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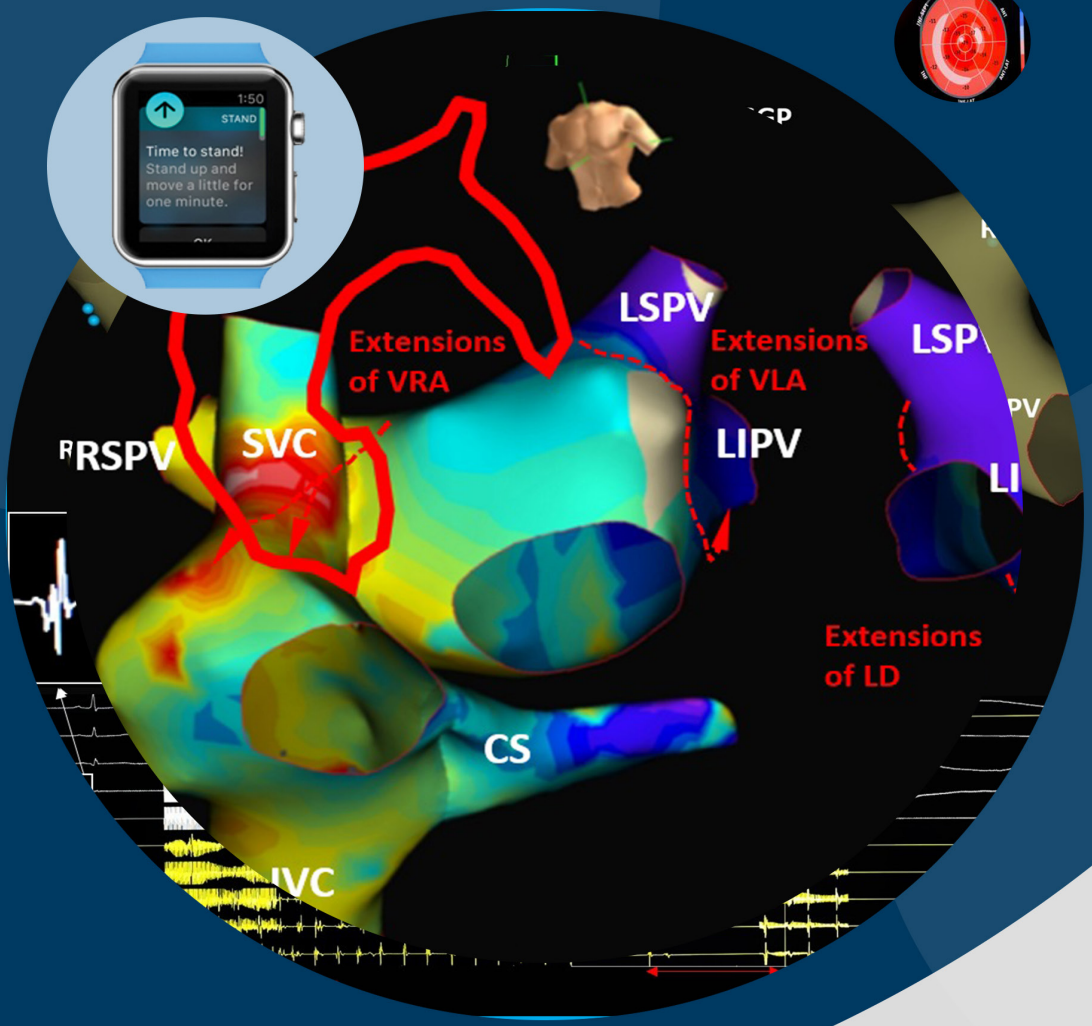

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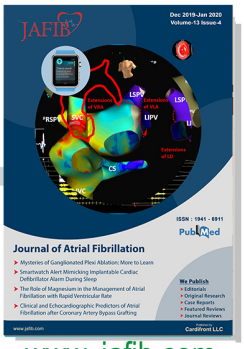

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There is Light at the End of the Tunnel

Journal of Atrial Fibrillation (JAFIB)

Dec 2020 - Jan 2021

Issue 4

Volume 13

Dear Colleagues

Welcome to the first issue of the Journal of Atrial Fibrillation in 2021. What a year that was in 2020! It was in many ways forgettable with historic events that will go down the history lane. It was the year where the world experienced a global pandemic of unprecedented magnitude in the modern history of human civilization. It was the very same year where we witnessed the incredible sacrifices of many of our colleagues in the healthcare field that saved millions of lives. We also saw how collective commitment could produce a vaccine for a tricky virus at warp speed. It was the year when the United States narrowly escaped the clutches of tyranny and democracy prevailed. This was the year that has taught us the spirit of humanity and resilience.

Congratulations to the organizers of EP-Live Austin on days of live cases. This was the 5th edition of the event where 20 lives and 15 recorded cases spanning the entire spectrum of clinical electrophysiology were displayed. Despite the limitations imposed by the pandemic, there were several thousand viewers from all over the world participating in this event.

In this issue of the journal, we have a wide variety of articles ranging from the risk of postoperative atrial fibrillation in patients undergoing open heart surgery to identification of ganglionated plexi for arrhythmia ablation. Finally, the journal has moved to a new platform which will be more robust and easier to navigate. There will be additional changes coming to the website and the editorial team as well. We appreciate your continued support of the journal and welcome your best work to be showcased for our audience. I wish you all a happy, health and prosperous 2021.

Sincerely
DJ Lakkireddy

Dhanunjaya (DJ)Lakkireddy
MD, FACC, FHRS
Editor-in-Chief, JAFIB

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Journal of Atrial Fibrillation

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Contemporary Anticoagulation Practices for Postoperative Atrial Fibrillation: A Single Center Experience

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Abstract

Aims: Postoperative atrial fibrillation (POAF) is a frequent in-hospital complication after cardiac surgery. Surprisingly, despite its prevalence, management of this condition has not been well studied. One promising approach that has been evaluated in a limited number of studies is use of anticoagulation. However, the trends and patterns of real-world use of anticoagulation in POAF patients has not been systemically investigated. In this study, we aimed to determine real-world patterns of anticoagulation use for patients with POAF.

Methods: We identified 200 patients undergoing coronary artery bypass (CABG) or cardiac valve surgery at University Hospitals Cleveland Medical Center over a 2 year period beginning January 2016 with new onset POAF. We reviewed charts to verify candidacy for inclusion in the study and to extract data on anticoagulation use, adverse outcomes, and CHA_2DS_2-VASc scores.

Results: Anticoagulation use was low after CABG, but high after bioprosthetic valve surgery. The most common anticoagulant used was warfarin. Anticoagulation use was not correlated with CHA_2DS_2-VASc score or cardioversion. Stroke and mortality were higher among patients not receiving anticoagulation, however, confirmation of this finding in larger randomized studies is warranted.

Conclusion: Anticoagulation use is low after CABG and this practice does not appear to be affected by CHA_2DS_2VASc score or cardioversion. This differs with previously reported provider attitudes towards management of this condition. Stroke and mortality appear to be elevated for patients not receiving anticoagulation but further investigation is required to confirm this observation.

Introduction

Postoperative atrial fibrillation (POAF) is a common in-hospital complication after cardiac surgery, affecting between 30-50% of patients undergoing the procedure, and is often managed by surgeons, internists, cardiologists, and critical care physicians or nurse practitioners.[1,2] Although this complication is commonly believed to be self-limited, multiple studies have demonstrated high rates of late recurrence of atrial fibrillation (AF) in these patients.[3-5] Importantly, POAF has repeatedly been associated with a higher incidence of mortality and multiple comorbidities, including stroke, heart attack, heart failure, and increased length of hospital stay.[6-11] Nevertheless, there is no consensus on the optimal short or long term management of this condition. Studies have shown promise for anticoagulation, as it has been associated with a reduced incidence of stroke and all-cause mortality.[12] These findings have not been consistently adopted into international guidelines, partly because of the lack of high quality randomized data, but likely also in part due to the general lack of information on this topic.[13-18] Furthermore, it has been previously shown that attitudes towards management of this condition vary substantially between providers.[19] In this study, we evaluate the real-world use of anticoagulation in a POAF cohort, specifically assessing the impact of cardioversion and the CHA_2DS_2-VASc score on use of anticoagulation, two important considerations in management of stroke prevention therapy.

Key Words

Postoperative Atrial Fibrillation, Anticoagulation, Cardiac Surgery

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Methods

Study Population

We included patients over 18 years of age who had undergone either coronary artery by pass (CABG) surgery or valve surgery (bioprosthetic valve in any position) and had a diagnosis of POAF. Patients with a pre-existing diagnosis of AF or a mechanical heart valve were excluded. We queried our internal cardiothoracic department surgery data base at University Hospitals Cleveland Medical Center to identify patients meeting these criteria between January 2016 and April 2017. These records were then manually reviewed to verify inclusion and exclusion criteria as noted above. Charts that met our criteria were then manually reviewed to extract remaining relevant data, including type of surgery, anticoagulant use and timing, chemical or electrical cardioversion, complications including death, stroke, or transient ischemic attack (TIA), risk factors including CHA_2DS_2-VASc score, and use of cardiac

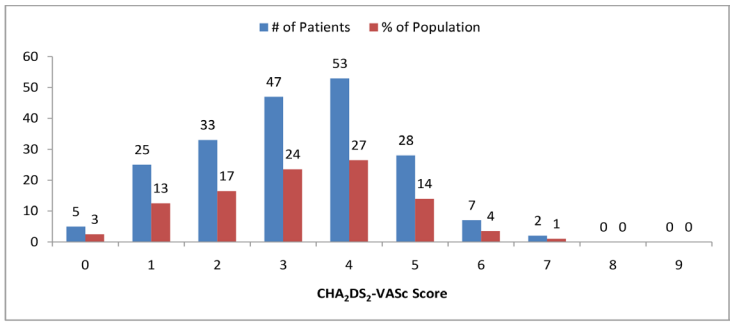

Figure 1: **Distribution of CHA_2DS_2-VASc scores among patients undergoing cardiac surgery.**

monitoring on discharge. Prescription of anticoagulation before discharge with no alternative indication for anticoagulation use was taken to mean anticoagulation for the indication of newly diagnosed POAF.

Outcomes

The primary outcomes of interest were the rates of anticoagulation use stratified by the type of cardiac surgery, CHA_2DS_2-VASc score, and the need for cardioversion. Additionally, we assessed the impact of anticoagulation on ischemic stroke and all-cause mortality at 30 days and one year after surgery. The follow up time accrued was from the date of surgery until the one year of follow up or death, whichever came first.

Statistical Methods

For rates of anticoagulation use, we excluded patients with contraindications or alternative indications for anticoagulation use. The proportion of POAF patients receiving anticoagulation was calculated for the remaining population, as well as in subgroups by type of surgery, CHA_2DS_2-VASc score, and cardioversion status. Additionally, the unadjusted incidence of stroke and mortality was calculated in the overall population, and in subgroups stratified by the use of anticoagulation. Stroke or TIA occurring on the day of surgery was considered procedure related, and excluded from analysis. All data analyses were performed using Microsoft Excel. Statistical analysis was performed using Chi-squared analysis. An alpha level of 0.05 was used for statistical significance. This study was approved by our institutional review board, and was found to be exempt from the need for informed consent.

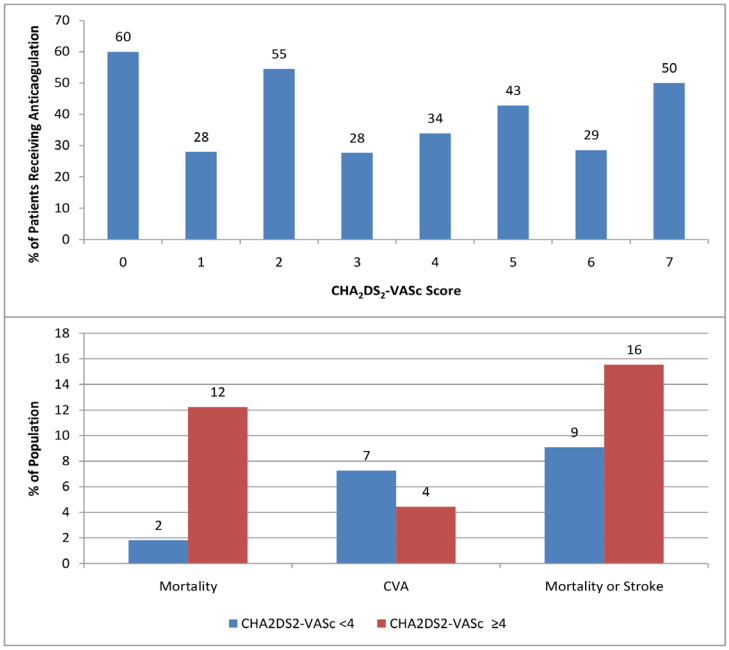

Figure 2: **Top: Percent of patients receiving anticoagulation by CHA_2DS_2-VASc score. Bottom: Percent of patients with complications by CHA_2DS_2-VASc score.**

Results

Cohort Characteristics

We included 200 eligible patients for the final analyses. Of these, 161 (81%) had CABG alone, and 39 (20%) had valve surgery either alone or in addition to CABG. The average patient age was 68 ± 12 years, and 39% of the patients were female. The average CHA_2DS_2-VASc score was 3.3 ± 1.5, with 47% of patients having a CHA_2DS_2-VASc score of 4 or greater. The distribution of CHA_2DS_2-VASc score in the overall population is outlined in Figure 1. Other demographic information can be found in Table 1.

Anticoagulation Use

Twenty three of 200 patients had a contraindication or alternative indication for anticoagulation, including mechanical valves, and were excluded. Overall, 81 of 177 patients (46%) received some form of anticoagulation, of which 80 (99%) received warfarin. For patients with valve surgery, 31 of 32 patients (97%) received anticoagulation compared to 50 of 145 patients (34%) with CABG alone. However, 55% of patients with bioprosthetic valve surgery or repair received anticoagulation before the diagnosis of AF was made. Anticoagulation use did not differ by CHA_2DS_2-VASc score (Figure 2; $\chi^2(7, 177) = 6.9$, $p = .44$).

Table 1: **Population Demographics**

		% of Population
Age		
-	<40	2.5%
-	40-50	4%
-	50-60	15.5%
-	60-70	31.5%
-	70-80	33.5%
-	>80	13%
Gender		
-	Male	61%
-	Female	39%
Hypertension		82.5%
Ejection Fraction		
-	<20%	3.5%
-	20-35%	18.5%
-	35-50%	16%
-	>50%	62%
Diabetes		39%
Prior Stroke		10.5%
Peripheral Vascular Disease		16%
Creatinine Clearance		
-	>60	75%
-	30-60	20%
-	<30	5%
Operation		
-	CABG	81%
-	Valve	20%
Cardioversion		48.5%
-	Chemical	42.5%
-	Electrical	6%

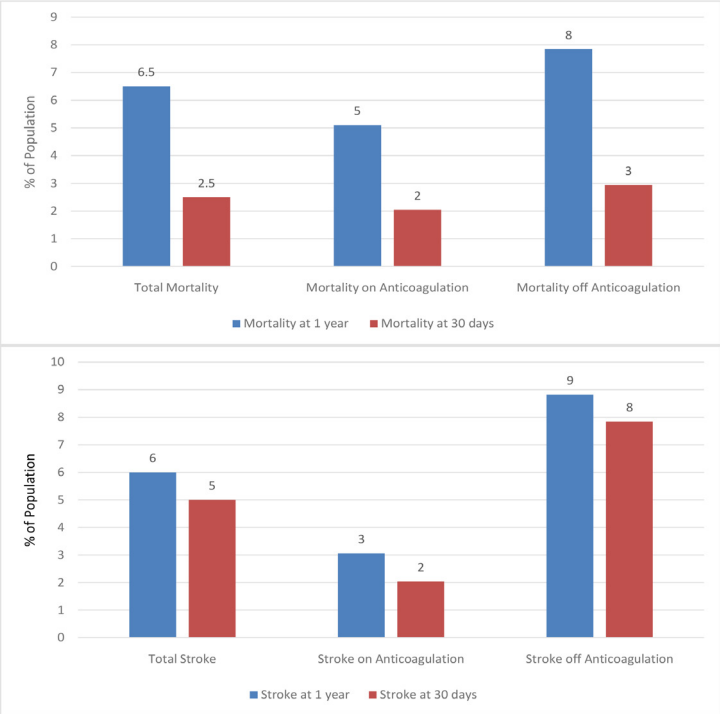

Figure 3: **Top: Percent of patients with mortality at 30 days and 1 year by anticoagulation status. Bottom: Percent of patients with stroke or transient ischemic attack at 30 days and 1 year by anticoagulation status.**

This finding remains after sensitivity analysis by excluding patients with valve surgery ($\chi^2(7, 145) = 5.9$, $p = .56$). Overall, anticoagulation use after chemical cardioversion was 47% and after electrical cardioversion was 63%. After removing patients with anticoagulation prior to AF diagnosis, these numbers drop to 43% and 57% respectively, and after removing all valve operations, they drop further to 37% and 50%, respectively. There was no statistically significant correlation between cardioversion and anticoagulation use among any of these groups. Of note, only one patient was discharged with cardiac monitoring (0.6%). This patient also received anticoagulation with warfarin prior to discharge.

Outcomes

The overall mortality rate in our cohort at 30 days and 1 year of follow up was 2.5% and 6.5%, respectively. Overall, 5.5% of patients suffered a stroke or TIA within 1 year of follow up, and 3.5% had a stroke or TIA within 30 days of surgery. Mortality was higher in the cohort with higher CHA_2DS_2-VASc scores (≥4), but no significant difference was observed for stroke or TIA (Figure 2; $\chi^2(1, 200) = 11.5$, $p < .001$ and $\chi^2(1, 200) = .53$, $p = .47$ respectively). Mortality and stroke or TIA were observed more frequently among patients not receiving anticoagulation compared with those who did (7.8% vs 5.1% and 7.8% vs 3.1% at one year respectively; Figure 3). These findings were not statistically significant ($\chi^2(1, 200) = .56$, $p = .45$ and $\chi^2(1, 200) = 2.1$, $p = .15$ respectively). There was again no difference on sensitivity analysis after excluding patients with valve surgery ($\chi^2(1, 200) = .009$, $p = .96$ and $\chi^2(1, 200) = 1.6$, $p = .24$ respectively). There was similarly no significant difference in mortality or stroke or TIA at 30 days in either the total cohort or CABG subgroup.

Discussion

Anticoagulation Use in POAF

Our primary objective was to evaluate the use of anticoagulation in a real-world cohort of POAF patients. We noted that overall, anticoagulation use was low in our patient cohort. This is not surprising given the lack of a robust evidence base and the conflicting recommendations from international guidelines.[13-18] However, our data demonstrate a higher rate of anticoagulation than in previous reports, even when limited to patients undergoing CABG alone.[12]

Role of CHA_2DS_2-VASc Score & Cardioversion

Interestingly, we found that the use of anticoagulation did not significantly increase in those who underwent a rhythm control strategy, including electrical cardioversion, although this may have been due to the small sample size in the latter group. Nonetheless, this suggests that care givers were less likely to view such interventions as an independent indication for anticoagulation. We also found no correlation between CHA_2DS_2-VASc score and anticoagulation use, signifying that this was not part of the decision algorithm among the majority of care givers. We suspect this is due to the lack of uniformity in guidelines specifically recommending this score for risk stratification in the POAF population. Alternatively, anticoagulation use may have been driven by concern for postoperative bleeding. We also saw a strikingly low rate of direct oral anticoagulant use compared with warfarin. These factors may be attributable to differences in surgeon preference at our institution.

A recent nationwide survey of provider attitudes found that there was substantial variation in practice patterns regarding management of POAF, further corroborating our findings that management of this disease process is inconsistent.[19] Interestingly, however, most providers in this survey reported using the CHA_2DS_2-VASc score for risk stratification as well as anticoagulation use after cardioversion. This stands in contrast to our findings that neither of these factors correlated with anticoagulation use. It is unclear if these differences were due to ideological differences between cardiologists (making up the majority of survey respondents) and cardiothoracic surgeons or critical care physicians (making up the majority of providers managing POAF at our institution) or if these differences reflect real world barriers for ideal management of this disease.

