incremental quality-adjusted life expectancy (years)	0.16	0.4	1.3
Incremental Cost per QALY ($)	37,713	Dominant	Dominant

Similarly, a budget impact model was constructed to project the 10 year cost-effectiveness of LAA closure (modelled using the PROTECT AFIB trial) as compared to warfarin and Dabigatran (modelled using the RE-LY trial).[41] The cost/benefit of LAA closure decreased with additional life years, becoming less expensive than Dabigatran at 8 years, and only 10% more expensive than Warfarin at 10 years (Figure 3).

Both studies showed that the majority of costs associated with LAA closure are borne early, mainly in the first year. However, in the long term, this modality becomes increasingly cost-effective and provides an opportunity for chronic healthcare savings. This information may provide the framework for physicians in assigning treatment strategies based on predicted life expectancy. From an economic standpoint, LAA closure may be ill advised in patients with a very low predicted life expectancy (<2-3 years). This is because a high expense will be met immediately, and patients are unlikely to benefit adequately from it within their lifetime.

Applicability of These Results to Other LAA Exclusion Devices.

At present, there is no CEA or CBA data pertaining to non-Watchman endocardial and epicardial (Lariat) LAA exclusion devices. With less established clinical efficacy parameters and different safety outcomes, it seems unlikely that the available results could be extrapolated to them.

The Lariat is associated with a lower rate of leaks at 1 year compared to Watchman.[42] On the other hand, manipulation of the LAA with the Lariat device is both endocardial and intrapericardial. This dual access approach widens the range of possible complications (ventricular puncture, epigastric vessel laceration, hemopericardium, pericarditis, and incomplete ligation). A retrospective, multicenter study of consecutive patients undergoing LAA ligation with the Lariat device[43] reported major complication occurrence in 15 patients (9.7%), and procedural success limited by bleeding. Such factors are likely to negatively impact the CEA and CBA.

Initial attempts to reduce stroke risks in patients with AF were made by cardiac surgeons performing excision, suture closure, or stapling of the LAA. These procedures have been performed for many decades in thousands of patients undergoing cardiac surgery for other conditions and, to a lesser extent, as standalone surgical procedures. Surprisingly, there is no data available indicating benefits in patients undergoing these procedures.[38] Indeed, the only randomized study on surgical LAA exclusion, published years ago, failed to show a reduction in stroke events in the treatment group.[1, 44]

It is clear that cost-effectiveness data extrapolated from Watchman trials cannot be generalized to all LAA exclusion strategies. Additional clinical efficacy data gathered over a significant follow-up period will be critical in establishing reliable cost effectiveness analyses for these intervention modalities.

Limitations in Available Data

Available LAA exclusion cost-effectiveness data have been extrapolated from the PROTECT-AF population. Given that CEA compares different treatments and their differences, it is unlikely

that using data from PREVAIL would yield a more favourable result for the Watchman device, considering the low rates of stroke in the control population of this trial.

As mentioned, one of the most prominent limitations to present cost-effectiveness analyses is the absence of a direct comparison between LAA exclusion and NOACs. These novel agents are gaining widespread acceptance, and are likely to become more affordable with time, factors that will surely sway CEAs in their favour. Similarly, many patients have absolute contraindication to oral anticoagulants, and so the alternative for these patients would be the receipt of no therapy at all. An ICER comparing LAA closure to non-therapeutic controls does not exist to date, but could be particularly useful for decision-making within this subset of patients.

Little attention has been given to LACA as a stroke prevention modality. Its utilization in the moderate to high stroke-risk population was shown to be cost-effective, and may present a reasonable alternative to LAA exclusion whose long-term clinical repercussions remain unclear. Furthermore, this modality may be used in patients with contraindication to anticoagulation, making a CBA of the two modalities more precise.

Conclusion

To date, cost-effectiveness data on LAA exclusion remain scarce. The limited studies available are heavily routed in Watchman clinical outcomes studies, and cannot be generalized to alternative LAA exclusion modalities. Available analyses however, have shown a cost-effective advantage to LAA exclusion, more prominently so in the long run.

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ICE Guided CRT: Is there Evidence of Reverse Remodeling?

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Abstract

Cardiac resynchronization therapy (CRT) is an accepted treatment for patients with heart failure (HF), impaired left ventricular (LV) function, and a wide QRS complex. However, more than 30% of eligible patients fail to benefit from CRT. It is clearly necessary to define the characteristics of the best candidates for this therapy. To this end, surface ECG and echocardiography have been tested. Unfortunately, however, neither of these examinations has proved sufficiently able to identify the best patients. A tailored approach based on the evaluation of both electrical and mechanical delay to guide LV lead placement seems to be the most reasonable strategy in order to increase the efficacy of CRT therapy. The good preliminary data that have been published suggest that using intracardiac echocardiography to define the mechanical delay could be an interesting option. Moreover, at present it is the only option available that can enable intraprocedural evaluation of the mechanical activation sequence. Naturally, further randomized studies with larger populations should be performed in order to ascertain the real benefit of this approach and to evaluate whether it will outweigh the additional cost of this technology.

Introduction

Cardiac resynchronization therapy (CRT) is an accepted treatment for patients with heart failure (HF), impaired left ventricular (LV) function, and a wide QRS complex. The paradigm for CRT is based on the evidence that conduction disturbances, in particular left bundle branch block (LBBB), lead to LV dysfunction.[1] In 1983, it was first reported that simultaneous septal and LV free wall contraction was hemodynamically superior to dyssynchronous contraction and that the best hemodynamic effect arose from fusion between intrinsic LBBB conduction and the LV pacing stimulus.[2] In accordance with this concept, and on the basis of the benefit observed in early hemodynamic studies[3-4] and the observation that delayed segments predominate at these sites, the conventional approach to resynchronization has involved directing the LV lead to the lateral and posterior walls.

In the last 20 years, several large randomized multicenter trials have shown the clinical benefits of CRT therapy on symptoms, exercise capacity, mortality and HF re-hospitalization.[5-11] In the CARE HF[10] and REVERSE[12] studies, substantial improvements in LV size and function, LVEF, RV function, LA size and mitral regurgitation severity were observed in patients treated with CRT in comparison with ICD only. These results provide consistent evidence of a substantial, progressive and sustained reverse remodeling effect conferred by CRT in the responder population.

The Dark Side: Non-Responder Population

However, more than 30% of eligible patients fail to benefit from CRT. The reasons for the high percentage of non-responders include inappropriate candidate selection, device programming and LV lead placement.[13] In general, the response to CRT is greatest when biventricular pacing serves to synchronize left ventricular contraction as much as possible. The two criteria for pacing sites that are generally held to optimize CRT response are: (1) pacing at areas of live, non-scarred myocardium, and (2) pacing at the area of the most delayed mechanical contraction or electrical activation. Echocardiography and MRI reveal both the regions of latest mechanical activation and areas of scarred, non-contractile myocardium.[14-15] By contrast, ECG excels in determining the regions of latest electrical activation; it also has some ability to distinguish areas of scarring, but is generally unable to guide lead placement.[16-17]

First Mission: Choose the Right Patient

It is clearly necessary to define the characteristics of the best candidates for this therapy. To this end, surface ECG and echocardiography have been tested. Unfortunately, however, neither of these examinations has proved sufficiently able to identify the best patients. Indeed, in candidate selection, electrocardiographic evidence of intraventricular conduction delay has been tested as a surrogate marker for mechanical interventricular and intraventricular dyssynchrony.[6,18] In patients with severe CHF symptoms, LBBB morphology and QRS width > 150ms have been shown to predict

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a greater likelihood of CRT benefit. On the other hand, in patients with mild heart failure, non-LBBB morphology has been shown to predict minimal CRT benefit, and potentially even harm due to LV pacing. However, a significant proportion of CRT patients fail to respond symptomatically, and an even a larger proportion do not display objective evidence of benefit.[7,10] Moreover, the utility of many echocardiographic measures of mechanical dyssynchrony that once held promise as predictors of response to CRT in single-center studies was tested by the PROSPECT (Predictors of Response to CRT) trial.[19] Even after validation by blinded core laboratories, no echocardiographic measure of dyssynchrony could reliably predict the response to CRT. Negative evidence also comes from the recent Echo CRT study, which failed to show a benefit from CRT-D in patients with QRS duration <130 ms and dyssynchrony assessed echocardiographically.[20] These results seem to suggest that the battle to select patients has been lost, a conviction that is underlined by the simpler CRT indications reported in the latest guidelines.[21] For this reason, research on LV lead placement has attracted considerable interest.

Second Mission: Choose the Right Vein

The standard technique of CRT implantation has remained substantially unchanged since it was first described in the 1990s.[22] A posterolateral position with acceptable pacing parameters and no diaphragmatic stimulation is usually considered a good angiographic result. However, several studies have reported a correlation between LV lead position and CRT outcome and mortality.[23-25] Derval and colleagues showed that the pacing site is the primary determinant of the hemodynamic response to LV pacing in patients with non-ischemic, dilated cardiomyopathy,[26] pacing at the best LV site being associated acutely with fewer non-responders. In another study, Duckett et al. reported that the acute hemodynamic response seemed to predict reverse remodeling both in ischemic and dilated cardiomyopathy.[27] In a smaller but significant group of patients, Spragg and colleagues assessed the greatest percentage rise in LV-dP/dtmax in a target other than the posterolateral and lateral veins. They reported that, in their institutional experience, 8 of 11 patients who underwent intraoperative hemodynamic measurements while being paced at various endocardial surfaces were found to have an optimal pacing site that was not at locations traditionally used for LV pacing.[28]

These data confirm the idea that even when the LV lead is deployed in a "good" fluoroscopic position, the response is variable. Thus, a concept has evolved according to which targeting segments of latest LV "activation" improves response. The ways of defining the optimal LV segment to pace are different.

Pacing at the Site of Latest Mechanical Activation

Dyssynchrony imaging, which plays a small role in patient selection, may be useful in LV lead deployment. In a prospective study, Ypenburg et al. found that pacing at the site of latest mechanical activation, as determined by speckle-tracking radial strain analysis, resulted in a superior echocardiographic response after 6 months of CRT and better prognosis during long-term follow-up.[29] In the TARGET randomized study, the authors showed that a targeted approach to LV lead placement based on the definition of the latest segment activated, as identified by speckle-tracking echocardiography, resulted in significant benefit in terms of LV reverse remodeling, clinical status and the long-term endpoint of combined death and heart failure-related hospitalization, in comparison with a standard approach.[30] The main limitation of that study was that speckle-tracking echocardiography could not be performed in all the patients. Secondly, despite targeting, the constraints of coronary venous anatomy appear to have restricted concordance to only two thirds of patients, and in 8% of all patients the LV lead was still placed at areas of scarring. Several data have suggested that the viability of the paced LV segment can influence the outcome of CRT. In this regard, pacing areas of scarring is associated with a worse response[31,32] than pacing viable myocardium. Increasing scar transmurality[31] and scar density[14] also portend a worse response. Another recent randomized study evaluated the impact of echocardiography-guided left ventricular lead placement with the aid of speckle-tracking echocardiography at the site of latest mechanical activation on the rate of freedom from appropriate CRT-D therapy for ventricular arrhythmias. The authors reported a higher percentage of CRT response in the echo-guided LV lead placement group (72% vs 48%, p = 0.006) with a consequent improved therapy-free survival rate.[33] When the trans-thoracic echocardiography approach is used, the best LV lead site is identified and implantation is performed at different times; it is therefore impossible to adjust the lead position if placement is suboptimal.

Pacing at the Site of Latest Electrical Activation

Another approach to identifying the right vein to pace is based on the evaluation of local ecg delay. The measurements of the QLV interval in each of the CS tributaries is the most used method to define the area of most delayed ventricular electrical activation. The QLV interval is defined as the time that elapses between the beginning of the QRS complex on surface ECG and the onset of the sensed electrogram at the LV lead. Placement of the CS lead at the site of the longest QLV interval is correlated with improved hemodynamics, including higher maximum dP/dT.[34] Moreover, a substudy of the SMART-AV trial showed that the length of the QLV interval was associated to a better outcome of CRT in patients with greater electrical dyssynchrony.[35] Similar results were observed also in the MADIT trial.[24]

This approach has the advantages of requiring minimal additional procedural time and it does not require the implementation of additional tests as echocardiography o cardiac MRI.

Another strategy was described in 2012 by Del Greco and colleagues, who demonstrated the ability of an electroanatomic navigation system (NavX system) to guide CRT–ICD implantation. The authors concluded that this approach was feasible and safe and reduced X-ray exposure both for patients and physicians. A further benefit was that the system provided more detailed information and accuracy during CS lead placement, in terms of both 3D visualization of anatomy and ventricular activation time, which optimize the pacing site choice.[36]

Currently, several additional studies are underway to correlate the QLV interval, as measured at the CS lead, and the clinical and echocardiographic response to CRT.

Intracardiac Echocardiography

In an early study conducted on dogs, Jiang et al. reported the feasibility and ability of intracardiac echocardiography in visualizing the left ventricle from the right ventricle and monitoring LV function.[37] Some years later, Saksena and colleagues proposed a clinical technique using intraoperative ICE to guide LV lead

positioning and CRT device optimization. In their study, ICE was used in 23 patients to assess baseline LV function and LVEF in the B-mode and/or M-mode view and to evaluate the stroke volume indirectly by means of aortic flow spectra from Doppler analysis. The final LV position was selected according to the greatest changes in LVEF and/or aortic flow parameters measured in each possible vein during CRT stimulation.[38] The same approach was also used for AV and VV optimization. Intracardiac echocardiographic visualization of LV function was achieved in all the patients. On using this approach, the authors reported a significant improvement in LVEF compared with the baseline evaluation (24±9% to 43±13%) and only one patient experienced worsening of heart failure during a follow-up of 11±5 months. On the other hand, ICE evaluation prolonged the procedure time by 45 minutes. The main limitations of that study were the small patient population and the inability to confirm the real benefit of ICE, owing to the study design.

In another study, Bai et al. proposed using ICE coupled with vector velocity imaging to evaluate LV dyssynchrony and to guide LV lead placement at the time of CRT implantation. Starting from a manual endocardial perimeter tracing of each B-mode LV image, the vector velocity imaging software creates 6-segment radial/longitudinal strain curves that enable LV dyssynchrony to be detected.[39] This analysis was performed in the basal condition, during LV only or during CRT pacing in at least 2 veins in the first 50 patients. These data were compared with those from the following 54 patients, in whom standard CRT implantation was performed. Reverse remodeling was observed in both groups, but the percentage of responders in the ICE group was significantly higher than in the standard group (82% vs 63%). In the ICE group, all the responders displayed optimal visual resynchronization on vector velocity imaging. The authors concluded that ICE-VVI analysis could be easily and safely performed during CRT implantation, and that its use was associated with a better outcome on CRT therapy during follow-up. Moreover, ICE guidance enablesthe final LV lead position to be chosed from among all candidate veins by means of "real-time" synchrony analysis. Alternatively, if optimal resynchronization cannot be achieved in the procedure, the patient may not be a suitable candidate for transvenous CRT.

Conclusions

Cardiac resynchronization therapy is the most powerful weapon to reduce morbidity and mortality in patients with symptomatic severe heart failure and ECG evidence of interventricular conduction delay. A tailored approach based on the evaluation of both electrical and mechanical delay to guide LV lead placement seems to be the most reasonable strategy in order to increase the efficacy of CRT therapy. The good preliminary data that have been published suggest that using intracardiac echocardiography to define the mechanical delay could be an interesting option. Moreover, at present it is the only option available that can enable intraprocedural evaluation of the mechanical activation sequence. Naturally, further randomized studies with larger populations should be performed in order to ascertain the real benefit of this approach and to evaluate whether it will outweigh the additional cost of this technology.

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Cardiac Resynchronization Therapy in Non-Ischemic Cardiomyopathy

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Abstract

Cardiac resynchronization therapy (CRT) is an established therapy for heart failure patients who remain symptomatic despite optimal medical therapy, have reduced left ventricular ejection fraction (<35%) and wide QRS duration (>120 ms), preferably with left bundle branch block morphology. The response to CRT depends on the cardiac substrate: presence of correctable left ventricular mechanical dyssynchrony, presence of myocardial fibrosis (scar) and position of the left ventricular pacing lead. Patients with non-ischemic cardiomyopathy have shown higher response rates to CRT compared with patients with ischemic cardiomyopathy. Differences in myocardial substrate may partly explain this disparity. Multimodality imaging plays an important role to assess the cardiac substrate and the pathophysiological determinants of response to CRT.

Introduction

Non-ischemic cardiomyopathy includes five major phenotypes: hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and left ventricular non-compaction.[1] The clinical manifestations of these cardiomyopathies vary largely within each form of cardiomyopathy. However, progression to overt heart failure and development of high likelihood of sudden cardiac death are common outcomes to these cardiomyopathies and cardiac resynchronization therapy (CRT) and implantable cardiac defibrillator (ICD) devices may be indicated in selected patients. The current review is focused on the experience with CRT in patients with non-ischemic cardiomyopathy.

The proportion of heart failure patients with non-ischemic cardiomyopathy who were included in large registries and landmark randomized controlled trials on CRT ranges between 33-66%.[2-4] CRT has demonstrated similar improvement in all-cause mortality and heart failure hospitalizations of patients with ischemic and non-ischemic cardiomyopathy.[4-6] However, in terms of left ventricular (LV) reverse remodeling and improvement in function, patients with non-ischemic cardiomyopathy exhibit larger benefit compared with patients with ischemic cardiomyopathy.[3-5, 7, 8] The underlying differences in demographics (sex and age), comorbidities and cardiac substrate including type of conduction abnormality (left versus right bundle branch block), the presence of mechanical dyssynchrony, the presence and extent of myocardial scar (or more specifically diffuse fibrosis), the varying cardiac venous anatomy, and the LV pacing lead location may all influence the effects of CRT. However, the specific weight of each of these parameters has not been extensively evaluated (and will be difficult to do). In addition, the relationship between CRT and the various phenotypes of non-ischemic cardiomyopathy remains unknown and is limited to small series and case reports.[9-16] Probably, the large majority of patients with non-ischemic cardiomyopathy who were enrolled in randomized trials on CRT, had dilated cardiomyopathy.

The present review article summarizes the evidence on the benefits of CRT in heart failure patients with non-ischemic (dilated) cardiomyopathy and discusses the potential role of imaging to improve selection of candidates for CRT.

Key Words:
Cardiac Resynchronization Therapy, Echocardiography, Magnetic Resonance Imaging , Heart Failure.

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None.

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Cardiac Resynchronization Therapy in Non-Ischemic Cardiomyopathy

Recent data from the National Cardiovascular Data Registry and the implantable cardioverter defibrillator (ICD) registry, including 31,892 heart failure patients treated with CRT, showed that the prevalence of non-ischemic cardiomyopathy was 43%.[3] CRT has demonstrated to improve heart failure symptoms and LV systolic function, induce LV reverse remodeling and improve prognosis of these patients.[5, 17, 18] In 191 patients with dilated cardiomyopathy,

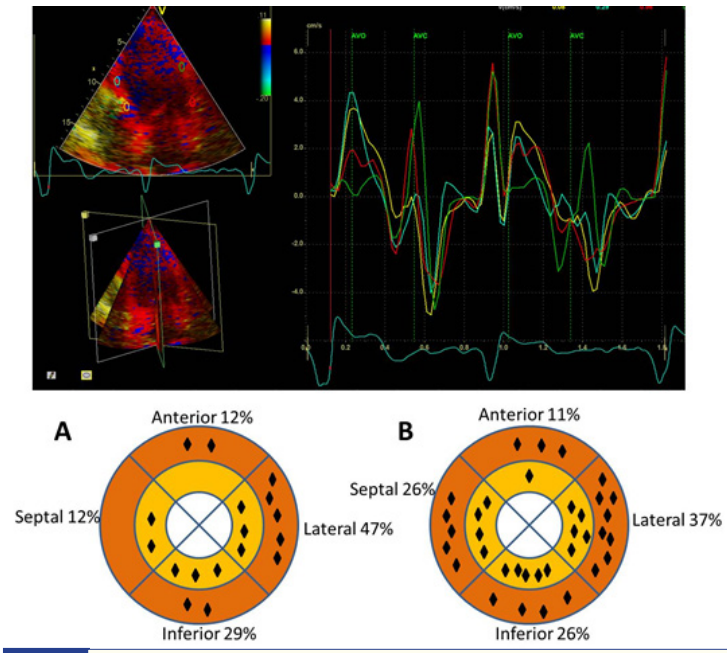

Figure 1: **Assessment of left ventricular (LV) dyssynchrony with triplane tissue Doppler imaging (TDI) in 17 patients with dilated cardiomyopathy and QRS duration >120 ms (A) and in 35 patients with ischemic cardiomyopathy and QRS duration >120 ms (B). The upper panel shows the assessment of LV dyssynchrony from the apical 4-chamber view placing 4 regions of interest in the basal and mid ventricular segments. The peak systolic velocity is measured for each mid and basal LV segment within the systolic interval demarcated in the time-velocity graph by the opening (AVO) and closing (AVC) of the aortic valve. The lower panel shows the distribution of the latest activated areas as assessed with triplane TDI in patients with dilated cardiomyopathy (A) and patients with ischemic cardiomyopathy (B). The basal lateral segment is more frequently the most delayed segment in patients with dilated cardiomyopathy whereas in ischemic heart failure patients the distribution is more variable**

McLeod et al. showed improvement in LVEF by 18.1±17.1% and mean reduction in LV end-diastolic volume of 60.2±75.1 ml/m2 after a median follow-up of 7 months. Similar results were observed in larger series such as the InSync/InSync ICD Italian registry which included 635 patients with dilated cardiomyopathy.[17] After a mean follow-up of 6 months, significant improvements in New York Heart Association (NYHA) functional class (from 3.0±0.6 to 2.0±0.8, p<0.05) and LVEF (from 26±7% to 35±11%; p<0.05) and reductions in LV end-systolic volume (from 147±93 ml to 118±82 ml, p<0.05) were observed. However, 37% of patients did not show any improvement in NYHA functional class or echocardiographic parameters or decrease in hospitalization for heart failure rates at follow-up. Similar percentages of non-response have been described in smaller series.[18] The analysis of the cardiac substrate by non-invasive cardiac imaging may provide further insight into CRT response (which may potentially help to select patients).

Assessment of Cardiac Substrate before CRT Implantation in Non-Ischemic Cardiomyopathy

Assessment of LV mechanical dyssynchrony, scar (fibrosis) burden and location in relation to the LV lead position are important in determining the response to CRT and the imaging techniques to evaluate them will be discussed in this section.

Left Ventricular Mechanical Dyssynchrony

Current recommendations include QRS duration and morphology as criterion for LV dyssynchrony.[19, 20] It has been demonstrated however, that QRS duration or morphology do not accurately reflect LV mechanical dyssynchrony.[21] Cardiac imaging conversely, permits characterization and quantification of LV mechanical dyssynchrony. Echocardiography remains the most widely used technique to evaluate LV mechanical dyssynchrony, and van de Veire et al. showed that in patients with dilated cardiomyopathy, the lateral wall is most often the latest activated segment, whereas the septum is the earliest activated segment (Figure 1).[22]

Different echocardiographic techniques have been used to assess LV dyssynchrony, including M-mode echocardiography or more sophisticated techniques such as tissue Doppler imaging (TDI) and 2D speckle tracking. Pitzalis et al. used M-mode echocardiography to show differences between the inward motion of the septum and the posterior wall, which correlated well with the reduction in LV end-systolic volume after CRT in 16 patients with dilated cardiomyopathy.[23] Likewise, TDI was used to demonstrate differences in timing of peak systolic velocity of the septum versus the lateral wall, which was associated with response to CRT in large populations of heart failure patients (with both ischemic and non-ischemic cardiomyopathy).[24] Patients with more than 60-65 ms difference between the peak velocities of the septum and lateral wall exhibited significant LV reverse remodeling after CRT.[25, 26] Despite significant evidence demonstrating the association between LV dyssynchrony and response to CRT, current guidelines do not include imaging techniques to improve patient selection for CRT.[19, 20] The results of the Predictors of Response to Cardiac Resynchronization Therapy (PROSPECT) trial showed limited reproducibility (high inter- and intra-observer variability) of the dyssynchrony parameters, and low predictive value (area under the curve ≤0.62 for all echocardiographic parameters) for clinical and echocardiographic improvement after CRT.[27] However, the PROSPECT study had various technical limitations, including the lack of standardized data acquisition and analysis, as well as the use of varying echocardiographic equipment (different vendors) which may have affected particularly the TDI results. In addition, novel techniques such as strain and 3D echocardiography may improve assessment of LV dyssynchrony. 2D speckle tracking has been used to compare regional differences in timing of peak strain (reflecting active deformation, whereas velocities reflect both active and passive motion). Lumens et al. evaluated 81 heart failure patients with this technique and demonstrated that the time difference between peak longitudinal strain of the septum and the lateral wall was significantly related with LV reverse remodeling at follow-up.[28] All these techniques rely on differences in timing of opposite walls rather than assessing the mechanical dispersion of the entire left ventricle. To overcome this limitation, 3-dimensional imaging (3D) has been used to derive a systolic dyssynchrony index, measured as the standard deviation of time to minimum regional volume of 16 segments (Figure 2); the larger the dyssynchrony index was, the more favorable the response to CRT.[29]

Other imaging techniques have also been proposed for assessment of LV dyssynchrony. Using MRI-myocardial tagging, Bilchick et al. proposed the circumferential uniformity ratio estimate (CURE) as a measure of LV dyssynchrony which is derived from the measurement of time to peak circumferential strain in 24 points of the LV myocardium in 3 evenly spaced myocardial slices.[30] A CURE value close to 1 indicates perfect synchronicity whereas a value close to 0 indicates complete dyssynchrony. In 20 patients

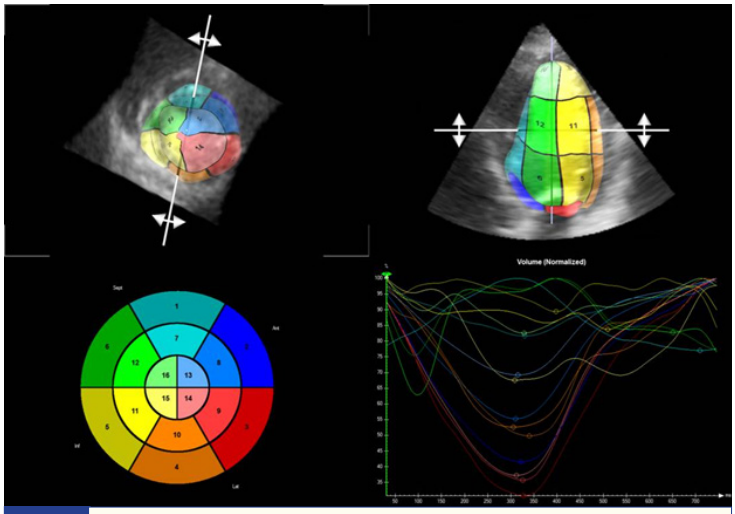

Figure 2: **Assessment of left ventricular dyssynchrony with 3-dimensional echocardiography. From the 3-dimensional full volume of the left ventricle, the time to minimum regional subvolume is calculated in 16 segments and the time-volume curves for each segment are plotted. The standard deviation of time to minimum regional subvolume of 16 segments is 13.8%**

undergoing CRT implantation (60% with dilated cardiomyopathy) a cut-off value of CURE <0.75 was associated with high probability of response to CRT.[30] Furthermore, LV dyssynchrony can be assessed with gated blood-pool ventriculography and single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) phase analysis.[31] A study of 64 patients (17 with non-ischemic cardiomyopathy) who met standard criteria for CRT and who underwent SPECT MPI demonstrated that the non-ischemic cardiomyopathy patients with QRS duration ≥150 ms had significantly more LV dyssynchronous activation than those with QRS duration between 120 and 150 ms.[32] A study of 32 patients with non-ischemic cardiomyopathy used equilibrium radionuclide angiography to quantify LV intraventricular dyssynchrony by measuring standard deviation of LV mean phase angle.[33] Receiver operating characteristics curve analysis demonstrated 95% sensitivity and 80% specificity at a cut-off value of 308 for standard deviation of LV mean phase angle in prediction of CRT response.[33] In addition, patients with dilated cardiomyopathy and left bundle branch block (LBBB) may show reduced work in the early activated septum which is associated with decreased glucose utilization as measured by septal F-18-fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET) relative to perfusion, a so-called reverse-mismatch.[34] This indirect marker of dyssynchrony was recently studied by Bernie et al. who showed that septal reverse mismatch <17.2% had good sensitivity (92%) and specificity (78%) to predict response to CRT (defined as reduction in LV end-systolic volume >10% or increase in absolute LVEF ≥5%) in patients with non-ischemic cardiomyopathy.[35]

Finally, pathophysiological characteristics may also have contributed to non-response of CRT. These factors include the extent and location of macroscopic fibrosis (scar); in patients with dilated cardiomyopathy, macroscopic focal fibrosis (scar) or diffuse microscopic fibrosis may limit CRT response, specifically if the LV pacing lead is positioned in an area of significant fibrosis. In addition, venous anatomy may also affect response to CRT: if the segment with the latest mechanically activation is not in the vicinity of cardiac veins, then this myocardium may not be reached for synchronization. Particularly, cardiac CT may non-invasively provide a roadmap for the location and extent of cardiac veins.

Location and Burden of Myocardial Fibrosis

The presence of replacement myocardial fibrosis has been associated with lower rates of response to CRT.[36, 37] Currently, late gadolinium contrast-enhanced MRI permits localization and quantification of myocardial replacement fibrosis with high spatial resolution. In contrast to patients with ischemic cardiomyopathy, where replacement fibrosis (scar) follows subendocardial or transmural distribution along coronary artery territories, in patients with non-ischemic cardiomyopathy the distribution of replacement fibrosis is variable, does not follow the coronary artery territory and depends on the underlying etiology. In idiopathic dilated cardiomyopathy, a characteristic midwall septal fibrosis can be observed in 30% of patients (Figure 3),[38] whereas patients with sarcoidosis commonly show patchy fibrosis located in the basal septum (involving the conduction system) and lateral wall, whereas in patients with cardiac amyloidosis, circumferential subendocardial fibrosis is characteristic. The association between myocardial replacement fibrosis and response to medical or device therapy has been investigated mainly in patients with idiopathic dilated cardiomyopathy.[39-42] In 97 patients with idiopathic dilated cardiomyopathy who received a CRT device, Leyva and coworkers reported a prevalence of midwall septal fibrosis on late gadolinium contrast enhanced (LGE) MRI of 21%.[41] Compared with patients without fibrosis, patients with midwall myocardial fibrosis showed significantly larger LV volumes and worse LVEF and functional status (with worse quality of life scores or 6-minute walk distance). In terms of clinical response (defined by freedom from heart failure hospitalization 1 year after implantation, improvement in ≥1 point NYHA functional class and ≥25% increase in 6-minute walk distance), the response rate was lower among patients with midwall septal fibrosis (65% vs. 80%) compared with their counterparts. In addition, patients with midwall septal fibrosis did not show significant reduction in LV volumes or improvement in LVEF at follow-up whereas patients without replacement fibrosis showed significant LV reverse remodeling with reductions in LV end-systolic volume of ≥15%. Interestingly, these differences were accompanied by significant differences in survival: after a median follow-up of 2.8 years, the all-cause mortality rate of patients with midwall septal fibrosis was 50% compared with 6.5% of patients without fibrosis. On multivariate analysis, the presence of midwall septal fibrosis was significantly associated with increased risk of all-cause mortality (hazard ratio 18.1, p<0.001).

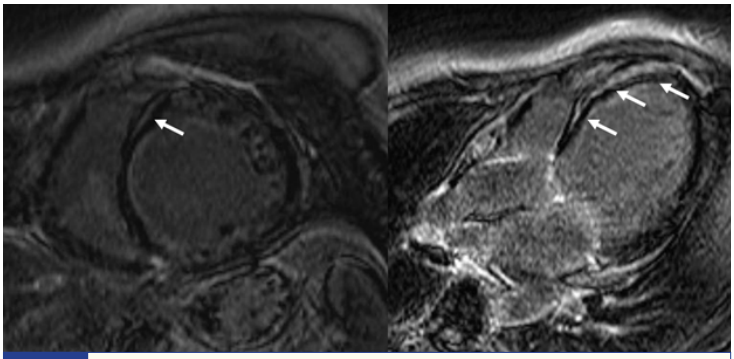

Figure 3: **Assessment of myocardial fibrosis with LGE-MRI in dilated ischemic cardiomyopathy. A 53 year-old male with dilated cardiomyopathy and midwall fibrosis extending along the septum (arrows)**

Nevertheless, in patients with dilated cardiomyopathy the amount of diffuse interstitial fibrosis may be larger than the presence of the focal fibrosis. Using T1 mapping MRI techniques, the extent of diffuse myocardial fibrosis can be quantified: in native data (pre-contrast), the T1 time values (relaxation of the myocardium) will increase along with the amount of diffuse fibrosis whereas in post-contrast data, the accumulation of gadolinium in the interstitial space will lead to a proportional decrease in T1 time values. Taking into consideration the hematocrit, the extracellular volume can be calculated from native and post-contrast T1 time values representing the amount of myocardial diffuse fibrosis. In 21 patients with dilated cardiomyopathy and 27 ischemic heart failure patients treated with CRT, Chen et al. showed that patients who showed LV reverse remodeling at follow-up tended to have lesser extent of diffuse fibrosis compared with patients who did not show LV reverse remodeling (0.30±0.06 vs. 0.34±0.06, p=0.043).[39] However, on multivariate analysis, the association between diffuse myocardial fibrosis and LV reverse remodeling was not significant, probably due to the stronger association between the presence of macroscopic focal replacement fibrosis and absence of LV reverse remodeling at follow-up. Additional studies including homogenous populations of patients with dilated cardiomyopathy treated with CRT and controlling for other confounding factors may help to better understand the correlation between diffuse myocardial fibrosis and response to CRT.

Cardiac Venous Anatomy

The conventional CRT practice places the LV lead in the (postero) lateral wall, which is presumably the site of latest mechanical activation due to LBBB and QRS prolongation. Lin et al. showed that such presumption may be more likely true in the non-ischemic cardiomyopathy patients.[32] Several studies demonstrated that a concordant LV lead position with the latest activated LV segments was associated with the greatest improvements in clinical status and LV performance in heart failure patients treated with CRT.[43-46] On the other hand, myocardial fibrosis (scar in ischemic heart failure patients) in the vicinity of the LV lead tip leads to a suboptimal response to CRT.[47-49] The myocardial fibrosis patterns observed in patients with dilated cardiomyopathy (more frequently midwall fibrosis of the interventricular septum) reduces the probability of placing the LV lead in an area of transmural fibrosis. Research has focused on the use of imaging techniques to guide lead placement to maximize the effects of CRT. Recently, two randomized trials (Targeted left ventricular lead placement to guide cardiac resynchronization therapy [TARGET] and Speckle tracking assisted resynchronization therapy for electrode region [STARTER]) showed that LV lead placement guided by the site of latest activation on speckle-tracking imaging resulted in a larger proportion of a favorable LV lead position, greater LV reverse remodeling and improved survival, compared to standard coronary venography guided placement of LV lead into the lateral, posterior, or posterolateral region.[44, 45] Long-term (39 months) follow-up in the TARGET trial demonstrated 70% survival rate in the patients with concordant/adjacent LV lead compared to 38% in the group with a remote LV lead position (p=0.003).[50] However, these studies included a majority of patients with ischemic heart disease. Experiences evaluating the role of non-invasive imaging to guide the positioning of the LV lead in non-ischemic cardiomyopathy patients are scarce.

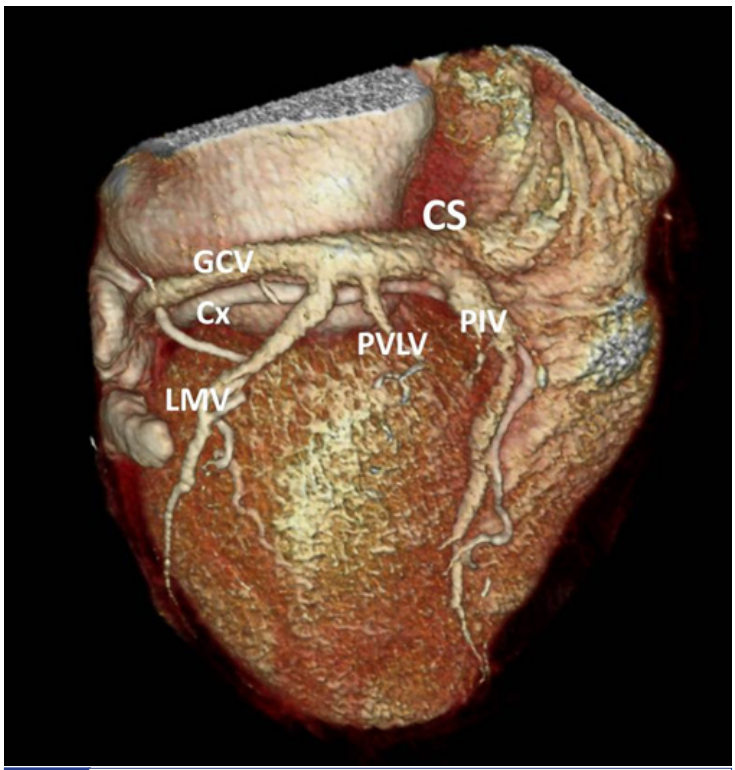

Figure 4: Assessment of cardiac venous anatomy with multi-detector row computed tomography. The 3-dimensional volume rendering shows the posterior aspect of the heart with the coronary sinus (CS) and its tributary branches: the posterior interventricular vein (PIV), the posterior vein of the left ventricle (PVLV) and the lateral marginal vein (LMV). Note the parallel course of the coronary sinus and the circumflex coronary artery (Cx)

The particular coronary vein used for the LV lead is dependent on individual cardiac venous anatomy. Retrograde venography via the coronary sinus is currently the standard technique for defining cardiac venous anatomy just prior to LV lead implantation. Cardiac computed tomography is increasingly utilized to visualize the coronary veins for pre-procedural planning of LV lead placement (Figure 4). Ricapito et al. demonstrated that cardiac CT was more sensitive for detecting posterior and left marginal veins compared to retrograde venography.[51] In addition, the left marginal vein was less likely observed in the patients with ischemic cardiomyopathy as compared with non-ischemic cardiomyopathy (42.9% vs. 66.7%).[51] In the study by van de Veire et al., the venous anatomy was strongly related to the presence of prior myocardial infarction, with left marginal vein present in only 22% of patients with anterior infarction and none of the patients with lateral infarction.[52] Coronary venous anatomy can also be reliably demonstrated using a comprehensive MRI protocol which includes myocardial perfusion, LV function and myocardial fibrosis.[53]

Even though the ability to secure LV leads in a major cardiac vein through coronary sinus cannulation is increasingly feasible, up to 10% of the patients undergoing CRT implantation have a failure of coronary sinus cannulation.[54] The possibility of direct surgical placement of the LV lead as rescue therapy for a failed transvenous approach has not only overcome the limitations imposed by coronary venous anatomy, but also potentially enabled easier targeting of the latest activated regions of LV.[55]

Conclusion

Current guidelines do not include imaging criteria to select heart failure patients for CRT.[19, 20] However, they underscore the evidence provided by several observational and prospective trials on the

relevance of LV dyssynchrony assessment, evaluation of myocardial scar and identification of the target region for LV lead placement. Design of new trials randomizing heart failure patients to CRT versus ICD alone or optimal medical therapy based on several imaging criteria (including assessment of LV dyssynchrony, myocardial scar, and the latest mechanically activated segment) would need a large number of patients, particularly if only non-ischemic cardiomyopathy patients are included, and may not be feasible in the near future. However, it remains important to accurately evaluate the patients who are candidates to CRT, and assess the different aspects that may influence the response to CRT. Availability of imaging techniques and local expertise will determine which imaging modalities can be used for the evaluation of CRT candidates.

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Atrial Fibrillation and Risk of Dementia/Cognitive Decline

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Abstract

Emerging evidence suggests a link between atrial fibrillation and subsequent development of dementia. While a majority of risk can be attributed to cardioembolic stroke secondary to atrial fibrillation, additional risk is apparent, and may be driven by vascular inflammation and changes in cerebral perfusion. Medical therapies including anticoagulation, statin therapy, and angiotensin-renin-aldosterone axis antagonists may reduce dementia risk. Procedural therapies such as atrial fibrillation catheter ablation and left atrial appendage closure may also prove to be important mediators of acute and long-term risk. In this paper, we review the data supporting a link between atrial fibrillation and dementia syndromes, pathophysiologic mechanisms and the potential roles of medical and procedural therapies at reducing such risk.

Introduction

Recent estimates indicate atrial fibrillation (AF) prevalence to be at epidemic levels, with further accelerated disease growth anticipated. Based upon a review from the Global Burden of Disease study,[1] it is estimated that the worldwide prevalence of AF is 596.2 and 373.1 per 100,000 men and women, respectively. In developed regions of the world, such as North America, the prevalence increases considerably: 925.7 and 520.8 per 100,000 men and women, respectively. The reasons for these high numbers are multifactorial and include an aging population and an increase in prevalence of AF risk factors such as obesity and hypertension. Incidence estimates from the Framingham study, 13.4/1000 for men and 8.6/1000 for women, suggest no coming relief from this growing tide.[2] Over the past 50 years, the incidence for men and women has increased by roughly 350 percent. Some effects of atrial fibrillation have been well described such as increased risk of stroke, heart failure and mortality. Dementia is an emerging novel morbidity.

Dementia represents an extreme on the cognitive decline spectra and is defined as a severe deficit of multiple domains of higher central nervous function (e.g. memory, cognition, apraxia, organization, speech, activities of daily living). In its most advanced stages, dementia is characterized by severe memory loss, difficulty with activities of daily living to include eating and speaking, loss of ambulation and bowel and bladder incontinence.[3] Hypertension, coronary artery disease, congestive heart failure, diabetes, and advanced age are each independently associated with AF and with dementia. The prevalence of dementia is estimated at 5 – 10 % in those aged 65 years or more, and doubles every five years after age of 65. The incidence increases with age as well, progressing from 0.1% at age 60-64 to >8% at age 95.[4] Alzheimer's disease (AD) and vascular dementia (VaD) comprise a large majority of dementia subtypes in adults over the age of 65. Considerable latency is present in AD, where brain imaging and CSF analysis may reveal elevated Amyloid β-protein (AβP) levels and plaques 20 years before clinically apparent dementia.[5] While specific etiologies are implicated in AD and VaD, anatomic pathology studies demonstrate that cerebrovascular insults and degenerative findings coexist in the majority cases.[6] The precise impact of cerebral infarction and secondary cognitive decline is difficult to predict, and is dependent on size, number and location of strokes.[7] Therapies aimed at disease regression have been disappointing,[8] resulting in increased interest in prevention by addressing modifiable risk factors: hypertension, diabetes, diet, hyperlipidemia, obesity and vascular insults, particularly earlier in life. Vascular insults include stroke, perhaps the most feared progeny of AF.

In 1997, Ott et al reported the association of atrial fibrillation with dementia in a population-based study comprised of 7983 residents of a suburb of Rotterdam, Netherlands.[9] Since that time, additional studies have indicated a similar risk, although causality remains a challenge to conclusively demonstrate. Several mechanisms have been proposed to explain the association between AF and dementia (see figure 1). The association of stroke and vascular disease with dementia has been recognized for more than 25 years. Here, the causation is simple to conceptualize: local neuron death leads to loss of function. Dementia results when brain centers responsible

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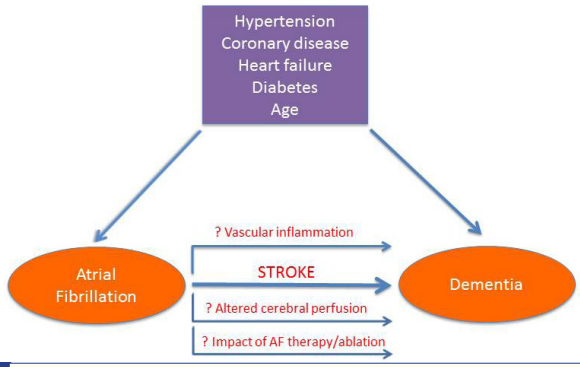

Figure 1: **AF and dementia share common risk factors. Additional mechanisms (horizontal arrows) might explain risk noted beyond that associated with coronary artery disease, heart failure, hypertension, diabetes and age**

for cognition, memory or processing lose function. Given the causal association between AF and cardioembolic stroke, a clear association of dementia and AF-associated silent and manifest stroke is not surprising. However, AF has also been associated with dementia in the absence of manifest or silent stroke.[10] In these instances, other mechanisms including altered cerebral perfusion and vascular inflammation have been proposed to explain the association between AF and dementia, particularly AD.[11] In this review, we will attempt to summarize the current evidence supporting an association between AF and dementia, both with and without stroke as a mediator, and the effect of medical and procedural AF therapies on reducing associated risks.

Are Atrial Fibrillation and Cognitive Decline /Dementia Associated?

Two recent meta-analyses have been published compiling the prospective and cross sectional studies examining atrial fibrillation and cognitive decline or dementia. Kalantarian et al. compiled 14 studies (85,414 patients), 9 of them prospective (74,358 patients) and demonstrated a weighted hazard ratio (HR) of 1.4 suggesting a modest association between AF and cognitive decline or dementia.[12] The HR was similar when looking at the 8 studies specifically assessing risk of dementia (HR 1.38) or cognitive decline (HR 1.5). The association was much stronger after a history of stroke, with a HR of 2.7 compared to a HR of 1.34 when comparing cognitive decline independent of stroke history. Santangeli et al. performed a similar meta-analysis limited only to prospective studies, which were identical to the 9 prospective studies examined by Kalantarian et al, with the inclusion of a 10th study which did not report an adjusted HR for baseline abnormalities between the comparator groups.[13] The HR of dementia/cognitive decline from these 10 prospective studies was 1.42 (see figure 2). Following the publication of these meta-analyses, Rusanen et al. have provided another important contribution in the work assessing possible associations. By assessing 1510 respondents among 2000 patients randomly invited to participate from four previous longitudinal population cohort studies, the authors were able to determine relative risk of dementia with AF diagnosed in mid-life compared to that diagnosed in late life.[14] The AF association with dementia was only present in the late life AF cohort. AF diagnosed in mid-life, quite surprisingly, did not predict later development of dementia. This finding is in contrast to subgroup analyses in the large prospective study by Bunch et al. where the highest association of AF with dementia was in the age group < 70yrs age, and the most commonly associated dementia type was Alzheimer's dementia.[15] A possible troubling explanation for the lack of association between AF diagnosed in mid-life with dementia reported by Rusanen et al. is the higher mortality rate noted in the Bunch cohort for younger patients developing AD or vascular dementia (HR 2.1 for both). Thus, attrition may reasonably be expected to diminish any possible association seen in the long-term follow up by Rusanen et al. Overall, the preponderance of the literature supports an increased risk of dementia or cognitive decline in patients with AF, with a HR of roughly 1.4, and which appears to be significantly higher in presence of stroke.

AF Associated Cognitive Decline/Dementia in The Presence of Stroke

The relationship of stroke and cognitive decline has been defined in much the same way as that of atrial fibrillation and dementia: case control series and longitudinal patient population studies. The population studies are most often derived from patients hospitalized with stroke, such as the ASPIRE-S cohort of 256 post-stroke patients. This study demonstrated a prevalence of mild to moderate cognitive decline of 41% at 6 months following stroke in a cohort that was considered functionally normal prior to stroke event.[16] When a longer view is taken, the cumulative incidence of dementia 25 years post-stroke was estimated at 48%.[17] A comprehensive meta-analysis of 30 studies of stroke related dementia revealed that post-stroke dementia prevalence is 20.3 % in hospital based studies and 7.4% in population based studies in the first year of follow up, excluding patients with pre-stroke dementia.[7] A nested case control study from the Framingham cohort revealed a HR of 2.4 for development of post-stroke dementia, even after adjustment for age, AF and DM. The HR was slightly higher with patients < 80 years old (HR 2.6).[18] A similar risk of 2.5 was noted in 10-year follow up from the Rochester Study.[17]

While a relationship between AF and stroke is clear, it is interesting that evidence indicates a link between AF and cognitive decline and dementia independent of stroke. In a pooled analysis of 7 studies, AF

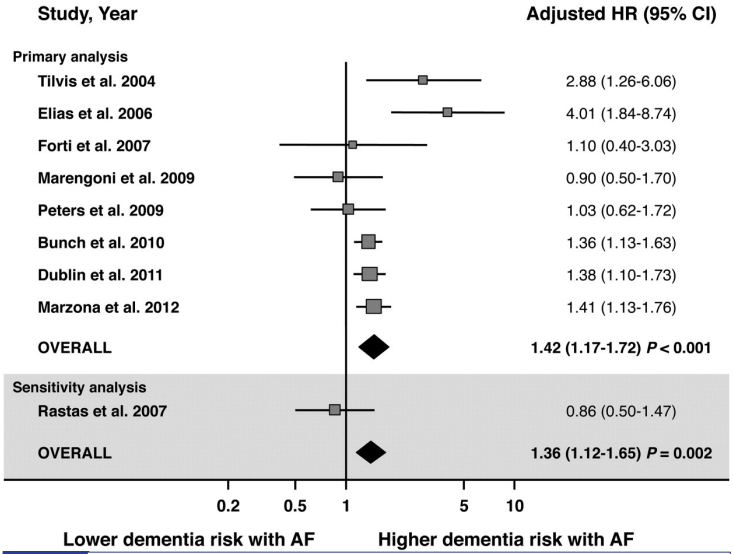

Figure 2: **Reproduced with permission from the publisher.[13] Forest plot showing the individual and pooled adjusted hazard ratios (HR) of dementia in patients with and without AF. Square boxes denote HR, dimension of each square box denotes weight of random effect analysis, and horizontal lines represent 95% confidence interval. Note, Rastas et al, did not report adjusted HR**

was associated with an OR of 1.64 for development of dementia in absence of stroke.[19] Similarly, patients with AF were noted to have a lower mini mental status exam score compared to a matched cohort without AF.[20] While AF was independently associated with pre and post stroke dementia, AF was also associated with more silent strokes seen on imaging, number and severity of stroke and recurrent stroke.[11, 21] In a review of brain magnetic resonance (MR) imaging, roughly 1/4th of patients with AF were noted to have silent cerebral infarction.[22] As a result, these features confound analysis. Chen et al described the importance of subclinical infarcts in predicting cognitive decline secondary to AF. In a study of 935 patients from the ARIC study without AF followed for 10.6 years, only patients with AF and subclinical infarcts on MRI imaging demonstrated higher rate of cognitive decline compared to the control cohort.[21] In conclusion, the association between stroke and subsequent dementia appears to be fairly robust and provides a strong causal link between AF and dementia.

Association between AF and Dementia in the Absence of Stroke

AF and Cerebral Perfusion

Because an increased risk of dementia/cognitive decline has been demonstrated in the absence of stroke, alterations in cardiac output have been theorized to provide an alternative mechanism by which AF might predispose to neurologic degeneration.[8, 23, 24] Analysis of roughly 1000 Framingham cohort patients undergoing cardiac MRIs and followed for a mean of 7.7 years demonstrated a HR of 1.7 for development of dementia in patients with a cardiac index (CI) of <2.5L/min/m2. CI remained significantly associated with dementia in patients without prevalent coronary artery disease or AF, suggesting an independent mechanism.[25] The underlying etiology behind this premise lies in the critical importance of unfettered cerebral perfusion to overall brain function. Local neural activation leads to increased local cerebral blood flow, in a manner akin to capillary recruitment dependent autoregulation seen in skeletal muscle.[26] It has been noted that white matter hyperintensities, lacunar infarcts and medial temporal lobe atrophy are found more frequently in patients with reduced CI.[8, 27] Medial temporal lobe atrophy and reduced metabolic activity is associated with mild cognitive decline, a precursor for AD.[28] From a cellular level, chronically reduced cerebral perfusion is associated with local acidosis and increase in oxidative balance. These features lead to dysregulation of tau protein, ultimately leading to hyperphosphorylation and development of tau oligomers and, later, neurofibrillary tangles.[29] Chronic hypoxia is also associated with alteration in blood brain barrier permeability. Reduced clearance of AβP[25] with secondary development of AβP plaques, secondary to a dysfunctional blood brain barrier is postulated as a primary etiologic mechanism for the development of AD.[30] Tau protein neurofibrillary tangles compromise the second major histopathologic finding of AD. Thus, it comes as little surprise that reduced cardiac index has been linked to dementia and AD in cross sectional study. Atrial fibrillation has been postulated to impose additional demands on the autoregulation process via direct loss of cardiac output from lack of atrial contribution to systole and from variability in RR intervals with resultant changes in ventricular loading and electromechanical coupling. As such, AF may act to independently worsen cerebral hypoperfusion injury, especially in the elderly, where cerebral autoregulation might already be impaired.

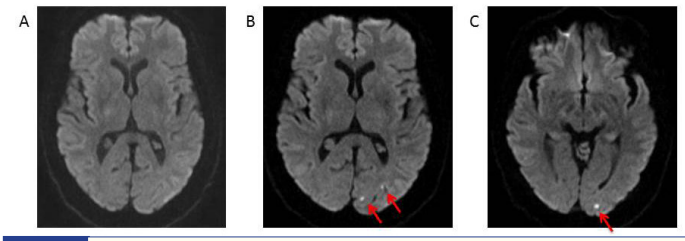

Figure 3: One day prior (panel A) and one day post -procedure (panels B and C) after atrial fibrillation ablation with a multi-electrode phased radiofrequency catheter. Panels B and C demonstrate three new punctate foci of diffusion restriction within the left occipital lobe without associated FLAIR hyperintensity. These foci are most in keeping with acute small vessel infarctions, likely associated with atrial fibrillation catheter ablation

There are a few studies available that have directly measured of cerebral perfusion in presence or absence of AF. Alosco et al performed thorough cognitive evaluation and middle cerebral artery Doppler evaluation on a cohort of 186 heart failure patients, of whom roughly 1/3rd had AF.[31] They found that the AF patients had lower cognitive testing scores in all domains assessed (global, executive function, memory, language) despite similar left ventricle ejection fraction (LVEF) (35-40%) and beta-blocker use. They noted that the cerebral blood flow velocity, as a surrogate for global cerebral perfusion, was significantly lower in the heart failure + AF cohort when compared to the heart failure without AF cohort. This relationship remained after adjustment for confounding variables and does provide support for abnormal cerebral perfusion in AF patients, although perhaps more readily identifiable in those with significant impairment to cerebral perfusion reserve i.e. systolic heart failure.