Role of Surgical Intervention

The frequency of anticoagulation use in patients with valve surgery was expectedly high given the guideline recommendation for routine short-term anticoagulation after bioprosthetic valve replacement, even in the absence of AF.[20,21] In our experience, this practice is care giver dependent. However, the high proportion of patients receiving anticoagulation before the diagnosis of AF in this cohort suggests that this may have been a predominant reason for anticoagulation in these patients at our institution. Sensitivity analysis demonstrated that CHA_2DS_2-VASc was not a driving factor for anticoagulation prescription, even after removing these patients.

Outcomes

This study was not powered to distinguish differences in outcomes by anticoagulation status or other risk factors, however, we report

this data to provide comparison with other published reports and add to the small body of work reporting such outcomes. Our data demonstrate a trend towards less stroke and mortality among patients receiving anticoagulation. This is consistent with previous reports that anticoagulation is associated with fewer complications in patients with POAF.[12] Interestingly, we did not see a clear trend towards a higher incidence of stroke among patients with higher CHA_2DS_2-VASc scores, although an increase in mortality was observed. To our knowledge, only one larger study reports outcomes in POAF by anticoagulation status with approximately 600 patients included.[12] This study reported a 22% relative risk reduction in mortality, similar to our findings. Nonetheless, other studies have shown no benefit of anticoagulation leaving the intervention in need of further study.[22] Our findings push the balance further in favor of anticoagulation.

Limitations

This study had several limitations, including the single center and retrospective nature of the study. These findings may not be generalizable to other institutions that may have different policies or culture with respect to anticoagulation use. Furthermore, we make assumptions regarding the goal of anticoagulation through evaluation of alternative indications and timing of medication prescription. This may not capture anticoagulation that was started after discharge or missed contraindications due to poor documentation. Finally, the small sample size does not allow for adequate power to determine significant differences in the outcomes of stroke or mortality, although this was not the primary purpose of this study.

Conclusion

This study confirms the overall low use of anticoagulation previously reported in the limited literature on POAF management. We also show that cardioversion and the CHA_2DS_2-VASc score do not seem to have a significant effect on the frequency of anticoagulation use, suggesting that POAF is thought of as a distinct entity from non-postoperative AF. Nevertheless, there is observational evidence to suggest a trend towards improved outcomes among those receiving anticoagulation, which is corroborated by our study. Furthermore, we identify discrepancies between provider attitudes towards treatment of POAF and real world management. These findings highlight the need for further randomized evidence to evaluate the role of anticoagulation in reducing stroke and mortality in this distinct condition, specifically among those in high risk groups such as those with a high CHA_2DS_2-VASc score or those requiring cardioversion.

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Computed Tomography-Derived Three-Dimensional Printed Models versus Two-Dimensional Transesophageal Echocardiography for Left Atrial Appendage Occlusion Device Planning: A Systematic Review and Meta-Analysis

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Abstract

Objective:This systematic review and meta-analysis compared computed tomography (CT)-derived three-dimensional (3D) modeling versus two-dimensional transesophageal echocardiography (TEE) for left atrial appendage occluder (LAAO) device planning.

Background:LAAO device planning is commonly performed with TEE. However, procedures often require multiple devices and deployments due to inaccurate sizing from TEE. The use of CT three-dimensional (3D) models for LAAO device planning may improve accuracy.

Methods:Four clinical studies that reported procedural and clinical outcomes for CT-derived 3D modeling versus TEE for LAAO device planning were identified. End points were accurate device sizing, procedure failure, number of devices used per procedure, fluoroscopy time, and post-procedure leak. Risk ratio (RR) and mean difference (MD) with a 95% confidence interval (CI) were calculated by the Mantel-Haenszel and inverse variance methods.

Results:A total of 166 participants were included. When compared with conventional imaging, the use of 3D printed models was associated with less fluoroscopy time (MD -6.98 minutes, 95% CI -12.68 to -1.28, p=0.02) and lower risk of occluder device peri-prosthetic leak (RR 0.23, 95% CI 0.07-0.73, p=0.01) for LAAO. There were signals towards lower number of devices per procedure (MD -0.56 devices, 95% CI -1.16-0.05, p=0.07) and less total procedure time (MD -13.50 minutes, 95% CI -28.14-1.14, p=0.07) with printed modeling for LAAO. There was no difference between modalities in rates of procedure failure.

Conclusions: CT-derived 3D printed models for LAAO device planning may offer the advantages of lower LAAO device peri-prosthetic leak and less fluoroscopy time when compared with conventional TEE guidance.

Background

Percutaneous left atrial appendage (LAA) device closure is a novel treatment for embolic stroke prevention in patients with non-valvular atrial fibrillation (AF). Studies have demonstrated that LAA closure with the Watchman device (Boston Scientific, Natick, MA) is non-inferior to long-term anticoagulation with warfarin for stroke prevention [1-7]. While anticoagulation remains the standard of care, device closure has now become an option for high-risk patients with contraindications to long-term anticoagulation [8].

Key Words

3D printing, computed tomography, left atrial appendage occlusion, transesophageal echocardiography

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LAA occlusion (LAAO) requires precise imaging to determine device sizing due to variability in size and shape of the LAA leading to differences in the orifice size and landing zone (9). Transesophageal echocardiography (TEE) is often used to determine appropriate sizing and target site for device deployment (10). However, LAAO procedures often require multiple devices and deployments for adequate occlusion predisposing to increased complications and cost. Recent studies have evaluated the use of three-dimensional computed tomography (3D-CT) and 3D-printing for pre-procedure planning to increase device implantation precision. However, data comparing CT-derived 3D models versus TEE for LAAO device selection and procedural efficiency is limited. This systematic review and meta-analysis sought to compare the impact of CT-derived 3Dmodeling versus TEE for LAAO device planning.

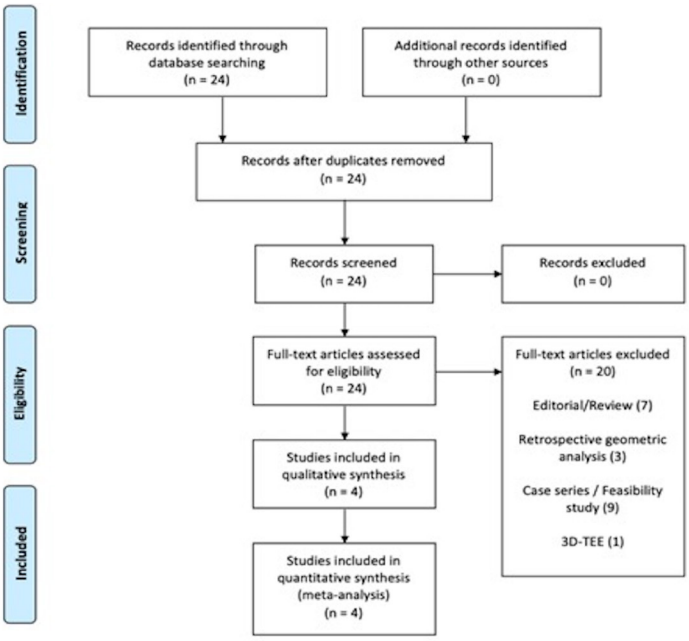

Figure 1: **Flow-chart of the included studies.**

A total of 24 abstracts were identified, and all were reviewed in detail. Shown above is the step-wise progression of the screening and selection process. Four studies were ultimately analyzed, which included two randomized trials and two retrospective analyses.

Methods

Search Strategy

The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement extension for network meta-analysis. The PRISMA flow diagram was used to depict the four phases of the review including identification, screening, eligibility and inclusion. The literature review identified randomized and nonrandomized clinical studies that reported comparisons between CT-derived 3D modeling versus TEE for LAAO device planning. Searches were limited to peer-reviewed primary research articles published in English, French and Spanish through July 2020. This research involved human subjects and described the impact of CT-derived 3D modeling versus TEE on device planning for patients who underwent LAAO. We developed the search strategy according to available guidance from the Cochrane Collaboration.

The search strategy in MEDLINE explored Medical Subject Heading (MeSH) terms related to CT-derived 3D modeling and TEE for LAAO device planning. The following Boolean strategy was applied to search PubMed/MEDLINE: ((((“printing, three-dimensional”[MeSH Terms] OR (“printing”[All Fields] AND “three dimensional”[All Fields])) OR “three-dimensional printing”[All Fields]) OR (“3d”[All Fields] AND “printing”[All Fields])) OR “3d printing”[All Fields]) AND ((“atrial appendage”[MeSH Terms] OR (“atrial”[All Fields] AND “appendage”[All Fields])) OR “atrial appendage”[All Fields]) AND ((((“transesophageal echocardiography”[All Fields] OR “echocardiography, transesophageal”[MeSH Terms]) OR (“echocardiography”[All Fields] AND “transesophageal”[All Fields])) OR “transesophageal echocardiography”[All Fields]) OR (“transesophageal”[All Fields] AND “echocardiography”[All Fields])). The articles found to be relevant during the search were stored in EndNote. Selected articles underwent full evaluation to assess their potential inclusion in the systematic review. Finally, the reference lists of all included studies were also cross-checked for publications not captured by the Boolean search strategy.

Study Selection

Articles were selected for inclusion based on the use of CT-derived 3D modeling compared to conventional TEE imaging for LAAO procedural and clinical outcomes. We excluded case reports and feasibility studies that did not compare outcomes with a control group. Three authors (S.I.Z., G.S.C., C.G.M.) independently read each full text article to assess their potential inclusion in the systematic review and meta-analysis. Risk of bias in the studies was assessed at the individual level of each study.

Statistical Analysis

Data were analyzed using Review Manager software 5.4. We used a random effects model to assess the combined risk and mean difference estimates. Study heterogeneity was evaluated using the I2 statistic. Analysis to determine sensitivity and publication bias was detected by funnel plots. A P-value <0.05 was considered statistically significant.

Results

Literature Search

A total of 24 abstracts were identified, and all were reviewed in detail. Four studies were ultimately included in the systematic review and meta-analysis; the studies by Li et al., and Eng et al., were prospective randomized studies, while the remaining 2 studies were retrospective

Table 1: **Patient demographics and characteristics in the studies meeting inclusion criteria for the systematic review and meta-analysis**

Study Author, Year	Location	N	3D Modeling Group	Patients	Age, Years	Female	CHF	Diabetes	HTN	HLD	CAD	CVA	CKD	BMI (kg/m2)	$CHADS_2$-VASC Score	HAS-BLED score
Obasare et al., 2017	USA	24	3D Modeling*	14	71 ± 9	36%	29%	36%	100%	57%	14%	36%	7%	29 ± 12	4.6 ± 1.3	3.8 ± 1.5
			No 3D Modeling	10	69 ± 13	50%	30%	30%	80%	70%	60%	10%	60%	31 ± 8	4.3 ± 2.2	3.5 ± 1.3
Eng et al., 2018	USA	24	3D Modeling	12	79.9 ± 6.7	33%	42%	42%	100%	NR	NR	17%	NR	28.51 ± 7.1	4.8 ± 1.4	4.8 ± 0.8
			No 3D Modeling	12	73.5 ± 7.6	50%	42%	25%	100%	NR	NR	33%	NR	26.6 ± 5.8	4.9 ± 0.9	4.4 ± 0.4
Ciobotaru et al., 2018	France	76	3D Modeling	21	78 ± 7	38%	29%	NR	NR	NR	NR	34%	39%	NR	4.9 ± 1.1	4.1 ± 0.8
			No 3D Modeling	55												
Li et al., 2017	China	42	3D Modeling	21	68.1 ± 6.9	52%	NR	29%	62%	NR	NR	24%	NR	24.5 ± 3.8	3.9 ± 1.2	3.1 ± 0.3
			No 3D Modeling	21	70.4 ± 8.6	48%	NR	24%	57%	NR	NR	19%	NR	24.5 ± 3.9	4.1 ± 1.6	3.2 ± 0.4

BMI=body mass index; CAD=coronary artery disease; CHF=congestive heart failure; CKD=chronic kidney disease; CVA=cerebrovascular accident; HLD=hyperlipidemia; HTN=hypertension; N=number; NR=not reported.

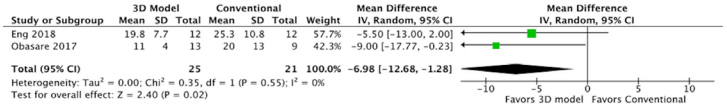

Figure 2: **Forest plot of fluoroscopy time for LAAO with and without 3D modeling**

Comparison of left atrial appendage occluder device planning using 3D computed tomography printed modeling versus conventional 2D transesophageal echocardiography on total procedural fluoroscopy time.

[11-14]. Figure 1 describes the flow-chart of included studies.

Baseline Characteristics of the Studies

Table 1 shows the baseline characteristics of the included studies. All studies were published between 2017 and 2019. The 4 studies included 166 patients with 68(41%) patients undergoing LAAO with CT-derived 3D modeling used for procedural planning. CT-derived 3D modeling was performed with ECG-gated 256-slice protocols in two studies;[13,14] no details were available in the remaining two.[11,12] The median age of the participants was 71.0 years (IQR, 69.7-75.8), and 48% were female. Clinical risk factors and co-morbidities included 90% hypertension, 29.5% diabetes, 37% coronary artery disease 30% congestive heart failure, and 39% chronic kidney disease. The median CHADS2-VASC score was 4.6 (IQR, 4.2-4.9), HAS-BLED score was 3.8 (IQR, 3.4-4.3), and body mass index 27.6 kg/m2 (IQR, 25.0-28.9). Single centers were sites for all of the included studies and the United States, France, and China were the countries represented.

3D Modeling versus TEE Imaging for LAAO

Ciobotaru et al., Eng et al., Li et al., and Obasare et al. reported various procedural outcomes in patients undergoing LAAO with CT-derived 3D modeling compared withTEE [11-14].Ciobotaru et al. found that CT-derived 3D modeling for LAAO double disc device planning decreased the number of prostheses, incidence of leaks, fluoroscopy time, and fluoroscopy dose when compared with conventional imaging [11]. Eng et al. found reduced number of utilized prostheses, guide catheters, and procedure time when CT-derived 3D modeling was compared with TEE for LAAO device planning [12]. Li et al. found that CT-derived 3D modeling for LAAO device planning significantly reduced radiation exposure compared with TEE [13]. Finally, Obasare et al. found reduced procedure time, anesthesia time, fluoroscopy time, and incidence of peri-device leak when CT-derived 3D modeling was compared with TEE for LAAO device planning [14].

Meta-analysis of the included studies revealed less fluoroscopy time (MD -6.98 minutes, 95% CI -12.68 to -1.28, p=0.02) with CT-derived 3D modeling for LAAO device planning as shown in the forest plot of 2 studies in Figure 2. Additionally, data from all 4 identified studies revealed the use of CT-derived 3D modeling decreased the incidence of peri-prosthetic leak (RR 0.19, 95% CI 0.07-0.51, p<0.01) when compared with TEE for LAAO device planning as shown in the forest plot in Figure 3. There were signals of a lower number of devices utilized per procedure (MD -0.56 devices, 95% CI -1.16-0.05, p=0.07) and less total procedure time (MD -13.50 minutes, 95% CI -28.14-1.14, p=0.07) when CT-derived 3D modeling was used for LAAO device planning as shown in Figures 4 and 5, respectively. There was no difference between modalities in rates of procedure failure as shown in Figure 6. None or low heterogeneity was detected for the outcomes of total fluoroscopy (I2=0%), peri-prosthetic device leak (I2=0%), and procedure failure (I2=0%). Moderate heterogeneity was detected for the outcomes of number of devices per procedure (I2=75%) and total procedure time (I2=55%).

Discussion

The present meta-analysis reported the pooled outcomes from 4 studies including 166 patients who underwent LAAO utilizing the Watchman occluder device. When compared with TEE, the use of 3D CT-derived printed modeling for device planning was found to confer the following: 1) less total required fluoroscopy time; 2) lower risk of occluder device peri-prosthetic leak; 3) numerically lower number of devices utilized and total procedural time; and, 4) a similar rate of successful device implantation.

Utilization of TEE is currently the conventional method for sizing of the LAA prior to occluder device implantation. However, the varied anatomy of the appendage, position of the ostium relative to the TEE probe, and individual cardiac positioning within the thoracic cavity often results in suboptimal LAA visualization. make it difficult to capture imaging of the LAA with TEE. Hemodynamic loading conditions and appendage contractile cyclesmay also resultin orifice size underestimation [15-17]. Indeed, registry data shows an average of 1.4 devices used per case for LAAO procedures planned with TEE [10]. Finally, there are also few consistent landmarks for determining the best landing zone for the occluder device [14].

CT scanning provides 3D reconstruction of the entire LAA with detailed depiction of LAA walls, lobes, and apex (Figure 7)[9]. Previous analyses have concluded that CT imaging alone improves LAAO device size prediction and procedural outcomes [18,19]. The studies included in the present meta-analysis took the additional step of creating 3D-printed models to aid in procedural planning. The 3D model can help operators visually assess device fit and determine the optimal landing zone. This translates to more time-efficient procedures with less devices used for successful implantation. The process of creating 3D models is relatively straightforward and quick. The included studies report needing approximately 6 to 10 hours to obtain the 3D printed model following the CT scan, and a cost of about $10 per patient [14]. This suggests that 3D modeling is likely cost effective given the reduction in procedure time and device deployments.

Several early feasibility studies evaluated the use of CT-derived 3D printing for LAAO device planning. Hell et al. found that 3D printing improved device sizing in a cohort of 22 patients undergoing LAAO. Predicted device size with the 3D model matched the final

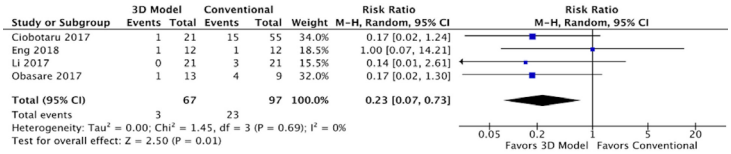

Figure 3: **Forest plot of post-procedure peri-prosthetic leak for LAAO with and without 3D modeling.**

Comparison of left atrial appendage occluder device planning using 3D computed tomography printed modeling versus conventional 2D transesophageal echocardiography on the presence of post-procedure peri-prosthetic leak.

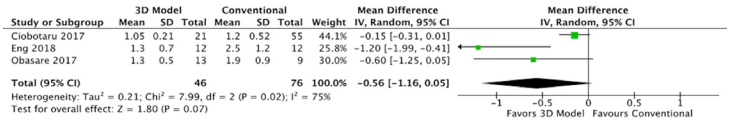

Figure 4: **Forest plot of number of devices per procedure for LAAO with and without 3D modeling.**

Comparison of left atrial appendage occluder device planning using 3D computed tomography printed modeling versus conventional 2D transesophageal echocardiography on the number of devices utilized per procedure.

implanted device in 21/22 patients (95%) compared with 10/22 (45%) of patients with device sizing planned by TEE [20]. In a cohort of 29 patients, Goiten et al., found good correlation between device sizing predicted by 3D modeling and the procedurally implanted device [21]. Hachulla et al. published a case series of 15 patients that found 3D printing to improve predicted device sizing [22]. The present findings support and expand upon this earlier data by analyzing studies with procedural outcome comparisons made between 3D print modeling and conventional imaging groups.

Fan et al. recently published a study using 3D-TEE data to create 3D printed models for LAAO device planning in 104 patients undergoing LAAO. Improved safety and efficacy was demonstrated for device selection with TEE 3D modeling-based sizing in patients undergoing LAAO [23]. The use of TEE-derived 3D models may be preferred to CT in patients whom contrast and radiation exposure is a concern, particularly in the setting of chronic kidney disease or contrast allergy. However, issues with complete visualization of the LAA by 2D TEE translate to 3D-TEE, with image dropout artifacts as the most common impediment to widespread application [14]. Nevertheless, in appropriate candidates with good imaging windows, 3D-TEE may be a viable alternative to 2D TEE or contrast-required 3D CT-derived printed modeling.

There are limitations to the present meta-analysis that should be considered when interpreting the data. Firstly, the sample size of the individual studies and pooled cohort was small, which limits power for statistical analyses. Furthermore, the outcome measures were not uniformly reported across all of the studies; this may be interpreted as a form of attrition or information bias. Secondly, between-center variability in procedural volume, assessment protocol for procedural results and outcomes, and availability of advanced imaging limits the generalizability of the results. These variables are closely related to and impact the learning curves for the structural interventionalist and imaging cardiologist, which introduces uncontrollable confounding. Thirdly, there are important knowledge gaps within the included studies that may bias the analyses. In the study by Obasare et al., there was a greater number of patients with chronic kidney disease in the non-3D (TEE) modeling group which may have led to avoidance of contrast

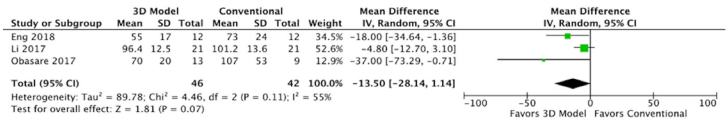

Figure 5: **Forest plot of procedure time for LAAO with and without 3D modeling.**

Comparison of left atrial appendage occluder device planning using 3D computed tomography printed modeling versus conventional 2D transesophageal echocardiography on total procedure time.

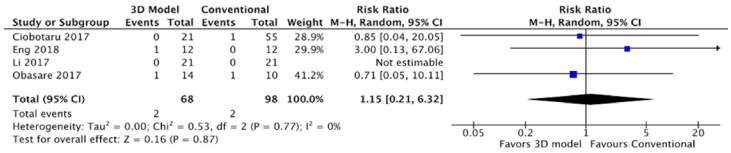

Figure 6: **Forest plot of procedure failure for LAAO with and without 3D modeling.**

Comparison of left atrial appendage occluder device planning using 3D computed tomography printed modeling versus conventional 2D transesophageal echocardiography on procedure failure.

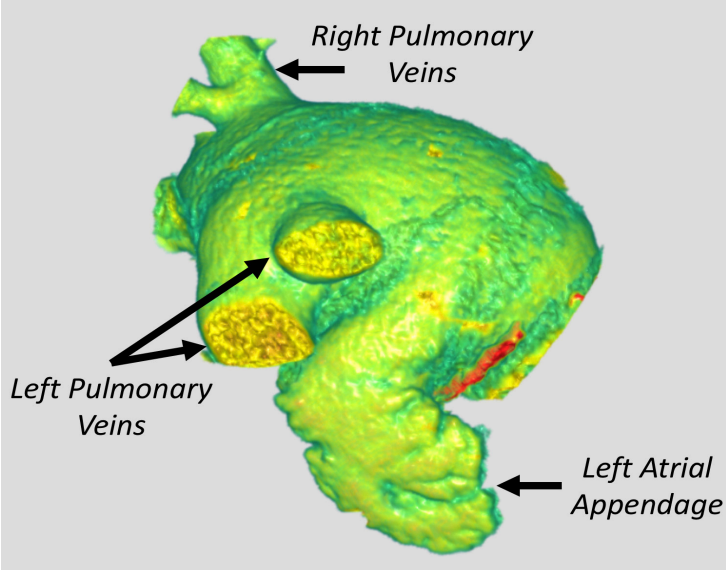

Figure 7: **Computed tomography-derived three-dimensional modeling.**

Depicted is a 'chicken wing' left atrial appendage and the left atrium. The left circumflex coronary artery is also shown in red in the left atrioventricular sulcus, which is an important landmark of in pre-procedural measurements and device sizing.

utilization and increased procedure time [14]. In the study by Eng et al., the time between CT scanning and modeling and LAAO was several weeks to months. The lack of standardization allows for the impact of possible anatomic changes, such as chamber size and function, on procedural planning and successful device implantation [12]. Finally, two of the studies included in the pooled analysis were retrospective in nature, which confers an inherent selection bias. However, these study designs are viewed as complementary. Observational investigations allow for external validation of randomized controlled data, provide insight into physician practice patterns, and represent an accurate patient population sample.

Conclusion

CT-derived 3D printed models for LAAO device planning may attenuate the risk of post-implantation device peri-prosthetic leak and decrease the procedure fluoroscopy time when compared with conventional TEE guidance. The current data is hypothesis-generating for larger confirmatory prospective and multi-center registry studies on the optimal method for LAAO device planning, which should also incorporate the use and further study of 3D TEE LAA modeling.

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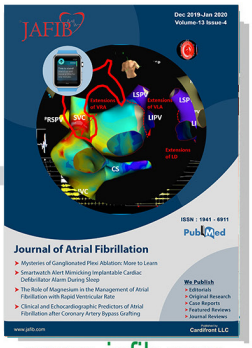

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Cardiac Resynchronization Therapy in continuous flow Left Ventricular Assist Device Recipients: A Systematic Review and Meta-analysis from ELECTRAM Investigators

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Abstract

Introduction: Whether cardiac resynchronization therapy (CRT) continues to augment left ventricular remodeling in patients with the continuous-flow left ventricular assist device (cf-LVAD) remains unclear.

Methods: We performed a systematic review and meta-analysis of all clinical studies examining the role of continued CRT in end-stage heart failure patients with cf-LVAD reporting all-cause mortality, ventricular arrhythmias, and ICD shocks. Mantel-Haenszel risk ratio (RR) random-effects model was used to summarize data.

Results: Eight studies (7 retrospective and 1 randomized) with a total of 1,208 unique patients met inclusion criteria. There was no difference in all-cause mortality (RR 1.08, 95% CI 0.86 – 1.35, p = 0.51, I2=0%), all-cause hospitalization (RR 1.01, 95% CI 0.76-1.34, p = 0.95, I2=11%), ventricular arrhythmias (RR 1.08, 95% CI 0.83 – 1.39, p = 0.58, I2 =50%) and ICD shocks (RR 0.87, 95% CI 0.57 – 1.33, p = 0.52, I2 =65%) comparing CRT versus non-CRT. Subgroup analysis demonstrated significant reduction in ventricular arrhythmias (RR 0.76, 95% CI 0.64 – 0.90, p = 0.001) and ICD shocks (RR 0.65, 95% CI 0.44 – 0.97, p = 0.04) in "CRT on" group versus "CRT off" group.

Conclusion: CRT was not associated with a reduction in all-cause mortality or increased risk of ventricular arrhythmias and ICD shocks compared to non-CRT in cf-LVAD patients. It remains to be determined which subgroup of cf-LVAD patients benefit from CRT.The findings of our study are intriguing, and therefore,larger studies in a randomized prospective manner should be undertaken to address this specifically.

Introduction

Despite advances in pharmacologic and device therapies, heart failure is one of the foremost causes of hospitalization in the United States, accounting for high morbidity, mortality, and increased burden to health care cost utilization. It is estimated that nearly 6 million Americans are currently affected by heart failure, a number that is expected to reach 8 million by 2030[1]. Studies have shown that cardiac resynchronization therapy (CRT) improves the quality of life, decreases heart failure hospitalization, reduces left ventricular dimensions and overall mortality in patients left ventricular ejection fraction (LVEF) ≤ 35%, NYHA functional class I-III and wide QRS in addition to guideline-directed medical therapy[2-4].

Given the limitations of organ availability, heart transplantation is not always the best therapeutic option in patients with ends stage heart failure. Left ventricular assist device (LVAD) has been a viable alternative and has been increasingly used as destination therapy (DT), bridge to transplant (BT), and bridge to recovery in end-stage

Key Words

Cardiac resynchronization therapy, LVAD, arrhythmias

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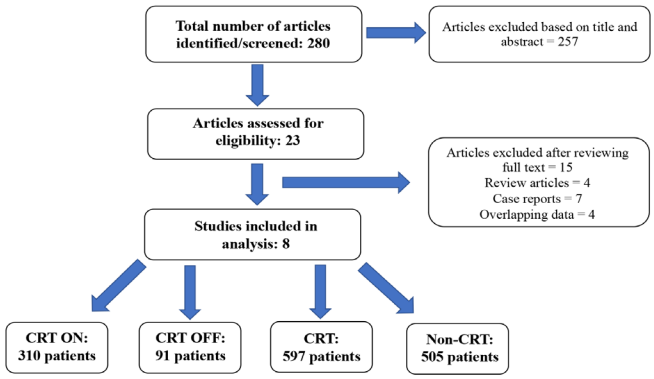


Figure 1: Flow Diagram illustrating the systematic search of studies

heart failure patients on guideline-directed medical therapy and CRT if indicated[5].However, whether CRT continues to augment left ventricular remodeling in patients with end-stage heart failure on LVAD remains unclear. Based on current available literature, there are no strict guidelines (limited to consensus statement regarding device and arrhythmia management in patients with LVAD)[6] on continued left ventricular pacing (as a part of CRT) in advanced heart failure patients with continuous-flow left ventricular assist device (cf-LVAD). Therefore, we performed a systematic review and meta-analysis of all the clinical studies examining the role of continued cardiac resynchronization therapy in end-stage heart failure patients with cf-LVAD.

Search Strategy

The reporting of this systematic review and meta-analysis complies with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines (Supplement Table 1)[7] and prospectively enrolled in the PROSPERO database.

We searched PubMed, Clinicaltrials.gov,the Web of Science, EBSCO database, Google Scholar, Cochrane Central Registry, and various major scientific conference sessions (American College of Cardiology, American Heart Association, Heart Rhythm Society, European Society of Cardiology and Cardiostim) for published abstracts and manuscripts until May 30, 2020. We used the following keywords and medical subject heading: "left ventricular assist device," LVAD", "CRT", "cardiac resynchronization therapy".

Study selection and data extraction

We included randomized clinical trials, prospective and retrospective studies. Considering the paucity of evidence, we decided to include abstracts. Any meta-analysis, review articles, studies with no comparator arm,or studies involving pulsatile flow LVAD (pf-LVAD) were excluded from our analysis. The data from included studies were extracted using a standardized protocol and a data extraction form. Any discrepancies between the two investigators were resolved through consensus and arbitration with the co-senior investigators (D.L and J.G).The following data were extracted: author name, study design, publication year, follow-up duration, number of patients, age, gender, biventricularpercent pacing, comorbidities, etiology of cardiomyopathy, INTERMACS score, indications of cf-LVAD, left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVEDD), ventricular arrhythmias, implantable cardioverter-defibrillator (ICD) shocks, medications, and outcomes. The Newcastle Ottawa Risk bias assessment tool was used to appraise the quality of non-randomized studies (Supplement Table2). The Cochrane – Risk bias assessment tool was used to appraise the quality of a randomized controlled trial (Supplement Table3).

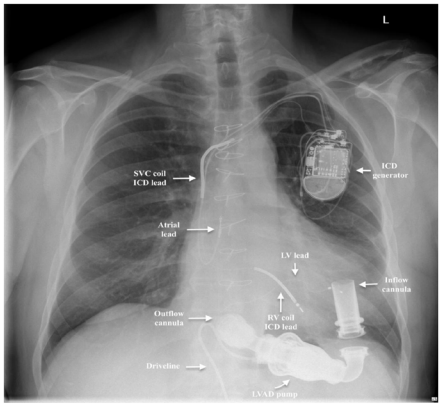
Clinical outcomes

The primary outcome of our study was – (i) all-cause mortality (ii) all-cause hospitalization (composite of heart failure and ventricular arrhythmia related hospitalization), (iii) ventricular arrhythmias,and (iv) appropriate ICD shocks between the CRT and non-CRT groups with cf-LVAD.

Subgroup analysis was performed comparing "CRT on" versus "CRT off" (to assess long term effect sequela ofwide QRS in cf-LVAD patients, if any). Outcomes studied were all-cause hospitalizations per patient, ventricular arrhythmia, and appropriate ICD shocks.

Statistical analyses

The meta-analysis was performed using a meta-package for R version 4.0 and Rstudio version 1.2. Mantel-Haenszel risk ratio (RR) random-effects model (DerSimonian and Laird method) was used to summarize data between the two group[8]. For continuous variables, weighted mean difference (WMD) was calculated to evaluate the difference in clinical outcomes between relevant subgroups in patients with cf-LVAD. Heterogeneity of effects among the included studies was assessed by Higgins I-squared (I^2) statistic[9]. A value of I^2 of 0–25% represented insignificant heterogeneity, 26–50% represented low heterogeneity, 51–75% represented moderate heterogeneity, and more than 75% represented high heterogeneity, as set forth by the Cochrane Collaboration. Publication bias was visually and formally assessed using funnel plots. A two-tailed $p < 0.05$ was considered statistically significant for all analyses.



	CRT versus non-CRT		"*CRT on*" versus "*CRT off*"	
Clinical Outcomes	**Risk Ratio (95% CI)**	**P Value**	**Risk Ratio (95% CI)**	**P Value**
All-cause mortality	1.08 (0.86 – 1.35)	P = 0.51	.	.
All-cause hospitalization	1.01 (0.76 - 1.34)	P = 0.95	-1.07 (-3.97 – 1.82)	0.47
Ventricular arrhythmias	1.08 (0.83 – 1.39)	P = 0.58	0.76 (CI 0.64 – 0.90)	**0.001**
Appropriate ICD shocks	0.87 (0.57 – 1.33)	P = 0.52	0.65 (CI 0.44 – 0.97)	**0.04**

Figure 2: Cardiac Resynchronization Therapy in end-stage heart failure patients with cf-LVAD

Table 1: Baseline characteristics of the studies included in our analysis

Study	Schleifer et al		Richardson et al		Roukoz et al		Choi et al		Kutyifa et al		Mai et al		Rao et al		Gopinathannair et al	
Study Period	2007-2012		2013 - 2016		2007 - 2015		2006 - 2009		2008 - 2014		2009 - 2015		2005 - 2013		2007 - 2015	
Type	Retrospective		Randomized controlled trial		Retrospective		Retrospective (abstract)		Retrospective (abstract)		Retrospective (abstract)		Retrospective (abstract)		Retrospective	
Follow up	2.1 years		11 (4-18)months		2.4 ± 2.0 years		49 days		25 months		59 days (median)		Up to 1 year		651 ± 528 days	
Biventricular pacing (%) Mean ± SD			99 (94-99)		96 ± 5.3										96 ± 5	
Groups	CRT on	CRT off	CRT on	CRT off	CRT on	CRT off	CRT	Non-CRT	CRT	Non-CRT	CRT	Non-CRT	CRT	Non-CRT	CRT	Non-CRT
N	39	26	20	21	251	44	22	13	61	130	40	47	135	118	280	106
Age Mean ± SD (years)	62±13	62±14	.	.	60±0.8	63±1.8	56±12		58.9±9.7		55.3±27		57.7	54.4	60±12	60±13
Males (N, %)	31 (79)	24 (92)	.	.	208 (82.9)	37 (84.1)	29 (total) (82.85)		162		74 (85.1)		.		232 (82.9)	86 (81)
Ischemic cardiomyopathy (N, %)	15 (38)	16 (62)	.	.	130 (51.9)	24 (54.8)	.		.		.		.		151 (53.9)	66 (62)
Hypertension (N, %)	11 (28)	8 (31)	.	.	174 (69.3)	23 (52.3)	.		.		.		.		185 (66.1)	78 (74)
Diabetes (N, %)	15 (38)	10 (38)	.	.	112 (44.6)	19 (43.2)	.		.		.		.		123 (43.9)	47 (44)
LVEF % Mean ± SD	17±6	18±6	.	.	15.8±5.8	16.6±7.7	.		.		20 (total)		16.9	19.1	16±6	16±6
LVEDD-mm Mean ± SD	72±9	71±12	.	.	72±10	73±12	.		.		.		71.4	67.8	70±10	70±10
Primaryprevention ICD (N, %)	33 (85)	17 (65)	.	.	139 (55.5)	15 (35.1)	.		.		.		.		.	.
Bridge to Transplant (N, %)	18 (46)	8 (31)	.	.	115 (45.7)	21 (48.8)	.		.		.		.		126 (45)	53 (50)
INTERMACS profile 1-2 (N, %)	.	.	.	.	71(28.1)	6 (14.3)	.		.		.		.		.	.
QRS duration (msec) Mean ±SD	141±27	138±43	.	.	160±29	152±29	.		.		.		.		159±29	155±26
Beta-blockers (N, %)	15 (38)	13 (50)			206 (82.3)	36 (81.8)									230 (82)	91 (86)
ACEi or ARB's (N, %)	.	.	.	.	139 (55.3)	26 (59.1)	.		.		.		.	.	109 (39)	42 (40)
Aldosterone antagonists (N, %)	.	.	.	.	56 (22.5)	8 (19.1)	.		.		.		.		.	.
Nitrates (N, %)	.	.		.	35 (14.1)	4 (9.5)	.		.		.		.		.	.
Hydralazine (N, %)	.	.	.	.	83 (33.2)	7 (16.7)	.		.		.		.		.	.
Antiarrhythmic drugs (N, %)	16 (41)	13 (50)	.	.	153 (60.95)	23 (52.27)	.		.		.		104 (77)	76 (64)	112 (40)	36 (34)

ACEi: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blocker

Results

Search results

A total of 280 citations were identified (Figure 1) during the initial search. Two hundred seventy-two records were excluded. After a detailed evaluation of these studies, eight articles: [7]retrospectives[10-16] and 1 randomized clinical trial[17] ultimately met the inclusion criteria, constituting 1,208 unique patients with a mean follow-up of 424.36±425.25 days. Table 1 summarizes the baseline characteristics of the included trials in our meta-analysis. Studies by Gopinathannair et al.(published in 2015 [18]and 2018[19]) enrolled patients from the same institution and overlapping years. Therefore, we only included the study by Gopinathannair et al published in 2019, as it was more contemporary of the three[16]. Patients in the "CRT off" subgroup were included in the non-CRT group for the overall analysis. Studies by Gopinathannairet al and Roukuz et al enrolled patients from the same

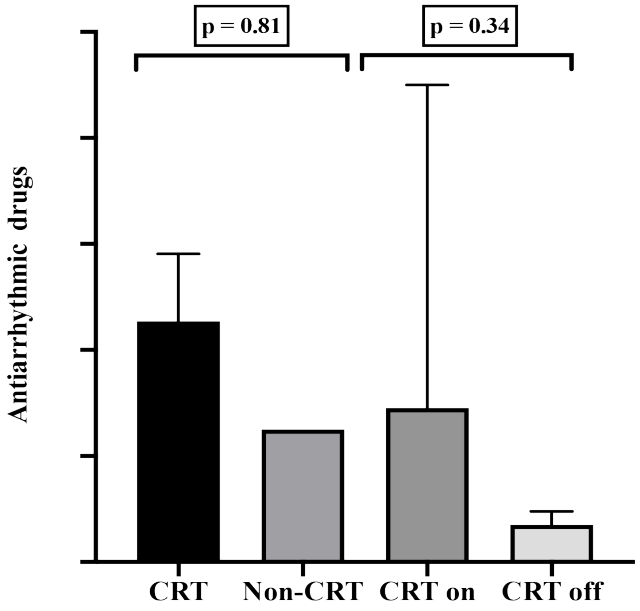


Figure 3: Antiarrhythmic drug use in end-stage heart failure patients on cf-LVAD.

institution and overlapping years; hence we included Gopinathannair et al for comparing CRT versus non-CRT and Roukuz et al for "CRT on"vs"CRT off".While comparing overall analysis (CRT vs. non-CRT), Roukuz et al was excluded due to overlapping data with Gopinathannair et al.

Study characteristics

Of eight studies included in our analysis, five studies evaluated CRT versus non-CRT in cf-LVAD patients (CRT = 597 patients, non-CRT = 505 patients) [12-16]; while 3 studies evaluated "CRT on" versus "CRT off" in cf-LVAD patients ("CRT on" = 310 patients, "CRT off" = 91 patients)[10,11,17].Overall, the mean age of the patients was 58.04 ± 12.84years. Bridge to transplantation (BTT)as the indication for LVAD placement was available in three trials (n = 341, 45.7%).[10,11,16]

Data on antiarrhythmic drugs was available only in 4 studies, with 51% patients (232/454) in CRT vs 50% patients (125/250) in non-CRT group (p=0.81); while 58.27% patients (169/290) in "CRT on" vs 51.42% (36/70) in "CRT off" sub-group (p=0.35) (Table 1 and Figure 3).