A second, cross sectional study of 952 healthy men from Sweden demonstrated that AF was associated with subcortical frontal lobe and executive functional decline, independent of stroke, hypertension or diabetes; however, treatment with digoxin in the AF cohort (n=44) mitigated the increased risk.[32] It is plausible that these findings might be reflective of reduced RR variability in AF following digoxin treatment, which would further support the role of cerebral perfusion derived insults in AF as a possible mechanism for secondary cognitive decline/dementia. Perhaps the most robust data comes from a 10 year prospective study originally designed to study the impact of ventricular rate on the progression of cognitive decline in patients with baseline mild cognitive impairment.[33] Among 358 patients (mean age 74), 44 developed AF. Ventricular rate was assessed as moderate (between 50 and 90) or low/high (lower than 50 or higher than 90). While AF was associated with progression of cognitive decline, it was more dramatically linked with low/high ventricular rate, with a HR of 7.7. This data would suggest that any significant deviation away from the normal heart rate where optimal diastolic and systolic loading would occur might be sufficient to perturb cardiac output and illicit chronic hypoxia and deterioration.

A sub-study from the AFFIRM trial,[34] however, demonstrated findings that contradict a perfusion model of atrial fibrillation induced cognitive decline.[35] In a study of 245 patients randomly selected to undergo MMSE periodically through the trial, no difference was found in the rhythm control arm vs. the rate control arm when analyzed by treatment intention or adjusted for actual rhythm. Although power may have been lacking to detect a difference in MMSE results associated with rhythm vs. rate control, the AFFIRM

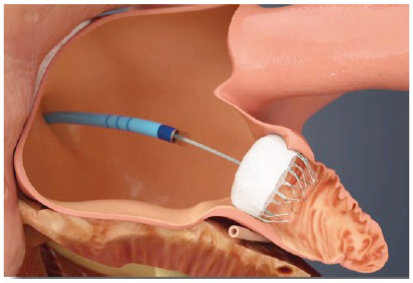

Figure 4: Watchman device is positioned via steerable sheath from femoral vein to the left atrial appendage, where it is released, sealing the LAA from the left atrium

sub-study results do not support a model of altered cerebral perfusion based on the presence of AF. Thus, while macroscopic changes in brain size and cognition have been correlated with low cardiac index,[27] and well-developed etiologic pathways are described to associate AF with cognitive decline via altered cerebral perfusion, there are mixed clinical data in support of the theory. Additional data are needed to clarify the role of atrial fibrillation in cerebral perfusion abnormalities and cognitive decline/dementia.

AF and Vascular Inflammation

Vascular dementia, as its name suggests, derives from the net result of multiple vascular insults. Recent evidence supports an early and crucial role for vascular factors in AD. Thus, for these two etiologies of dementia, compromising a majority of the cases occurring in the older adult population, a vascular model has developed. Specifically, vascular inflammation and endothelial dysfunction have been implicated as key events allowing for onset of clinical cognitive decline and dementia. AβP plaques are associated with up-regulation of IL-1, IL6, and TNF-α, and the levels increase with disease severity.[36] Clarifying cause vs. effect is observation of glial activation even prior to AβP plaque formation. Direct disruption of the blood brain barrier secondary to local extracellular deposition of AβP (amyloid angiopathy) further exposes the CNS to a wider host of pro-inflammatory mediators.[5] Atrial fibrillation is associated with, though not necessarily caused by, a pro-inflammatory systemic milieu, including postoperative AF and lone AF.[37-39] It has been postulated that increased permeability of the blood brain barrier along with increases in activated monocytes, prostaglandins and other pro-inflammatory mediators may act synergistically to hasten progression of dementia in the vascular model.[40] Thus, while it has not been determined definitively that the increased systemic vascular inflammatory cytokines noted in AF would hasten progression of cognitive decline, a common pathophysiologic pathway exists between the two allowing for a compelling clinical model. Similar changes are noted to result from local reactive oxygen species formation in response to hypo-perfusion. Sequestration of nitric oxide and up-regulation of endothelin lead to decreased vascular compliance and additional loss of auto-regulation reserve in areas of vascular inflammation and endothelial dysfunction, which are driven in part by hypoxia and hypo-perfusion. Thus, an etiologic and epidemiologic association for vascular inflammation and oxidative stress exists for atrial fibrillation and both VaD and AD.

Impact of AF Therapy on Dementia

Anticoagulation Therapy

Anticoagulation is recommended for all patients who are not determined to be "low risk" by risk prediction schemes. The current risk prediction algorithm recommended by US and European guidelines is the CHA2DS2-VASc tool, which assigns points for congestive heart failure, hypertension, age, diabetes, stroke or TIA, vascular disease, or female gender.[41] Generally, it is recommended to anticoagulate any patient who is not determined to be low risk for thromboembolism, as defined by a score of 2 or greater.[41]

Because the strongest association of dementia with AF is mediated by stroke, the benefit of anticoagulation therapy to prevent subsequent dementia has been explored. Jacobs, et. al., reviewed dementia risk based upon time in therapeutic range from a 2600 patient cohort derived from the large Intermountain Heart Cohort.[42] Roughly 70% of the cohort had a CHADS2 score of ≥ 2 and equal representation of genders was present. When divided into quartiles of time in therapeutic range (i.e. <25%, 26-50% and 51-75%) and compared to the cohort demonstrating >75% time in therapeutic range, a linear relationship of risk of dementia was demonstrated with HRs of 5.3, 4.1, and 2.6, respectively. The increased risk of dementia was 1.7-1.8% for every percentage point increase in time out of range, high or low. However, the risk associated with time out of therapeutic range was present only in those patients < 80 years of age. These findings complement the noted higher risk of AF related dementia in patients < 70yrs of age by Bunch et. al.[15]

Novel Oral Anticoagulant Therapies

Assessment of dementia incidence following wider adoption of novel oral anticoagulation (NOAC) agents should further clarify the role of anticoagulation in development of dementia. Compared with warfarin therapy, several agents are now available which demonstrate at least non inferiority for stroke prevention compared to warfarin with similar or improved safety profiles.[43] These drugs have not been studied specifically for impact on long term cognition. A prior study demonstrated an additive benefit of direct thrombin inhibition using nautrally occuring hirudin combined with donepezil in AD patients.[44] The benefits were noted to dissipate during washout of the hirudin. Thrombin upregulation has been demonstrated in patient's with AD, and thrombin inhibition has been shown to reduce CNS inflammation in animal models.[45] Such data has not been presented with Factor Xa, thus dabigatran may be an attractive agent for future study. Presently, however, insufficient data is available to comment definitively on the role of NOAC agents in reducing risk of dementia.

Statin Therapy

Statin therapy exerts pleiotropic effects predominantly modulating vascular inflammation and reduced oxidative stress.[46] The impact of statin therapy on dementia rate is informative in assessing the role of vascular inflammation on AF associated dementia.[47] In a large review of a national database of more than 50,000 Taiwanese patients, the use of a statin was associated with a small reduction in risk of non-vascular type dementia.[48] This study was limited secondary to increased rates of warfarin, aspirin and clopidogrel use in the statin treated arm. A small study assessing atorvastatin and ezetimibe therapy in patients with AF showed improvement in measures of cognition and better preservation of medial temporal lobe size.[49] Similar results were noted in a second, small study of 34 patients again treated with combination atorvastatin and ezetimibe. In this study (mean age of 73), markers of inflammation were reduced and measures of cognition were improved after 1 year of treatment with the combination therapy.[50] The seemingly positive effects of statin based therapy on brain function, volume and dementia progression,

including non-vascular dementia, would further support a role of pro-inflammation and oxidative stress. As it is also demonstrated that levels of inflammation rise during AF episodes, there is at least reasonable expectation that this pathway might be more than simply an epiphenomenon. While design and execution of clinical trials to further explore this are challenging, this remains an area of active research.

Renin-Angiotension-Aldosterone Axis Modulation

The ONTARGET and TRANSCEND trials studied the impact of angiotensin conversion enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) therapy on cardiovascular outcomes in at risk patients.[51] In total, over 31,000 patients were enrolled in these studies, and a subset underwent additional MMSE testing periodically through the median follow time of 56 months. In this study, lack of ACEI or ARB therapy was associated with an increased mean HR for development of a decrease in MMSE by ≥ 3 points, dementia, loss of independence or admission to long term care facility, though none of these HRs reached statistically significance.

Catheter Ablation of Atrial Fibrillation

Atrial fibrillation catheter ablation (AFCA) has emerged as an important treatment option for management of symptoms in patients with AF, particularly among those with symptoms refractory to pharmacologic therapy. Clinical data suggests that AFCA is superior to continued pharmacologic therapy;[52-54] however, AFCA is associated with important procedural complications, some of which may have an impact on cognitive outcomes. The introduction of catheters into the left atrium and the creation of pro-thrombotic ablation lesions may create a nidus for embolic peri-procedural transient ischemic attack and cerebrovascular accident (TIA/CVA). Large registry studies have demonstrated that the incidence of symptomatic peri-procedural TIA/CVA associated with AFCA is approximately 0.5-1%.[55-58] Fortunately, the long-term prognosis for cognitive and functional recovery among those who experience a symptomatic TIA/CVA associated with AFCA appears to be excellent, regardless of the severity of the peri-procedural event.[58] AFCA has also been associated with more subtle forms of post-procedural cognitive impairment, although the incidence of subtle impairments, detected only through formal testing, is less well described. In an important study of 60 patients undergoing AFCA, the incidence of sub-clinical post-procedure cognitive impairment identified by a battery of neuropsychological testing was significantly higher among those undergoing AFCA at both 48 hours and 90 days post procedure, compared to control patients undergoing ablation for supraventricular tachycardia (SVT) or AF patients awaiting AFCA.[59] On univariate analysis, the only predictor of cognitive impairment at both 48 hours and 90 days was duration of left atrial access, suggesting a potential role for strategies aimed at reducing the risk of thromboembolic events associated with left atrial access in minimizing adverse cognitive outcomes. Beyond 90 days, the long-term impact of such subtle cognitive decline associated with AFCA is not well defined. Lastly, in addition to clinically evident TIA/CVA and more subtle but still clinically detectable forms of cognitive impairment, AFCA has also been associated with completely asymptomatic embolic events which are only identified by brain magnetic resonance imaging (MRI) (see figure 3). The incidence of these asymptomatic cerebral emboli (ACE) associated with AFCA has been estimated at anywhere from 7-38%, depending in part on the specific MRI protocols used to identify acute embolic lesions and also whether imaging was performed both before and after or only after AFCA.[60] Much of the concern regarding ACE stems from data in non-AF patients demonstrating an increased long-term risk of dementia in those with silent cerebral infarcts (defined as T2 hyperintensity on brain MRI).[61] Whether a similar association exists between ACE associated with AFCA and long-term dementia risk is unclear. A small number of studies have performed follow-up MRIs on patients with ACE detected post-AF ablation and in the vast majority of these studies, the acute MRI lesions associated with ACE regress during long-term follow-up without leaving evidence of a chronic glial scar.[60] Therefore, the incidence of chronic cerebral infracts following AFCA is significantly lower than the incidence of ACE detected on MRI performed within 24-48 hours post-ablation.

Limited data exists on the long-term impact of AFCA on cognitive outcomes. One large prospective registry compared outcomes in 4212 patients undergoing AFCA to 16,848 age and gender matched patients with AF who did not undergo ablation. At three years, the incidence of CVA or dementia was significantly lower among those undergoing AFCA.[62] In a similar multicenter registry from the United Kingdom and Australia, the incidence of stroke during a mean follow-up of 3.1 years was significantly lower among those undergoing AFCA compared to medically treated AF patients.[63] Although these data suggest that the short-term risk of emboli associated with AFCA may be offset by a beneficial effect of AFCA on long-term neurologic outcomes, the lack of a randomized control group in these studies raises concern for residual confounders, which may differentiate between AF patients who are or are not referred for AFCA. On-going randomized trials of AFCA, which are powered to assess clinical outcomes such as stroke, will hopefully provide additional data.

Given the concern that AFCA may be associated with at least a short-term risk of symptomatic and asymptomatic cerebral events, a number of technical strategies have been proposed to mitigate the risk of thromboembolism associated with AF ablation including performing the procedure with uninterrupted oral anticoagulants, higher intra-procedural activated clotting time (ACT) targets, systemic anticoagulation with heparin prior to left atrial access and avoidance of intra-procedural cardioversion.[60] Specific ablation energy sources may also carry different levels of thromboembolic risk, although robust data are lacking in this regard. Pre-clinical studies suggest that cryo-energy lesions may be less thrombotic than radiofrequency (RF); however, clinical studies have not demonstrated any significant difference in the incidence of asymptomatic embolic events associated with cryo-ablation compared to irrigated RF.[60] In contrast, phased RF technology with multi-electrode catheters may pose an increased risk of thromboembolic events, although a number of changes to the phased RF platform have recently been introduced which may reduce that risk. The impact on cognitive outcomes of these technical approaches to mitigating thromboembolic risk has not been well validated.

Left Atrial Appendage Closure

Because the left atrial appendage (LAA) has been identified as the source of cardioembolism in approximately 90% of non-valvular atrial fibrillation,[64] LAA closure is an area of rapid development and research to reduce risk of stroke. Given that stroke is a strong effector of subsequent cognitive decline/dementia, it is certainly plausible that LAA closure might reduce subsequent cognitive impairment. The Watchman device (Boston Scientific, Natick MA) is a small

transfemoral device which is delivered into the LAA and is designed to seal the LAA from the remainder of the left atrium (figure 4). The 2.3 year follow up from the Protect AF study of the Watchman closure device showed significant reductions in composite endpoint of stroke, systemic embolization or cardiovascular death, driven by reductions in hemorrhagic stroke rates.[65] The 4 year follow up, however, showed only a trend toward reduced stroke, again driven by reduced hemorrhagic strokes. Large/debilitating strokes were, however, less common in the Watchman cohort.[66] Thus, it is not clear how LAA closure will impact subsequent development of dementia compared to warfarin therapy.

Conclusions

AF has been linked to cognitive decline through numerous cross sectional population studies. Definitive association through prospective study is challenging secondary to multiple common shared risk factors. Several pathways have been offered to explain the noted association including direct neuronal cell death via stroke, altered cerebral perfusion leading to white matter loss, medial temporal lobe atrophy, and increased oxidative stress states. There is clear benefit to oral anticoagulation therapy in reducing risk of stroke and reducing risk of attendant dementia. This benefit is further correlated with time in therapeutic range in patients treated with warfarin. AFCA is noted to perhaps increase risk of mild cognitive dysfunction acutely, mainly through cerebral embolism, but the middle and long-term outcomes appear more favorable. Truly randomized data is limited in this regard; however, registry data suggests that durable establishment of sinus rhythm following ablation may improve cognitive function. Statin therapy appears to yield some benefit in improving cognitive outcomes, while outcomes of other forms of AF therapy remain unclear. Cognitive decline/dementia is an important outcome in patients with AF, with striking impact on quality of life and overall health care costs associated with management. It is important for clinicians treating AF to be aware of the association with cognitive decline for counseling and monitoring purposes and to be aware of possible means of reducing risk.

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Ablation of Atrial Fibrillation in Combination with Left Atrial Appendage Occlusion in A Single Procedure. Rationale and Technique

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Abstract

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and is associated with a fivefold increase in the risk of ischemic stroke and systemic embolism.

Left atrial appendage (LAA) is the source of thrombi in up to 90% of patients with nonvalvular atrial fibrillation (AF). Although thromboembolic prophylaxis by means of oral anticoagulants (OAC) has been shown to be very effective (OAC), they also confer an inevitably risk of serious bleeding.

Catheter ablation (CA) is an effective treatment for symptomatic AF but its role in stroke prevention remains unproved. Recently, LAA percutaneous occlusion has been demonstrated to be equivalent to OACs in reducing thromboembolic events.

The aim of this review is to describe the rationale, feasibility, outcomes and technique of a combined procedure of AFCA and percutaneous LAAO, two percutaneous interventions that share some procedural issues and technical requirements, in patients with symptomatic drug-refractory AF, high risk of stroke, and contraindications to OACs.

Introduction

Non-valvular atrial fibrillation (AF) is associated with a fivefold increase in the risk of ischemic stroke and systemic embolism that causes increased mortality and morbidity and higher medical expenses.[1] Hence, assessment of thromboembolic risk and the use of adequate prophylactic anticoagulation is mandatory in the proper clinical management of AF.

Although anti-vitamin K drugs or the more recently introduced factor II/Xa inhibitors can significantly reduce the risk of stroke in at-risk patients with AF, these oral anticoagulants (OAC) medications are associated with severe hemorrhagic adverse effects[2] On the other hand, atrial fibrillation catheter ablation (AFCA) is an effective rhythm control strategy for patients with symptomatic, drug-refractory AF but its role in stroke prevention remains unproved.[3]

Key Words:
Atrial Fibrillation Ablation,Left Atrial Appendage Closure, Thromboembolism.

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These challenges have led to interest in mechanical exclusion of the left atrial appendage (LAA), that has been shown to be the source of thrombi in up to 90% of the patients with non-valvular AF, as an interventional, ¨local¨, method to prevent thromboembolism in AF. Devices for percutaneous occlusion have shown efficacy and safety in achieving this goal when OAC is contraindicated or declined by the patient.[4]

Combining AFCA and LAAO, two percutaneous interventions that share some procedural issues and technical requirements, could reduce the incidence of stroke in selected high-risk patients while simultaneously relieving AF symptoms in a single session. The aim of this review is to describe the rationale, feasibility, outcomes and technique of a combined procedure of AFCA and percutaneous LAAO.

Limitations of Anticoagulation and Rhythm Control Strategies to Prevent Thromboembolism

Although thromboembolic prophylaxis by means of OAC was shown to be very effective, leading to a 60% relative risk reduction of stroke compared to placebo,[2] vitamin K antagonists, principally warfarin, have some significant deficiencies such as slow onset of action, narrow therapeutic windows, need for regular blood sampling to monitor the international normalized ratio, marked inter-individual variations in drug metabolism, overlap with parenteral

Table 1: Suggested indications for left atrial appendage occlusion[22]

1.	**As alternative to oral anticoagulation when oral anticoagulation is possible**
•	Patient refusal of (N)OAC despite adequate information and physician advice
2.	**As replacement for anticoagulation when anticoagulation is not possible**
2a	**Patients with a contraindication to anticoagulation**
•	Patients with a high thromboembolic risk (CHA2DS2-VASc score of ≥ 2) but contraindication to (N)OAC
2b	**Patients with an increased bleeding risk under systemic anticoagulation**
•	HAS-BLED score ≥ 3
•	Need for a prolonged triple anticoagulation therapy (e.g. recent coronary stents)
•	Increased bleeding risk not reflected by the HAS-BLED score (e.g. thrombopenia, cancer, or risk of tumour-associated bleeding in case of systemic OAC)
•	Severe renal failure as contraindication to NOAC
3.	**As a complement to anticoagulation**
•	Patients with embolic events despite adequate OAC provided no other plausible cause
4.	**As adjunct to ablation of atrial fibrillation**
•	Patients with a significant risk of thromboembolic events (CHA2DS2-VASc score of ≥ 2) undergoing an ablation procedure to treat symptomatic atrial fibrillation, who, in addition, have a strict or relative contraindication to (N)OACs

(N)OAC: (Novel) oral anticoagulant

anticoagulants and multiple drug and food interactions, all of which lead to an incomplete protection or an increased risk of bleeding.[5] For these reasons, as many as 65% of patients with indications for such treatment do not receive it, while the international normalized ratio (INR) is estimated to be out of range in a further 19% of patients.[6]

Recent clinical trials have found that newer, target-specific oral anticoagulants (NOACs) such as direct thrombin inhibitors (dabigatran) and Xa inhibitors (rivaroxaban, apixaban and edoxaban) which do not require monitoring and have fewer drug interactions, offer efficacy and safety equivalent to, or better than, those of warfarin for reducing the risk of stroke in patients with non-valvular AF.[7-10] But like warfarin, and due to the inherent nature of anticoagulation, they also confer an inevitably risk of serious bleeding. Moreover, although the inclusion of NOACs in the secondary prevention of systemic embolism has increased the safety of chronic anticoagulant therapy in patients with NVAF, roughly 20% of patients resign from these new agents within 2 years of therapy due to complications or poor tolerance.[11] For example, in the RELY trial,[7] 10% of patients receiving dabigatran and 17% of those receiving warfarin stopped the treatment within 1 to 2 years. In the ROCKET-AF study,[8] 24% of those treated with rivaroxaban and 22% of those treated with warfarin stopped treatment during the study, in the ARISTOTLE trial,[9] 25% of patients discontinued apixaban and 28% discontinued warfarin and during the ENGAGE study,[10] 34% of patients stopped warfarin and 19% interrupted edoxaban.

Apart from OAC, different strategies of maintenance of sinus rhythm with antiarrhythmic drugs or catheter ablation have been studied as another means to reduce the incidence of stroke in atrial fibrillation patients. Although it seems logical that the risk of systemic embolism may be lessened if the atrial fibrillation burden can be reduced or eliminated by rhythm control (antiarrhythmic drugs or AFCA), many clinical trials have failed to demonstrate a difference between rhythm control with antiarrhythmic drugs in reducing rates of stroke or systemic embolism[12] probably due to the low effectiveness for maintaining sinus rhythm or the high rate of discontinuation of antiarrhythmic drugs. Regarding AFCA, and although low stroke risks were reported by observational studies in patients who maintained sinus rhythm after ablation despite OAC cessation, most current guidelines.[3,13] recommend that systemic anticoagulation should be continued indefinitely in patients with a high risk for stroke, due to several facts. First of all, recurrences (not only symptomatic but also silent) of AF are common both early and late following AF ablation. Secondly the ablation procedure itself destroys a portion of the atria and, finally, the impact of this on stroke risk is uncertain and it has not been addressed by large randomized prospective trials designed to assess the safety of stopping anticoagulation after AF catheter ablation. For all these reasons, nowadays, AFCA is considered a symptomatic treatment and the consensus is that it should not be indicated with the sole purpose of stopping anticoagulation.[3,13,14]

Left Atrial Appendage Closure for Stroke Prevention

The LAA has long been recognized as the site of clot formation in most patients with nonvalvular AF and in fact, it has been shown that 90% of thrombus in patients with AF form in this cul-de-sac structure.[15] Thus, LAAO to preventing thromboembolism has important theoretical basis in patients with AF.

Due to the aforementioned concerns with anticoagulation, interventional alternatives for the prevention of thromboembolism in patients with NVAF, such as the exclusion of the left atrial appendage (surgically or percutaneously using different dedicated devices) have been explored (Figure1). The main body of scientific evidence comes from the PROTECT-AF cohort, the most relevant randomized clinical trial that has compared both strategies. In the PROTECT-AF trial, 707 patients from fifty-nine centers in the USA and Europe were prospectively randomized in a 2:1 ratio in an unblinded fashion to LAAO with the Watchman device versus standard warfarin therapy.[16] The trial was designed to examine the efficacy and safety of percutaneous closure of the LAA in patients with nonvalvular AF (not contraindicated for warfarin) and to assess noninferiority of the WATCHMAN LAA occluder device to standard warfarin therapy, which was the control arm. The first publication,[16] showed that the efficacy of percutaneous closure of the LAA with WATCHMAN device was non-inferior to that of warfarin therapy. Importantly, when follow-up was extended from 600 to 2621 patient-years (3.8 years),[4] LAAO reduced the relative risk of the primary end point (the composite of stroke, systemic embolism, and cardiovascular death) by 40% (1.5% absolute reduction) compared with the warfarin control arm. Furthermore, the device-based strategy was associated with a 60% relative risk (1.4% absolute reduction) of cardiovascular death and 34% relative reduction (5.7% absolute reduction) in all-cause death, strongly suggesting for the first time a survival benefit for the Watchman group when compared with the control warfarin. Longer follow-up results, up to 5 years, were recently communicated (Reddy et al, data not published) showing similar results. It should be noted that the mean follow-up in this trial exceeded by far that of most contemporary stroke prophylaxis trials,[7-10] such as RELY (2.0 years), ROCKET-AF (1.9 years), ARISTOTLE (1.8 years) and ENGAGE (2.8 years)

Although in the PROTECT-AF there was an initial higher rate of adverse safety events in the intervention group than in the control group,[17] the positive effect of increased operator experience and overcome of the learning curve was clearly demonstrated in the CAP registry with shorter implant time, higher implant success and warfarin discontinuation rate, and lower complication rates.[15] The PROTECT-AF trial also found that, regardless of whether

Table 2: Results of combining LAAO and AF ablation in a single session

	Type	n	AF type	CHADS2-VASC	HASBLED	Technique	Procedure time (min)	LAAO success 3-m (%)	1-yr OAC freedom(%)	1-yr AT freedom (%)	Complications
Swaans et al[23]	Observational	30	Px/Ps	3 (1-5)	2 (1-3)	PVAC ± MASC Watchman	97 (75-115)	97	77	70	1 late dislodgement 1 tongue hematoma 2 groin hematoma
Calvo et al[24]	Observational	35	Px/Ps/LSPs	3.1±1.1	3.1±1	RF PVI ± roof line Watchman/ACP	160±33	100	97	78	3 pericardial effusions
Romanov et al[25]	Randomized	89	Px/Ps	2.2±0.6	3.5±0.8	RF PVI Watchman	189 ± 29	87	79	59	2 groin hematoma

AF: atrial fibrillation, AT: atrial tachycardia, LAOO: left atrial appendage occlusion, LSPs: long-standing persistent, OAC: oral anticoagulation, Px: paroxysmal, Ps: persistent, PVI: pulmonary vein isolation, RF: radiofrequency

the enrolled patients had received prior warfarin therapy, the LAA closure significantly improved the quality of life of patients.[18]

The ASAP registry focused on the effects of LAAO in those patients who cannot tolerate warfarin even in the short term. In 150 patients followed for a mean of 14.4 (± 8.6), the authors found a a 77% reduction from the expected stroke rate of 7.3% based on the CHADS2 scores of the patient cohort.[19]

The Watchman device received the FDA approval in 2015,[20] "to reduce the risk of thromboembolism from the left atrial appendage (LAA) in patients with non-valvular atrial fibrillation who:

• Are at increased risk for stroke and systemic embolism based on CHADS2 or CHA2DS2- VASc scores and are recommended for anticoagulation therapy;

• Are deemed by their physicians to be suitable for warfarin; and

• Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin".

There are no available data coming from randomized trials related to other occlusion devices or LAA ligation techniques. Initial results with the ACP/Amulet occluder, described from some observational studies and multicentric registries are promising, indirectly comparable to some extent to the Watchman device, but to date there is no available head-to-head comparison of the Amplatzer devices with oral anticoagulation.[21]

Typical indications for percutaneous LAAO include patients with a high thromboembolic risk (CHA2DS2-VASc score of .2) but with a contraindication to systemic anticoagulation. This subset of patients represent the most accepted clinical indication for LAA occlusion, albeit by having to extrapolate the results of the PROTECT AF study to that specific cohort, that was specifically excluded from this trial. In addition, the results of the ASAP registry would support this indication.[19] According to the 2012 ESC Guidelines for the management of atrial fibrillation this indication has a class IIb recommendation.[3]

Other recommended indications for the use of LAA occluders, based in an expert consensus statement published recently[22] are summarized in table I.