Outcomes (Figure 4-6, Supplement figure 1-2)

All-cause mortality

The data for all-cause mortality was available in 3 trials[13,15,16].The presence of CRT was not associated with any difference in all-cause mortalityas compared to non-CRT in patients with cf-LVAD (30.67% vs.27.4%, RR 1.08, 95% CI 0.86 – 1.35, p=0.51). No heterogeneity was observed between trials (I^2 =0%)(Figure 4).

All-cause hospitalization

Two studies reported data on all-cause hospitalization[15,17]. Rates of hospitalizationwere not significantly different between CRT and non-CRT group in cf-LVAD patients (67.10% vs. 68.88%, RR 1.01, 95% CI 0.76-1.34, p = 0.95, I2 =11%) (Figure 5A).

In studies comparing "CRT on" vs "CRT off"[10,11], all-cause hospitalization per patient was not significantly different between "CRT on"versus "CRT off"in cf-LVAD patients (WMD -1.07, 95% CI -3.97 – 1.82, p = 0.47, I2=63%) (Figure 5B).

Ventricular arrhythmias

The data forthe incidence ofventricular arrhythmias after cf-LVAD was available in 5 trials[10,12,14-16].The CRT group was not associated with increased risk of ventricular arrhythmias as compared to the non-CRT group in cf-LVAD patients (44.76% vs.40.32%, RR 1.08, 95% CI 0.83 – 1.39, p=0.58).Moderateheterogeneity was observed between trials (I^2 =50%) (Figure 6).

When comparing "CRT on" vs."CRT off"10,11, "CRT on" group was associated with a lower incidence of ventricular arrhythmias as compared to "CRT off" group in cf-LVAD patients (57.9% vs. 75.7%, RR 0.76, 95% CI 0.64 – 0.90, p = 0.001). No heterogeneity was observed between trials (I^2 =0%) (Supplement Figure 1).

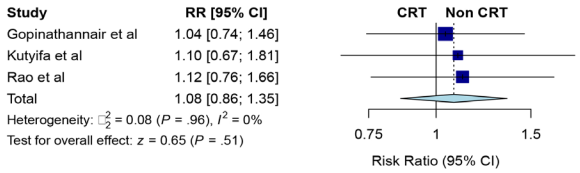
Appropriate ICD shocks

Four studies reported data on the ICD shocks[10,15-17]. The incidence of ICD shocks did not differ between CRT and non-CRT group in cf-LVAD patients (35.86% vs 33.58%, RR 0.87, 95% CI 0.57 – 1.33, p = 0.52). Moderate heterogeneity was observed between trials (I^2 =65%). (Figure 7).

In studies comparing "CRT on" versus "CRT off"[10,11,17], "CRT on" group was associated with a lower incidence of ICD shocks as compared to "CRT off" in cf-LVAD patients (33.87% vs. 47.25%, RR 0.65, 95% CI 0.44 – 0.97, p = 0.04). Mild heterogeneity was observed between trials (I^2 =28%). (Supplement Figure2).

Discussion

The main findings in this analysis are: (1) all-cause mortality and hospitalizations did not differ between CRT and non-CRT groups



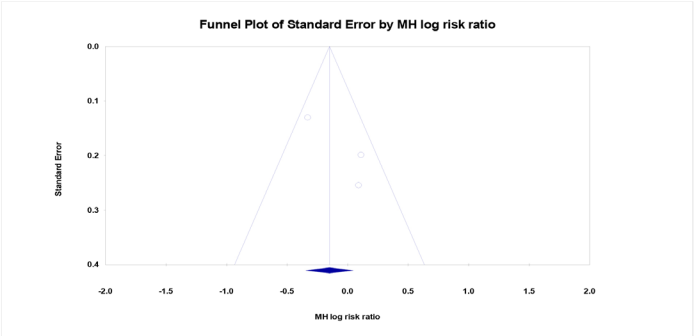


Figure 4: All-cause mortality.The Forest plot shows the outcomes of the individual trials as well as the aggregate. Point estimates to the left favors CRT. The funnel plot demonstrates no publication bias.

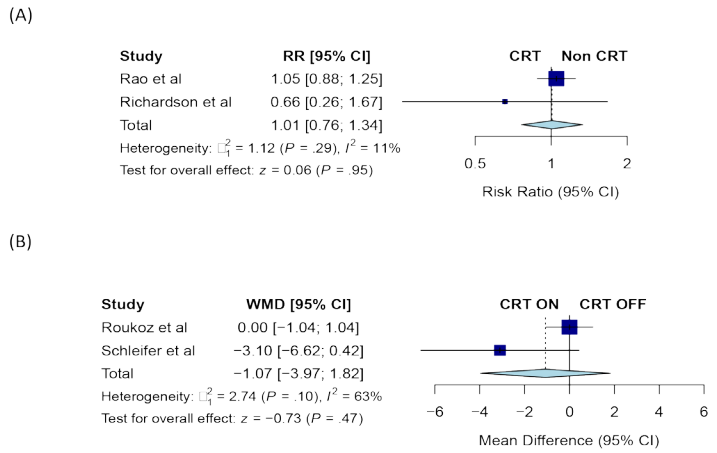


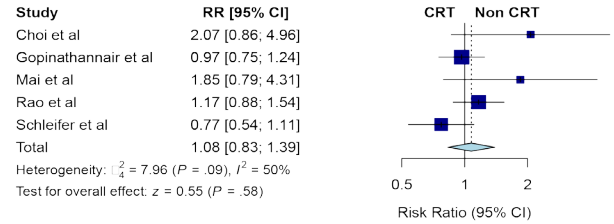
Figure 5: **All-cause hospitalization. (A) The Forest plot shows the outcomes of the individual trials as well as the aggregate. Point estimates to the left favors CRT. (B) The forest plot shows all-cause hospitalization per patient was not significantly different between "CRT on" versus "CRT off" in cf-LVAD patients. Point estimates to the left favor "CRT on".**

in end-stageheart failure patients with cf-LVAD; (2) no reduction in ventricular arrhythmias and ICD shocks was observed; (3) Significant reduction in ventricular arrhythmias and ICD shocks was observed in cf LVAD patients with "CRT on" as compared to "CRT off" (Figure 2). The findings of our study are important clinically and indicate that cf LVAD patients with active CRT did not derive any long term any benefit with continued LV pacing; however, there was significant reduction in ventricular arrhythmias and ICD shocks in cf-LVAD patients with "CRT on" versus "CRT off". Nonetheless, due to reduction in battery longevity requiring multiple procedures, risks and benefits must be judiciously contemplated.

MADIT-CRT post hoc analysis demonstrated that patients with ≥97% biventricular are at reduced risk of heart failure hospitalization and mortality as compared to patients with < 97% biventricular pacing[20]. In addition, cf-LVAD improves overall survival in end-stage heart failure patient; however, the benefit of CRT in cf-LVAD may not be additive.Whether or not continued LV pacing post LVAD implantation for maximal LV remodeling remains controversial.There are several potential explanations for the findings observed in our study. First, lack of randomized clinical trials may have caused a selection bias towards sicker patients, resulting in no observed mortality benefit with CRT. Second, advanced heart failure patients on cf-LVAD are at increased risk of mortality from non-arrhythmic causes such as device infection, pump failure, or pump thrombosis, factors that may outweigh the net clinical benefits of CRT. Third, hemodynamic effects observed with cf-LVAD might offset the electromechanical effects and the long-term sequelae seen with CRT. The RV and LV shares oblique fibers within the interventricular septum, thereby augmenting RV contractility with LV contraction[21,22]. With a decline in LV function, oblique septal fibers orient in a more transverse orientation due to spherical shaped LV (given volume overload), thereby reducing RV contractility. Therefore, CRT (in non-LVAD patients) by reverse LV modeling may in turn improve septal fibers orientation and improve RV function. It is worthwhile to notice that hemodynamic benefits of CRT in improvement on LV systolic function are predominantly mediated by the improvement of electrical dyssynchrony resulting in improved mechanical synchrony in a setting of wide QRS. Acute LV unloading, change in LV fiber orientation/cardiac chambers from LVAD inflow cannula, and limited pulsatility of LV might counterpoise the hemodynamic effect and long-term sequelae observed with CRT [16,23]. Fourth, improved patient care, care transition teams, and improvement in LVAD design (over the last decade), resulting in enhanced patient survival, might offset the effects of biventricular pacing.

Studies have shown that CRT may exhibit proarrhythmic effect [24][thought to be due to differential activation and creation of two different wavefronts (from RV and LV pacing), resulting in a unidirectional functional block and initiating reentrant arrhythmias], with an increased risk of ventricular arrhythmias in CRT non-responders[25].Besides, ventricular arrhythmia prior to LVAD implantation is an independent predictor of recurrent arrhythmia after LVAD implantation[26]. In our pooled analysis, although the non-CRT group had a lower incidence of ventricular arrhythmias and ICD shocks, it did not reach statistical significance. The findings of our study corroborate with the study from Gopinathannair et al. demonstrating no significant association between QRS duration or RV pacing or LV pacing on long term outcomes (i.e.,hospitalization or development of ventricular arrhythmias)[16].

It is well known that a wide QRS (left bundle block or right bundle branch block) and resultant inter/intraventricular dyssynchrony is associated with adverse clinical outcomes in patients with heart failure[27,28]. Acute LV unloading, thereby reducing wall stress from cf-LVAD,surpasses the potential electrical remodeling benefit derived from either narrow QRS or biventricular pacing. However, in subgroup analysis, there was a statistically significant reduction in episodes of ventricular arrhythmias and ICD shock in "CRT on" group versus "CRT off". The precise pathophysiology of the observed finding remains unclearand could represent Type 1 error. Also, there was



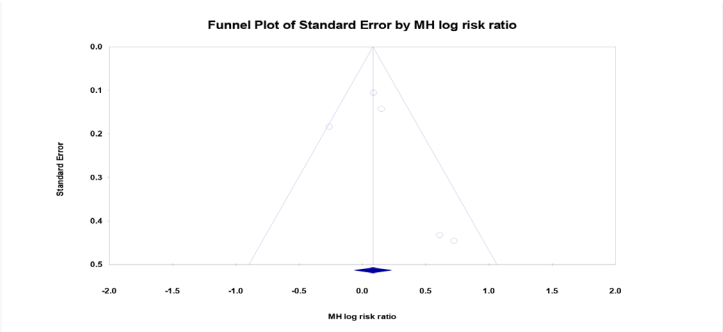
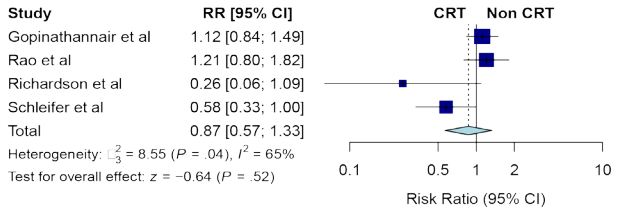


Figure 6: **Ventricular arrhythmias.The Forest plot shows the outcomes of the individual trials as well as the aggregate. Point estimates to the left favors CRT. The funnel plot demonstrates no publication bias.**



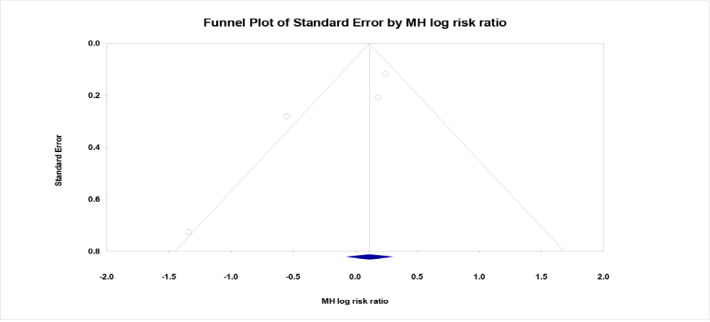


Figure 7: **Appropriate ICD shocks.The Forest plot shows the outcomes of the individual trials as well as the aggregate. Point estimates to the left favors CRT. Funnel plot demonstrates publication bias**

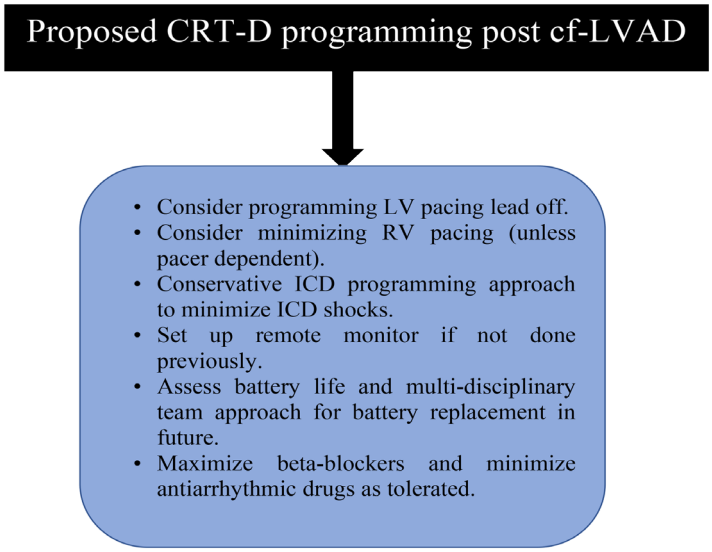


Figure 8: **Clinical practice approach on CRT-D in patients with cf-LVAD [6]**

a substantially higher number of primary prevention ICDs in the "CRT on" patients which could contribute to the lower incidence of ICD shocks and ventricular arrhythmias in those groups as opposed to the "CRT off" group.Variation in device programming could be another potential explanation for the differences in arrhythmia detection in both groups. Also, no significant difference was observed in terms of antiarrhythmic use between the "CRT on" and "CRT off" groups (Figure 3). If the antiarrhythmic effect of CRT is the possible explanation for the reduction in ventricular arrhythmias and ICD shocks as highlighted by Richardson et al.[17], then similar findings should have been observed in CRT versus non-CRT group in our analysis. The findings of our study are intriguing, and therefore, we feel that larger studies in a randomized prospective manner should be undertaken to address this specifically.

Because of the lack of definite clinical data assessing the role of CRT in LVAD patients, it remains controversial at this time regarding optimal device programming settings. Therefore, in our clinical practice, we typically deactivate the LV pacing (and reprogram to minimize RV pacing unless otherwise pacer dependent) to preserve battery life and minimize generator changes[19], which by themselves carry a risk of infections or anticoagulation related issues (pocket hematoma or LVAD pump thrombosis) in this high-risk population (Figure 8).

This systematic review and meta-analysis has several important limitations.First, patient selection bias due to limited data (retrospective nature of included studies and conference abstracts) could not be excluded. Also, the trials that evaluated "CRT on" versus "CRT off" had a small size and lacked sufficient statistical power to draw realistic conclusions. Second, information on arrhythmia burden/morphology and its timing in relation to LVAD were obscure. Third, variations in the LV lead position depending underlying anatomy and operator experience, device programming parameters in cf-LVAD patients were not well defined. Fourth, QRS duration, change in QRS post LVAD, and change in LVEF was not available in all trials to thoroughly understand hemodynamic effects between CRT on and off groups. Fifth, data on antiarrhythmic and other medications, etiology of death (cardiac, or non-cardiac), generator changes, and LVAD/CRT related complications were not outlined in all trials.Finally,patient-level data to perform more detailed analyses are not available.

Conclusion

Cardiac resynchronization therapy was not associated with a reduction in all-cause mortality, increased risk of ventricular arrhythmias, and ICD shocks as compared to non-CRTin end-stage heart failure patients with cf-LVAD. However, it remains to be determined which subgroup of cf-LVAD patients may benefit from cardiac resynchronization therapy.Future research should be directed to study the role of CRT in end-stage heart failure patients with cLVAD in a dedicated randomized controlled study.

Please Click for Supplemental Material

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Incidence of Early Atrial Fibrillation After Transcatheter versus Surgical Aortic Valve Replacement: A Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: Post-operative atrial fibrillation (POAF) is common after aortic valve replacement (AVR) and is associated with worse outcomes. We performed a meta-analysis of randomized controlled trials comparing Surgical Aortic Valve Replacement (SAVR) and Transcatheter Aortic Valve Replacement (TAVR) for incidence of POAF at 30 days.

Methods: We searched databases from 1/1/1990 to 1/1/2020 for randomized studies comparing TAVR and SAVR. POAF was defined as either worsening or new-onset atrial fibrillation. Random effects model was used to estimate the risk of POAF with TAVR vs SAVR in all trials, and in subgroups (low, intermediate, high risk, and in self-expandable vs balloon expandable valves). Sensitivity analysis was performed including only studies reporting new-onset atrial fibrillation

Results: Seven RCTs were identified that enrolled 7,934 patients (3,999 to TAVR and 3,935 to SAVR). The overall incidence of POAF was 9.7% after TAVR and 33.3% after SAVR. TAVR was associated with a lower risk of POAF compared with SAVR (OR 0.21 [0.18-0.24]; P < 0.0001). Compared with SAVR, TAVR was associated with a significantly lower risk of POAF in the high-risk cohort (OR 0.37 [0.27-0.49]; P < 0.0001), in the intermediate-risk cohort (OR 0.23 [0.19-0.28]; P < 0.0001), low-risk cohort (OR 0.13 [0.10-0.16]; P < 0.0001). Sensitivity analysis of 4 trials including only new-onset POAF showed similar summary estimates (OR 0.21, 95% CI [0.18-0.25]; P< 0.0001).

Conclusions: TAVR is associated with a significantly lower risk of post-operative atrial fibrillation compared with SAVR in all strata. Further studies are needed to identify the contribution of post-operative atrial fibrillation to the differences in clinical outcomes after TAVR and SAVR.

Introduction

Transcatheter aortic valve replacement (TAVR) has emerged as an alternative to surgical aortic valve replacement (SAVR) [1,2] for treatment of patients with symptomatic severe aortic stenosis (AS) in all risk cohorts [3-5] with short-term follow-up indicating durable results with TAVR. Recent trials comparing TAVR vs SAVR also showed that early and late outcomes are better in TAVR vs SAVR, and that stroke risk at one year is notably lower with TAVR vs SAVR [6].

Key Words

TAVR, SAVR, Atrial Fibrillation, Meta-Analysis

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Post-operative atrial fibrillation (POAF) is common after TAVR and SAVR[7]. The incidence of POAF has been reported in 20-40% of SAVR and 5-40% of TAVR patients and has been associated with risk of early and late stroke in both TAVR and SAVR[8-10]. POAF is also associated with prolonged hospital stay as well as increased morbidity and mortality[11].

While prior observational studies reported lower risk of POAF after TAVR vs SAVR, these studies are limited by design. We performed a meta-analysis of randomized trials to examine the incidence of POAF at 30 days after TAVR and SAVR.

2. Methods

2.1 Data sources and eligibility criteria

We conducted and reported this meta-analysis according to the Cochrane Central Register of Controlled Trials (CENTRAL). We

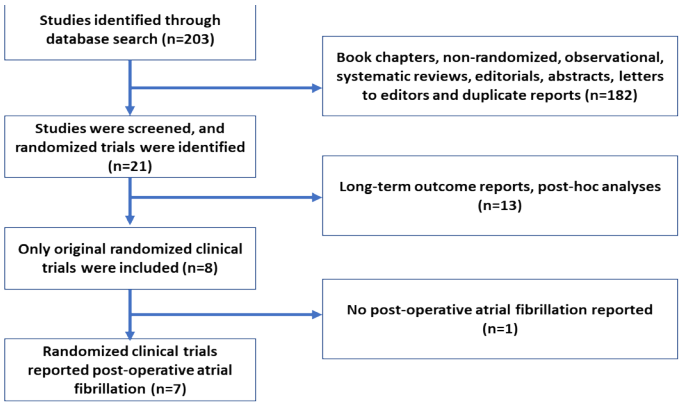

Figure 1: **CONSORT diagram**

performed a systematic computerized search through the MEDLINE, EMBASE, and COCHRANE databases from January 1st, 1990 to January 1st, 2020 using the following search terms separately and in combination: "randomized trial," "TAVR," "SAVR," "Atrial fibrillation," "Complications," and "Aortic stenosis." We performed the same search strategy for abstracts of the major scientific sessions, and ClinicalTrials.gov for any relevant studies. This was complemented with a manual search of PubMed and Google Scholar. Bibliographies of retrieved studies and review articles were searched to identify any additional relevant studies. Authors, country, study population, and affiliated institutions were screened to exclude duplicate studies. Our search was limited to manuscripts in English language. Only randomized studies comparing TAVR vs SAVR were included in this analysis. The search strategy, study selection, and analysis adhered to QUORUM (Quality of Reporting of Meta-Analysis) guidelines for meta-analyses.

2.2 Data extraction, outcome definition, and quality assessment

Two independent investigators (HA, RM) extracted the data, including baseline study characteristics, demographics, and outcomes of interest from the retrieved studies. There was good inter-rater agreement between the reviewers with respect to inclusion of studies, study quality, and data abstraction (k> 0.85). The outcome was POAF, which was defined as new or worsening AF within 30 days post AVR (TAVR or SAVR). The definition of worsening AF was included in three clinical trials (Supplemental Table 1), while the remaining trials did not have a clear definition. Atrial fibrillation was diagnosed as any arrhythmia within hospitalization that has the ECG characteristics of atrial fibrillation (or flutter) and lasts sufficiently long to be recorded on a 12-lead ECG, or at least 30 seconds on a rhythm strip in some of these trials. No specific methods for AF detection were provided in other trials. Supplemental Table 1 lists the definition of POAF in each trial. Cochrane risk-of-bias tool for randomized trials (RoB 2) was used to describe trial bias.

2.3 Data synthesis and statistical analysis

Continuous variables are expressed as means ± standard deviation and categorical variables as counts and percentages. Summary results are presented as mean differences. Random and fixed effects model was used to calculate Odd Ratios (OR) and corresponding 95% confidence interval (CI) given high heterogeneity (I2> 50% in all analyses). Publication bias was examined by funnel plots and Egger's test.[12] Subgroup analysis was conducted for high, intermediate and low risk cohorts, and valve type (balloon-expandable and self-expandable TAVR). Sensitivity analysis was performed by limiting analysis to trials that included only new-onset AF. Data collection, study selection, processing of the data, and reporting of results were performed according to accepted principles of systemic review and meta-analysis[13] All P-values were two-tailed, with statistical significance set at 0.05, and CIs were calculated at the 95% level. Review Manager software (Version 5.3.5. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to perform the analysis.

3. Results

3.1 Search Results

The database search identified 203 relevant references or citations (Figure 1). After duplicate removal and title and abstract reading, 182 records were excluded, and 8 were considered for full-text analysis. Of these, 1 article was excluded because it did not report POAF, and 7 studies were selected for the meta-analysis (PARTNER 1[14], CoreValve[15], NOTION[16], PARTNER 2[17], SURTAVI[18], PARTNER 3[19], Evolut[20]).

3.2 Characteristics of the studies

A total of 7 randomized trials with 7,934 patients met our selection criteria. Of these, 3,999 patients were randomized to TAVR and 3,935 were randomized to SAVR. The baseline patient characteristics are listed in Table 1. Males constitute 59.0% of the cohort, 29.2% had a previous history of atrial fibrillation (AF), and 8% of patients had known prior history of a cerebrovascular accident. The Society of Thoracic Surgeons (STS) perioperative risk of mortality ranged from low (1.9%) in the "low-risk" TAVR trials to high (11.8%) in the "high-risk" studies. Transfemoral access was used in 90% of patients in the composite analysis.

3.1 Outcomes

POAF at 30 days was defined as either new onset AF or worsening of AF. The composite incidence of POAF at 30 days was 9.7% (377/3900) after TAVR and 33.3% (1224/3680) after SAVR (Figure 2). In a fixed-effect meta-analysis including all 7 trials, TAVR was associated with a lower risk of 30-day POAF compared with SAVR (OR 0.21, 95% CI [0.18-0.24]; P < 0.0001, I2 = 86%) (Figure 3). The lower incidence

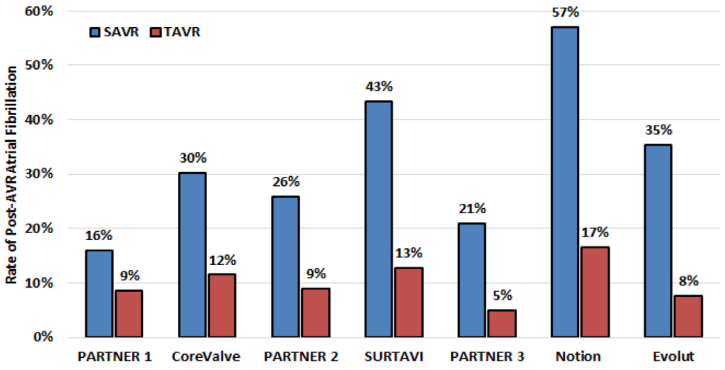

Figure 2: **Incidence of post-operative atrial fibrillation at 30 days with TAVR and SAVR Across the Randomized Clinical Studies**

Table 1: Baseline Characteristics of the 7 studies

	High risk				Intermediate risk				Low risk					
	Partner 1		CoreValve		Partner 2		SURTAVI		Partner 3		Evolut		Notion	
	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR
Trials' characteristics														
Recruitment period	2007-2009		2011-2012		2011-2013		2012-2016		2016-2017		2016-2018		2009-2013	
Longest follow-up, year	5		3		2		2		1		2		2	
Design	Non-inferiority		Non-inferiority		Non-inferiority		Non-inferiority		Non-inferiority and Superiority		Non-inferiority		Superiority	
ITT patients	348	351	394	401	1011	1021	864	796	503	497	734	734	145	135
As-treated patients	344	313	391	359	994	944	863	794	496	454	725	678	142	134
Patients' characteristics														
Age, mean (SD)	83.6 ± 6.8	84.5 ± 6.4	83.5 ± 7.1	83.5 ± 6.3	81.5 ± 6.7	81.7 ± 6.7	79.9 ± 6.2	79.7 ± 6.1	73.3 ± 5.8	73.6 ± 6.1	74.1 ± 5.8	73.6 ± 5.9	79.2 ± 4.9	79.0 ± 4.7
Women, n (%)	147 (42.2%)	153 (43.6%)	183 (46.4%)	189 (47.1%)	463 (45.8%)	461 (45.2%)	366 (42.4%)	358 (45.0%)	161 (32.0%)	131 (26.4%)	261 (35.6%)	229 (31.2%)	67 (46.2%)	64 (47.4%)
STS, mean ± SD	11.8± 3.3	11.7 ± 3.5	7.3 ± 3.0	7.5 ± 3.2	5.8 ± 2.1	5.8 ± 1.9	4.4 ± 1.5	4.5 ± 1.6	1.9 ± 0.7	1.9 ± 0.6	1.9 ± 0.7	1.9 ± 0.7	2.9 ± 1.6	3.1 ± 1.7
CKD, n (%)	38 (10.9%)	24 (6.8%)	48 (12.2%)	52 (13.0%)	51 (5.0%)	53 (5.2%)	14 (1.6%)	17 (2.1%)	1 (0.2%)	1 (0.2%)	3 (0.4%)	1 (0.1%)	2 (1.4%)	1 (0.7%)
PVD, n (%)	148 (42.5%)	142 (40.5%)	163 (41.4%)	169 (42.1%)	282 (27.9%)	336 (32.9%)	266 (30.8%)	238 (29.9%)	34 (6.8%)	33 (6.6%)	54 (7.4%)	56 (7.6%)	6 (4.1%)	9 (6.7%)
Prior CVA, n (%)	95 (27.3%)	87 (24.8%)	51 (12.9%)	53 (13.2%)	NK	NK	57 (6.6%)	57 (7.2%)	17 (3.4%)	23 (4.6%)	74 (10.1%)	80 (10.9%)	24 (16.6%)	22 (16.3%)
Prior CABG, n (%)	147 (42.2%)	152 (43.3%)	117 (29.7%)	121 (30.2%)	239 (23.6%)	261 (25.6%)	138 (16.0%)	137 (17.2%)	NK	NK	18 (2.5%)	14 (1.9%)	NK	NK
Prior CAD, n (%)	201 (57.8%)	198 (56.4%)	207 (52.5%)	187 (46.6%)	548 (54.2%)	560 (54.8%)	498 (57.6%)	438 (55.0%)	335 (66.6%)	323 (65.0%)	464 (63.2%)	449 (61.2%)	78 (53.8%)	71 (52.6%)
Prior PCI, n (%)	116 (33.3%)	110 (31.3%)	133 (33.8%)	152 (37.9%)	274 (27.1%)	282 (27.6%)	184 (21.3%)	169 (21.2%)	NK	NK	103 (14.0%)	87 (11.9%)	11 (7.6%)	12 (8.9%)
Known AF or flutter, n (%)	80 (23.0%)	73 (20.8%)	161 (40.9%)	190 (47.4%)	313 (31.0%)	359 (35.2%)	243 (28.1%)	211 (26.5%)	78 (15.5%)	85 (17.1%)	111 (15.1%)	98 (13.4%)	40 (27.6%)	34 (25.2%)
Prior pacemaker, n (%)	69 (19.8%)	76 (21.7%)	92 (23.4%)	83 (20.7%)	118 (11.7%)	123 (12.0%)	84 (9.7%)	72 (9.0%)	12 (2.4%)	13 (2.6%)	NK	NK	5 (3.4%)	6 (4.4%)
Intervention's characteristics														
Valve Type	Edwards Sapien	NA	Corevalve	NA	Sapien XT	NA	CoreValve, Evolut R	NA	Sapien S3	NA	Corevalve, Evolut R, Evolut Pro	NA	Corevalve	NA
Transfemoral access, n (%)	244 (70.1%)	NA	394 (100.0%)	NA	775 (76.7%)	NA	809 (93.6%)	NA	490 (97.4%)	NA	727 (99.0%)	NA	145 (100.0%)	NA
Transthoracic access, n (%)	104 (29.9%)	NA	0 (0.0%)	NA	236 (23.3%)	NA	55 (6.4%)	NA	0 (0.0%)	NA	7 (1.0%)	NA	0 (0.0%)	NA

Abbreviations. TAVR = Transcatheter aortic valve replacement; SAVR: Surgical aortic valve replacement; STS PROM= Society of Thoracic Surgery perioperative risk of mortality score; CVA = cerebrovascular accident; CKD = chronic kidney disease; PVD = Peripheral vascular disease; CABG = Coronary artery bypass grafting; PCI= percutaneous coronary intervention; AF= Atrial fibrillation; NA= Not applicable; NK= Not known.

of POAF at 30 days was noted across different risk strata: high-risk cohort (23.2% vs 10.2%, OR 0.37, 95%CI [0.27-0.49]; P < 0.0001, I2 = 62%), intermediate-risk cohort (33.4% vs 10.8%, OR 0.23, 95% CI [0.19-0.28]; P < 0.0001, I2 = 77%), and low-risk cohort (39.1% vs 7.8%, OR 0.13, 95% CI [0.10-0.16]; P < 0.0001, I2 = 55%). Similarly, the lower incidence in 30-day POAF with TAVR was significant in trials using both self-expanding valves (41.1% vs 12.9%, OR 0.21 [0.17-0.25], P<0.0001, I2=62%) and balloon-expandable valves (29.2% vs 7.9%, OR 0.21 [0.18-0.25], P<0.0001, I2=92%). The reported incidence of stroke, mortality and readmission at 30 days in TAVR vs SAVR are showed in Supplemental Table 2.

3.2 Sensitivity analysis

Four trials [Evolut[20], PARTNER 1[14], PARTNER 2[17], PARTNER 3[19]] reported incidence of "new-onset" AF. The risk of new onset AF at 30 days in TAVR group was lower than SAVR group (OR 0.21, 95% CI [0.18-0.25]; P< 0.0001, I2 = 92%), Figure 4. Calculation of summary effects with fixed- and random-effects yielded similar results (Supplemental Table 3).

4. Discussion

This study demonstrates a lower overall cumulative incidence of worsening and new-onset atrial fibrillation after TAVR compared with SAVR. The lower risk of POAF extends to all risk categories and TAVR valve types. Similarly, we also demonstrate a lower incidence

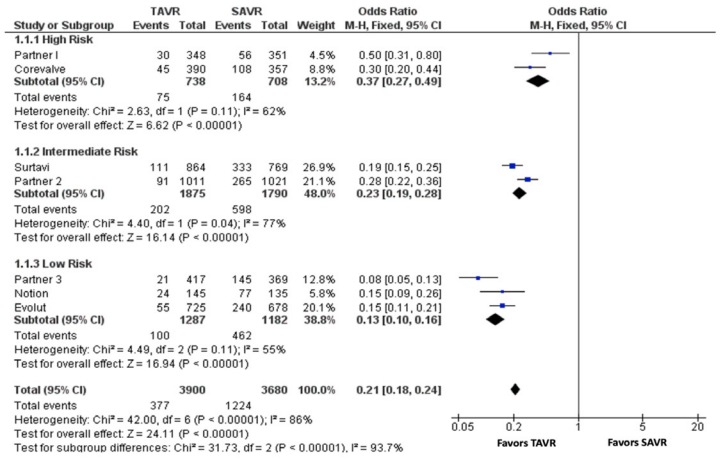

Figure 3: **Forest plot of studies comparing post-operative atrial fibrillation at 30 days in TAVR versus SAVR in high, intermediate, and low risk cohort. CI = confidence interval; TAVR = transcatheter aortic valve replacement; SAVR = surgical aortic valve replacement.**

of new onset post-operative atrial fibrillation after TAVR compared with SAVR.

The incidence of POAF is reported to be between 20% and 50%, and it varies by the procedure type [21-23]. Prior single-center studies consistently showed that TAVR is associated with a lower risk of AF compared with SAVR. In a single center study of 170 patients undergoing AVR (84 TAVR, 86 SAVR), a lower risk of new onset AF was noted in the TAVR group compared with SAVR group (6% vs 33.7%, P<0.05)[24]. Non-femoral access routes used in TAVR seemed to be associated with higher risk of POAF. In a retrospective single-center cohort study of 231 patients undergoing TAVR, POAF occurred in 53% after transapical TAVR, 33% after transaortic TAVR, and 14% after transfemoral TAVR. AVR without pericardiotomy was associated with a lower risk of AF, with an adjusted OR (adjusted OR: 0.18; 95% CI: 0.05 to 0.59) similar to the summary effect observed in our analysis. These studies, however, are limited by the different baseline characteristics of patients undergoing TAVR vs SAVR, and the non-randomized nature of the analyses predisposing to significant bias. Only randomized studies were included in the current metanalysis, therefore minimizing bias and balancing confounders. [25]

Studying the incidence of POAF is important as it is associated with worse clinical outcomes after AVR (TAVR and SAVR). In a study of 24,076 patients undergoing TAVR in the US, post-TAVR AF was associated with increased risk of stroke and readmission[26]. Similarly, other studies showed that new-onset AF after TAVR is associated with increased risks of systemic embolization and stroke [27], and short-term[10] and long-term mortality[25].

Our findings have important clinical implications. The key differences in complications rates of TAVR and SAVR, including the risk of POAF, should be part of the shared-decision making process between the patient and the Integrated Heart Team. Furthermore, differences in the incidence of POAF between the two AVR approaches may provide some insight into POAF mechanism. POAF is generally thought to be multifactorial: inflammatory response triggered by pericardiectomy and cardiopulmonary bypass, catecholamine surge, pericardial inflammation, and the overall hemodynamic burden of surgery. Patients with preexisting atrial remodeling seem to have higher risk of POAF after TAVR[28]. Transfemoral TAVR is a less invasive procedure, with a significantly reduced hemodynamic burden, no compromise of the pericardium, and a reduced inflammation and sympathetic tone. Our findings further confirm the importance of these contributing factors and procedure type on POAF.

Notably, there is uncertainty on the role of anticoagulation in post-operative AF. POAF has been linked with early and late stroke after both TAVR and SAVR[8,29]. Most patients with POAF after TAVR receive anticoagulation whereas anticoagulation for SAVR is much less common[30]. Whether POAF and/or anticoagulation mediates short and long-term stroke risk and other outcomes after TAVR vs SAVR remains to be elucidated.

In the current meta-analysis, the odds ratio of POAF with TAVR vs SAVR is lower with decreasing surgical risk: (high risk OR 0.37 [0.27-0.49]; intermediate risk OR 0.23 [0.19-0.28]; and low risk OR 0.13 [0.10-0.16]). The lower rate of POAF with TAVR vs SAVR may be due to the decreased utilization of "alternative" access use (ex. trans-apical or trans-aortic) in the lower risk population, in addition to the improved overall TAVR techniques in the lower risk studies. As such, differences in POAF between TAVR and SAVR could be magnified. Additionally, patients in the higher risk trials have higher prevalence of comorbidities including cardiomyopathy and atrial remodeling, and peri-procedural AF may reflect paroxysmal AF that was not detected, and thus diluting the effect of post-AVR pericardial inflammation. The contribution of reduced POAF burden to the improved outcomes (especially stroke and rehospitalization) noted with low-risk TAVR compared with SAVR should needs further investigation.

5. Study limitations

We acknowledge the limitations inherent to meta-analyses. The validity of our results is dependent on the validity of the studies included. We do not have access to patient level data in order to perform individual-level meta-analysis. Nevertheless, by limiting included studies to RCTs we minimize variability in burden of comorbidities between TAVR and SAVR groups and as a result decrease the possibility that differences could be due to confounding. The included studies did not entirely differentiate between new onset and provoked AF, and none of the included studies reported time to and duration of AF. Finally, not all the patients in these trials had continuous monitoring such as implantable loop recorders or pacemakers, and methods for AF detection may not have been standardized across studies, which may have led to underdiagnosis of AF. While the overall implications for post-procedural management may be similar, there are different implications for underlying mechanism and for the role of long-term

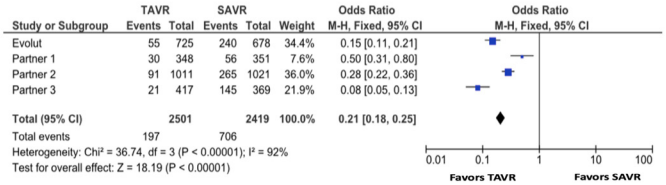

Figure 4: **Forest plot of studies comparing the risk of new onset atrial fibrillation at 30 days in TAVR versus SAVR.CI = confidence interval; TAVR = transcatheter aortic valve replacement; SAVR = surgical aortic valve replacement.**

anticoagulation. The definition of POAF was not standardized across trials, and thus a level of heterogeneity is expected due to different definitions. We address this shortcoming by conducting a sub-analysis with only the studies that reported new onset POAF specifically and demonstrate that the results are consistent with our overall findings.

6. Conclusions

TAVR is associated with a significantly lower risk of post-operative atrial fibrillation compared with SAVR in all risk strata and valve types. Further studies are needed to identify the contribution of post-operative atrial fibrillation to the clinical outcomes observed after TAVR and SAVR.

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Effect of Intensive Blood Pressure Lowering on Incident Atrial Fibrillation: A Systematic Review and Meta-Analysis

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Abstract

The effect of intensive versus standard blood pressure (BP) lowering on the risk of atrial fibrillation (AF) is uncertain. Intensive BP lowering is associated with a lower risk of AF among patients with hypertension. We searched PubMed, EMBASE, and CENTRAL (inception to June 5, 2020) for randomized controlled trials evaluating the effect of intensive versus standard (target systolic BP < 140 mmHg) BP lowering on incident AF. We assessed heterogeneity using the I2 statistic then usedfixed-effects meta-analysis models to report pooled treatment effects and 95% confidence intervals. We also tested for publication bias by three funnel plot-based methods. The quality of each study was assessed with the Cochrane Risk of Bias tool. We assessed 16 candidate studies for eligibility from 2,312 published articles, but only three randomized clinical trials were eligible for inclusion and included a combined 12,219 participants with hypertension: Cardio-Sis (Studio Italiano Sugli Effetti Cardiovascolari del Controllo della Pressione Arteriosa Sistolica), ACCORD-BP (Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial), and SPRINT (Systolic Blood Pressure Intervention Trial). The target systolic BP in the intensive BP arm was <120 mmHg for participants in SPRINT and ACCORD-BP, but <130 mmHg for participants in Cardio-Sis. Participants randomized to intensive BP lowering had significantly lower risk of incident AF compared with those randomized to standard BP lowering (AF incidence 2.2% vs. 3.0%, respectively; pooled hazard ratio (95% confidence interval): 0.74 (0.59 – 0.93)).Intensive BP lowering is associated with a significantly lower risk of incident AF in patients with hypertension. These findings add to the current evidence supporting the benefits of intensive BP control.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia and is associated with a five-fold increased risk of ischemic stroke and a two-fold increased risk of death.[1-4]The prevalence of atrial fibrillation continues to increase and is projected to exceed 12 million in the US alone by 2030,[5,6] which has led to calls for additional research exploring primary prevention of AF.[7] In observational studies, there is a strong relationship between blood pressure and the risk of AF, with hypertension accounting for the largest population attributable fraction of risk of incident AF.[8] There is mounting evidence that intensive blood pressure lowering can decrease the risk of death, atherosclerotic cardiovascular disease, heart failure, and stroke.[9,10] However, the extent to which the risk of AF can be decreased by intensive blood pressure lowering remains uncertain.[11, 12] Therefore, a systematic review and meta-analysis was performed to determine whether intensive blood pressure lowering is associated with a reduced risk of incident AF.