Rationale and Possible Indications for the Combination of Laao and AF Ablation

In view of the above, the combination of LAA occlusion with catheter ablation might be a comprehensive way to improve the symptoms of AF while at the same time reducing the incidence of stroke in selected high-risk patients in a single session. Theoretically speaking, and assuming that the abscence of randomized data and/or cost-effectiveness studies supporting this strategy do not allow a broad recommendation, this hybrid procedure would cover the full clinical spectrum of AF in terms of antiarrhythmic and symptomatic effects (CA) as well as an anti-embolic intervention (LAAO) for selected patients.

Provided that the patient has a formal indication for both procedures, and specially if they have high stroke or bleeding risk and an anticipated reduced efficacy of CA alone, the combination of PV isolation with LAA closure in a single session could reduce the need and risks of a repeated left atrial intervention, a new transseptal puncture, perhaps general anaesthesia, and probably a new anticoagulation perioperative period should LAAO become desirable during follow-up.

Based on the expert consensus, in single-center observational series and in personal communications, the EHRA/EAPCI document on catheter-based LAA occlusion[22] suggests that patients with a significant risk of thromboembolic events (CHA2DS2-VASc score ≥2) undergoing an AFCA procedure, who also have a strict or relative contraindication to OACs, might be acceptable candidates for the combination of LAA occlusion and AF ablation in a single procedure.

Results of Combining Laao and AF Ablation in a Single Session

So far, few data on the combination of LAA occlusion and AF ablation in a single session have been published (Table II).

The first report of this strategy comes from a series of 30 consecutive patients with documented paroxysmal, or (longstanding) persistent, non-valvular AF with a CHADS2 score ≥1 or (relative) contraindication for OAC.[23] The authors performed pulmonary vein isolation (PVI) with the phased multipolar ablation system (PVAC)® in all the patients and additional complex-fractionated atrial electrograms ablation with the MASC and MAAC in 8 cases immediately followed by LAAO with the Watchman device. The median CHADS2 and HAS-BLED scores were 2.5 and 2, respectively. Twenty-three patients (77%) had a history of stroke, of whom 9 (30%) had a stroke under oral anticoagulation. Eight patients (27%) had a relative contraindication for VKA that was due to bleeding or failure to achieve an adequate international normalized ratio, and 2 patients had both. The median total procedure time was 97.3 minutes (38 minutes for LAAO). A median of 1.5 devices per patient were required to reach an optimal LAAO and at the end of the procedure, 3 patients had minimal residual flow (flow ≤5 mm). There were only 3 minor perioperative complications. At the 12-month follow up, 70% of the patients were free from atrial arrhythmias, 13% of the patients underwent a redo procedure, 23% of the patients did not discontinued Warfarin (1 due to late device embolization, 1 for dense spontaneous contrast in the left atrium, 1 due to pulmonary embolism, and in 4 patients, due to their treating cardiologist's preference on the basis of recurrent or persistent AF). During follow-up none of the patients had thrombus formation on the surface of the device and no thromboembolic events had occurred.

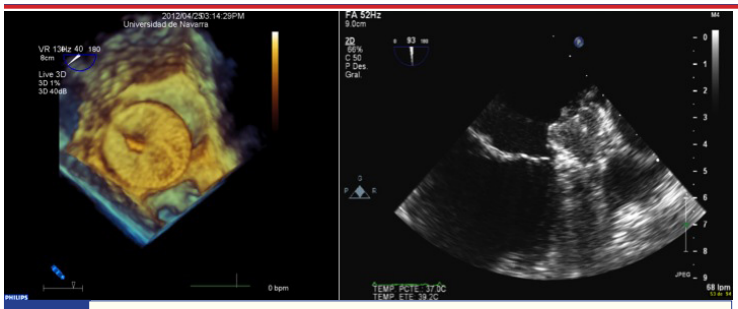

Figure 1: **Transoesophageal echocardiography images during the combined ablation procedure and LAAO**
Left panel: three-dimensional TEE views after an ACP device were released Right panel: two-dimensional TEE images during the deployment of a Watchman device. Optimal position and compression was confirmed with no residual leaks and a tug test was performed demonstrating simultaneous movement of the device and LAA before releasing the device

Three patients had a severe non-procedural bleeding event.

We reported our experience on 35 consecutive patients with symptomatic drug-refractory AF, a CHADS2 score of ≥1, a CHA2DS2-VASc score ≥2 and relative or absolute contraindications for OACs, or who refused OAC therapy despite adequate information.[24] Patients underwent a combined procedure of PVI ± roof line and LAAO with the Watchman or the ACP device, depending on the LAA anatomy. Median score was 3 on both CHA2DS2-VASc and HAS-BLED. Persistent or long-standing persistent AF was present in 71% of the patients. Nine percent of the patients had a prior stroke under OAC, and 48% had bleeding complications. The mean total combined procedure time was 160.5 ± 33.75 min, while the mean subsequent LAAO procedure time was 42.05 ± 11 min. A Watchman device was implanted in 29 (82%) patients and an ACP in 6 (18%) patients. A median of 1.3 devices per patient was used in this series. The periprocedural complications included three cases of severe pericardial effusion successfully treated by percutaneous pericardiocentesis (1 presumably due to the PVI procedure and 2 to the LAAO procedure). There were no device embolization events during follow-up. One patient died 17 days after the procedure, while on OAC and aspirin, due to an intracerebral hematoma associated to extremely high INR. At 3-month follow-up, all 35 patients (100%) met the criteria for successful sealing of the LAA. At a mean follow-up of 13 months (3–75), 78% of patients were free of arrhythmia recurrences and 97% discontinued OAC. There was one case of transient ischemic attack at 2 years post-procedure. The transesophageal echocardiograpy (TEE) did not reveal LA thrombus and there was complete closure of the LAA. This patient was placed on clopidogrel for secondary prevention. In our series, the observed ischaemic stroke rate was 2.6% per year representing 42.3% fewer events than expected according to the predicted ischemic stroke rate of this cohort taking from historical series.[24]

Finally, Romanov et al[25] recently published a trial on 89 patients with paroxysmal or persistent AF and high thromboembolic and bleeding risk, that were randomized to either PVI or PVI + LAAO with the Watchman occluder. The aim of the study was to assess the impact of LAAO added to PVI in terms of the antiarrhythmic response of PVI. Ninety-eight percent of the patients received and implantable loop recorder. Briefly, The closure device was successfully implanted after PVI in 39 (87 %) of the 45 patients assigned to the intervention group, there were no statistical differences between both groups in terms of procedure-related complications, and LAAO was not observed to influence the success of PVI (evaluated by time to the first recurrence of any atrial tachyarrhythmia and the AF burden) after the blanking period.

Taken together, this results suggest that the combination of LAAO with different PVI techniques in a single session can be performed successfully and safely, do not interfere with repeat PV isolation, and do not seem to influence the long-term success of PVI in patients with symptomatic refractory AF.

Technical Challenges of The Combined Procedure

The completion of combined CA and LAAO in a single session involves some technical modifications compared to the standalone procedures that have to be taken into account. Regarding the pre-procedural assessment, and although it is not mandatory, we perform routinely a multi-slice cardiac CT scan in all the patients. A 3D reconstruction of the left atrium is useful to assess the morphologic features of the LAA (type, measurements, presence of challenging anatomies, etc). Although the final decision on device size is based on information collected with both intraoperative TEE and/or fluoroscopy, CT scan allows to choose in advance the type of the occluder, hints to the device size and is helpful to rule out the presence of thrombi, therefore avoiding the need of the preoperative TEE. Another additional advantage of the CT scan for the combined procedure is its subsequent use for image integration with the non-fluoroscopy navigation system during the AFCA procedure.

Regarding the type of the device, in our institution the ACP/Amulet devices are usually indicated for appendages shorter than wide or with very complex anatomies, while the Watchman device is implanted in the rest of the patients. Although there is no definitive evidence, the physical structure of the Watchman occluder, without a disk covering the pulmonary ridge, and the lower incidence of late embolization whith this device, could facilitate a hypothetical redo procedure.

The LAAO procedure tipically requires continuous intraoperative TEE guidance and therefore, general anesthesia. Although we perform our standard AFCA under simple conscious sedoanalgesia, and we do not use TEE guidance for the transseptal punctures, during the combined procedures we prefer to perform both interventions under general anesthesia from the beginning. First of all, TEE is extremely useful to titrate the location of the transeptal puncture, since an inferoposterior access and the avoidance of a PFO entrance is essential. Secondly, from the logistic point of view and due to the need TEE guidance during transseptal puncture and LAAO we feel more comfortable with the patient under general anesthesia throughout the entire procedure.

Post-procedural anticoagulation with warfarin is recommended for the Watchman device to avoid thrombus formation on the device until completion of endothelization, provided there are no contraindications to anticoagulation. However, in the ASAP registry, patients received clopidogrel for 6 months and ASA indefinitely without OAC, and the ischaemic stroke rate was only 1.7% compared with 2.2% in the PROTECT AF device group. The postprocedural anticoagulation strategy for the ACP device banks on the good record regarding low thrombogenicity of the Amplatzer device family, and indicates in its instructions for use DAT only without an oral anticoagulant. Therefore, a standalone LAAO can be managed without postoperative anticoagulation. However, after a combined procedure, patients should receive systemic anticoagulation for two

months, according to the 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation.[26] For these reason, whenever possible, we use warfarin or a dose-adjusted regimen of low-molecular weight heparin during this period and we perform the follow-up TEE after two months, shifting to (dual) antiplatelet therapy upon its result. Note that due to the need of a short period (1-3 months) of anticoagulation after a left linear atrial ablation, caution should be taken before indicating a combined procedure in patients with an absolutely strict contraindication for short-term oral anticoagulation.

Finally, and needless to mention, the multidisciplinary nature of this combined intervention requires the availability of an appropriate team with specific training and experience in both AFCA and LAAO procedures, including an anesthesiologist, an experienced echocardiographer, and nursing and technical staff who are familiar with every procedural step.[22]

Conclusions

The combination of AFCA and percutaneous LAAO in a single procedure is a feasible strategy in patients with symptomatic drug-refractory AF, high risk of stroke, and strict or relative contraindication to OACs. This strategy will undoubtedly undergo further scrutiny in future randomized trials and cost-effectiveness studies but is highly attractive for its potential as a combined antiarrhythmic and antithrombotic intervention in high-risk patients.

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A Patient With Asymptomatic Cerebral Lesions During AF Ablation: How Much Should We Worry?

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Abstract

Silent brain lesions due to thrombogenicity of the procedure represent recognized side effects of atrial fibrillation (AF) catheter ablation. Embolic risk is higher if anticoagulation is inadequate and recent studies suggest that uninterrupted anticoagulation, ACT levels above 300 seconds and administration of a pre-transeptal bolus of heparin might significantly reduce the incidence of silent cerebral ischemia (SCI) to 2%.

Asymptomatic new lesions during AF ablation should suggest worse neuropsychological outcome as a result of the association between silent cerebral infarcts and increased long-term risk of dementia in non-ablated AF patients. However, the available data are discordant. To date, no study has definitely linked post-operative asymptomatic cerebral events to a decline in neuropsychological performance. Larger volumes of cerebral lesions have been associated with cognitive decline but are uncommon findings acutely in post-ablation AF patients. Of note, the majority of acute lesions have a small or medium size and often regress at a medium-term follow-up.

Successful AF ablation has the potential to reduce the risk of larger SCI that may be considered as part of the natural course of AF. Although the long-term implications of SCI remain unclear, it is conceivable that strategies to reduce the risk of SCI may be beneficial.

Introduction

Catheter ablation (CA) is a recognized treatment for patients with symptomatic atrial fibrillation (AF) refractory to drug therapy.[1-6] However, the complexity of the procedure may expose patients to a considerable number of complications.[7-10] Stroke and thromboembolisms are among the most worrisome periprocedural complications following left atrial (LA) catheter ablation. Recent evidence suggests that clinically apparent cerebral ischemia is only the "tip of the iceberg" because an higher than expected rate of subclinical cerebral emboli can be detected by imaging after LA ablation, opening up a discussion about their clinical relevance and how to reduce them.[11]

Key Words:
Asymptomatic Cerebral Embolism, Silent Cerebral Ischemia, Atrial Fibrillation Ablation, Magnetic Resonance Imaging, Stroke.

Disclosures:
None.

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Clinical thromboembolic events after AF ablation typically occur within the first 24h of the procedure with a high-risk period extending for the first 2 weeks.[12] Periprocedural stroke incidence rate has been estimated to be between 0.1 and 0.8% in AFCA patients, and a similar incidence rate has been observed for periprocedural transient ischemic attacks (TIA).[11-13] Surprisingly, it is becoming increasingly evident that AF ablation may cause silent ischemic lesions (Figure) in up to 40% of the cases.[11,14] The incidence of periprocedural silent ischemic lesions varies considerably, depending upon several factors among which the ablation procedure and periprocedural anticoagulation strategy play a pivotal role.

Mechanisms and Procedure Related Risk Factors of Periprocedural Brain Lesions

Thrombus formation during and after LA ablation might result from platelet and coagulation system activation either directly at the catheter surface or at the site of endothelial application. Additional potential mechanisms may account for the risk of silent cerebral ischemia (SCI) associated with AFCA. Air microemboli may be introduced into the blood stream through sheaths and catheters

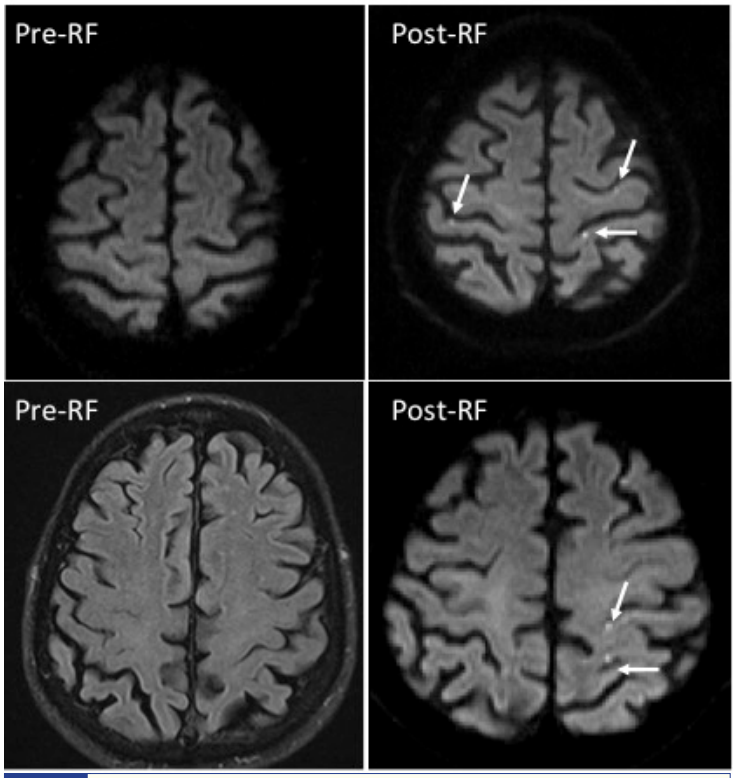

Figure:1 **Selected MR-images from a patient, displaying small and clinically silent ischemic lesions (indicated by arrows) detected 2 days after the ablation procedure.**

or developed during ablation as a result of blood boiling during radiofrequency catheter ablation.[15] Furthermore, a residual iatrogenic atrial septal defect after trans-septal puncture might increase the risk of paradoxical embolism. However, recent evidence suggests a high sealing rate of the defect (66%) immediately after the procedure and a very low incidence of persisting inter-atrial shunt (4-7%), predominantly left-to-right, at 12 months of follow-up[16-17] which is not associated with an increased risk of symptomatic cerebral/systemic embolism.

The source of ablation energy may play an important role in the genesis of periprocedural brain lesions. Most ablation procedures are being performed with closed- or open-irrigation radiofrequency energy (RF) catheters, which are capable of focal ablations. Balloon and coil platforms, using different energy sources, are being tested as potential alternatives for focal RF catheters, with the hope to optimize efficacy and minimize complications.[18-22] Cryo-balloon PV isolation is promising because of the low thrombogenicity and the lower risk of PV stenosis. Results from clinical studies showed that the use of cryoablation for pulmonary vein isolation (PVI) is associated with a low risk of endothelial disruption, thrombogenicity, and pulmonary vein stenosis compared to RF ablation.[23,24] Sauren et al. have analyzed the incidence of cerebral microembolic signals via transcranial Doppler monitoring in patients undergoing PVI with three different ablation procedures: segmental PVI using a conventional radiofrequency ablation catheter, segmental PVI using an irrigated radiofrequency tip catheter and circumferential PVI with a cryoballon catheter.[25] When compared to an irrigated radiofrequency tip catheter and a cryoballon catheter, the use of a conventional radiofrequency catheter for PVI was associated with a significantly higher incidence of cerebral microembolic signals. Other brain magnetic resonance imaging (MRI) studies showed a similar risk of SCI between open-irrigated RF and cryoballoon technologies.[26-27]

In contrast, the risk associated with phased RF multi-electrode catheters (PVAC) has been consistently higher than other forms of ablation energy.[28-30] In order to reduce the thromboembolic risk of PVAC technology, Verma et al.[31] recently demonstrated in 60 patients undergoing PVAC ablation that the use of three specific procedural interventions (ACT >350 seconds with uninterrupted oral anticoagulants (OAC), underwater loading, distal or proximal electrode deactivation to prevent overlapping) significantly reduces the SCI incidence to 1.7%.

Other procedure-related factors linked to an increased risk of subclinical cerebral lesions are additional LA substrate ablation (e.g. adjunctive ablation at sites exhibiting complex fractionated atrial electrograms), regardless of LA time (time spent with catheters in the LA) and the occurrence of intraprocedural cardioversion.[32] Cardioversion during AF ablation might increase the risk of clinically evident and silent embolism. Specifically, emboli can be released from LA after sinus rhythm restoration as well as impaired LA diastolic function following cardioversion may promote thrombus formation in the LA appendage. Although data are still inconsistent, the incidence of silent cerebral lesions seems to be lower in patients remaining in stable sinus rhythm throughout ablation than in patients undergoing periprocedural cardioversion. A recent study has reported a 2.75-time increase in the risk of subclinical cerebral embolism related to periprocedural cardioversion.[11] Analogously, Ichiki et al.[33] found that the use of cardioversion during the procedure was the most important predictor of cerebral thromboembolism after AF ablation (OR, 3.31). In this perspective, it would be worth trying to restore sinus rhythm with catheter or postponing cardioversion until after the procedure once atrial lesions are healed.[11] However, the question has to be resolved yet because the association between brain lesions and periprocedural cardioversion was not as evident in a few studies.[34-36]

Periprocedural Anticoagulation: New Data, Still Open Questions

It is still unclear which is the best anticoagulation approach to reduce the incidence of neurological sequelae during AF ablation. Embolic risk is higher if anticoagulation is inadequate and concerns underscore the importance of uninterrupted anticoagulation in the peri-ablation period. In a large, high-risk patient population, the COMPARE trial has recently demonstrated that performing catheter ablation of atrial fibrillation without warfarin discontinuation reduces the occurrence of peri-procedural stroke/TIA.[37] Periprocedural symptomatic thromboembolic events occurred in 39 patients (4.9%) off-warfarin and in 2 patients (0.25%) without warfarin discontinuation. Therefore warfarin discontinuation had a ten-fold higher chance of cerebral thromboembolism. In the light of these results, it is noteworthy that published studies that investigated MRI-detected brain lesions after AF ablation included a range of anticoagulation strategies that may not reflect the current best practices (Table 1). Indeed, in most of these studies patients had warfarin discontinuation before the procedure. It is plausible that keeping patients on continuous OAC, as opposed to interrupted anticoagulation, protects against the risk of periprocedural silent brain infarcts, and warrants further investigation.[36] Di Biase et al.[36] demonstrated that performing AF ablation with "therapeutic INR" and pre-transseptal catheterization

Table 1: Published studies evaluating the incidence of silent cerebral thromboembolic lesions after atrial fibrillation ablation

Study (Reference)	Patients (n)	AF type	Periprocedural anticoagulation, %	Technology used for LA ablation	Silent Strokes
Lickfett et al. 2006[61]	20	paroxysmal	OAC held with bridging	Irrigated RF (PVI only)	10%
Gaita et al. 2010[11]	232	59% paroxysmal 41% persistent	OAC held with bridging	Irrigated RF (PVI, lines and CFAE ablation)	14%
Schrickel et al. 2010[14]	53	89% paroxysmal 11% persistent	OAC held with bridging	Irrigated RF (PVI only)	11%
Herrera et al. 2011[28]	74	paroxysmal	OAC held with bridging	Irrigated RF/Cryo/PVAC (PVI only)	37,5% (PVAC) 4.3% (cryoballoon) 7.4% (irrigated RF)
Gaita et al. 2011[29]	108	paroxysmal	OAC held with bridging	Irrigated RF/Cryo/PVAC (PVI only)	38.9%(PVAC) 8.3%(irrigated RF) 5.6%(cryoballoon)
Deneke et al. 2011[59]	86	64% paroxysmal 36% persistent	OAC held with bridging	Irrigated RF/PVAC (PVI only)	38%
Neumann et al. 2011[26]	89	81% paroxysmal 19% persistent	OAC held with bridging	Irrigated RF/Cryo (PVI, lines)	8.9% (Cryoballoon) 6.8% (irrigated RF)
Scaglione et al. 2012[62]	80	paroxysmal	OAC held with bridging	Irrigated RF (PVI only)	6%
Ichiki et al. 2012[63]	100	50% paroxysmal 50% persistent	Uninterrupted OAC	Irrigated RF (PVI/CFAE ablation)	7%
Martinek et al. 2013[32]	131	60% paroxysmal 40% persistent	Uninterrupted OAC	Irrigated RF (PVI, lines and CFAE)	12%
Schmidt et al. 2013[27]	99	paroxysmal	Uninterrupted OAC	PVAC (PVI only)	22%
Ichiki et al. 2013[33]	210	53% paroxysmal 47% persistent	Uninterrupted OAC/Dabigatran	Irrigated RF (PVI/CFAE ablation)	12%
Haeusler et al. 2013[35]	37	paroxysmal	OAC held with bridging	PVAC (PVI only)	41%
Wieczorek et al. 2013[58]	37	paroxysmal	Uninterrupted OAC	PVAC (PVI only)	27%
Verma et al. 2013[31]	60	paroxysmal	Uninterrupted OAC	PVAC (PVI only)	1.7%
Di Biase et al. 2014[36]	146	26% paroxysmal 32% persistent 42% Long-standing persistent	Uninterrupted OAC and heparin bolus pretranseptal puncture	Irrigated RF	2%

Abbreviations: OAC=oral anticoagulants; RF= Radiofrequency; PVI= pulmonary vein isolation; PVAC =phased RF multi-electrode catheters

intravenous heparin bolus with ACT > 300 seconds significantly reduces the prevalence of SCI (2%) compared to patients off warfarin and those non-compliant with the anticoagulation protocol. Similarly, Verma et al showed that new post-procedural SCI occurred in only 1.7% of patients undergoing AF ablation with therapeutic INR and ACT > 350 seconds.[33]

A recent study[38] confirmed that an aggressive anticoagulation strategy during RF catheter ablation (ACT >320s) reduces the number of microembolic signals on transcranial Doppler compared to a conventional one (ACT >250s). Of note, this study showed that the majority of microemboli during AF ablation are gaseous or non-thrombotic particulate debris, regardless of the technology and the anticoagulation strategy; as a consequence, their occurrence cannot be reduced with aggressive anticoagulation.

Vitamin K antagonists (VKA) have been the standard of care for stroke prevention in AF patients for decades. Multiple new oral anticoagulants (NOACs) have been developed as potential replacements for VKAs for stroke prevention in AF. These newer agents have been demonstrated to be non-inferior to VKAs in many treatment areas and have become available as an alternative to VKAs for prevention of thromboembolism. With the increasing use of these agents, several key issues have also emerged. The feasibility and safety of periprocedural newer anticoagulants in AF ablation have been controversial in several previous studies.[39-43] Ichiki et al.[33] compared the incidence of asymptomatic cerebral microthromboembolism between warfarin therapy and dabigatran therapy in 210 consecutive patients undergoing AF ablation. New microthromboemboli were detected in 10.0% of patients undergoing AF ablation with uninterrupted warfarin versus 26.7% of patients with perioperative dabigatran therapy ($P < 0.05$) Similarly, Dentali et al. reported that the incidence of symptomatic cerebral thromboembolism after AF ablation was higher in the dabigatran group than in the warfarin group.[43] On the other hand, Kaseno et al. reported that the incidence of symptomatic and asymptomatic cerebral thromboembolism after AF ablation was comparable in the dabigatran and warfarin groups.[42] In addition it is important to note that to maintain ACT levels above 300 seconds during the AF ablation procedures, a higher amount of heparin is needed both for factor II and factor Xa inhibitor when compared to warfarin.[44]

Data on NOACs are still conflicting and further evaluation is needed to optimize safety profile of these novel anticoagulants.[45-48] Current evidence suggests that Dabigatran therapy may not be an effective alternative to periprocedural warfarin therapy in AF ablation, especially in patients who undergo cardioversion during the procedure. The role of the newer oral anticoagulants in AF ablation requires further investigation in high risk patients and should be compared to continuous on warfarin treatment. Very recently, the VENTURE-AF trial demonstrated that the use of uninterrupted

oral rivaroxaban was feasible in patients undergoing AF ablation and event rates were similar to those for uninterrupted VKA therapy.[49]

Subclinical Brain Lesions and Cognitive Dysfunction: The Sound of Silence

Clinically evident stroke is not the only neurological consequence of AF. Atrial fibrillation adversely impacts neurocognitive function, and it is associated with all forms of dementia, including Alzheimer's disease.[50] Multiple studies have demonstrated an increasing association between AF and cognitive impairment. This association was first observed in the Rotterdam study,[51] a large cross-sectional, population-based study, which reported an age- and sex-adjusted odds ratio for dementia and impaired cognitive function of 2.3 (95 % confidence interval, 1.4-3.7) and 1.7 (95% confidence interval, 1.2-2.5), respectively. Interestingly, the authors observed that this association was present even if no clinical stokes have occurred. Bunch et al. in their retrospective study of 37,000 patients showed that AF patients younger than 70 years were at the greatest risk of premature dementia.[50]

Silent brain infarcts assessed by brain MRI may be associated with dementia and cognitive decline.[52-54] Prevalence of silent cerebral infarction on MRI in AF patients varies between 5.8% and 28.3%. For example, Cha et al. found silent strokes in 28.3 % of AF patients compared to 6.6 % for non-AF patients.[55] In a population-based study that enrolled 15000 patients Vermeer et al[52] showed that the presence of silent brain infarcts on MRI at baseline doubled the risk of dementia in the general population. The infarcts were more often located in the basal ganglia (52%), followed by other subcortical and cortical areas.[56] Age, size, severity, and location of the brain lesion might also influence the onset and severity of dementia.[57] Elderly patients might be more vulnerable to cognitive decline due to lower cortical volumes.

Asymptomatic Cerebral Events During AF Ablation: Do not Worry, It is Not all Worrisome

Brain MRI has identified a high incidence of acutely detected ischemic embolic lesions after catheter ablation of AF (Table 1).[11,14,28,29,35,58-63] Whether post-operative silent cerebral infarction results in cognitive dysfunction is not well established. Asymptomatic ischemic cerebral lesions have been documented by diffusion-weighted MRI after many invasive cardiac procedures. Sauren et al[25] found 3,908 +/- 2,816 (mean,SD) microembolic signals within the basal cerebral arteries during AF ablation; this number is comparable to patients subjected to major cardiac surgery and suggests that neuropsychological change, probably similar to major cardiac surgery, can be expected during the catheter ablation process.

Several studies evaluated the prevalence of post-operative cognitive dysfunction in patients after RF ablation for AF. Medi et al. showed that AF ablation is associated with a 13% to 20% prevalence of post-operative cognitive dysfunction that persists at 90 days after the procedure.[64] Increased LA access time was significantly associated with post-operative cognitive dysfunction on univariable analysis. Schwarz et al.[65] compared the results of neurocognitive testing of 21 patients undergoing AF ablation with those of 23 non-AF controls. Overall, 56.5% of patients who underwent ablation deteriorated from baseline on the verbal memory tests, compared with 17% of controls. Interestingly, in this study the decline was not explainable by evidence of micro embolic lesion as detected on MRI; it is possible that decline in cognitive functions is multifactorial and not correlated to focal lesions only.

Very recently Madhavan et al.[66] performed neuropsychological testing in 28 patients before and after AF ablation. No correlation between SCI and cognitive decline was noted. These data indicate no relevance of the small number of SCI produced during ablation to neurocognitive dysfunction. Similarly, the association between post-operative silent cerebral infarction and dementia was not evident in other studies.[35,59,67] Irrespective of the severity of periprocedural stroke, Patel et al. reported a complete functional and neurocognitive recovery over 38.4 ± 24 months of follow-up, in most patients who had an acute cerebrovascular event secondary to AF ablation.[67] Notably, Vermeer et al[52] showed that the risk of cognitive decline is confined to people who had additional silent brain infarcts during follow-up. AF patients continue to have additional brain infarcts, both silent and symptomatic, that decrease their cognitive function. It would be logical to think that successful AF ablation may attenuate the risk of developing dementia by reducing the risk of subsequent brain infarcts. To date, no study has definitely linked post-operative MRI brain lesions to decline in neuropsychological performance. Furthermore, only limited knowledge on the histopathological significance of MRI-detected brain lesions exist.

Notably, the majority of acute MRI lesions observed after AF ablation regress without evidence of chronic glial scar when reassessed at short-term follow-up.[32,59,68] Post-ablation lesions might recognize different histopathological mechanisms compared to the lesions documented in patients naïve to LA interventions. MRI-detected brain lesions might be the common imaging endpoint of different mechanisms including thrombus, air, tissue or fat embolism during an AF ablation procedure. Micro-embolic lesions related to air embolism may cause less brain damage compared to solid embolic events. The mechanism of brain signals in non-ablated AF patients remains still unclear but may be due to small haemorrhagic infarcts and/or small embolic infarcts.

Deneke et al. evaluated the clinical course and longer-term characteristics of post-ablation MRI detected asymptomatic cerebral lesions.[59] In post-ablation MRI, 50 new brain lesions were identified in 14 patients. Follow-up MRI after a median of 3 months revealed 3 residual lesions corresponding to the large acute postablation lesions (>10 mm). The remaining 47 small or medium-sized lesions were not detectable at follow-up evaluation.

Larger volumes of cerebral lesions have been associated with cognitive decline and are uncommon findings acutely in post-ablation AF patients. Whether larger MRI-detected lesions represent the effect of solid thrombotic embolism and smaller lesions the endpoint of gaseous embolic events remains speculative. Most lesions heal in the short-term and although LA ablation is associated with small or medium-size SCI events, AF-ablation may prevent development of additional larger lesions occurring during the natural course of the AF disease. Of note, an apparent reduction in the risk of additional brain lesions was documented on follow-up MRI after AF-ablation.[35,59,69] Using a large database, Noseworthy, et al. recently evaluated 'real world' stroke rates in AF patients who underwent catheter ablation or cardioversion.[70] Among 24,244 patients, included in this propensity-matched analysis, the authors found that ablation is associated with a significant higher initial risk of stroke/TIA within the first 30 days (RR 1.53; p=0.05). However, over longer-term follow-up, ablation is associated with a slightly lower rate of non-TIA stroke (RR 0.78; p=0.03). Beyond symptomatic relief, AF ablation may provide

additional benefits;[71-74] although speculative, it is intriguing to propose that AF ablation may reduce the likelihood or delay the onset of dementia over the long-term[69] and warrants further investigations.

Since silent cerebral events secondary to AF ablation are common but not associated with impaired cognitive function, we do not believe that follow-up cerebral MRI should be routinely performed after AF ablation. It is possible that decline in cognitive functions is multifactorial and not correlated to focal lesions only. Post-ablation MRIs can be however considered to assess the potential embolic risk of new ablation devices/technologies for LA ablations.

Conclusions

Appropriate management of AF-patients has been engaging clinicians for many years. Diffusion-weighted MRI has documented asymptomatic ischemic cerebral lesions after most invasive cardiac procedures, including AF ablation. Given the heightened risk of dementia in AF patients not undergoing ablation, the relationship between AF and SCI is an old issue but only larger volumes of cerebral lesions have been associated with cognitive decline. From a pathophysiological point of view, new ischemic lesions on MRI after AF ablation, should suggest worse neuropsychological outcome; however, the available data are discordant. Most silent MRI-detected lesions observed acutely after AF ablation procedures are small or medium-size events and the majority of acute lesions regress at medium-term follow-up.

AF patients continue to have additional brain infarcts, both silent and symptomatic, that decrease their cognitive function. In this way, successful AF ablation has the potential to reduce the risk of cerebrovascular events that may be considered as part of the natural course of AF.[70,75,76] Although the long-term implications of SCI remain unclear, it is conceivable that strategies to reduce the risk of SCI may be beneficial.

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Contact Force and Atrial Fibrillation Ablation

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Abstract

Catheters able to measure the force and vector of contact between the catheter tip and myocardium are now available. Pre-clinical work has established that the degree of contact between the radiofrequency ablation catheter and myocardium correlates with the size of the delivered lesion. Excess contact is associated with steam pops and perforation. Catheter contact varies within the left atrium secondary to factors including respiration, location, atrial rhythm and the trans-septal catheter delivery technology used. Compared with procedures performed without contact force (CF)-sensing, the use of this technology has, in some studies, been found to improve complication rates, procedure and fluoroscopy times, and success rates. However, for each of these parameters there are also studies suggesting a lack of difference from the availability of CF data. Nevertheless, CF-sensing technology has been adopted as a standard of care in many institutions. It is likely that use of CF-sensing technology will allow for the optimization of each individual radiofrequency application to maximize efficacy and procedural safety. Recent work has attempted to define what these optimal targets should be, and approaches to do this include assessing for sites of pulmonary vein reconnection after ablation, or comparing the impedance response to ablation. Based on such work, it is apparent that factors including mean CF, force time integral (the area under the force-time curve) and contact stability are important determinants of ablation efficacy. Multicenter prospective randomized data are lacking in this field and required to define the CF parameters required to produce optimal ablation.

Introduction

Traditionally, operators were reliant on indirect measures of the contact between the tip of the ablation catheter and myocardium, such as the fluoroscopic appearance of the catheter and tactile feedback, to guide ablation. With the advent of contact force (CF)-sensing catheters, this is no longer the case, as these data are now directly measured and available in real-time during a procedure. In this review, we present the preclinical work correlating CF and lesion sizes, the factors determining catheter contact in the human left atrium (LA), the impact of CF-sensing on the atrial fibrillation (AF) ablation procedure, and review work focused on establishing optimal CF parameters for ablation.

Catheter-Based Contact Force Sensing Technologies

The first of the catheter-based technologies to obtain a CE mark (2009) was the TactiCath® (St Jude Medical Inc., St Paul, MN, USA). This catheter uses three optical fibers between the second and third electrodes of the catheter and an elastic polymer catheter tip.[1] The latter undergoes micro-deformations in response to contact which changes the wavelength of reflected infrared light transmitted by the optical fibers. The magnitude and orientation of the contact force may then be derived from the wavelength of reflected light at the three fibers.[1]

The most recently CE marked of the contact force sensing technologies is the ThermoCool® SmartTouch™ Catheter (Biosense Webster Inc., Diamond Bar, CA, USA). Here the catheter the tip electrode is mounted on a precision spring permitting a small amount of electrode deflection. By measuring this deflection using location sensor coils at the proximal end of the spring, the system can calculate the force being exerted (and its orientation) using the known characteristics of the spring. The SmartTouch catheter integrates with the Carto[3] (Biosense Webster Inc.) electroanatomic navigation system. During a case, the magnitude of contact force and its vector are displayed in real-time on the Carto[3] display screen as well as the contact force waveform (Figure 1).

For the SmartTouch catheter, the reported sensitivity reported by the manufacturer is less than 1g of contact force. Data has been published for the Tacticath, where a comparison has been made between the measurements made by the catheter and a calibrated balance: this demonstrated the measurements by the catheter were highly sensitive and accurate (mean error ≤1g).[1]

Contact Force and Ablation

In vitro work with non-irrigated catheters using temperature-

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Table 1: Clinical studies assessing ablation efficacy with respect to catheter contact force: methods used to assess efficacy and cut off values for effective ablation

Author	Number of Patients	Operator Blinded to CF	AF Subtype	Method to judge ablation efficacy	Suboptimal Ablation	Effective Ablation
Reddy[40]	32	No	PAF	12 months recurrence of symptoms	CF <10g; FTI<500g.s	CF>20g FTI>1000g.s
Haldar[28]	40	In half of cases	35% PAF	Acute PV reconnection in a 7 segment model per PV pair	CF 14.5g	CF 19.6g
Kumar[27]	12	Yes	PAF	Acute PV reconnection in a 5 segment model per PV pair	LPV: CF 9g, FTI 173g.s RPV: CF 11g, FTI 282g.s	LPV: CF 20g, FTI 436g.s RPV: CF 24g, FTI 609g.s
Kumar[47]	20	Yes	PAF	EGM criteria for transmurality[46]		CF>16g, FTI >404g.s
Neuzil[39]	40	Yes	PAF	PV reconnection at 3 month protocol-driven restudy in a 5 segment model per PV pair	CF 15.5g Minimum CF 3.6g Minimum FTI 118g.s	FTI>400g.s CF 19.5g Minimum CF 8.1g Minimum FTI 232g.s
Ullah[29]	60	No	Persistent AF	Reconnecting segments in a 12 segment model per PV pair at redo procedure (median 8 months from index procedure)	CF 11.5g FTI 231g.s	CF 12.5g FTI 231g.s
Sohns[53]	6	No	PAF	MRI-defined scar in 5mm2 zone		>1,200g.s

EGM=Electrogram; PV=Pulmonary Vein; CF=Contact Force; FTI=Force Time Integral; LPV=Left Pulmonary Vein; RPV=Right Pulmonary Vein

controlled ablation demonstrated a linear relationship between CF and lesion size, with the largest difference between no contact and being in contact with tissue.[2] Over a wide range of contact forces (0-400N), there was an increase in lesion size with increasing CF (as long as the electrode tip temperature was maintained at the pre-set value and contact was maintained).[2] The increase of lesion size with force is small such that a in a study comparing 10g to 20g of contact, no difference in lesion size was found.[3] Because the power output of non-irrigated catheters is controlled by the catheter temperature the effect of changes in contact force is minimized. Poorer contact entails more power output to reach the same temperatures[2] and since lesion size relates to temperature at the electrode tip,[4] similar lesion sizes are therefore produced.

Conversely, if power controlled ablation is used, there is a significant relationship between lesion size and tissue contact.[5] High contact and increased power is associated with an increase in steam pops and impedance rises following rapid, excessive electrode temperature rises.[5] Irrigated ablation is not temperature controlled and thus lesion size is significantly greater at a force of 30g compared to 10g in vitro.[6] Even with temperature-controlled power-limited ablation, in an in vitro model, where fluid flow external to the catheter is utilized to cool the catheter tip, lesion size increases with catheter contact before a plateau is attained.[7]

These proof of principle studies used catheter rigs where catheter tip force was extrapolated from the force loaded onto the catheter. Similar technologies in vivo demonstrate that increased CF is associated with larger and more transmural lesions[8] but also more steam pops.[9] These systems have the limitation that force measurement is not as accurate because of friction between the catheter and the sheath which varies with sheath deflection. Irrigated tip force-sensing catheters have further examined the impact of different levels of CF on lesion size and also the interplay of this variable with the ablation power. Increased CF is associated with increased tissue temperature at 3 and 7 mm away from the ETI, and is associated with increased lesion size at a given level of CF, as is increasing ablation power.[1] Increasing CF is also associated with an increased incidence of thrombus formation at the electrode edge, especially with increasing power, and a similar relationship is also apparent for steam pops.[1,10]

Within the beating heart, even within the fibrillating atrium, it would be expected that contact will be dynamic rather than static. Such dynamic contact has been simulated in an in vitro setting where constant (static) contact has been found to produce the largest lesions while variable and intermittent contact produce progressively smaller lesions.[11] Therefore, the dynamic quality of contact between the electrode and tissue is also of great importance in the efficacy of lesion formation. A measure termed the force time integral (FTI) has therefore been proposed as a measure of catheter contact during ablation. This is the area under the force-time curve and incorporates both the variation in CF during an ablation and also ablation duration. The FTI has been found to correlate with the lesion volume in in vitro experiments.[11]

Contact Force in The Left Atrium

Better electrode-tissue contact results in a greater proportion of the delivered power contributing to the resistive heating of the tissue, rather than wasted in the blood stream. Consequently, this can lead to larger, more likely transmural lesions but also increases the risk of complications through excessive tissue heating. In an *ex vivo* porcine heart study, a force of 417±167g could perforate un-ablated left atrium, while ablation reduced the force needed to perforate.[12] A further study of *in vivo* porcine hearts found that the lowest CF recorded to cause perforation was 77g, with a force of 158.4 ± 55.4 needed to perforate unablated left atrium.[13] A study in patients undergoing AF ablation demonstrated that the actual contact forces exerted on the myocardium vary significantly among operators during mapping and ablation when they were asked to maintain what they perceived (without CF-sensing technology) to be 'good contact'.[14] This included multiple high force events defined as the contact force exceeded 100g for 200ms, with six of the thirty four patients having over 40 such instances.[14] These episodes occurred during catheter manipulation as well as ablation. A further study where operators also blinded to CF measurements mapped around the pulmonary veins specifically found a significant variation in the CF by location, with points taken around the left veins having lower CF than the right side, and the LA/left atrial appendage ridge points having the lowest CF.[15]

One would assume that having access to CF data would therefore reduce the risk of complications such as cardiac perforation, as high force episodes could be reduced. A retrospective study including 557 patients undergoing AF ablation demonstrated that the use of CF-sensing catheters was associated with a significant reduction in the rate of major complications (2.1 vs 7.8%, p=0.01) including

cardiac perforation (0 vs 3.3%, p=0.021).[16] However other studies have shown no reduction in complications with CF-sensing data available.[17–19]

There are areas around the pulmonary veins which are more resistant to electrical isolation[20] and have a higher frequency of both acute and chronic reconnection.[21] The intervenous ridges and pulmonary vein-left atrial appendage ridge are important areas in this respect.[20,21] The reason for this locational variation in the efficacy of ablation may relate variation in wall thickness and texture,[22] resulting in differences in the compliance of different regions,[23–26] thus changing the quality of the contact with the catheter. While availability of CF data could affect the CF applied by the operator during LA mapping and ablation, there are other additional factors which also play a role in determining contact in the LA. Respiratory motion may affect CF, with lesions delivered during apnea having a higher average contact force and force time integral than those during ventilation.[27] During wide area circumferential ablation, the CF varies by location, with lower forces on the left side and anteriorly.[26,28] In those ablated with the operator blinded to CF data, the CF is significantly lower during ablation around the LA/left atrial appendage ridge compared with cases where CF data was available.[28] The type of trans-septal sheath used to deliver the ablation catheter during ablation, whether manual non-steerable or steerable also affected the distribution of contact forces around the WACA (Figure 2).[29]

The quality of contact between the catheter and myocardium is not just reflected by the mean CF but also by the stability of the contact force waveform, quantified as the CF variability (CFV) (Figure 3).[26]

The greater the mean CF applied, the greater the CFV. This may be because at low CF the myocardium has a large capacity for stretching and can buffer sources of variability such as cardiac motion from affecting contact with the catheter; at higher CF, CFV increases, suggesting that less of this variability is buffered by the tissue and more transmitted to the catheter tip. Other factors have also been found to increase the CFV: sinus rhythm rather than AF (presumably because of increased cardiac movement); stiffer robotic sheaths, and LA location. Apnea has also been found to be associated with a reduction in the variability of the applied CF.[27] This variability of the CF is of relevance to ablation as there is evidence that for the same FTI, a higher CFV can result in a lower ablation efficacy (Figure 4).[26]

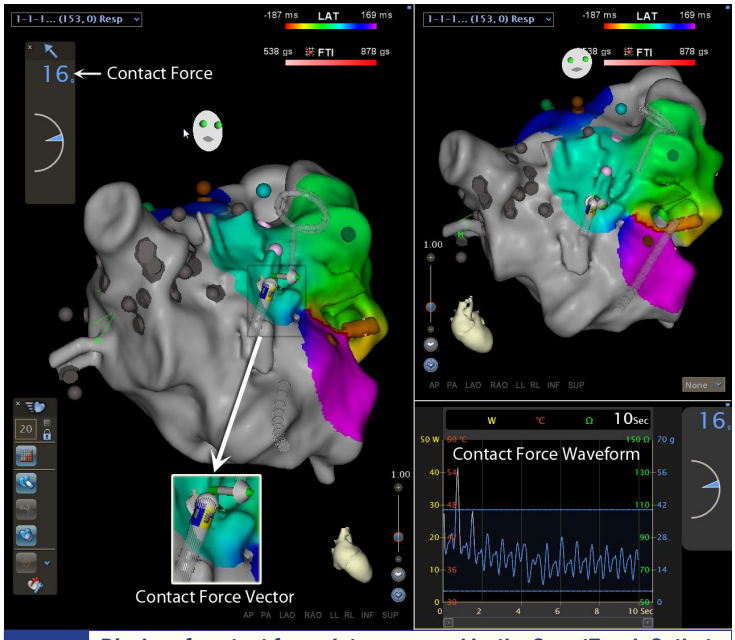

Figure 1: **Display of contact force data measured by the SmartTouch Catheter on the Carto3 screen**
Displayed is a left atrial geometry created using the Carto3 electroanatomic navigation system. Highlighted are the contact force, contact force vector and the contact force waveform for the contact between the catheter and the myocardium

Impact of CF-Sensing on Clinical AF Ablation

One single center 38 patient prospective randomized study has been published assessing the impact of CF-sensing on AF ablation. A non-randomized prospective single-arm study in which 160 patients were ablated at 21 sites has been also published[30] as well as prospective, non-randomized studies enrolling around 20-30 patients in the CF-sensing arm and comparing with a non-CF sensing group.[28,31–34] Aside from these, multicenter registries,[16,17,19] including 200-600 patients have also been published. The results from these studies are discussed below.

A limitation in all but two[18,28] of the two arm studies published to date is that there has been some variation in the equipment used in the two study groups, namely the ablation catheter or mapping systems. This could introduce bias based on the handling characteristics of the CF-sensing catheter itself compared with non-CF sensing catheters, rather than its ability to measure CF. Moreover, the use of CF-sensing generally requires the most up to date iterations of electroanatomic navigation systems. In non-CF sensing groups, some of the cases could conceivably be performed using older systems - previous studies have demonstrated differences in procedural parameters between different mapping systems[35] and different versions of the same mapping system.[36]

The use of CF-sensing catheters has been described to be associated with a reduction in fluoroscopy times,[17,19,32,34] though in two studies fluoroscopy times were found to be longer in the CF-sensing group.[16,31] Procedure times were also shorter in the CF-sensing arms of the above studies,[17,32–34] other than in one study where it was significantly longer where CF data were available.[31] In the randomized trial, procedure but not fluoroscopy times were shorter when CF data were available to the operator.[18]

While the above procedural parameters are of importance, a key factor determining the utility of CF-sensing is clinical efficacy. Success rates have been compared in some of the publications to date.[17–19,31,32,34] In some cases, there was an improvement in success rates with the use of CF-sensing.[17,19,31,32] In one of these studies, a benefit in terms of success rates was only observed for patients in PAF rather than persistent AF.[19] In another study, exclusively examining persistent AF patients, an improvement in ablation success rates was only observed when CF-sensing was used with the remote robotic navigation system and not when used with manual ablation.[17] Other studies, including the prospective randomized one, have not observed an improvement in success rates when CF-sensing was used.[18,34]

CF-sensing catheters have also been found to be associated with a reduction in procedure times in hybrid epicardial (using a bipolar RF catheter)/endocardial AF ablation procedures, in a study comparing the data with a historical cohort where a non CF-sensing catheter was used for the endocardial ablation.[37] On comparison with the second generation cryoballoon, in a multicenter non-randomized study of 376 patients with PAF, the procedure times for CF-sensing catheters are significantly longer without a difference in fluoroscopy or overall complication rates, and with no difference in success rates

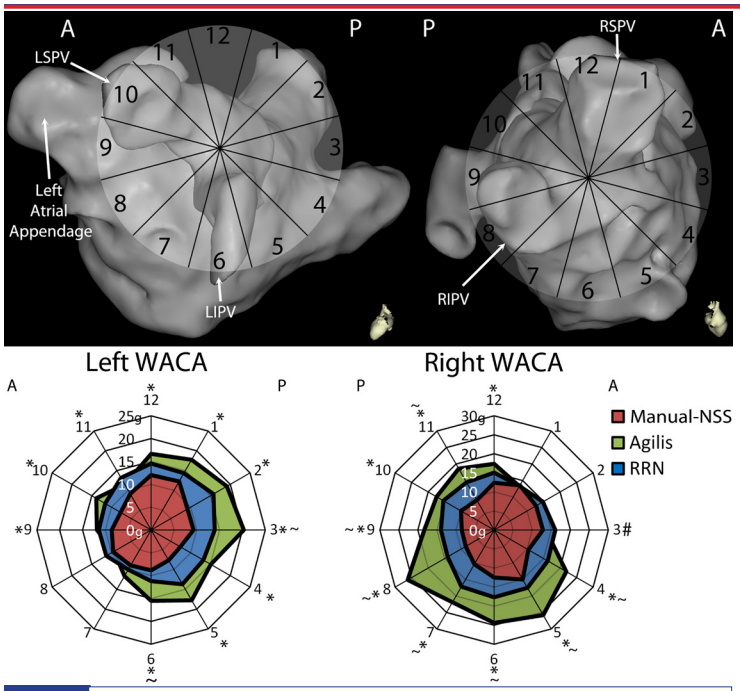

Figure 2: **Distribution of contact force in the right and left WACA**
Upper figure demonstrates a clock face scheme for segmenting each WACA, left pulmonary veins on the left, right pulmonary veins on the right. Lower figure demonstrates radar plots of the distribution of contact forces during initial pulmonary vein encirclement for 60 patients with persistent AF using different trans-septal sheaths. The outer edge represents the WACA location according to the clock face segmentation. The further from the center of the plots, the higher the median contact force in grams
A=Anterior; P=Posterior; Manual-NSS=Manual Non-steerable sheath group; RRN=Remote Robotic Navigation
***=Significant difference between Manual-NSS and steerable sheath groups (p<0.05); #=Significant difference between RRN and Manual-NSS groups (p=0.009); ~= Significant difference between RRN and Agilis group (p<0.05); +=Significant difference between indicated groups (p<0.05)**
(Reproduced from Ullah et al,[29] Journal of Cardiovascular Electrophysiology, Wiley, with permission)

at 18 months.[38]

Clearly, further, larger prospective randomized and preferably multicenter trials are needed to clarify the impact of CF-sensing on procedure parameters and success rates.

Optimizing CF Parameters During Ablation

An important point with regard to the success rates from AF ablation procedures is that it is unlikely that simply having CF-data available will improve outcomes: it more likely that using the data to maintain optimal ablation CF will make the difference. In this respect it is interesting that in the SMART-AF trial, cases where the operator had maintained the CF within their self-determined optimal range ≥80% of the time were associated with a significant improvement in success rates, with such procedures over 4 times as likely to be successful than those where this was not the case.[30] This then raises the important question as to what the optimal CF parameters for ablation should be.

Contact force during ablation predicts acute wide area circumferential ablation (WACA) reconnection in patients with PAF, with sites of pulmonary vein reconnection having a lower average contact force[27,28] and FTI during ablation.[27] At 3 months' follow up, segments within a WACA line ablated with a minimum force time integral below 400g.s had a greater chance of reconnection among PAF patients.[39] At 12 months of follow up, the average contact force, FTI and incidence of low CF during ablation are predictive of procedural success in PAF patients.[40]

The aim of a radiofrequency application during AF ablation is the generation of a transmural lesion. This results in a persistent barrier to electrical conduction or the elimination of a driver. At a procedural level, this is best reflected by an improvement in the single procedure success rate for the ablation. Clearly, this is the most relevant outcome measure clinically. CF parameters have been compared between cases with and without a recurrence of symptoms by Reddy et al.,[40] (Table 1), with higher CFs during ablation observed in those without recurrence. An improvement in success rates may not necessarily mean that the ablation procedure has been more efficient: this would be reflected by a reduction in the procedure length, for example. In order to make procedures more efficient, the aim should be for every radiofrequency application to be contributory to the success of the procedure. This would lead to shorter procedures and potentially less risk of complications. Moreover, suboptimal applications may lead to short term procedural success but long-term failure – by causing tissue edema and an incomplete transmural lesion. Consequently, it is useful to be able to assess the efficacy of individual radiofrequency applications.

In preclinical studies, the efficacy of an individual ablation is relatively straightforward to judge as histological lesion dimensions are available.[2,41] Lesion histology is not available for clinical studies though, and therefore alternative measures of the effect of ablation are used. Classically, the attenuation of the electrogram has been used to judge the efficacy of an individual ablation. Unipolar atrial electrogram attenuation has been found to be associated with transmurality of ablative lesions.[42] Significantly more amplitude reduction in the bipolar signal during sinus rhythm and AF with transmural lesions is seen in vitro, with a reduction of ≥ 60% having a high specificity for lesion transmurality.[43] In clinical studies, an ≥80% reduction in electrogram amplitude has been targeted.[21,44] Electrogram attenuation has been found to correlate poorly with CF applied during ablation.[26,45] Changes in sinus rhythm electrogram

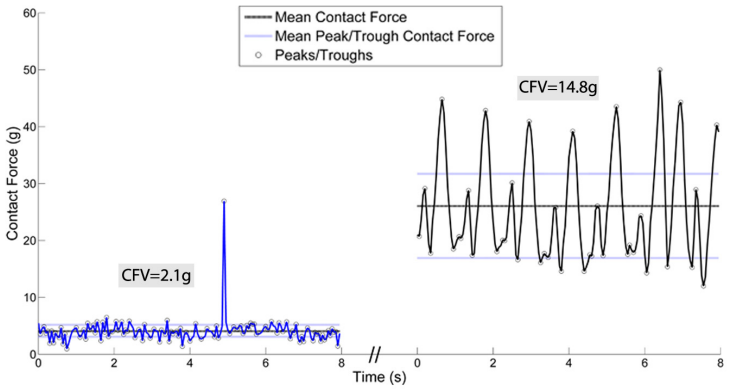

Figure 3: **Contact force variability**
Contact force (CF) waveform over time at two mean contact forces – the contact force variability (CFV) is the difference between the mean trough and peak CF. The mean CF is indicated by the solid line while the mean peak and trough CFs are indicated by the dotted lines. On the left of the image is a waveform at low mean CF with low CFV, while on the right is a waveform at higher CF with higher CFV
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morphology have been shown to be predictive of transmurality of ablation lesions in a porcine model by Otomo et al.,[46] In this case, for unipolar signals a loss of a negative deflection was associated with transmurality, while in the case of bipolar signals, the changes associated with the latter were dependent on the orientation of the catheter to the myocardium. One group has used these criteria for bipolar signals to judge ablation efficacy and found that CF parameters were sensitive and specific for identifying transmurality based on electrogram parameters.[47] Another group found no relationship between CF parameters and transmurality as suggested by the above electrogram morphology changes.[26]

The most commonly employed model for assessing ablation efficacy is reconnection of the WACA lines[27,28,39] (Table 1). In this approach, the ipsilateral WACA is divided into five to twelve segments and efficacy is based on whether that segment reconnects or not. The disadvantage here is that target parameters for individual radiofrequency applications are being assessed based on the response of a region, quite often with overlapping lesions, to ablation. In most of these studies, operators were blinded to CF measurements (Table 1): such blinding serves to exaggerate the differences between ineffective and effective ablations as a lack of knowledge of CF allow for a greater range of CF to be applied and therefore makes it difficult to establish where the actual threshold for effective ablation lies. Based on these studies, a mean ablation CF of at least 15g and FTI of >400gs would appear to be associated with a reduced risk of an ablation being in a reconnecting segment.