Key Words

Atrial Fibrillation, Blood Pressure, Hypertension, Intensive, Meta-Analysis

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Methods

We performed a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[13] We searched PubMed, EMBASE, and CENTRAL for articles published from inception to June 1st, 2020, without language or other restrictions. Search terms included: atrial fibrillation AND (blood pressure OR hypertens* OR antihy pertens* OR anti-hypertens*) AND (placebo OR control*) AND random. One author (MJS) screened titles and abstracts. For relevant articles, full texts were retrieved and reviewed. The reference lists from all included trials were also reviewed for relevant articles. Trials were eligible for inclusion in the meta-analysis if they were randomized clinical trials comparing two intensities of blood pressure management and included incident AF as a reported outcome in any analysis of the trial. Secondary prevention trials of blood pressure lowering for reducing the risk of recurrent AF after catheter ablation were excluded. Control was defined as the standard blood pressure lowering according to the blood pressure guidelines at the time of conducting the study.

Data were extracted by author MJS using a standardized data extraction form. All included studies and their extracted data were independently reviewed by JY and ES. The primary out come of this meta-analysis was incident AF. We utilized the Cochrane Risk of Bias tool version 2 to assess the quality of the included studies.[14] Domains of assessment included selection bias, performance bias, detection bias, attrition bias, and reporting bias. Hazard ratios (HRs) and 95% confidence intervals (95% CI) were taken from each trial. Chi-squared analysis was used to quantify the degree of heterogeneity between included studies, with a pre-specified p-value of 0.10 used to define significant heterogeneity. Variability and heterogeneity across studies was further assessed using a forest plot and I2 statistics. Weighted pooled treatment effects were calculated using a fixed-effects meta-analytic model given the low between-study heterogeneity.[15] Publication bias was assessed using Egger's funnel plot.[16] Pooled absolute and relative risk reductions were calculated. Statistical analysis was performed using RevMan 5.3.[17]

Results

The systematic search strategy of published articles yielded 3,142 articles for review (Figure 1). After excluding duplicates, 2,312 articles were considered for inclusion by reviewing their titles and abstracts. Full texts were retrieved for 16 candidate studies. Of these, one was excluded for being a secondary prevention trial, nine were excluded for not randomizing participants to antihypertensive therapies, and three were excluded for randomizing to a specific class of antihypertensive agent, rather than intensity of therapy, leaving three trials eligible for inclusion in the meta-analysis: Cardio-Sis (Studio Italiano Sugli Effetti Cardiovascolari del Controllo della Pressione Arteriosa Sistolica),[18] ACCORD-BP (Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial),[19] and SPRINT (Systolic Blood Pressure Intervention Trial).[20]

A descriptive analysis of the participants eligible for this analysis who were initially free of AF from each of the included studies is provided in Table 1. All included studies were open-label randomized clinical trials comparing two intensities of blood pressure control. Two of three were conducted in the USA, while the third was conducted in Italy. Important differences include diabetes being one of the inclusion criteria in ACCORD-BP, but an exclusion in SPRINT and Cardio-Sis. Also, the target systolic blood pressure for the intensive arm was < 120 mmHg in SPRINT and ACCORD-BP, but < 130 mmHg in Cardio-Sis.

Between the three included trials, there were 12,219 participants. The mean age of trial participants was 66.1 ± 8.3 years and 41.0% were women. The mean baseline systolic and diastolic blood pressures were 141.4 ± 15.1 and 79.0 ± 10.9 mmHg, respectively (Table 2). The median duration of follow-up was 3.8 years. The publication year ranged from 2009 to 2020. Risk of bias was assessed in all included studies, with the overall risk being low in all three studies in all domains assessed (Figure 2). The funnel plot was not suggestive of publication bias, with relative symmetry about the cumulative effect size (Figure 3).

Participants assigned to intensive blood pressure lowering achieved lower systolic and diastolic blood pressures than those assigned to standard blood pressure lowering by 12.4 and 7.1 mmHg, respectively.

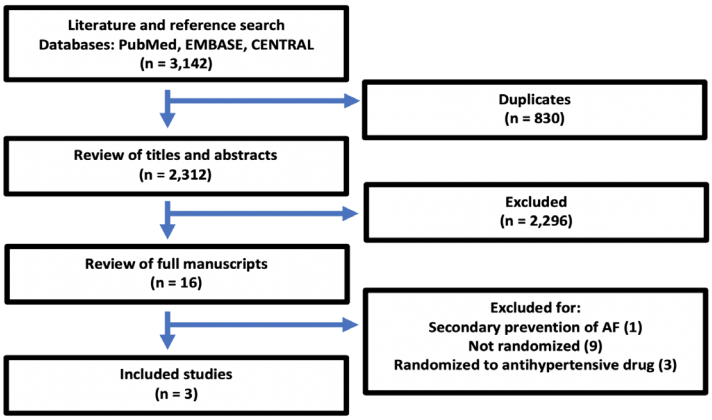

Figure 1: Study flow for systematic review and meta-analysis.

Of 2,312 unique articles found during the literature search, 16 full-texts were retrieved and 3 studies met criteria for inclusion in the meta-analysis.

Incident AF was diagnosed in 135 of 6,111 participants in the intensive blood pressure lowering group and 184 of 6,108 in the control group. The effect sizes as hazard ratios ranged from 0.46 to 0.87. In a fixed-effect meta-analytic model, intensive blood pressure lowering was associated with a decreased risk of incident AF (2.2% vs. 3.0%; hazard ratio 0.74, 95% confidence interval 0.59 – 0.93; absolute risk reduction 0.8%, relative risk reduction 27%; Figure 4). The effects were fairly

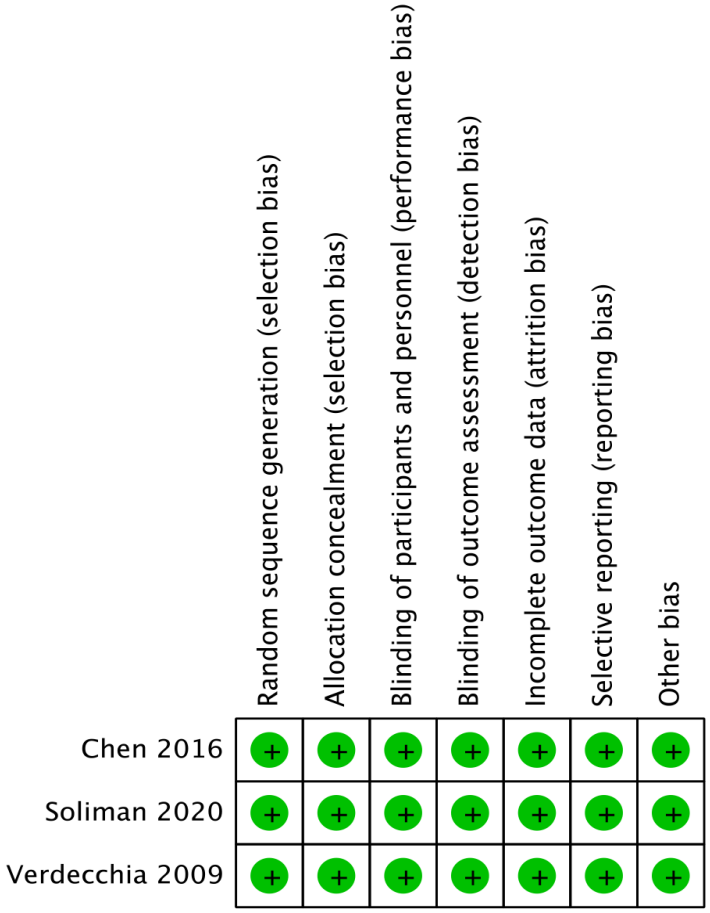

Figure 2: Risk of bias of included studies.

All included studies had a low risk of bias in all domains assessed.

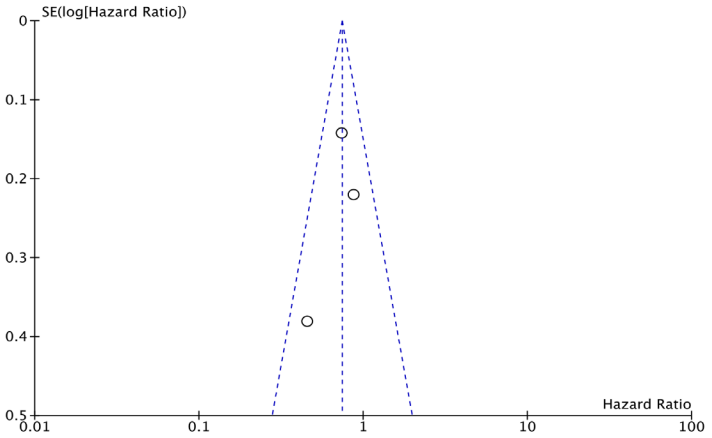

Figure 3: Funnel plot of included studies.

Funnel plot depicting the relationship between treatment effect and study precision is not suggestive of publication bias.

consistent across trials with low heterogeneity (I2 = 5%).

Discussion

Principal Findings

This systematic review and meta-analysis, which included three trials with 12,219 participants, found intensive blood pressure lowering compared with standard blood pressure control results in a 26% decreased risk of incident AF. The low degree of heterogeneity suggests that this effect is conserved across multiple patient populations. This meta-analysis adds to the known epidemiological association of blood pressure and AF risk in the literature by providing further evidence that intensive blood pressure lowering as a therapeutic strategy that may lower the risk of AF.

In aggregate, the evidence available from the epidemiological literature strongly supports the association between higher blood pressure and increased risk of incident AF. However, the question of whether intensive blood pressure lowering decreases the risk of incident AF, or if the propensity for AF might be irreversible such that intensive lowering of blood pressure might not have salutary benefits in prevention of AF, has been un answered.[11] Our findings of a consistent benefit of intensive blood pressure lowering in attenuating the risk of AF lends support to the idea that aggressive control of hypertension may decrease the societal burden of AF.

How Low Is Too Low?

Though intensive blood pressure lowering was found to decrease the risk of AF in our analysis, it remains unclear whether there is a lower limit of blood pressure below which there is no further reduction in AF risk, or even an increased risk. This is particularly important if intensive blood pressure lowering is to be considered as a tool for lowering the risk of AF, as the target blood pressure depends on the shape of the curve relating blood pressure to AF risk. One study found evidence of a J-shaped curve relating blood pressure to AF risk, such that patients receiving treatment for hypertension with achieved systolic blood pressure< 120 had double the risk of AF compared to those with achieved systolic blood pressure 120 – 129, though the case-control design may allow for residual confounding.[21] In contrast, in the Women's Health Study, a 10 mmHg increase in systolic blood pressure was associated with a 12% increase in risk of AF.[22] Importantly, this dose-risk relationship was conserved in all strata of blood pressures tested, with continuously-decreasing risk of AF with progressively decreasing blood pressures, including an systolic blood pressure< 120 mmHg stratum. Findings were similar in a study of Norwegian men, with those in the lowest quartile of systolic blood pressure (88 – 116 mmHg) having the lowest risk of AF.[23] An analysis from the ONTARGET/TRANSCEND trials found the group with systolic blood pressure< 120 had the lowest risk of AF.[24] Overall, the epidemiological literature suggests that there is no lower limit of blood pressure target below which the benefit in AF prevention is lost, and these findings are in agreement with the result of our meta-analysis.

Less Benefit In Diabetes?

Of the three trials included in this meta-analysis, only ACCORD-BP did not individually demonstrate a statistically-significant reduction in the risk of incident AF with intensive blood pressure control. This may be explained by ACCORD-BP being underpowered for incident AF, though it should be noted that there were more cases of incident AF in ACCORD-BP than Cardio-Sis. As an alternative explanation, since ACCORD-BP only included participants with diabetes and the other trials specifically excluded participants with diabetes, it is possible that the benefits of intensive blood pressure lowering in decreasing the risk of AF in those with diabetes are less than that seen in those without diabetes. The presence or absence of diabetes may influence the effects of intensive blood pressure lowering on the risk of AF, particularly in light of the fact that intensive blood pressure control has been shown to be beneficial in those without diabetes, but not in those with diabetes, when comparing the SPRINT and ACCORD-BP trials in their primary outcomes.[10,25] It should be noted, however, that although the ACCORD-BP study did not reach statistical significance for reduction in risk of AF, the direction of association still suggested a benefit of intensive blood pressure lowering and the magnitude of the

Study	Intensive BP Control Events	Intensive BP Control Total	Standard BP Control Events	Standard BP Control Total	O−E	Variance	Weight	Hazard Ratio Exp[(O−E) / V], Fixed, 95% CI	Year
Cardio-Sis (Verdecchia, 2009)	10	557	21	553	−5.35	6.89	9.0%	0.46 [0.22, 0.98]	2009
ACCORD-BP (Chen, 2016)	37	1551	45	1536	−2.86	20.54	26.8%	0.87 [0.56, 1.34]	2016
SPRINT (Soliman, 2020)	88	4003	118	4019	−14.78	49.07	64.1%	0.74 [0.56, 0.98]	2020
Total (95% CI)		**6111**		**6108**			**100.0%**	**0.74 [0.59, 0.93]**	
Total events	135		184						

Heterogeneity: $Chi^2 = 2.10$, df = 2 (P = 0.35); $I^2 = 5\%$
Test for overall effect: Z = 2.63 (P = 0.009)

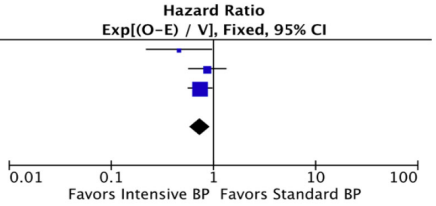

Figure 4: Association of Intensive Blood Pressure Lowering with Incident Atrial Fibrillation

The blue squares and bars represent the mean values and 95% confidence intervals of the effect sizes, with the area of the blue squares reflecting the weight of the studies. The black diamond represents the combined effect, with the vertical line representing no association.

Table 1: Participant Baseline Characteristics of Studies Included in Systematic Review and Meta-Analysis of the Association of Blood Pressure Lowering with Incident Atrial Fibrillation

Trial	Trial Design	Country	Study Population	Intervention	Control	Participants	Age mean, SD	Female
Cardio-Sis[18] (2009)	**Open-label randomized clinical trial**	Italy	Age ≥ 55, SBP ≥ 150 mmHg, no diabetes, no AF	**Goal SBP < 130 mmHg**	**Goal SBP < 140 mmHg**	**1,111**	**67.0 (7.0)**	**59.0%**
ACCORD-BP[19] (2016)	Open-label randomized clinical trial	USA	Diabetes, SBP 130 – 180 mmHg, high CVD risk	Goal SBP <120 mmHg	Goal SBP < 140 mmHg	3,087	62.2 (6.6)	48.2%
SPRINT[20] (2020)	Open-label randomized clinical trial	USA	No diabetes, no stroke, LVEF ≥ 35%, SBP 130 – 180, increased CVD risk	Goal SBP <120 mmHg	Goal SBP 135 – 139	8,022	67.7 (9.2)	35.5%

Cardio-Sis – Studio Italiano Sugli Effetti Cardiovascolari del Controllo della Pressione Arteriosa Sistolica
ACCORD-BP – Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial
SPRINT – Systolic Blood Pressure Intervention Trial
SD – standard deviation; SBP – systolic blood pressure (mmHg); AF – atrial fibrillation; CVD – cardiovascular disease; LVEF – left ventricular ejection fraction

association was only slightly less than that seen in the meta-analysis as a whole.

Benefit In Diverse Populations

The fact that intensive blood pressure lowering appears to confer a lower risk of AF in each of the included trials, despite the differences in their inclusion criteria and participant characteristics, is noteworthy. While ACCORD-BP included 39.2% non-white and SPRINT included 31.6% black participants, Cardio-Sis was a study of nearly all white participants. Since the incidence of AF is approximately 50% higher in whites than blacks,[26] the larger magnitude of beneficial effects from intensive blood pressure lowering found in the Cardio-Sis trial may be explained by the predominantly white study population. The mean BMI was 27.8 in Cardio-Sis, 29.9 in SPRINT, and 32.1 in ACCORD. While we cannot exclude an interaction between BMI and intensive blood pressure lowering with regard to AF risk, prior studies have found that the benefits of intensive blood pressure lowering appear to be conserved across all tested BMI strata.[27] The proportion of participants with prevalent cardiovascular disease also differed between trials. Only 12% of Cardio-Sis participants had baseline cardiovascular disease, but 19.5% of SPRINT participants and 30.9% of ACCORD-BP participants had prevalent cardiovascular disease. Taken together, the overall consistency of the relationship between intensive blood pressure lowering and AF risk, despite the differences in study populations, is reassuring and increases the generalizability of this finding.