While histological lesion parameters are not available for clinical cases, work has been done using cardiac MRI to attempt to image ablation lesions. McGann et al., described a methodology for imaging LA scar using delayed enhancement MRI (DE-MRI) following pulmonary vein isolation, and the burden of LA scar they observed correlated with arrhythmia recurrence.[48] This group went on further to demonstrate that areas of DE-MRI enhancement correlate with areas of electrical scar (R2=0.57) and that DE-MRI imaging could be used to identify breaks in the pulmonary vein isolation lines.[49] In a blinded analysis using pre- and post-ablation MRI images, another group found that investigators were able to identify ablated LA myocardium in only 60% of cases, with a poor ability to distinguish ostial from circumferential ablation lesions.[50] This contrasts with another report in which ablated myocardium could be identified in 100% of cases on DE-MRI.[51] These findings suggest MRI may be useful in determining the sites of ablation lesions but the difference in the reported reliabilities may relate to the signal intensity thresholds being used to assign scar on MRI. To address this, recent work has correlated macroscopic scar volumes with DE-MRI imaging scar volumes in the right atria of 8 swine: based on this, DE-MRI signal intensity thresholds have been proposed which allow the best approximation of the macroscopic scar volume.[52]

Contact force parameters have been compared with MRI-imaged atrial scar by Sohns et al.[53] Table 1. In this study of six patients, the FTI of ablation was correlated with DE-MRI scar. In order for this comparison to occur though, the FTI was not examined from the perspective of a single radiofrequency application, but in a subdivision of 1cm zones. Increasing FTI above 1,200g.s was associated with a significant increase in the proportion of a 5mm2 region of myocardium exhibiting DE-MRI scar (below this FTI value, the increase in the scar burden in that zone with an increase in FTI was small). This study therefore raises the possibility of using cardiac MRI to assess

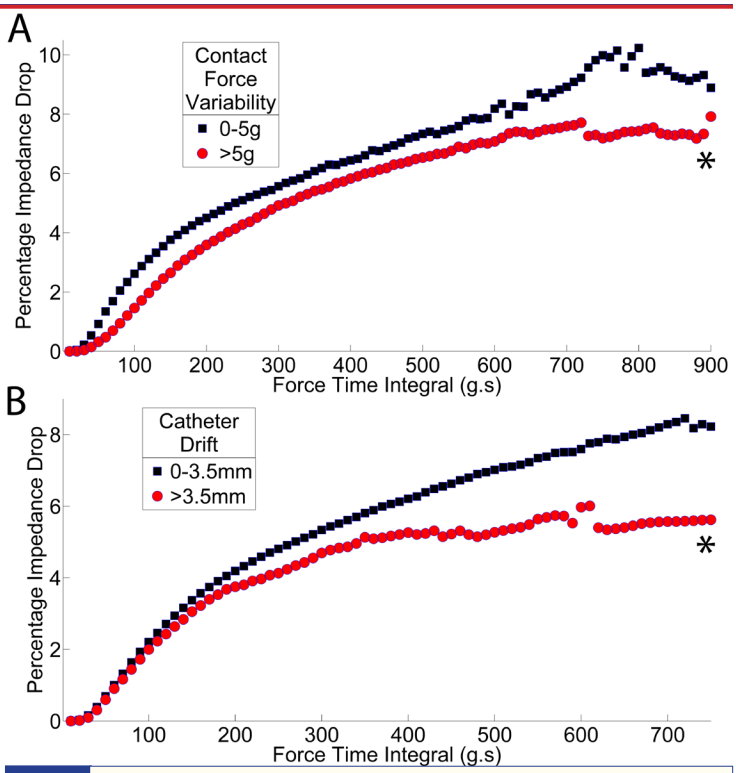

Figure 4: **Factors affecting impedance drop during ablation (A) Contact Force Variability and (B) Catheter drift. Each point is the mean of at least 10 ablations. *p<0.0005 (Reproduced from Ullah et al,[26] Journal of Cardiovascular Electrophysiology, Wiley, with permission)**

ablation efficacy clinically. The drawback here though is that the efficacy is being assessed at a MRI-zone level (albeit a small zone) rather than an individual radiofrequency application. This therefore relies on extremely accurate registration of each radiofrequency application between the electroanatomic navigation system and the MRI being used to judge scar. Moreover, this method is unable to account for any overlap in applications (for example through catheter drift even during a putative static application). It may be for these reasons that the threshold for effective ablation is much higher in this study compared with the other work presented in Table 1.

An alternative approach to clinically assess the efficacy of each individual radiofrequency application based on the impedance drop/FTI relationship has also been used.[26,45] For persistent AF patients, the relationship was found to be logarithmic with a plateau at 500g.s.[45] This method was also used to investigate the impact of contact force variability and catheter drift on the efficacy of ablation (Figure 4).[26] Based on this work, maximal efficacy is provided by parallel catheter contact with CFV ≤5g, catheter drift ≤3.5mm and there is no benefit in terms of biophysical efficacy from ablation beyond 500g.s.

Such detailed optimisation of catheter contact during ablation is now possible with the introduction of automated lesion marker placement software such as the Visitag upgrade for Carto.[3] In a study by Anter et al.,[54] such an algorithm was used and found to be associated with lower rates of acute pulmonary vein reconnection but not improved success rates at 6 months. The limitation of that study though was that only catheter displacement and impedance drop were used by the annotation algorithm. The incorporation of CF parameters could be used to further refine the targets for ablation. A randomized trial where one group was ablated with optimised CF

targets and the other without CF sensing could be conducted to definitively prove the utility of CF-sensing to the ablation procedure.

Conclusions

The availability of real time catheter-based CF-sensing holds great potential for improving the safety and success rates of AF ablation procedures by reducing suboptimal and excessive CF during ablation. Optimal CF parameters for ablation remain to be established, and one would hope that their adoption would help to optimize each individual radiofrequency application, improving procedural efficacy. Multicenter prospective randomized data are lacking in this field and are required to definitively prove the argument for the adoption of this technology and the CF thresholds required during ablation.

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Atrial Fibrillation Ablation in Adults With Repaired Congenital Heart Disease

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Abstract

The incidence of atrial fibrillation (AF) in congenital heart disease (CHD) adults has increased in the past decades due to a longer life expectancy of this population where the subjects are exposed to cardiac overflow, overpressure and structural changes for years.

The literature regarding AF ablation in repaired CHD adults emphasizes the importance of intracardiac echocardiography (ICE) to perform the transseptal puncture and the ablation procedure in the left atrium (LA), both effectively and safely. In small case control studies, where the predominant congenital cardiomyopathy was the atrial septal defect, the most common strategy for ablation was antral isolation of the pulmonary veins showing results, at one year follow-up, similar to those in the general population.

The positive results of AF ablation so far, in this specific population, widen the range of therapeutic options for a group of patients whose only chance has been pharmacological treatment, which has proved to be inefficacious in most of the cases and not free from adverse events.

Introduction

The management of congenital heart diseases (CHD) has much changed during the past few decades. The advances in surgical techniques and treatment of the associated comorbidities have significantly increased the life expectancy of this population. Consequently, the incidence of atrial arrhythmias, and especially atrial fibrillation (AF), has also increased as more patients reach the adulthood.[1] The most studied and prevalent arrhythmia in CHD patients has always been the intra-atrial reentrant tachycardia which is closely related to the surgical procedure , but this is probably about to change as the incidence of AF in these patients is growing independently of the surgery.[2,3,4,5] The prevalence of AF for the CHD population varies in the literature between 3.7 to 15%, a notoriously higher percentage than that of the general population which is around 0.95%.[6,7,8] A different pathophysiology and the conjunction of risk factors (those factors present in the general population and those unique for these patients) could explain the increased prevalence. In a recent multicenter cohort of adults with tetralogy of Fallot, AF was the most prevalent atrial tachyarrhythmia over the age of 55 years.[9] The presence of a higher thromboembolic risk, the higher morbidity and mortality and the increased risk for heart failure in CHD patients deserve special attention.[10,11] Antiarrhythmic drugs have been for a long time the only treatment used in CHD patients, not always with success. Koyak et al. in 2013 investigated the efficacy of antiarrhythmic drugs in 92 CHD patients with new onset supraventricular tachycardia, and 68% of them were AF.[3] Class III drugs were the most effective to prevent recurrences but at the same time they were the drugs with more side effects (dizziness, bradycardia, intolerance) and all patients taking amiodarone presented thyroid toxicity, representing an important limitation for the treatment of this young population. Class I, II and IV antiarrhythmic drugs were not superior in preventing recurrences than no antiarrhythmic therapy. In addition, class I drugs are contraindicated in most cases due to the presence of structural heart disease and ventricular dysfunction. Therefore, sotalol remains the only option of treatment as it is one of the most effective drugs with no extra-cardiac toxicity (2/3 of patients were free from arrhythmia for at least one year follow-up). The limitations of antiarrhythmic drugs pave the way for AF ablation as an alternative of treatment, although the associated technical difficulties prevent its introduction in the majority of the EP labs.

Key Words:
Atrial Fibrillation, Ablation, Congenital Heart Disease.

Disclosures:
None.

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Pathophysiology

The initiation of AF in CHD adults can be the result of several factors: a) left atrial (LA) dilation due to volume overload in the increased right-sided flow CHD or secondary to high systemic blood pressure or left ventricular dysfunction; it is well known the relationship between atrial dilation and the development of

Table 1: Summary of the three publications with the largest number of CHD repaired patients who underwent atrial fibrillation ablation

	Number of CHD patients	Groups	Type of AF	Ablation strategy	Success
Philip et al. 2012	36	All kind of CHD vs non-congenital structural heart disease (NCSHD)	Paroxysmal (72%) Persistent (27.7%)	PVI +SVC +other LA lines	84% patients free of symptomatic AF vs 86% in NCSHD at 300 days
Santangeli et al. 2011	39	Percutaneous device in ASD due to ostium secundum	Paroxysmal (33%) Persistent (67%)	PVI + SVC in paroxysmal/ PVI+SVC+post wall+septal LA+CFAEs in persistent or long standing AF	77% patients free of symptomatic and/or documented AF at 14+months
Lakkireddy et al. 2008	45	Surgical or percutaneously treated ASD and PFO patients vs age-gender matched controls	Paroxysmal (60%) Persistent (26%) Permanent (14%)	PVI + CTI	76% patients free of symptomatic and/or documented AF vs 82% in the control group at 15+4 months

fibrosis and electrical heterogeneity which is the cornerstone for the perpetuation of AF; LA dilation has been observed either in pre and post repaired patients, as surgery cannot prevent the initiation of atrial arrhythmias in most cases,[8,12] b) incisional scarring predisposing to reentrant circuits (percutaneous closure of septal defects has been observed as a protector against AF); this circuits could explain the common coexistence of AF and atrial tachycardia that has been observed in these patients,[13] c) sinus node disease (either primary or post surgery) which facilitates the activation of other atrial triggers, d) blood desaturation in chronic cyanotic patients has been reported as a possible independent factor for the development of AF, although this has not been demonstrated due to its relation to complex CHD and Eisenmenger syndrome with hemodynamic worsening.[8]

Risk Factors for The Development of Atrial Fibrillation

As previously mentioned, adult CHD patients are subjected to the usual risk factors of the general population (age, hypertension, functional class, obesity, diabetes…) and to some particular risk factors that only affect this group of patients: age at surgery, complexity of the CHD, complexity of surgery, diseases with increased right-sided flow or blood desaturation, among others. Gender seems not to play a role in CHD adults as it does in the general population.

In a study, conditions disproportionately associated with atrial fibrillation were left-sided obstructive lesions, incompletely palliated CHD, and, to a lesser extent, Fontan surgery.[14] Older age, left atrial enlargement, lower left ventricular ejection fraction, and number of cardiac surgeries have been independently associated with AF.[9] Atrial fibrillation is a well-recognized sequela of large, unrepaired atrial septal defects in adults. Early but not late (i.e., >40 years) closure of the atrial septal defect reduces its prevalence postoperatively.[15,16]

Transseptal Puncture

One reason for many physicians to not include AF ablation in the treatment of CHD patients is the difficulty in performing the transseptal puncture. The modified anatomy makes the usual anatomical references and maneuvers to identify the fossa ovalis for a safe puncture useless.

All publications regarding transseptal puncture in complex CHD or in simple CHD in which the atrial septum and/or its adjacent structures have been modified, are using intracardiac echocardiography (ICE) to access the left atrium. After femoral venous puncture, a phased-array ultrasound imaging catheter is advanced into the right atrium to obtain a direct view of the atrial septum and to localize a safe site for the puncture, as the usual pull back from the superior vena cava and jump into the fossa ovalis are not applicable. The transseptal puncture is performed as usual using a long transseptal sheath and a long needle.

The transseptal puncture technique using ICE has also been described in big detail and proved safe in patients with surgical interatrial patches and closure septal devices, the last ones more and more frequently used due to the widespread of percutaneous techniques. ICE is used to identify the portion of the septal wall not covered by the device, which can be found in a posteroinferior position in a majority of cases as the device is normally anterosuperiorly oriented[17](Fig. 1). When a free portion of the wall is not present, transseptal puncture can be done through the closure device and ICE provides an essential support to directly visualize the appropriate site for the puncture. The technique for the perforation of percutaneous closure devices was first described in 2011 by Santangeli et al.[12] Briefly, once the needle had crossed the device, the 8Fr dilator was removed and an upsized 11Fr dilator was advanced over the wire to dilate the access site across the device. Finally, the transseptal sheath was introduced into the left atrium. No shunt was observed in the follow-up of these patients.

Another handicap when crossing a repaired interatrial septum is its thickness and/or stiffness. In some cases there can be also calcification of the patch or the septum itself. In these cases, perforation of the septum with the usual needle may not be possible. The use of a RF-assisted transseptal needle[18] or a surgical electrocautery pen in the cut mode placed on the proximal hub of the needle while tenting of the septum can solve this problem.

Atrial Fibrillation Ablation Strategy and Results

Publications about AF ablation in CHD adults are scarce. With

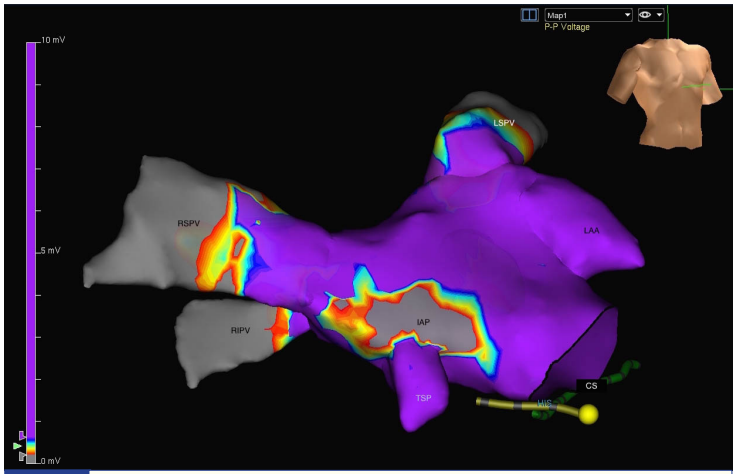

Figure 1: Left atrium voltage map in a right anterior oblique view. A surgical interatrial patch (IAP) can be seen as a grey spot as it has no electrical conduction. The transseptal puncture was performed posteriorly to the patch where the native tissue was thinner and easier to puncture. RSPV: right superior pulmonary vein; RIPV: right inferior pulmonary vein; LSPV: left superior pulmonary vein; LAA: left atrial appendage; IAP: interatrial patch; TSP: transseptal puncture; CS: coronary sinus

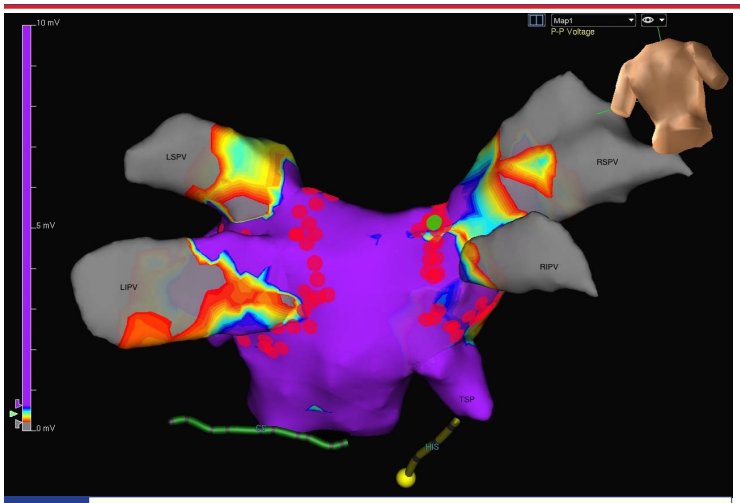

Figure 2: **Left atrium voltage map in a posteroanterior view. The red dots represent the lines of radiofrequency ablation in a circular antral modality around the pulmonary veins ostia. RSPV: right superior pulmonary vein; RIPV: right inferior pulmonary vein; LSPV: left superior pulmonary vein; LIPV: left inferior pulmonary vein; TSP: transseptal puncture; CS: coronary sinus**

respect to catheter ablation of AF, operators have largely mimicked and adapted standard strategies, including isolation of pulmonary venous antra (Fig. 2), connecting lesion sets to the left-sided AV annulus, and cavotricuspid isthmus ablation.[1] These complex procedures require careful anatomic planning and ideally utilize techniques for real-time and/or registered volume imaging of the heart to facilitate visualization of relevant anatomy.

There are only three reports with a considerable number of patients which are summarized in Table 1. The largest report was published in 2012 by Philip et al. who included all kind of CHD (61% of patients had an atrial septal defect) and reviewed prospectively 36 patients.[19] A total of 34 patients had undergone some kind of reparation, a surgical intervention in the majority of them. These patients were compared to a control group of 355 patients with non-congenital structural heart disease (57% valvular heart disease). The last group was slightly older and had a higher prevalence of diabetes, hyperlipidemia and hypertension. Paroxysmal AF was the predominant type of AF in both groups. ICE was used during the transseptal puncture and to guide the position of the ablation catheter during ablation. An 8mm tip RF ablation catheter (70W, 55°C) was used to isolate the four pulmonary veins targeting the pulmonary vein antrum in all cases. The second site most approached was the superior vena cava. Other sites were the LA septum, the mitral isthmus or the coronary sinus. Intravenous heparin was administered during the procedure to maintain an activated clotting time of 350 to 400 seconds. After a mean of 300 days of follow-up, 84% of patients in the CHD group and 86% of patients in the non-congenital structural heart disease group were free of symptomatic AF under antiarrhythmic therapy. After 4 years, the proportion was 61 and 69%, respectively. The procedure failed in the only patient with Tetralogy of Fallot and also in a patient with transposition of the great vessels due to technical problems to reach the LA with the ablation catheter.

There are two other studies focused in adult patients with repaired atrial septal (ASD) defects. In 2008 Lakkireddy et al.[17] reported 45 patients with atrial septal defect or patent foramen ovale repair, 22 surgically and 23 percutaneously. Pulmonary vein antral isolation was performed in all patients. Additional lines were done if required (cavotricuspid isthmus in 6 patients and a figure of 8 flutter ablation in one case). The ablation catheter used was either an 8-mm non-irrigated or a 3.5-mm irrigated catheter. Warfarin was not discontinued for the procedure and additional enoxaparin was administered when the international normalized ratio (INR) was under.[2] The mean follow-up duration was 15+ 4 months. Failure was defined as any documented and/or symptomatic atrial arrhythmia. The repaired ASD patients were compared to an age-gender-AF type matched controls. Failure between 3 and 12 months after the procedure was slightly higher in ASD patients than in the control group (24% vs 18%, P=0.7). Recurrence rates were also higher in the non-paroxysmal group compared with the paroxysmal patients (33% vs 19%, P≤0.4) as in the general population.

In 2011, Santangeli et al.[12] published a study including 39 patients with percutaneous atrial septal closure devices due to ostium secundum defects. ICE was used as a guide for the transseptal puncture as previously described. In paroxysmal AF patients pulmonary vein antrum isolation and isolation of the superior vena cava were performed. In persistent and long-standing persistent AF patients applications on the entire posterior wall to the coronary sinus and the left side of the septum and ablation of complex fractionated atrial electrograms in the left atrium and the coronary sinus were added to PV and superior vena cava isolation. At the end of the procedure an infusion of isoproterenol was administered to show vein reconnection or extra pulmonary vein firing. Warfarin was not discontinued and intravenous heparin was administered during ablation to reach an activated clotting time >300. At mean follow-up of 14 + months, 77% of patients were free from atrial arrhythmia recurrence (defined as any atrial arrhythmia lasting for at least 30 seconds).

The presence of a persistent left superior vena cava has been described as a trigger for AF. Its isolation has been performed in small case series[20] by advancing a circular mapping catheter into the left superior vena cava and eliminating all fractionated signals inside the vein by pulling back an irrigated RF catheter. Isolation of the left superior vena cava has been also performed with cryothermal energy when the diameter of the proximal coronary sinus allows the introduction of a cryoballoon.

Summary

The prevalence of AF in CHD adults is increasing due to longer life expectancy, the presence of more cardiovascular risk factors (hypertension, diabetes, obesity) in older ages and intracavitary pressure changes and cardiac remodeling. Antiarrhythmic drugs are less efficacious to prevent recurrences in CHD patients and drugs have side effects which are not desirable in this young population who need a long-term treatment. AF ablation can be an option to help improving the efficacy of antiarrhythmic drugs or even as a single treatment.

The major difficulty to perform the AF ablation procedure is the distortion in the cardiac anatomy that makes the usual position and maneuver of the catheters unhelpful. The changes in the anatomical references are especially relevant during the transseptal puncture and to guide the position of the catheters during ablation. Therefore, the use of ICE to have a direct visualization of the anatomical structures is almost imperative. An additional barrier is the presence of interatrial septal patches or closure devices. Again, ICE and the use of radiofrequency energy to perforate the septum can help

overcoming these obstacles.

There are only few studies with small samples or case reports about AF ablation in CHD adults. The majority of patients in these publications have repaired atrial septal defects, who have less anatomical changes than major congenital heart defects, and paroxysmal AF. The standard strategy for ablation in all cases was antral PV isolation but the additional applications or atrial lines were heterogeneous between the different studies. Although CHD patients are more vulnerable for presenting a thromboembolic event and therefore the strategy for anticoagulation during ablation was aggressive, no complication related to the procedure was reported in any case.

The clinical results reported from the available publications are promising, with similar success rates when compared to the general population. However, the fact that the authors are all members of experienced teams should be kept into account. A review of eight prospective randomized trials in the general population, comparing AF ablation with antiarrhythmic drug therapy or rate control agents alone, reported a success rate of 77.8% in the AF ablation arm.[21] In line with these results, the success rate for AF ablation in CHD patients ranged from 76% to 84%.

It has been observed a higher incidence of recurrences in the long-term follow-up of postoperated CHD patients after atrial flutter ablation,[4,5] however, information about the outcomes during the long-term follow-up after AF ablation for CHD patients is missing. For patients with drug refractory AF or those not suitable for catheter ablation, AV nodal ablation might be considered. AV nodal ablation with post ablation ventricular pacing in patients with CHD has been reported in a small series,[22] but, again, information on the long term is very limited.

In conclusion, the use of AF ablation in the CHD population looks promising and safe, nevertheless, more studies are needed to provide further learnings and conclusions.

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Clinical and Economic Implications of AF Related Stroke

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Abstract

A major cause of morbidity and mortality among patients with atrial fibrillation (AF) relates to the increased risk of stroke. The burden of illness that AF imparts on stroke is likely to increase with our aging populations and increasingly sophisticated cardiac monitoring techniques. Understanding the clinical and economic differences between AF related ischaemic stroke and non-AF related stroke is important if we are to improve future cost effectiveness analyses of potential preventative treatments, but also to help educate clinical and policy decision makers on use or availability of treatments to prevent AF related stroke. In this article we review the existing evidence that highlights differences in the clinical characteristics and outcomes between AF and non-AF stroke, as well as differences in their economic impact and discuss ways to improve future economic analyses.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with a prevalence that increases from 5% in those over 65 years to 10% in those over 80 years.[1,2] These figures are expected to rise exponentially as the population ages such that 7 million Americans will suffer from AF by the year 2020, and 16 million by the year 2050.[1] Indeed, the age-adjusted prevalence of AF has already quadrupled in the US over a period of 50 years from 1958 (20.4 cases per 1000-person years) to 2007 (96.2 cases per 1000-person years),[3] and in the 10 years from 2000 through 2010, AF-related hospitalisations in the US rose by 23%, with increasingly complex and costly admissions.[4] The diagnosis confers significant impairment of quality of life in addition to morbidity and mortality from heart failure, systemic embolisation (SE) and stroke in particular.[5,6] Stroke is the 3rd leading cause of death and the leading cause of serious adult disability in the United States (US) and the United Kingdom (UK).[7,8] Atrial fibrillation is a major risk factor for stroke, generally increasing the risk of ischaemic stroke fivefold,[9] however, age further increases this risk in the setting of AF. The Framingham heart study showed that attributable risk of stroke increases from 1.5% age 50-59 years to 23.5% age 80-89 years,[5] with AF accounting for nearly 25% of strokes in those over the age of 80 years compared to between 10–15% across all age groups.[10] Furthermore, contrary to younger populations, dyslipidaemia and hypertension are less significant risk factors relative to AF in the very old.[11-13] These facts, along with the aging population here in the UK, suggest AF will play an increasingly larger role in contributing to the overall burden of stroke disease.