Mechanisms

The mechanisms of the observed benefits of intensive blood pressure lowering on reducing AF risk likely involve several pathophysiological pathways.[11] Animal studies of the effects of chronic hypertension and its treatment on atrial myocardium have demonstrated that spontaneously hypertensive rats have higher incidence and duration of pacing-induced atrial tachycarrhythmias, with associated deranged calcium handling and increased interstitial fibrosis.[28] In an experimental rat model of hypertension in which the atria from rats with surgically-induced partial aortic stenosis were compared with controls, increased after load led to atrial fibrosis, reduced vectorial conduction velocity, reduced calcium content in the cardiomyocyte sarcoplasmic reticulum, and heterogeneity of conduction velocity, as well as heightened susceptibility to pacing-induced AF and more persistence in AF.[29,30] It is likely that intensive blood pressure lowering either slows progression of these processes or even leads to partial reversal. While it remains unproven that treatment of hypertension can lead to reversal of atrial cardiopathy,[31] this is a plausible explanation as there are several studies describing how treatment of hypertension can lead to regression of electrical and structural remodeling in the ventricle, including regression of left ventricular hypertrophy, decreases

Table 2: Outcomes of Studies Included in Systematic Review and Meta-Analysis of the Association of Blood Pressure Lowering with Incident Atrial Fibrillation

Trial	Follow-up years, median	Intervention Group BP (mean, SD)			Control Group BP (mean, SD)			Difference in BP Difference	Cases Intensive vs. control	HR (95% CI, p-value)
		Baseline	Follow-Up	Difference	Baseline	Follow-Up	Difference			
Cardio-Sis[18] (2009)	2.0	Systolic: 163.3 (11.3) Diastolic: 89.6 (8.8)	Systolic: 136.0 Diastolic: 79.2	Systolic: 27.3 (11.0) Diastolic: 10.4 (7.5)	Systolic: 163.3 (11.1) Diastolic: 89.7 (8.8)	Systolic: 139.8 Diastolic: 80.0	Systolic: 23.5 (10.6) Diastolic: 8.9 (7.0)	Systolic: 3.8 Diastolic: 1.5	10 vs. 21	0.46 (0.22 – 0.98, 0.044)
ACCORD-BP[19] (2016)	4.4	Systolic: 139.0 (15.0) Diastolic: 77.5 (9.5)	Systolic: 119.3 Diastolic: 64.4	Systolic: 19.7 Diastolic: 13.1	Systolic: 139.4 (15.5) Diastolic: 76.0 (10.2)	Systolic: 133.5 Diastolic:70.5	Systolic: 5.9 Diastolic:5.5	Systolic: 13.8 Diastolic: 7.6	37 vs. 45	0.85 (0.55 – 1.32, 0.48)
SPRINT[20] (2020)	3.8	Systolic: 139.5 (15.7) Diastolic: 78.2 (11.8)	Systolic: 121.5 Diastolic: 68.7	Systolic: 18.0 Diastolic: 9.5	Systolic: 139.6 (15.3) Diastolic: 78.1 (11.8)	Systolic: 134.6 Diastolic: 76.3	Systolic: 5.0 Diastolic: 1.8	Systolic: 13.0 Diastolic: 7.7	88 vs. 118	0.74 (0.56 – 0.98, 0.037)

Cardio-Sis – Studio Italiano Sugli Effetti Cardiovascolari del Controllo della Pressione Arteriosa Sistolica
ACCORD-BP – Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial
SPRINT – Systolic Blood Pressure Intervention Trial
BP – blood pressure (mmHg); SD – standard deviation; HR – hazard ratio; 95% CI – 95% confidence interval

in left ventricular mass, and improvement in diastolic function.[32,33]

Limitations And Strengths

Our findings should be interpreted in the context of their limitations. We cannot exclude the possibility that there may be additional studies of intensive blood pressure lowering that reported incident AF as an outcome that were not captured by our search strategy. In addition, despite querying PubMed, EMBASE, and CENTRAL, we found only three studies eligible for inclusion in our meta-analysis, providing us with limited ability to perform more detailed analysis and meta-regression. Surveillance for AF was limited to study electrocardiography in the included studies, so subclinical AF may have escaped detection, though we would not expect a differential effect by intensity of blood pressure lowering. Our data did not include further characterization of AF as paroxysmal or persistent, so any benefits of intensive blood pressure control on slowing progression from paroxysmal AF to persistent AF would not be appreciated in our study. The lack of sex-specific and race/ethnicity-specific event data precludes us from assessing for interaction between demographic characteristics and intensive blood pressure lowering. Since prevalent diabetes was an inclusion criteria for ACCORD and an exclusion criteria for Cardio-Sis and SPRINT, it is possible that the difference in effect size of intensive blood pressure control may be explained by prevalent diabetes serving as a residual confounder, and our meta-analytic methodology with the three included studies does not allow us to teasing out the differential effects in those with and without diabetes. Our study also does not address the effect of intensive blood pressure control on the risk of recurrent AF in patients who have had a prior episode of AF, as Cardio-Sis did not include any participants with prevalent AF and the analyses from ACCORD-BP and SPRINT specifically excluded participants with prevalent AF. Study strengths include the methodological rigor of the underlying randomized controlled trials, rigorous search strategy, inclusion of over 12,000 eligible participants, and the consistent direction of effect observed with low heterogeneity.

Conclusion

This systematic review and meta-analysis of randomized clinical trials published to date demonstrates that intensive blood pressure lowering compared with standard blood pressure control results in a 26% decreased risk of incident AF, and that this effect appears to be consistent in multiple patient populations. Further studies exploring the utility of intensive blood pressure lowering for primary prevention of AF are needed.

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The Role of Magnesium in the Management of Atrial Fibrillation with Rapid Ventricular Rate

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Abstract

Background: Atrial fibrillation is currently managed with a variety of rate controlling and antiarrhythmic agents. Often, magnesium is used as adjunctive therapy, however, the benefit it provides in managing Afib with RVR has been debated. This study aimed to determine if IV MgSO4 administration in conjunction with standard therapy provides any synergistic effect in acute and prolonged control of Afib with RVR.

Methods: This was a retrospective study involving ninety patients with episodes of Afib with RVR during their hospitalization. The treatment group included those that had received magnesium (n=32) along with standard management and the control group (n=58) received only standard management. Heart rates at different time intervals were collected. Dose dependent effects of IV MgSO4 on heart rates were also evaluated.

Results: Patients that received magnesium had a lower mean heart rate (85 BPM versus 96 BPM, P<0.05) 24 hours after onset of the episode. Also, in the last 16 hours of observation, it appeared that administration of higher levels of magnesium resulted in statistically lower heart rates. In the group of patients that received 2 grams of magnesium, the mean heart rate at 8 hours was 103.4 beats/min and 84.8 beats/min at 24 hours (p<0.01). This same trend was not seen in patients that received 1 gram of magnesium or in the control group.

Conclusion: Overall, the use of IV MgSO4 as an adjunctive treatment permitted normalization of the heart rate progressively that continued to at least 24 hours.

Introduction

Atrial Fibrillation (Afib) is the most commonly managed heart arrhythmia[1,2]. It is classified as a supraventricular arrhythmia which involves desynchronized atrial activation resulting in poor mechanical function. Characteristic identification of this arrhythmia on electrocardiogram (ECG) is highlighted by the lack of consistent P waves. Dependent on the condition of the AV node itself and its response to vagal and sympathetic tones, this rhythm can lead to a rapid ventricular response (RVR). Afib with RVR shortens ventricular filling time, increases myocardial oxygen demands and can potentially induce tachycardia cardiomyopathy[3].

A variety of rate controlling agents and antiarrhythmic agents including ß-blockers, calcium channel blockers, digoxin, and amiodarone are commonly used to control Afib with RVR[4]. Often, magnesium is seen being used as an adjunctive therapy, however, the benefit it provides in managing Afib with RVR has been debated. The rationale behind magnesium use is based on the physiological and pharmacological properties of the element[5]. Magnesium directly acts on myocardial potassium channels and has voltage dependent and indirect effects on sodium and calcium channels. Additionally, it can act as a calcium antagonist capable of inhibiting L-Type calcium current channels in myocardial cells. In theory, this property can lead to decreased frequency of sinus node depolarization and a prolonged refractory period of the AV node[6].

Evidence has emerged over the years supporting magnesium supplementation when trying to prevent or treat arrhythmias[6-9]. A meta-analysis by Onalen et al indicated that intravenous magnesium sulfate (IV MgSO4) provides a synergistic effect with standard rate controlling agents in acute management of Afib with RVR[10]. As a complement to rate control, a meta-analysis of 5 randomized trials (n=380) demonstrated that magnesium administration led to improved heart rates by a factor of 3 compared to placebo[11]. However, there are some studies that demonstrate that magnesium use does not provide any benefit in managing Afib with RVR[12-14]. For example, a meta-analysis of 10 randomized controlled trials by Kwok et al demonstrated that supplementing digoxin or ibutilide with IV MgSO4 provided no benefit in controlling Afib with RVR[13]. In addition, Lancaster et al., observed higher serum potassium and magnesium levels being associated with increased risk of postoperative atrial fibrillation[14].

This study aimed to determine whether IV MgSO4 provides a synergistic affect when combined with rate controlling or anti arrhythmic agents in achieving acute and prolonged control of episodes

Key Words

Atrial Fibrillation, Magnesium

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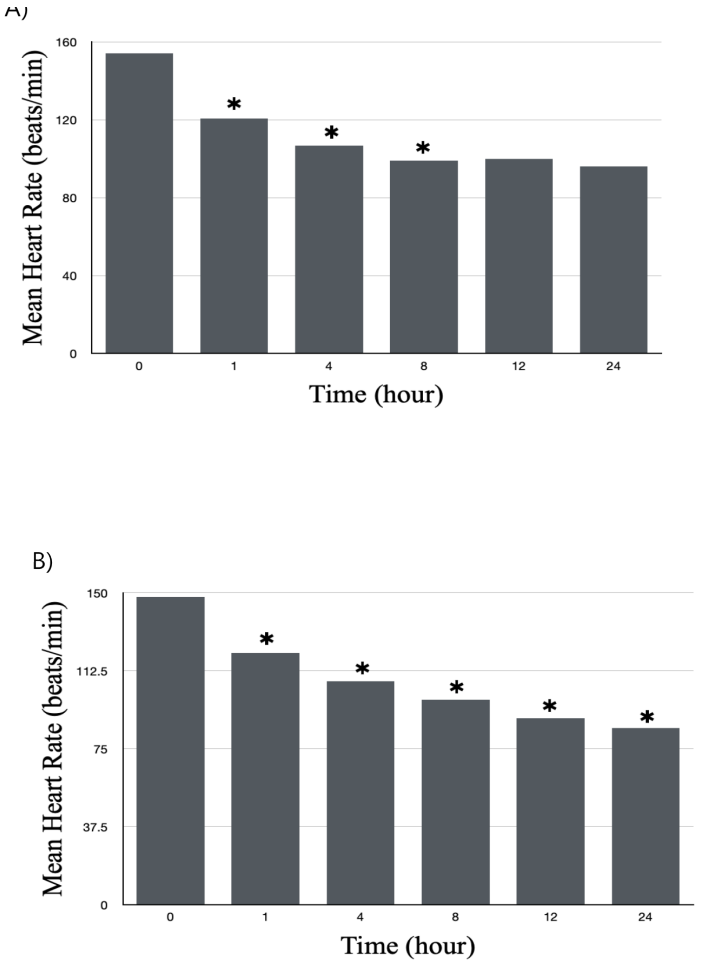

Figure 1: **A) Mean heart rate in relation to time for patients in the control group; patients that did not receive magnesium. B) Mean heart rate in relation to time in patients that received magnesium. *P<0.05**

of acute atrial fibrillation with rapid ventricular rate.

Methods

This was a retrospective study conducted at SUNY Upstate Medical University, Syracuse, NY. The patients selected for this study were those who had episodes of atrial fibrillation with RVR during their inpatient admission. A total of 90 patients were included for the study and data was collected through chart review. Each patient that was found to have Afib with RVR had a rapid response team come in to address the clinical situation. Heart rates for these patients were collected at onset of the episode, and subsequently at 1 hour, 4 hours, 8 hours, 12 hours and 24 hours after onset of the episode.

Patients were divided into two groups: those that received intravenous magnesium during the episode of atrial fibrillation with RVR and those that did not. Patients were given magnesium as per the preference of the physician in charge of care at the time. The patients that did not receive magnesium served as the control group for the study. Additional data gathered included whether patients in both groups were given any nodal blocking agents or antiarrhythmic agents. To determine whether the effect of magnesium is dose dependent, the heart rates of patients that received 1 gram of magnesium were compared to those that received 2 grams of magnesium.

Statistical analysis

The mean heart rate at onset of atrial fibrillation with RVR, at 1 hour, 4 hours, 8 hours, 12 hours and 24 hours were calculated. Student's T test was used to compare the means in group of patients that received magnesium to those in the control group. The decrease in heart rate from one-time interval to another within each group was also evaluated using paired student's T test analysis. The proportional receipt of beta blockers, diltiazem, digoxin and amiodarone among these two groups was calculated and their frequency of use was compared using the Chi-square method. The group of patients that received magnesium was further subdivided into groups based on the amount of magnesium given. One group was created of those patients that had received 1 gram of magnesium while another group was created of those that had received 2 grams of magnesium. The mean heart rates after magnesium administration in each group at onset of atrial fibrillation with RVR, at 1 hour, 4 hours, 8 hours, 12 hours and 24 hours were compared. A multiple linear regression analysis was also performed. A P value <0.05 was considered significant.

Results

Characteristics of Patients Enrolled in the Study

A total of 90 patients were enrolled in this study; of these, 32 patients had received magnesium during episodes of atrial fibrillation with RVR while 58 patients did not.

Patient baseline characteristics were similar in both groups (Table 1). A beta blocker was administered to 25 (78%) patients that

Table 1: **Demographic and Clinical Characteristics of Patients**

	Control (n=58)	Magnesium (n=32)
Age (years), median, SD	68 + 11.2	71 + 9.0
Sex		
Male	36 (53%)	19 (59%)
Female	32 (47%)	13 (41%)
History of heart disease No. (%)	26 (38%)	13 (41%)
Mean Estimated GFR (ml/min/1.73m^2)	43.5*	51†
Paroxysmal atrial fibrillation	19 (33%)	11 (34%)
Chronic atrial fibrillation	19 (33%)	7 (22%)
Valvular atrial fibrillation	2 (3.6%) **	1 (3.6%) ††
Average left atrial diameter (cm)	3.71**	3.85††
No prior history of atrial fibrillation	25 (43%)	18 (56%)
Diuretics No. (%)	16 (28%)	8 (25%)
Mean Serum magnesium (mg/dl)	1.79	1.8
Beta blockers No. (%)	40 (69%)	25 (78%)
Calcium channel blocker No. (%)	23 (40%)	7 (22%)
Digoxin No. (%)	4 (7%)	2 (6%)
Amiodarone No. (%)	3 (5%)	3 (9%)
Patients with repeat episodes of atrial fibrillation with RVR No. (%)	15 (26%)	7 (22%)

SD, Standard Deviation
*14 patients were not included in this calculation as they were above 80 years of age. GFR was estimated using the CKD-EPI equation which may not provide accurate assessments in patients greater than 80 years of age.
†7 patients were not included in this calculation as they were above 80 years of age.
**3 patients were not included as they did not have any cardiac imaging.
††4 patients were not included as they did not have any cardiac imaging.

Table 2: Mean heart rate in relation to time in patients that received magnesium compared to those that did not.

Time interval (hour)	Mean Heart Rate in the Control Group, beats/min (SEM)	Mean Heart Rate in the Magnesium group, beats/min (SEM)	Significance
0	154.21 (+2.54)	148.19 (+3.29)	NS
1	120.57 (+3.31)	121.23 (+3.93)	NS
4	106.86 (+3.24)	107.45 (+4.45)	NS
8	99.13 (+2.74)	98.72 (+4.55)	NS
12	99.87 (+2.94)	89.66 (+5.25)	NS
24	96.00 (+2.92)	85.03 (+4.44)	p<0.05

NS, no significant difference between the two groups

received magnesium and to 40 (69%) patients that did not receive any magnesium. In addition, 7 (22%) patients that received magnesium and 23 (40%) patients that did not receive magnesium were given calcium channel blockers. Digoxin and amiodarone were used less frequently, regardless, the frequency of use of these medications was comparable in both groups. Overall, when comparing the two groups of patients, there was no significant difference in the number of patients who received beta-blockers, calcium channel blockers, digoxin, or amiodarone.

Furthermore, the mean serum magnesium level was observed to be similar in both group of patients. Specifically, the group of patients that was given magnesium had a mean serum magnesium level of 1.8 mg/dl prior to the episode of Afib with RVR, while the control group was noted to have a mean of 1.79 mg/dl.

Lastly, the mean estimated GFR in the group of patients that received magnesium was noted to be 51 ml/ min/ 1.73m2, compared to a mean of 43.5 ml/min/1.73m2 in the control group. It should be noted that 7 patients from the group treated with magnesium and 14 patients from the control group were excluded from the calculation above as they were above 80 years of age.

Main results

Patients that received magnesium had a lower mean heart rate after 24 hours of the onset of the atrial fibrillation with RVR episode compared to the patients that did not receive magnesium. The average heart rate 24 hours after the episode in patients that received magnesium was 85 beats/min, whereas the average heart rate for patients that did not receive magnesium was 96 beats/min (P<0.05) (Table 2).

The control group demonstrated a statistically significant progressive decrease in the heart rates between onset of the episode to 1 hour after episode (p<0.001), 1 hour to 4 hours after episode (p<0.001) and 4 hours to 8 hours after episode (p<0.001) (Figure 1A). However, the decrease in heart rate between 8 hours to 12 hours and 12 hours to 24 hours was not statistically significant. On the other hand, the magnesium group showed similar trends as there were also significantly lower heart rates at the intervals of 1 hour, 4 hours and 8 hours after the onset of episode (Figure 1B). Unlike the control group however, the magnesium group continued to demonstrate a statistically significant decline in the heart rate beyond 8 hours. The average heart rate at 12 hours was 89.66 beats/min and was statistically lower than the average heart rate of 98.72 beats/min at 8 hours (p<0.05). Also, at 24 hours, the average heart rate was 85.03 beats/min and was lower than the average heart rate of 89.66 beats/min at 12 hours (p<0.05). In brief, it appears that that the addition of magnesium permits normalization of the cardiac rate in a progressive way that continues up to 24 hours.

A deeper comparison was done on the 34 patients that received magnesium; 17 patients were given 1 gram of magnesium and 17 were given 2 grams of magnesium. Upon comparison, it was noted that the mean heart rate after 24 hours in the low magnesium group was 87.1 beats/min, whereas in the high magnesium group, the mean heart rate at 24 hours was 84.8 beats/min; this difference did not achieve statistical significance (Table 3). However, in the last 16 hours of observation, between 8 hours of the onset of the episode and 24 hours, it appeared that administering higher levels of magnesium had an advantage (Figure 2). The mean heart rate in the control group and the low magnesium group at 8 hours was 99.2 beats/min and 94.1 beats/min, respectively. At 24 hours, the mean heart decreased to 96 beats/min in the control group and to 87.1 beats/min the in low magnesium group, and these decreases in heart rate were not statistically significant. On the other hand, in the group of patients that received 2 gm of magnesium, the mean heart rate at 8 hours was 103.4 beats/min and 84.8 beats/min at 24 hours (p<0.01). In brief, the mean heart rate decreased by 3 beats/min in patients that did not receive any magnesium, 7 beats/min in those that received 1 gram of magnesium and 18.2 beats/min in those that received 2 grams of magnesium between 8 and 24 hours after onset of Afib with RVR.

As this study involved the use of other rate controlling agents in association with magnesium, a multiple linear regression analysis was also performed to determine whether magnesium has an independent effect on rate response. An analysis including all rate controlling agents and magnesium at 24 hours resulted in R=0.29 (p<0.05). A backward stepwise regression analysis, removing the effect of one rate controlling agent at a time, concluded that magnesium alone was still important in determining the heart rate (R=0.22, p<0.05). Furthermore, it was determined that the effect magnesium had on rate response is dependent on the amount of magnesium administered. A significant regression equation was found (95.6-0.77(milliequivalents of magnesium)) with a R of 0.27 (p<0.05). The heart rate decreased by

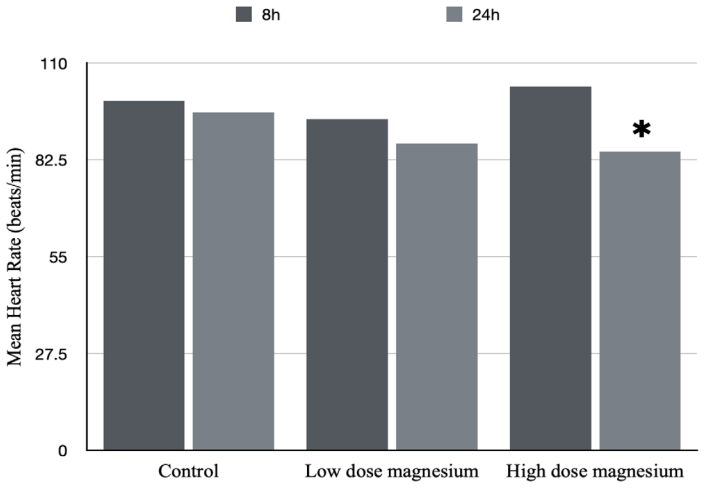

Figure 2: Mean heart rates in the control group, the low dose magnesium group, and the high dose magnesium group at 8 hours and 24 hours after onset of Afib with RVR. *P<0.01

Table 3: Mean heart rate over time in patients that received 1 gram of magnesium (low dose magnesium group) and 2 grams of magnesium (high dose magnesium group).

Time interval (hour)	Mean Heart Rate in the Low Magnesium Group, beats/min (SEM)	Mean Heart Rate in the High Magnesium Group, beats/min (SEM)	Significance
0	147.5 (+4.0)	147.4 (+5.0)	NS
1	117.4 (+5.4)	124.5 (+5.5)	NS
4	104.2 (+4.7)	111.7 (+7.6)	NS
8	94.1 (+5.3)	103.4 (+7.2)	NS
12	91.1 (+8.5)	90.7 (+5.9)	NS
24	87.1 (+7.0)	84.8 (+5.2)	NS

NS, no significant difference between the two groups

0.77 beats/min for each milliequivalent (mEq) of magnesium used;of note, 8 mEq of magnesium is equivalent to 1 gram of magnesium. In brief, the infusion of magnesium leads to a predictable decrease in heart rate and this response is independent of the other medications butis dependent on the dosage of magnesium used.