Anticoagulation with dose adjusted warfarin has been shown to reduce the risk of stroke in AF by around two-thirds.[14-18] Unfortunately numerous studies have shown that utilisation of anticoagulation thromboprophylaxis in AF remains sub-optimal with less than 60% of eligible patients receiving anticoagulation,[19] dropping to around 20% in those over the age of 80 years.[20-22] The introduction of the novel oral anticoagulants (Dabigatran, Rivaroxaban, Apixaban and Edoxaban) may help improve these figures with their relative ease of use and improved intracranial bleeding profiles,[23] however, the costs of their use are increasingly scrutinised among differing health economies. This is understandable in the current economic climate although such economic analyses run the risk of underestimating the cost effectiveness of these agents if they do not utilise AF stroke specific cost data. This is due to the growing body of evidence that suggests patients with AF tend to have larger strokes,[24] that are more severe,[25] and result in higher mortality rates,[26, 27] longer lengths of hospital stay[25] and higher rates of discharge to institutional care,[26] than their sinus rhythm (SR) counterparts. This is likely to result in increased health and societal costs.

In this review we discuss the differences in clinical outcome after stroke among patients with and without AF, what economic implications this imparts and considerations required for future economic evaluations.

Clinical Consequences of AF Stroke

A systematic review of literature investigating differences in stroke

Key Words:
Atrial Fibrillation, Stroke Outcomes, Costs, Cost Effectiveness.

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None.

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outcomes among patients with and without AF was undertaken using PUBMED and MEDLINE databases with search criteria consisting of the terms: 'stroke' AND 'outcome' AND 'severity' AND 'atrial fibrillation'. This identified 385 articles, from which 356 were excluded from the title and abstracts alone. Two further reports were excluded due to high patient selectivity.[24,27] This left 27 studies for the final analysis that reported primary data analysis and good (>80%) case inclusion (table 1).

Stroke Severity

The association between AF and increased stroke severity has been suggested in the literature for the last 45 years. Analysis of some of the earliest published reports, such as that of Marquardsen,[29] however, were limited because of their retrospective nature, poor case ascertainment and the limited diagnostic capabilities of the era. It was not until the early 1980's that systematic analyses of patients were reported and highlighted real differences in stroke severity between those with and without AF (Table 1). The Scandinavian Stroke Scale (SSS)

Table 1: Studies comparing stroke outcomes amongst patients with and without AF

Study	Country	Methods/Population	Sample size (AF vs non-AF)	Outcome Measures	Results (AF vs non-AF)	Sig (P, CI)
Wolf et al (1983) Framingham study[46]	US	Prospective observational evaluation of population based cohort who developed stroke	59 vs 442	30 day mortality 6 month stroke recurrence	17% vs 19% 47% vs 20%	NS <0.05
Britton & Gustafsson (1985)[36]	Sweden	Prospective, consecutive inpatient analysis	92 vs 196	Neurological score (0 – 100 where 100 is normal) Reduced conscious level (%) Inpatient mortality (%)	53 vs 67 33% vs 10% 26% vs 5%	<0.001 <0.001 <0.05
Candelise et al (1991)[47]	Italy	Prospective consecutive stroke admissions	211 vs 837	Severe motor deficit (broad class) 1 month mortality 6 month mortality	54% vs 46% 27% vs 14% 40% vs 20%	NS <0.05 <0.05
Gustafsson & Britton (1991)[48]	Sweden	Retrospective observational analysis of consecutive stroke admission	88 vs 188	1 month - recurrent stroke / SE - mortality 5 year – recurrence stroke / SE - mortality	13% vs 2% 35% vs 7% 26% vs 25% 78% vs 52 %	<0.01 <0.01 NS <0.01
Broderick et al (1992)[49]	US	Retrospective analysis of consecutive hospital and community stroke patients	318 vs 1064	Mortality – 30 days - 1 year - 3 years	23% vs 8% 44% vs 18% 77% vs 43%	<0.001 <0.001 <0.001
Sandercock et al (1992)[50]	UK	Prospective community based registry data of consecutive strokes	115 vs 560	30 day mortality	23% vs 8%	<0.05
Anderson et al (1994)[51]	Australia	Prospective population based registry analysis of consecutive stroke patients	Total 321	1 year mortality	Adjusted RR 2.0	CI (1.1-3.5)
Lin et al (1996) Framingham study[37]	US	Prospective community based observational study	103 vs 398	Proportion stroke severe or fatal (%) – broad classification. Mortality – 30 day - 1 year 1 year stroke recurrence Functional dependence (severe BI): - acute period - 3 months - 6 months - 12 months	39% vs 28% 25% vs 14% 63% vs 34% 23% vs 8% 73.3% vs 32.5% 58.3% vs 16.3% 36.4% vs 15.8% 30% vs 10.9%	<0.05 <0.05 <0.05 - <0.01 <0.01 0.05 NS
Jørgensen et al (1996) Copenhagen stroke study[25]	Denmark	Prospective community based analysis of consecutive stroke admissions	217 vs 968	Admission – stroke severity (SSS) - functional dependence (BI) Inpatient mortality (%) Length of hospital stay (days) Discharged to own home (%)	29.7 vs 37.5 34.5 vs 51.7 33% vs 17% 50.9 vs 39.8 48% vs 69%	<0.0001 <0.0001 <0.0001 <0.001 <0.0001
Vemmos et al (2000)[52]	Greece	Prospective population based registry	189 vs 366	1 year disability (MRS > 2)	Adjusted RR 1.8	CI (1.1-3.2)
Lamassa et al (2001) European biomed study[26]	7 countries in Europe	Prospective multi-centre registry of consecutive first time stroke patients	803 vs 3659	Stroke severity (%) – TACI - LACI Mortality – 28 day - 3 month Length of hospital stay (days) Discharge to own home (%) Functional dependence – 3 month (BI)	33.8% vs 25.1% 16% vs 29.2% 19.1% vs 12% 32.8% vs 19.9% 23.9 vs 22.7 61.4% vs 71.4% 12.8 vs 15.3	<0.001 <0.001 <0.001 <0.001 NS <0.001 <0.001
Saxena et al (2001)[35]	Worldwide multi-centre	Retrospective analysis of stroke patients randomised to IST1	3169 vs 15282	Stroke severity (%) – TACI - LACI - reduced GCS Stroke recurrence at 2 weeks Mortality at 2 weeks	36% vs 21% (OR 2.1) 13% vs 26% (OR 0.4) 37% vs 20% (OR 2.4) 1.2% vs 0.7% 17% vs 7.5% (OR 2.5)	CI (2 – 2.3) CI (0.4- 0.5) CI (2.2- 2.6) NS CI (2.2-2.8)
Appelros et al (2002) & (2003)[53,54]	Sweden	Population based analysis of consecutive stroke patients – second analysis with 12 months follow up	90 vs 287	Stroke severity – NIHSS > 6 Mortality – 28 days - 1 year Dependency at 1 year (MRS >2)	Adjusted OR 1.9 Adjusted OR 2.4 Adjusted HR 2.4 Unadjusted OR 1.6	CI (1.2-3.1) CI (1.3-4.5) CI (1.6-3.6) NS
Dulli et al (2003)[55]	US	Retrospective analysis of consecutive stroke patients admitted to hospital	216 vs 845	Bedridden state (MRS = 5) at discharge	41.2% vs 23.7%	<0.0005
Steger et al (2005)[30]	Austria	Prospective multi-centre hospital based registry of consecutive stroke patients	304 vs 688	Stroke severity – NIHSS > 21- admission MRS >4	13% vs 6% 52% vs 31%	<0.004 <0.004
Kimura et al (2005)[31]	Japan	Prospective multi-centre hospital based registry of consecutive stroke patients	3335 vs 12496	Stroke severity – NIHSS > 23 -NIHSS < 6 Length of hospital stay (days) Mortality at 28 days	19.7% vs 4.5% 31.3% vs 64.4% 40.5 vs 34 11.3% vs 3.4%	<0.0001 <0.0001 <0.0001 <0.0001

Study	Country	Methods/Population	Sample size (AF vs non-AF)	Outcome Measures	Results (AF vs non-AF)	Sig (P, CI)
Ghatnekar & Glader (2008)[56]	Sweden	Prospective multi-centre hospital based registry of consecutive stroke patients	1619 vs 4992	Length of hospital stay (days) Mortality – 28 days - 3 years	22.4 vs 20.9 13% vs 7% 43% vs 25%	<0.01 <0.01 <0.01
Thygesen et al (2009)[32]	Denmark	Prospective multi-centre hospital based registry of consecutive stroke patients	741 vs 3108	Stroke severity – SSS < 30 Length of hospital stay (days) Mortality – 30 days - 1 year	28.3% vs 13% 15 vs 9 14.7% vs 5.8% 31.7% vs 13.7%	- - <0.05 <0.05
Hannon et al (2010) & (2014)[38,39]	Northern Ireland	Population based prospective cohort study of all stroke patients	177 vs 391	Stroke severity – NIHSS at 72 hrs - MRS at 72 hrs Mortality – 28 days - 3 months	7 vs 5 3.8 vs 3.0 15% vs 12.2% 23.1% vs 16.4%	0.005 <0.001 NS NS
Tu et al (2011)[57]	World-wide multi-centre	Analysis of all placebo controlled arms of 6 RCT's from the VISTA collaborators database	819 vs 2046	Stroke severity – NIHSS Mortality at 3 months Dependency at 3 months (MRS)	15 vs 12 25.2% vs 13.6% 4 vs 3	<0.001 <0.001 <0.001
Saposnik et al (2013)[58]	Canada	Prospective multi-centre hospital based registry of consecutive stroke patients	2185 vs 10501	Mortality – 30 day - 1 year Death or disability (MRS >2) at discharge	22.3% vs 10.2% 37.1% vs 19.5% 69.7% vs 54.7%	<0.0001 <0.0001 <0.0001
Mcgrath et al (2013)[59]	Canada	Prospective multi-centre hospital based registry of consecutive stroke patients	Total 10528	Mortality – 30 day - 1 year Dependency at discharge (MRS 4-5)	Adjusted OR 1.36 Adjusted OR 1.25 Adjusted OR 1.19	CI (1.2-1.6) CI (1.1-1.4) CI (1 – 1.4)
Andrew et al (2013)[60]	Australia	Prospective multi-centre hospital based registry of consecutive stroke patients	2049 vs 3424	Mortality at 1 year	Adjusted OR 1.46	CI (1.1-2.0)
Ali et al (2015)[33]	UK	Prospective observational hospital cohort study consecutive stroke patients	78 vs 135	Stroke severity – NIHSS: - Mild-Mod (0-15) - Severe (>16) - Oxford: LACS TACS Inpatient mortality Length of hospital stay (days) Discharged to own home	11 vs 7 68.1% vs 88.1% 31.9% vs 12.2% 12.6% vs 40.4% 31% vs 18.8% 19.2% vs 4.9% 16 vs 7 38.4% vs 71.5%	<0.001 <0.001 <0.001 <0.001 <0.001 0.001 <0.001 <0.001

SE – systemic embolism; RR – relative risk; OR – odds ratio; HR – hazard ratio; CI – confidence interval, NS – non-significant; BI – Barthel Index; SSS – Scandanavian Stroke Scale; MRS – Modified Rankin Score, TACI – total anterior circulation infarct; LACI – lacunar infarct; GCS – Glasgow coma scale; NIHSS – national institute of health stroke scale

and National Institute of Health Stroke Scale (NIHSS) are widely used and validated measures of stroke severity. Four studies reported patients with AF to be 3-4 times more likely to suffer strokes categorised as severe according to these scales as compared to patients in SR.[30-34] The Oxford classification divides strokes into 4 groups depending on the combination of neurological impairments. This classification has a strong correlation with prognosis, with total anterior circulation syndrome (TACI) exhibiting the worst prognosis (1year mortality ~ 60% and dependency ~ 35%), and lacunar syndromes (LACI) exhibiting the best (1 year mortality ~ 10% and dependency ~5%).[34] Analysis of patients from the European biomed study,[26] and patients randomised in the first international stroke trial (IST1)[35] both showed that 30-40% of patients with AF suffered TACI strokes compared to between 20% and 25% of patients in SR, while the proportion of LACI strokes was significantly smaller for patients with AF (13-16% AF vs 26-29% SR). AF stroke is associated with lower levels of consciousness[35,36] and greater initial functional impairments as assessed by Modified Rankin scores (MRS) and Barthel indices (BI).[25, 27, 37-39]

A number of mechanisms have been postulated to explain these differences in stroke severity. Firstly, cardioembolic strokes secondary to AF typically result from embolisation of fibrin rich (red) clots from the left atrium, 90% of which come from the left atrial appendage.[40] These are typically larger than the platelet rich (white) clots associated with atheromatous disease and are more likely to occlude a larger vessel calibre resulting in more severe stroke.[35] A post-hoc analysis of patients undergoing magnetic resonance (MR) diffusion and perfusion imaging prior the thrombolysis in a phase 2 RCT, the EPITHET trial, showed that patients with AF typically had greater volumes of infarction (52mL vs 16mL, p< 0.05), higher rates of haemorrhagic transformation (63% vs 38%, p< 0.01) and greater volumes of brain undergoing severe post infarct hypoperfusion, than in patients in sinus rhythm.[42] This later finding of post infarct hypoperfusion suggests that a second mechanism for greater stroke severity may come from the fact that while atheromatous disease develops gradually, allowing greater brain collaterals to develop, this is unlikely to occur in AF strokes due to the abrupt nature of vessel occlusion. Indeed, the quality of collateral circulation at the time of stroke has itself been shown to predict patient outcome particularly when the extent of penumbral schema is high.[43] A further factor potentially contributing to the state of severe hypoperfusion in AF related stroke is a reduced cardiac output. We typically attribute 15-20% of cardiac output to atrial contraction,[44] which is lost in chronic AF, and results in reduced regional cerebral blood flow even before a stroke occurs.[45]

Disability and Mortality

A greater index stroke severity is likely to result in greater disability, and indeed 8 of the 9 studies reporting on functional outcomes revealed a significantly greater dependency, as measured by MRS or BI, at 3, 6 and 12 months following AF stroke.[26, 37, 52-55, 57-59] Lin and colleagues[37] performed a very comprehensive comparative analysis of function following stroke showing AF stroke to be associated with at least double the proportion of patients classed as severely dependent compared to non-AF stroke at 3, 6 and 12 months following stroke, but that this difference declined with time and was not statistically significant at 12 months. This may be related to a higher early mortality of severely impaired AF stroke patients that excluded these patients from longer term follow up.

Twenty-one studies reported on differences in mortality, from 1 month up to 5 years, and all but 2[38, 46] suggested significantly higher mortality rates in patients with AF compared to those without. The analysis by Wolf and colleagues[46] included patients suffering transient ischaemic attacks (TIA's) representing 10% of the cohort, which may have contributed to why no difference was seen. Pooling

Table 2: Pooled analysis of mortality rates following stroke in patients with and without AF

	AF	Non-AF
30 day mortality rate (%)*	16.3	7.5
1 year mortality rate (%)**	37.4	19.5

* Candelise et al,[47] Gustaffson & Britton,[48] Broderick et al,[49] Sandercock et al,[50] Lin et al,[37] Lamassa et al,[26] Kimura et al,[31] Ghatnekar et al,[56] Thygesen et al,[32] Hannon et al,[38] Saposnik et al.[58]

** Broderick et al,[49] Lin et al,[37] Thygesen et al,[32] Saposnik et al.[58]

the data from 11 of the studies that prospectively or retrospectively reported absolute figures for 1 month mortality, and 4 studies reporting the same for 1 year mortality, reveals that overall, stroke associated with AF is twice as likely to be fatal compared to non-AF stroke (table 2). Although the majority of difference seen in disability and mortality between AF and non-AF stroke can be attributed to stroke severity and age, it is interesting to note that some of the more recent published analyses,[32, 58, 59] report an increased death and disability in patients with AF stroke even when age and stroke severity were adjusted for in multivariate models. This may be related to an increase in cardiac complications following stroke. In fact, Tu et al[57] investigated the rate of serious cardiac adverse events (SCAE's) following stroke in nearly 3000 patients from 6 RCT registries and found an independent association with AF stroke patients, which included acute coronary syndromes, pulmonary oedema, ventricular tachycardia/fibrillation and cardiac arrest.

Length of Stay and Discharge Destination

An increased stroke severity and inpatient dependency associated with AF stroke is reflected in longer lengths of hospital stay, and was reflected in all 6 studies that reported this outcome comparison.[25, 26, 31, 32, 33, 56] The overall average lengths of hospital stay (LOHS) vary dramatically between studies (9 days to 51 days), and are likely to reflect differences in the models of care provided for stroke in different cities and countries. The studies by Jørgensen et al,[25] Lamassa et al,[26] and Ali et al[33] also highlight that patients suffering AF related stroke are significantly more likely to require institutional care on discharge. Both hospital stay and institutional care are likely to incur significant direct healthcare and societal costs.

Longer-Term Prognosis

The effect of atrial fibrillation as an independent predictor of longer-term mortality has been studied. Long term follow up of patients evaluated in the Copenhagen stroke study revealed atrial fibrillation to be an independent predictor of survival at 5 years but not 10 years.[61] A similar study from Norway failed to show that atrial fibrillation was associated with overall mortality at 12 years following stroke,[62] suggesting this lack of association may be explained by the high early attrition rate in patients with AF.

The risk of stroke recurrence also appears to be higher in patients with AF. The Framingham analyses by Wolf et al[46] and Lin et al[37] both show higher rates of stroke recurrence at 6 and 12 months, while a retrospective evaluation of a Spanish stroke cohort of 915 patients (22% AF) suggested this association persists for up to 5 years.[63] Reassuringly however, they also showed that stroke recurrence rates in patients with AF could be reduced to non-AF rates by the use of anticoagulation.

Effect of AF on The Cost of Stroke

We found 9 studies that directly compared the costs of stroke among patients with AF or cardioembolism (CE) and those without. These are highlighted in table 3. Studies distinguishing cardioembolic stroke have been included as AF tends to account for 75-80% of these.[38, 64] Studies vary in their methodology, perspective, duration, and cost inclusions. Cost studies can be generated in two ways. 'Top down' analyses utilise epidemiological data and diagnoses related cost to produce data that are usually generalisable across a broad group of individuals e.g. national, but may compromise on accuracy. 'Bottom up' studies, often undertaken prospectively, apply a unit cost to all aspects of care associated with a diagnosis, that cumulatively produce a more accurate account of true costs, but are less generalisable across differing health and social economies. Both can provide useful insights into cost differences for patients with AF.

Acute Costs

Acute care costs were reported by 6 studies, all of which reported significantly higher costs among patients with AF/CE than without.[33, 38, 64-67] Although overall costs vary significantly between differing countries and according to study methodology, strokes related to AF/CE are associated with a 25-37% increase in inpatient costs compared to stroke patients without AF/CE. Although the study by Diringer et al[65] did not report actual cost differences, they did show that AF was an independent predictor of inpatient cost along with length of stay, NIHSS, heparin use, male sex and history of ischaemic heart disease (IHD). Studies that included post-acute rehabilitation phases[33, 64] also revealed cost increases of 50-60% compared to non-AF patients. In a UK analyses, Ali et al[33] estimated that the adjusted independent effect of having AF on costs was an additional £2,173 (95% confidence interval 91-4,254), which represented nearly 40% of the costs for non-AF stroke. Wang et al[67] also reported the presence of AF to independently add 26% to the acute costs of stroke in a US 'top down' study, however they excluded patients over the age of 65 years, and thus are likely to underestimate the cost differences between these groups as AF related stroke is likely to be more prevalent among this older excluded cohort.

Longer Term Costs

Four of the studies analysed cost data for periods of up to 3 years, and also report higher costs among patients with AF/CE. Luengo-Fernandez et al[68] performed a population-based prospective study to analyse predictors of 1-year direct stroke costs in the UK. They followed 346 patients suffering ischaemic or haemorrhagic stroke, as well as subarachnoid haemorrhage, through the Oxford Vascular Study between 2002 and 2004, and showed 1 year costs to be significantly higher among patients with AF (£9,667 vs £5,824, p=<0.001). While univariate analysis did indicate AF to be a predictor of 1-year costs, the significance of this association disappeared when adjustments were made for stroke severity (NIHSS), which accounted for approximately 50% of cost variance. The Berlin Acute Stroke Study[69] was one of the first cost comparative studies to include both direct and indirect costs. They reported higher total 1 year costs among patients with AF compared to those without (€ 14,924 vs € 13,330, p=<0.01), driven by differences in direct costs. Indirect costs were greater among non-AF patients as they were younger and more likely to be in paid employment at the time of stroke. They did not however include the indirect costs of loss of productivity from informal care arrangements which may have influenced this finding. The only study comparing costs up to 3 years post stroke utilises national registry data from Sweden.[56] Atrial fibrillation was present in 24.5% of the 6,611 patients studied and was associated with higher 1 year (€ 9,012 vs € 8,447, p= <0.001) and total discounted 3-year costs (€ 10,192 vs € 9,374, p= <0.001), but cost differences in years 2 and 3 were not

Table 3: Summary of studies comparing costs of stroke in patients with and without AF and cardioembolic (CE) stroke. Both 'bottom up' and 'top down' studies included.

Study	Country (year)	Mean age (yrs)	Design	Diagnosis		N	% AF	Time period	Cost inclusion	Costs of IS (£)		Comments
				AF/ CE	Stroke					AF/CE	SR	
AF vs SR												
Diringer et al (1999)[65]	USA 1996 Tertiary centre	70 yrs	Prospective hospital cohort	ECG	Assessment and imaging	191	7.3%	IP stay	IP direct costs excluding physician fees	-	-	AF independently associated with IP cost. High use of ICU (16%) but low proportion of patients with AF. Average IP cost of stroke £3,871 ($4408)
Luengo-Fernandez et al (2006)[68]	UK 2002	75 yrs	Population based prospective cohort	ECG	Assessment and imaging	346	21 %	1 year	Direct health and social costs	£9667	£5824	Association of AF with 1 year costs lost significance in multivariate analysis.
Bruggenjurgen et al (2007)[69]	Germany 2001 Tertiary centre	74 yrs	Prospective cohort	ECG	Assessment and imaging	367	19.3%	1 year	Direct indirect Total	€11,979 €3125 €14,924	€88117 €4513 €13330	AF independent predictor of acute care costs. Indirect costs for patients with SR> AF. Excluded patients that died (7.5%)
Ghatnekar & Glader (2008)[56]	Sweden 2001	74 yrs	Retrospective evaluation of national registry data - top down	ECG	ICD – 10 codes 161/163/164	6611	24.5%	1 year	DRG related direct health costs	€ 9012	€ 8447	Direct costs for first year significantly higher for AF patients but not for second or third year. At 3 years, still significant difference overall.
								3 year	As above	€10,192	€ 9374	
Hannon et al (2014)[39]	Ireland 2006	71 yrs	Prospective population cohort	ECG, Clinical records	Assessment and imaging	568	31%	IP stay	Direct costs 'bottom up'	$15,025	$11,196	Cost differences were statistically significant (p<0.005). Proportion of patients in work significantly lower among patients with AF prior to index stroke. Indirect costs included.
								2 yrs	Direct and indirect costs 'bottom up'	$36,865	$18,691	
Ali et al (2015)[33]	UK 2012	75 yrs	Prospective hospital cohort	ECG, clinical record, exam	Assessment and imaging	213	37.3%	IP and OP care costs	Direct costs 'bottom up'	£9,083	£5,729	Significant differences in direct costs (p=<0.001). Adjusted independent effect of AF was an additional £2,173.
Wang et al (2015)[67]	US 2010-12	54 yrs	Retrospective evaluation of national commercial claims data	DRG code	DRG code of follow up events	33,500	7.2	IP stay – first stroke	Direct costs 'top down'	$23,770	$18,779	Cost differences statistically significant (p=<0.002). Excluded patients aged > 65 yrs, therefore likely underestimate of costs differences. Adjusted independent effect of AF was an additional $4,905 for first time stroke & $3,315 for repeat stroke.
								IP stay – repeat strokes	Direct costs 'top down'	$24,199	$20,929	
CE vs Non-CE												
Yoneda et al (2003)[66]	Japan 2000 Tertiary centre	70 yrs	Prospective hospital cohort	ECG, records, clinical exam	Assessment and imaging	179	33% (27% AF)	IP stay	IP direct costs excluding meals	$8356	$6163	Significant differences cost of CE stroke vs non-CE stroke. High rates of ICU use (55%), low mortality (3%), younger population.
Winter et al (2008)[64]	Germany 1999 Tertiary centre	68 yrs	Prospective hospital cohort	ECG, records, clinical exam	Assessment and imaging	379	26.7% (20% AF)	IP stay	IP direct costs – only PT & SALT	€ 4890	€ 3550	Duration of post acute care not documented. Cost differences statistically significant.
								Post acute period	IP rehab facility or therapy clinic	€16,480	€10,500	

CE – cardioembolic; ECG – electrocardiogram; IS – ischaemic stroke; IP – inpatient; PT – physiotherapy; SALT – speech and language therapy; ICD – international classification of diseases; ICU – intensive care unit; DRG – diagnosis related group; > - more than

significantly different to those without AF. Costs however only included recurrent inpatient admissions and excluded outpatient visits, rehabilitation, social care costs and indirect costs, which may explain the apparent small differences seen. Despite this, AF remained an independent predictor of 3-year costs after adjustment for age, sex, co-morbid disease, stroke recurrence, mortality, institutionalisation and healthcare region. More recently, Hannon et al[39] undertook a well conducted, prospective, population based, 'bottom up' comparison of direct and indirect costs after stroke among patients with and without AF in Ireland. Costs among patients with AF were double those of non-AF patients ($ 36,865 vs $ 18,691, p= <0.001) despite fewer patients in paid employment at the time of stroke in the AF group.

Economic Implications of AF-Stroke

The evidence to date thus suggests that strokes due to AF are significantly more costly than non-AF stroke. This is important for a

number of reasons. First, as our population ages, the proportion of stroke due to AF will undoubtedly increase, and without significant improvements in the use of anticoagulation, overall costs of stroke to health and social economies are likely to rise. Studies already inform us that AF-strokes account for 40-50% of an economy's total stroke costs, despite making up only a third of these patients.[33,39] Second, this increase in AF burden may be accelerated by the increasing use of prolonged cardiac monitoring techniques, particularly among patients with cryptogenic stroke. Studies have suggested that the use of 30-day cardiac monitors post cryptogenic stroke can uncover a diagnosis of AF in over 10% of patients;[70] this compares to less than 2% using only 24 hours of monitoring.[71] Third, if we are to undertake cost effectiveness analyses for interventions aimed at preventing AF-stroke, then cost of stroke data should be AF specific. Such economic analyses compare changes in health state as a result of an intervention with the associated change in the total cost to the economy. Taking anticoagulants for example, using general cost of stroke data may underestimate their cost effectiveness, as anticoagulants aim to prevent AF-stroke, a more costly health outcome to the economy, than non-AF-stroke. In a recent systematic review of 18 cost effectiveness studies of the novel oral anticoagulants for stroke prevention in AF, only 2 utilised stroke cost data that were AF specific.[72] Further, the distribution of stroke severities among patients anticoagulated for AF that are used in these economic analyses are generally derived from randomised control trial (RCT) data. A unit cost is then applied to these stroke severities e.g. mild, moderate, severe or fatal. This may not translate into what is seen in clinical practice due to the selection bias among RCT participants (younger and fitter), and due to the fact that anticoagulation control among warfarin users is often better among trial participants. For patients who suffer strokes while on warfarin, early and late outcomes are improved if INR is therapeutic on admission.[73] It is not surprising thus to find that stroke severity distributions among patients with AF from epidemiological data reveal greater proportions of severe and fatal strokes than reported in RCT data (45% vs 7-34%).[74] Thus, unless analysts use real-life data on stroke severity distribution among patients with AF, they further risk underestimating cost effectiveness of preventative strategies. Such analyses are now available, from UK cohorts at least.[39, 75] These are timely developments given the introduction of even newer oral anticoagulants to healthcare markets (e.g. Edoxaban), as well and the emergence of novel convenient patch cardiac monitors (e.g. Zio patch monitor©), and endovascular approaches to stroke prevention (e.g. Watchman©). Cost effectiveness analyses of all of these interventions will enable policy decision makers to make informed decisions regarding their provision and use.

Conclusion

AF is a growing problem across both developed and developing countries. Patients with AF are likely to suffer strokes that are more severe than patients without AF, and are twice as likely to be dead at 30 days and at 1 year. Stroke sufferers are more disabled and more costly to their health and social care economies as a consequence of their AF. Unfortunately, economic studies often underestimate the cost effectiveness of interventions such as anticoagulants to prevent stroke among these patients as they do not take into account the excess costs of AF related stroke. Despite the clinical evidence to support anticoagulation in patients with AF, anticoagulation use in this population remains sub-optimal, and suggests an ongoing need to educated clinical decision makers. Adjustment of future economic analyses of interventions to prevent AF-stroke to improve accuracy of cost effectiveness, may help improve the availability of such interventions, and ultimately help reduce the disease burden.

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Value of The Wearable Cardioverter Defibrillator (WCD) as a Bridging-Therapy before Implantation of a Cardioverter Defibrillator (ICD)

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Abstract

Wearable cardioverter defibrillators (WCD), initially available in 2002, have recently experienced more routine use in many institutions as a means of preventing sudden cardiac death (SCD) prior to implantable cardioverter defibrillator (ICD) evaluation or implantation. WCD differ from ICD by their noninvasive nature, making them well suited for patient populations who have a chance for significant cardiac recovery (such as after an acute myocardial infarction).

Despite their noninvasive nature, WCD treatment of sustained ventricular tachyarrhythmias is highly successful. An additional feature is the use of response buttons, which reduces the number of conscious shocks. Duration of use varies by condition but is typically several weeks to several months. Numerous studies have shown good compliance with WCD use and excellent efficacy. Although few prospective studies have been published, several are in progress including a randomized control trial of high risk patients after myocardial infarction.

WCD use is rapidly gaining popularity for patients with recent myocardial infarction, recent-onset cardiomyopathies, and acute or subacute myocarditis. Surgical delays in implanting an indicated ICD or after ICD removal are also common. WCD removal occurs when the patient either qualifies for an ICD implantation or is determined to no longer have elevated SCD risk.

Introduction

Sudden cardiac death (SCD) is a common mode of mortality in Western countries, reported to account for 81 deaths per 100,000 person-years in Germany.[1] While SCD may result from bradyarrhythmias, the most common initial life-threatening arrhythmias are believed to be ventricular tachyarrhythmias.[2,3] Defibrillation therapy, if provided timely, is highly effective in reversing ventricular tachyarrhythmias and aborting SCD.[4]

Implantable cardioverter defibrillators (ICD) have demonstrated efficacy in reducing SCD and mortality in general among specific populations identified to have high SCD risk.[5,6,7,8,9,10] However, ICD therapy is not without hazards and due to its invasive nature is generally reserved for patients with permanent SCD risk.

Key Words:
Implantable Cardioverter Defibrillator, Sudden Cardiac Death, Wearable Cardioverter Defibrillator, Ventricular Tachyarrhythmia.

Disclosures:
None.

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Still, there remain patient populations with high SCD risk that are temporary or changeable due to evolving cardiac conditions, and may be better served by non-invasive therapy. For some patients hospitalization for cardiac monitoring (with defibrillation therapy provided by medical personnel) is a rational choice, but in general this solution cannot be justified for long periods of time (i.e., weeks or months). The gap between hospitalization and ICD implantation remains a difficult decision for physicians. During this time a wearable cardioverter defibrillator (WCD) is an appropriate therapeutic option for many patients.

Since first FDA approved in 2001 and CE marked the same year, the WCD has been used on more than 150,000 patients[12] and use continues to grow in Europe and the USA. However, few prospective studies and no randomized trials have been published. In this article the WCD will be reviewed using published data as well as personal experience.

Device Description

The WCD has been described in technical detail several times[13,14,15,16] [figure 1]. In general, it functions similarly to an ICD in that it automatically detects and treats ventricular tachyarrhythmias (VT/VF). However, it has several important differences. First, the WCD delivers a sequence of escalating alarms whenever VT/VF is detected. These alarms are a minimum of 30 seconds in duration. As a result the typical time from arrhythmia onset to shock delivery

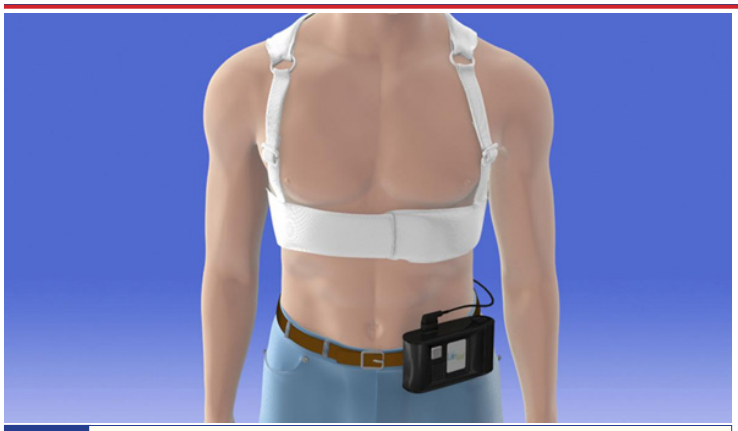

Figure 1: WCD device

is 45 seconds (detection and confirmation time included). As the detection algorithm operates continuously through the alarms, non-sustained arrhythmias (i.e., less than 30 seconds in duration) are not treated by design. Second, a conscious patient may prevent a shock by holding the two response buttons of the WCD. Thus, almost all treated ventricular arrhythmias occur in unconscious patients who generally do not remember the treatment itself. This combination (unconscious, sustained VT/VF) meets the classic definition of sudden cardiac arrest.[17]

The treatment shock (150 joules in a truncated exponential biphasic waveform) delivered by a WCD is similar to many external defibrillators. However, the 98% first shock success in commercial use[12] is higher than generally reported during resuscitation trials whether community-based or inpatient.[18] This success is in part due to the speed by which defibrillation occurs, although other factors such as the apex-posterior defibrillation pathway may contribute.[19] In a study of induced VT/VF, WCD defibrillation using 70 joules was successful in 10/10 attempts.[20] Hence, 150 joules likely represents a reasonable margin of safety for WCD users.

The WCD is presently available from only one manufacturer (ZOLL, Pittsburgh, USA). From the time of commercial introduction to the present LifeVest 4000 device, the size and weight of the design has decreased significantly while maintaining the essential features of detection and treatment of VT/VF. Additional enhancements were also added such as automatic downloading of device-stored information, increased stored memory and improvements to benefit patient-device interactions.

The manufacturer has maintained a website since inception for viewing downloaded information including daily use and ECG recordings of alarms received by patients. In the current version of the website it is possible to arrange for automated alerts (email or fax messages) of treatments, compliance and other data. In our practice, we do not use the automation and instead rely instead upon surveillance of the website at a time of our convenience. We find that significant events requiring immediate attention, such as treatments, are reported rapidly by patients and/or witnesses.

Prior Studies

There are a few prospective studies of WCD performance and many retrospective analyses of specific populations. The regulatory approval study for the FDA (WEARIT/BIROAD) reported 6 of 8 VT/VF events were successfully resuscitated and only 6 inappropriate shocks occurred over 900 patient-months of monitoring.[21] The study was designed to compare WCD resuscitation rates to a historical control of 25% success. Longer term mortality was not a study feature, as successful resuscitation in these populations (transplant listed, acute myocardial infarction with ventricular dysfunction, or recent CABG surgery with ventricular dysfunction) would lead to ICD implantation rather than continued WCD use. In essence, the WCD was considered bridge therapy to cardiac transplantation, ICD implantation, or improvement in cardiac function.

The WEARIT II registry has completed US enrollment of 2,000 patients and is awaiting completion of one year follow-up data collection. An interim report after all subjects completed WCD use revealed that there were 120 sustained VT/VF episodes during WCD use in 41 patients (2% of the patient population). Interestingly, only 30 of the episodes were actually treated by the WCD. The other 90 sustained VT/VF episodes were not treated due to response button use by conscious patients.[23]

There are two randomized control trials of WCD use that are currently enrolling subjects. The Vest Prevention of Early Sudden Death Trial (VEST) will examine whether WCD use can reduce SCD among patients with an ejection fraction ≤35% during the initial three months following myocardial infarction. Started in 2008, the study plans to compete enrollment of 1900 subjects in 2016. In the background of DINAMIT[24] and IRIS[25] failing to show utility of ICD implantation early after myocardial infarction in similar patients, the results will be of great interest to the medical community.

The second randomized control trial, WCD use in hemodialysis patients (WED-HED), began enrolling in 2015 and plans to complete enrollment of up to 2,600 subjects by 2019. It will examine the effect of WCD use on SCD among patients 50 years of age or older during the first six months after hemodialysis initiation. In contrast to most trials of primary prevention of SCD, subjects must have an ejection fraction over 35%. Hemodialysis patients are well known to have a high mortality rate, particularly during the first months after initiation, and sudden death accounts for about 25% of mortality regardless of ejection fraction.[26]

There are numerous retrospective analyses using commercial data prospectively collected by the manufacturer. Most are collections of smaller specific patient subgroups such as congenital heart disease[27] or children[28, 29] but three deserve mention as significant evidence of safety and efficacy in real-world application.

The first involves 3,569 patients, which represented all US WCD users between 2002 and 2006.[30] These patients had a median daily use of 21.7 hours and a mean duration of use of 52 days. While wearing the WCD, 59 patients had 80 VT/VF treated. Of 80 VT/VF events, 79 were converted on the first shock. However, 8 patients died after treatment (4 while under medical care, 2 due to signal disruption, 1 pacemaker interaction, and 1 bystander interference). Other deaths during WCD wear were due to asystole (17 deaths), respiratory arrest (2 deaths) and pulseless electrical activity (1 death). This analysis indicates that the large majority of patients are able to use the WCD properly, that most sudden cardiac arrests begin as VT/VF events, and that the WCD is highly effective in converting such arrhythmias. Lastly, the authors compared WCD use to ICD use and found similar survival.

Another study by the same group compared propensity-matched revascularized (post-CABG surgery or PCI) patients who either used a WCD or were part of a registry maintained by the institution.[31] All patients had significant ventricular dysfunction (ejection fraction

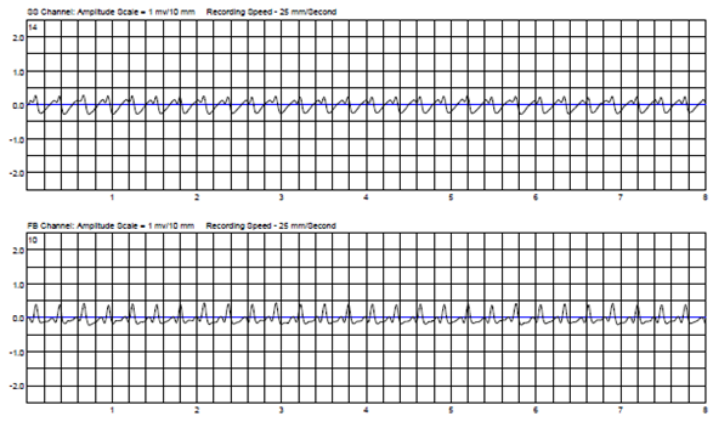

Figure 2: ECG of patient's VT event

≤35%). The mortality at 90 days was found to be lower for WCD users (7% mortality compared to 3% in WCD users for CABG patients, 10% to 2% for PCI patients) and this effect persisted after propensity matching. The improved survival was not entirely attributable to the detection and treatment of V/VF events as only 1.3% of patients had an appropriate therapy. The authors speculated the larger than expected difference may have been due to the fact that WCD users received more consistent follow-up for ICD evaluation and/or that the ECG monitoring may have revealed additional treatable conditions. Notably, monthly mortality was significantly higher in the first three months of follow-up for both groups.

The final study used the outcomes of 8,453 patients who wore a WCD after acute myocardial infarction.[32] A total of 133 patients (1.6%) were appropriately treated and 91% were successfully resuscitated. The time from index myocardial infarction to treatment was a median of 16 days, with 75% of treatments occurring in the first month and 96% within the first three months. This parallels the well-known early mortality of these patients. Patients who were resuscitated had a one year survival rate of 71%. This study demonstrates that patients selected for SCD risk are most likely to have a sudden cardiac arrest event early, before ICD consideration, and that resuscitated patients have a promising survival trend after WCD use has ended.

First-Hand WCD Experience

At our institution, we have used the WCD on a regular basis since mid-2010. Our experience with over 225 patients mirrors the commercial findings of the US, that is, we find the WCD is well tolerated by patients. A subset was presented during the 2013 fall meeting of the Germany Cardiology Society. In that subgroup, patients used the WCD a median of 22 hours per day and the average duration of use was 72 days. There were no treatments, but one patient experienced a conscious VT and successfully used the response buttons for 55 minutes, preventing a conscious shock [figure 2]. This patient subsequently received an ICD. This patient exemplifies two points. First, the WCD may deliver fewer appropriate shocks than an ICD as conscious patients can prevent being shocked on VT. Reducing the numbers of shocks in ICD patients delivered has recently been found to improve mortality.[33,34,35,36,37,38] Second, without the monitoring of the WCD this event may have been missed and the patient would have not received an ICD. Monitoring for sustained VT is an underappreciated, yet very valuable, aspect of WCD therapy.

As only 43% of our patients needed permanent protection with an ICD, one of the major advantages of WCD use lies in the fact that it was easily removed after medical optimization or simple time permits cardiac function to recover. An extra 2 to 3 months is a significant amount of time for evaluation before deciding on permanent therapy that is not completely benign. While ICD therapy clearly improves survival in defined populations for some patients, other patients will experience unnecessary painful shocks, device infections, and other morbidities.[39]

Discussion/Patient Selection

The WCD is best utilized as a method of bridging patients over high risk periods for SCD until ICD implantation or evaluation can occur. At our institution, we most frequently use the WCD for patients who have significant ventricular dysfunction, thus raising SCD risk, but also have a reasonable chance of recovering cardiac function. In addition, we use the WCD when patients have an uncertain risk of SCD, such as patients who may have a genetic predisposition to SCD but have not yet undergone a full evaluation, and for discharging patients safely when an ICD is indicated but cannot be implanted due to a surgical contraindication.

Patients who have a chance of cardiac recovery are perhaps the most exciting use for WCD. These patients have experienced a recent cardiac event (acute myocardial infarction, revascularization, or diagnosis of non-ischemic cardiomyopathy), have dilated cardiomyopathy requiring medical optimization, or have acute or subacute myocarditis. In all of these patients groups, immediate ICD implantation is not recommended until disease stabilization is established.[40,41]

In our case series, myocarditis was a frequent diagnosis, accounting for 45% of the patients. Prior to the WCD, myocarditis patients presented a difficult decision as the majority will recover yet significant SCD risk exists regardless of ejection fraction. Thus ICD implantation during the acute/subacute period is currently reserved for those who have a secondary prevention indication. As the disease progresses only about 21% of patients will develop dilated cardiomyopathy[42] and require permanent SCD protection through ICD implantation. Patients with late gallium enhancement during cardiac magnetic resonance imaging appear to have higher risk of mortality and SCD during the recovery phase[43] but screening for SCD is not well defined at this time. We frequently rely on WCD use for such patients until either risk resolves or the requirements for an ICD are met.

For decades, the initial months after an MI has been recognized as an especially high risk period for SCD.[44] As a clinical strategy, the sizeable proportion of patients recovering ventricular function after MI makes the choice of a WCD particularly attractive in the post-infarction period. Still, trials of ICD use early after MI (DINAMIT and IRIS) have not proven beneficial.[24, 25] This lack of benefit has been ascribed to insufficient power, competing risks of mortality, the risk of surgical implantation close to the time of the cardiac event, and/or negative effects of ICD shocks leading to increased heart failure.[24,45,46,47] Although the outcome of VEST remains in the future, the 2014 HRS/ACC/AHA Expert Consensus[40] acknowledged that patients with significant ventricular dysfunction may benefit from WCD use prior to ICD evaluation.

The question of why WCD use may be successful when ICD implantation has failed in two trials is a valid one to ask. First, the differences in treatments between ICD (VT/VF) and WCD

(unconscious, sustained VT/VF) may result in fewer appropriate WCD therapies.[23] In our patient population, a conscious patient with a sustained VT used the response buttons until the VT spontaneously terminated, nicely demonstrating how the reduction in therapies may occur. This is an important aspect as ICD shocks were associated with increased non-sudden cardiac mortality in DINAMIT and IRIS, even as SCD was reduced. Second, it has been suggested that defibrillation lead implantation may cause local irritation of the myocardium, triggering VT/VF early after the procedure.[48] This issue does not exist with the non-invasive WCD and again may result in fewer defibrillation therapies. Lastly, transthoracic defibrillation may have a different clinical impact than intracardiac defibrillation on recently infarcted hearts. Shocks from ICD leads appear to result in the release of cardiac enzymes significantly more than higher energy shocks from subcutaneous defibrillators,[49] presumably due to the high focal energy gradients within the heart.[50] This incremental trauma may play an important role in the recently infarcted heart. Thus, there is good reason to anticipate better outcomes from WCD use than the results of ICD studies for this important group of patients.

Like their ischemic counterparts, many patients with non-ischemic cardiomyopathy recover significant ventricular function after diagnosis. Peripartum cardiomyopathy and chemically-induced cardiomyopathy (e.g., alcoholic cardiomyopathy) are associated with up to 90% recovery after causative factors are removed. Even patients with idiopathic dilated cardiomyopathy commonly improve with medical optimization.[51] Early protection from SCD remains important as SCD occurs during the optimization period without SCD protection[51] and, if an ICD is implanted, those with recently diagnosed non-ischemic cardiomyopathy are just as likely to experience ICD shocks.[52] It has also been noted that patients who improve ventricular function after ICD implantation receive shocks at similar rates to those who do not improve.[53,54] Based on the number of articles demonstrating that non-ischemic cardiomyopathy patients frequently improve after ICD implantation, it may make sense to use a WCD for longer periods of time - perhaps up to a year - in patients who tolerate it.[40]

Conclusion

The WCD is a welcome additional to the therapeutic options for SCD prevention. Its non-invasive nature and effectiveness in terminating VT/VF make it an excellent choice for patients that do not yet meet the indications for permanent SCD protection afforded by ICD implantation. Although prospective studies are few, many retrospective analyses indicate that 1) patient acceptance and compliance with use is excellent, 2) effectiveness in terminating VT/VF is high, and 3) shocks are minimized by allow conscious patients to use response buttons. Patients with myocarditis, acute myocardial infarction with ventricular dysfunction, and cardiomyopathy with ventricular dysfunction may benefit by WCD use until the potential for recovery has been determined.

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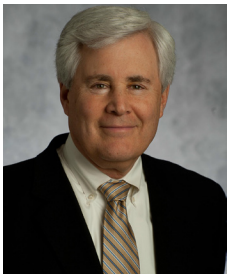
Dr. Petras Stirbys, MD, PhD

Clinician, cardiosurgeon, implantologist of cardiovascular electronic devices, arrhythmologist, researcher. Former Vice-Rector for clinical affairs of Kaunas Medical Academy, Head of Cardiac Pacing clinic. Currently working as implanting cardiosurgeon in the Dept. of Cardiology, Hospital of Lithuanian University of Health Sciences, Kaunas Clinics, Kaunas, Lithuania.

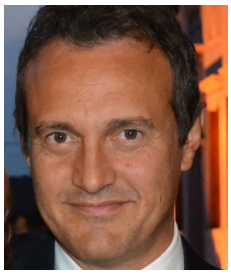


Dr. James A. Reiffel, MD

Dr. Reiffel's current research interests include the optimum management of patients with atrial fibrillation and flutter; studies in cardiac repolarization as relates to dysrhythmias and gender differences in proarrhythmic risk; and the development of new antiarrhythmic and anticoagulant pharmaceuticals.

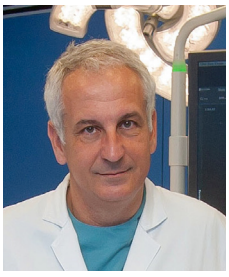
Dr. Dierk Thomas, MD, FAHA, FESC, FHRS

Dr. Thomas is head of electrophysiology at the Department of Cardiology, University of Heidelberg, Germany. His research interests include molecular mechanisms of atrial fibrillation and novel therapeutic strategies.



Dr. Giovanni Battista Forleo, MD, PhD

Dr. Giovanni B Forleo received his Medical Degree at the University of Florence, Italy. Subsequently he completed his Residency at the Catholic University in Rome. After the clinical fellowship, he obtained the PhD and has been appointed Adjunctive Professor at the University of Rome "Tor Vergata". Dr. Forleo currently serves as cardiac electrophysiologist at the University Hospital of Tor Vergata in Rome. His major area of research is related to cardiac pacing and electrophysiology. His research work has been published in a variety of international journals and was presented in many international conferences.

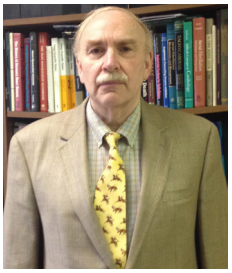


Dr. Ignacio García-Bolao, MD, PhD, FESC

Ignacio García-Bolao is Head of Cardiac Electrophysiology and Director of the Cardiology and Cardiac Surgery Department at the Clinica Universidad de Navarra. He is Full Professor at the University of Navarra. He is highly experienced in catheter mapping and ablation of atrial and ventricular complex arrhythmias, percutaneous left atrial appendage closure and CRT.

Dr. Ignasi Anguera, MD, PhD

Associate Professor of Medicine, University of Barcelona. Dr. Ignasi Anguera is the Director of Cardiac Electrophysiology Laboratory at the Bellvitge University Hospital, Barcelona, Spain. Dr Anguera is a graduate from University of Barcelona. He did cardiology training in the Hospital Clinic, Barcelona, Spain; where he was awarded a PhD. He has been faculty and staff electrophysiologist at Bellvitge University Hospital for last 10 years.



Dr. John Somberg, MD

John Somberg is currently a Professor of Medicine and Pharmacology at Rush University in Chicago. He also serves as Chief the Division of Clinical Pharmacology and the Director of the Masters in Clinical Research Program at Rush University. Dr. Somberg is the Editor of the American Therapeutics and has served for 14 years on the Circulatory Device Advisory Panel with the FDA. Dr. Somberg completed a cardiology fellowship at the Peter Bent Brigham Hospital, Harvard Medical School, ran the Cardiac Arrhythmia Service at Albert Einstein and was the Chief of Cardiology at the Chicago Medical School prior to his current position. His areas of specialization are anti-arrhythmic pharmacology and drug and device development.

Dr. Angelo Biviano, MD, MPH

Angelo Biviano, is an Esther Aboodi Assistant Professor of Clinical Medicine at NewYork-Presbyterian Hospital, Columbia University Medical Center. A clinical cardiac electrophysiologist, his research interests include the diagnosis and treatment of atrial fibrillation and atrial flutter using ECG surface waveform and intracardiac electrogram signal processing techniques.

Dr. Ali N Ali, MBChB, MRCP, MSc

Consultant Stroke, Geriatrics and General Internal Medicine. Honorary Senior Clinical Lecturer and Department Research Lead Sheffield Teaching Hospitals Foundation NHS Trust and University of Sheffield, UK. Main research interests include health economics, effects of aerobic exercise after stroke, and rehabilitation devices in stroke and geriatrics.

Dr. Murat SUCU, MD

He is a Professor Doctor of Cardiology. He is working Department of Cardiology and Director of Clinical Electrophysiology at the University of Gaziantep in Turkey. Dr. Sucu's clinical interests of clinical an invasive electrophysiology including both device implantation and catheter ablation therapies. Dr. Sucu has published more than 70 national and international scientific manuscripts.

Dr. Antonio Rossillo, MD

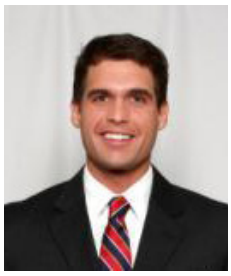
Staff member EP Section of Cardiology Department, San Bortolo Hospital of Vicenza, Italy. Medicine Graduation in 1999, University of Milan, Italy. Cardiology Degree in 2003, University of Padua, Italy. Chairman of Young EP section of Italian Society of Arrhythmology and Cardiac Pacing. Scientific Secretary of Venice Arrhythmias congress. Clinical Experience in Electrophysyology and Catheter Ablation, Cardiac Pacing and Transvenous Lead Extraction. Author or co-author of more than 40 of published articles on pacing and electrophysiology.

Dr. Bahij Kreidieh, MD

Dr Kreidieh is a Medical graduate of the American University of Beirut in Lebanon. He is currently completing his post-doctoral fellowship in Cardiac Electrophysiology at the Houston Methodist Debakey Heart and Vascular Center. His research interests include Brugada syndrome, Inappropriate sinus tachycardia, Catheter ablation techniques and Atrial fibrillation, particularly centered about the role/impact of the left atrial appendage?. Dr Kreidieh will commence Internal Medicine residency training in the University of Miami/JFK Medical Center in June, 2016.

Dr. David Delurgio, MD

Emory Saint Joseph's Hospital welcomes David B. DeLurgio, MD as the new director of Electrophysiology (EP) at the Emory Heart and Vascular Center. DeLurgio joins 17 other physicians with the Emory Heart and Vascular Center and Emory Cardiovascular Specialists in a new shared location at 5671 Peachtree Dunwoody Road, Suite 300. This suite provides a seamless patient care experience by offering a variety of cardiology services that can be managed in this convenient location.



Dr. Robert Tonks, MD

Dr Robert Tonks completed Internal Medicine residency at New Hanover Regional Medical Center in Wilmington, NC in 2014 and is currently completing post-doctoral advanced heart failure clinical research at Duke University, Division of Cardiology, Clinical Research Unit in Durham, NC. He will begin general cardiology fellowship at the University of Tennessee in Knoxville in 2016.

Dr. Tom Wong, MD

Dr Tom Wong, Consultant Cardiologist and Electrophysiologist, is the chief of the arrhythmia and device services at the Royal Brompton and Harefield Hospitals in London. His clinical expertise and research interest are in the area of arrhythmia interventions.

Dr. Ujjwal Rastogi, MD

Ujjwal Rastogi is currently the congestive heart failure fellow at the James J Peter VA Medical Center affiliated with Mount Sinai School of Medicine, New York. He completed his residency in internal medicine at Saint Peters University Hospital, New Jersey.

Dr. Jeroen J Bax, MD

Jeroen J Bax is professor of Cardiology and Director of non-invasive cardiac imaging, at the department of Cardiology, Leiden University Medical Center, The Netherlands. He has been working intensively with the European Society of Cardiology (ESC), and is currently serving as President Elect of the ESC. He has been Associate Editor of the American College Cardiology, and is currently Associate Editor of the European Heart Journal. He has co-authored numerous scientific articles, has guided many PhD fellows and his main interests of research include imaging in heart failure, stable coronary artery disease, valvular heart disease and atrial fibrillation.