Lastly, the number of repeat episodes of atrial fibrillation during the patient's hospitalization were also analyzed. In the group of patients that received magnesium, 7 (22%) patients had repeat episodes before discharge, compared to 15 (26%) patients in the control group.

Discussion

Atrial fibrillation has become a major public health burden and its prevalence is projected to continuously increase[18]. The associated costs continue to strain a struggling healthcare system with increasing needs in medications, management of the extensive complications such as heart failure and stroke, and the significant morbidity and mortality caused simply due to the prevalence of the condition. Additional options for management of this arrhythmia may help with the overall burden, and magnesium, being a drug that is easily available and uncostly, may provide some support.

Magnesium is viewed to act as a calcium channel blocker; hence, it should theoretically function as an AV nodal blocker. However, there have been mixed results regarding the benefit of magnesium use in helping control atrial fibrillation with RVR in prior studies. Most of these studies have also been limited to post-cardiac surgery patients, limiting the generalizability of their findings[14-17]. With such contrasting studies, electrolyte supplementation for management of atrial fibrillation remains conflicting in both medical and surgical wards.

The patients included in this study were not post-surgical, rather patients from all wards within the hospital that developed acute episodes of atrial fibrillation with rapid ventricular rate. The results of this study indicate that magnesium may play an important role in helping maintain a lower heart rate for longer periods of time. Also, it seems that magnesium may help decrease heart rates at a faster rate. In the different groups that were analyzed, when magnesium was given, there was a greater decrease in heart rates 1 hour from the onset of the episode and onwards. In addition, it should be noted that the mean serum magnesium levels prior to the onset of the episode, were within normal range for both the control group and the group of patients that received magnesium. Interestingly, the patients that did receive magnesium still achieved a statistically significant lower mean heart rate after 24 hours of the onset of the atrial fibrillation with RVR episode compared to control group despite normal serum magnesium levels. This study also indicates that there is a possibility that the impact of magnesium may be dose dependent as the rate of decrease in heart rate was noted to be higher in patients that were given a higher dose of magnesium.

Limitations

There were limiting factors that played a role in this study. For instance, patients had received other drugs during their episodes of Afib with RVR; some received rate controlling agents, while others received antiarrhythmic agents. The dosage administered for these other drugs may have also varied in the different groups. To further add to the limitations, some patients that had repeat episodes of Afib with RVR, were administered additional medications and this may have hindered the overall response to magnesium administration.

Conclusions

Overall, our results seem to indicate that magnesium has a role to play in the management of atrial fibrillation with RVR. Larger randomized studies are still needed to further support and clarify its role. Additional areas for future studies that may be worth looking into include determining the impact of magnesium when combined with specific AV nodal blockers or antiarrhythmics. Last but not least, further studies are needed to determine effective dosages of magnesium and to help determine whether there are any adverse effects of high dose magnesium use in such patients.

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Intraluminal Esophageal Temperature Monitoring Using the CircaS-Cath™ Temperature Probe to Guide Left Atrial Ablation in Patients with Atrial Fibrillation

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Abstract

Backgrounds: Radiofrequency catheter ablation is a common treatment for atrial fibrillation (AF), during which thermal esophageal injury may rarely occur and lead to an atrio-esophageal fistula. Therefore, we studied the utility of the Circa S-Cath™ multi-sensor luminal esophageal temperature (LET) probe to prevent esophageal thermal injury.

Methods and Results: Thirty-sixpatients, enrolled prospectively, underwent circumferential or segmental pulmonary vein isolationfor treatment of AF. A maximum ablation electrodetemperature of 42ºC was programmed for automatic power delivery cutoff. In addition, energy delivery was manually discontinued when the maximum LET on any sensor of the probe rose abruptly (i.e. >0.2ºC) or exceeded 39ºC. Esophagoscopy was performed immediately after ablation in 18 patients (with the temperature probe still in place) and at approximately 24 hours after ablation in 18 patients. Esophageal lesions were classified aslikely traumatic or thermally related. Of the 36patients enrolled in the study, 21 had persistent and 15 had paroxysmal AF,average LVEF 57±16% and CHA_2DS_2VASc score 1.6±1.2 (range 0-4). Average maximum LET was 37.8±1.4ºC, power delivery 31.1±8 watts and ablation electrode temperature 36.4±4.1ºC. Average maximum contact force was 44.5±20.5 grams where measured. Only 1patient (<3%) had an esophageal lesion that could potentially represent thermal injury and4patients(11.1%) had minor traumatic mechanical injury.

Conclusion: LET guided titration of power and duration of energy application, using an insulated multi-sensor esophageal temperature probe, is associated with a low risk of esophageal thermal injury during AF ablation. In only rare cases, LET monitoring resulted in the need to manipulate the esophagus to avoid unacceptable temperature rises, that could not be achieved by adjustment of power and duration of energy application.

Introduction

Radio frequency catheter ablation (RFCA) to electrically isolate the pulmonary veins from the left atrium (LA) has become a first-line treatment for symptomatic atrial fibrillation(AF).[1] However, damage to the esophagus, may occur during ablation of the posterior LA wall, leading to the potentially fatal complication of atrio-esophageal (AE) fistula.[2,3,4] Esophagoscopy (EG) following AF ablation has revealed an incidence of thermal injury up to 47% following RFCA for AF.[5-11]. Fortunately, AE fistula is a rare complication of AF ablation, with a reported incidence of only 0.03–0.2%.[12-14] The mortality rate from AE fistula is very high, and thus preventing its occurrence is critically important.

Key Words

Atrial fibrillation, Ablation, Esophagus, Esophageal temperature probe, Atrio-esophageal fistula

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Several strategies have been implemented to decrease the risk of esophageal injury, including limitation of power in the posterior LA wall, perpetual motion of the ablation catheter, identifying the anatomic location of the esophagus during RFCA and avoiding it entirely, displacement of the esophagus away from the ablation catheter, and intra-luminal cooling of the esophagus.[15-18] Luminal esophageal temperature (LET) monitoring to limit power and duration of ablation in proximity to the esophagus, and to indicate the need for esophageal manipulation to avoid LET rises, is another alternative approach available during AF ablation procedures. Monitoring LET with a single sensor temperature probe, may be ineffective and inconvenient due the need to continually move the temperature probe relative to a rapidly moving ablation catheter. Furthermore, even with the use of a single sensor LET monitor, esophageal ulceration has still been reported.[7-9,11] Therefore, a new, multi-sensor esophageal probe (Figure 1), which monitors LET at 12 insulated temperature sensors placed uniformly along the length and width of probe, eliminating the need to continuously move the probe once in place, has been developed by Circa Scientific, LLC (Circa Scientific, Inc., Englewood, CO, USA).

Although we currently use the Circa S-Cath™ esophageal temperature probe to monitor esophageal position and LET in all of our AF ablation cases, this study was designed to evaluate the ability of the CircaS-Cath™ multi-sensor LET probe to prevent esophageal thermal lesions, as observed by esophagoscopy, in a prospective series of patients undergoing RFCA for AF.

Methods

Patient Population

Thirty-six patients undergoing RFCA for symptomatic, drug-refractory AF, were enrolled in this study. Ablations were performed by three experienced electrophysiologists, with two electrophysiologists performing primarily wide are acircum ferential pulmonary vein (WACA) ablation and one electrophysiologist performing both segmental ostial PV isolation (SPVI) and WACA. Consequently,3 patients underwent SPVI and 33 patients underwent WACA.

Temperature Monitoring

For LET monitoring a Circa S-Cath™ esophageal temperature probe with 12 sensors (Circa Scientific, Inc., Englewood, CO, USA) was used to continuously record the intraluminal esophageal temperature (Figure 1). The probe was inserted orally by the anesthesiologist, under fluoroscopic guidance and advanced into the esophagus, after general anesthesia and endotracheal intubation. The probe was advanced with its stylet in place to straighten the probe, until the temperature sensors spanned the left atrium from the cranial to caudal direction (approximately from the left main-stem bronchus to the coronary sinus), and then the stylet was removed and the probe visualized fluoroscopically to ensure adequate positioning. The probe has a sinusoidal shape, which may be variably distorted by esophageal pressure, but is usually retained after placement (Figure 1). The accuracy of the thermistor is reported by the manufacturer to be ±0.3°C. The 12 temperature sensors are 2.5 mm in length and separated byapproximately 10 mm when deployed. The multi-sensor probe was connected to the Circa Temperature Monitoring System (CS-1000 Circa Temperature Monitoring System, Circa Scientific, Inc., Englewood, CO, USA) with continuous maximum temperature displayed.

Ablation Procedure

All patients in this study underwent general anesthesia prior to ablation. Anticoagulation was administered prior to ablation in a standard manner. Via the left femoral vein asteerable decapolar catheter (Webster CS catheter, Biosense Webster, Inc, Diamond Bar, CA, USA or Polaris catheter, St. Jude, St. Paul, MN, USA) was placed in the coronary sinus for pacing and recording,and an intracardiac ultrasound (ICE) catheter (AccuNav, Siemens, Mountain View, CA, USA) was positioned in the right atrium toguide the trans-septal puncture. Via the right femoral veintwotrans-septal sheaths were positioned in the LA. Intravenous heparin was administered prior to trans-septal puncture followed by a continuous infusion, to maintain an activated clotting time of 300–350 seconds. Using acircular mapping catheter (Lasso™, Biosense Webster, Inc., Diamond Bar, CA, USA) electroanatomical maps and a 3D geometry were created using the Carto (BiosenseWebster, Inc., Diamond Bar, CA, USA),Ensite Velocity or Precision systems (St. Jude Medical, St. Paul, MN, USA). An externally irrigated ablation catheter (Thermocool Smart Touch™ or ST/SF™, BiosenseWebster, Inc., Diamond Bar, CA, USA or TactiCath™, St. Jude Medical, St. Paul, MN, USA) was used for ablation. The PVs were isolated by delivery of RF applications circumferentially or segmentally to the antral or ostial regions of the PVs, respectively, as required to produce a minimum of entrance block for at least 30 minutes, confirmed during isoproterenol infusion at 20 mcg/min. Either a Stockert™ generator (Biosense Webster, Inc.™, Diamond Bar, CA, USA)or CoolPath™ generator (St. Jude Medical, Inc., St. Paul, MN, USA) was used to deliver RF energy, depending on the type of ablation catheter used. Catheter tip temperature, power, and impedance were recorded for each RF energy application. The power delivered to the posterior LA wall during each ablation was varied

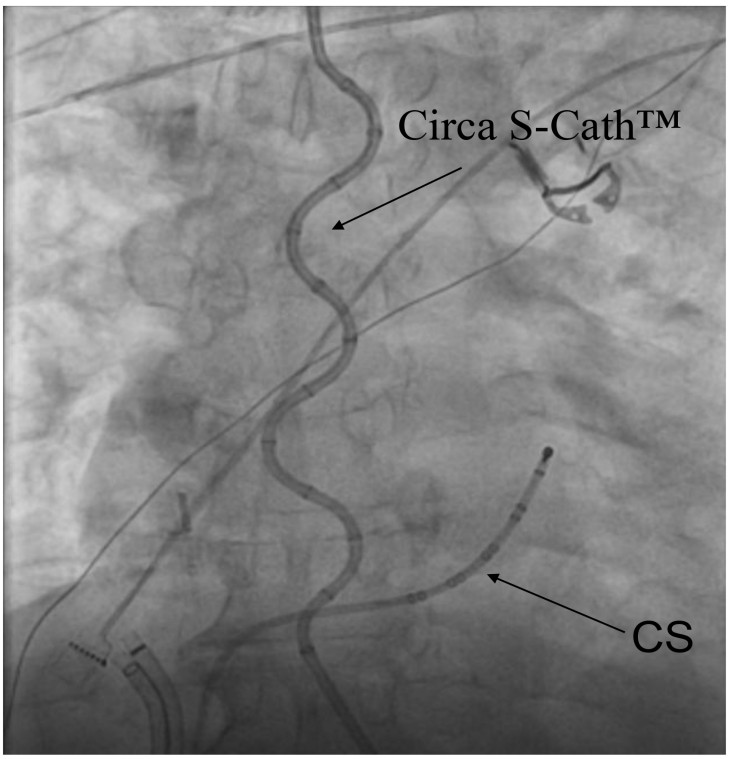

Figure 1: AP fluoroscopic image of Circa temperature probe (Circa S-Cath™) in the esophagus during AF ablation procedure, with asteerable deca-polar catheter in the coronary sinus (CS).

Table 1: Baseline Characteristics

Patients	36
Age	64.2 ± 9.8 years
Gender (Male)	31 Male / 5 Female
LVEF	56.5 ± 16.2%
CHA_2DS_2VASc Score	1.6 ± 1.2
Female Gender	5 pts
Age >=65 &<=74	15 pts
Age >75	5 pts
CHF	7 pts
HTN	23 pts
DM	5 pts
CVA/TIA/TE	2 pts
Vascular Disease	1 pts

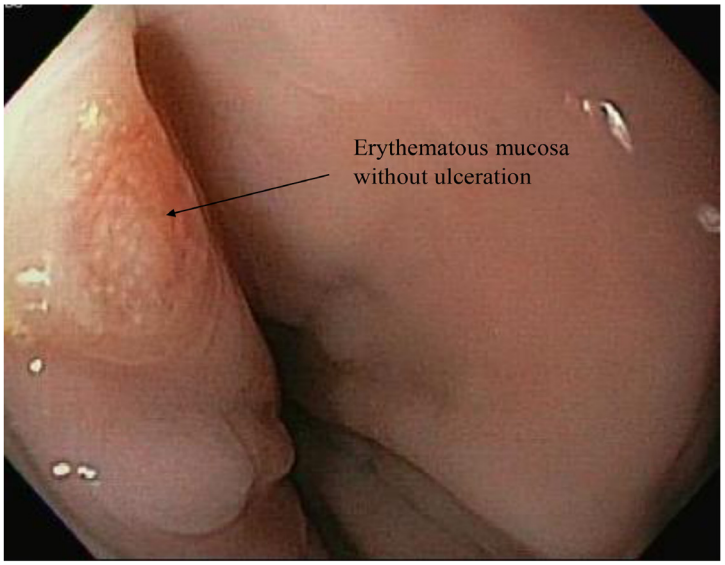

Figure 2: Esophagoscopy image showing a 3 mm edematous mucosal lesion at 32 cm from the incisors that could possibly be related to thermal injury to the esophagus.

according to the LET measured by the Circa S-Cath™ esophageal temperature probe, with a maximum power of 30-40 watts (30 watts for ThermocoolST/SF™ catheters) and maximum electrode-tissue interface temperature of 42°C. Energy delivery was discontinued immediately in all cases when the maximum LET on any sensor of the Circa S-Cath™ temperature probe rose abruptly (i.e. by >0.2°C/sec, due to manufacturer stated device accuracy of ±0.3°C) or exceeded 39° C. These parameters were used due to the fact that, in our clinical experience prior to this study, if the LET rose abruptly or approached 39° C, it would typically continue to rise and often exceed these limits for several seconds after energy delivery was interrupted. If energy delivery was interrupted due to the LET exceeding these parameters during initial ablation at any location, ablation was resumed at the same area after LET returned to baseline measurement, but at a lower power (i.e usually in increments of 10 watts lower than initial power). If LET then again rose above the limits stated above, ablation was terminated immediately, and the esophagus manipulated away from the ablation catheter (using the same endoscope subsequently used to evaluate the esophagus for any lesions created during the ablation procedure as described in the next paragraph) in order to avoid further LET rises and complete the pulmonary vein isolation (PVI) procedure. Esophageal manipulation was only required however in two patients in the entire study (as noted below). When LET rises were not observed during the procedure, ablation energy was delivered for up to 30 seconds at each locationuntil there was complete PVI.

Endoscopic Evaluation

Esophagoscopy was performed in all patients by a trained interventional endoscopist, either immediately after the ablationwith the temperature monitoring probe still in place (18 patients) or the day after ablation (18 patients). Lesions were identified,photographed, and classified by the endoscopist performing the esophagoscopy immediately after the study. Any esophageal lesions observed were classified as pre-existing diagnostic abnormalities, or either traumatic or thermally related to the procedure.

Follow-Up

After discharge, as part of our standard-of-care, patientswere seen in the outpatient arrhythmia clinic at 1, 6, 12 and 24 months for any possible procedure related complications,and to assess for any AF recurrence (not reported in this study).

Table 2: Procedure Data

Pt	Ablation Type	Catheter Type	Circa Temp Maximum (C)	Catheter Temp Maximum (C)	Catheter Power Maximum (W)	Contact Force Maximum (g)
1	SVPI	ST	38.00	41.00	40.00	66.00
2	WACA	ST	38.90	36.00	35.00	32.00
3	WACA	ST	38.40	40.00	36.00	42.00
4	WACA	ST	37.70	42.00	50.00	45.00
5	WACA	ST	36.90	40.00	40.00	69.00
6	WACA	ST	38.20	40.00	25.00	47.00
7	WACA	ST	37.00	41.00	44.00	39.00
8	WACA	ST	38.10	37.00	30.00	47.00
9	WACA	TactiCath	38.10	36.00	20.00	NA
10	WACA	ST	37.10	38.00	30.00	NA
11	WACA	ST	38.30	37.00	25.00	NA
12	WACA	ST	38.50	41.00	40.00	NA
13	WACA	ST	38.20	38.10	41.00	73.00
14	WACA	ST	37.40	39.00	30.00	59.00
15	WACA	ST	37.90	39.00	40.00	NA
16	WACA	ST	39.00	32.80	21.00	NA
17	WACA	ST	37.70	39.00	30.00	NA
18	WACA	ST	37.20	36.00	25.00	67.00
19	WACA	ST	38.20	35.50	36.00	43.00
20	WACA	ST	37.40	42.00	42.00	24.00
21	WACA	ST	37.90	39.10	36.00	23.00
22	WACA	ST	38.20	28.80	25.00	39.00
23	WACA	TactiCath	38.50	38.00	25.00	13.00
24	WACA	TactiCath	37.50	33.00	40.00	32.00
25	WACA	TactiCath	38.50	37.90	20.00	22.00
26	WACA	TactiCath	37.80	38.00	30.00	20.00
27	SVPI	TactiCath	37.30	37.70	30.00	46.00
28	WACA	ST	38.00	30.90	30.00	53.00
29	WACA	ST	30.40	37.70	20.00	55.00
30	WACA	ST	39.50	30.50	15.00	24.00
31	WACA	ST	37.50	24.00	25.00	20.00
32	WACA	ST	38.00	32.80	31.00	67.00
33	WACA	ST	39.00	32.90	26.00	98.00
34	WACA	TactiCath	39.40	34.00	30.00	36.00
35	WACA	ST	37.60	31.40	31.00	68.00
36	SPVI	TactiCath	37.90	32.00	25.00	21.00
Avg			37.81	36.36	31.08	44.48
SD			1.42	4.10	8.02	20.46

All values represent the average of the maximum observed during each ablation, for each patient. WACA = wide area circumferential pulmonary vein ablation, SPVI = semgmental pulmonary vein isolation, NA = not available, Safire™ = 8 mm solid tip ablation catheter from St. Jude, Inc., ST = SmartTouch, gms =grams, TactiCath™ = Irrigated force sensing catheter from St. Jude, Inc., Temp = Temperature in degrees centigrade

Statistical Analysis

Continuous variables have been expressed as the mean±one standard deviation, and statistical significance was calculated using the Student's t-test. Categorical variables have been expressed as absolute numbers or percentages, and statistical significance was calculated using the Chi-squared test. A statistically significant difference between variables required a p value ≤0.05. All statistical analysis was performed using Microsoft Excel 2010.

Approval

Participation in the study was entirely voluntarily and all participants provided written informed consent prior to enrollment. The study was approved by the UCSD Institutional Review Board and registered with Clinical Trials.Gov (IRB#150018, CT.GOV#NCT02467166).

Results

Patient Characteristics

Thirty-sixpatients, 31 males and 5 females, average age 64.2±9.8years, with an average LVEF of 56.5±16.17% and an average CHA2DS2VASc score of 1.6±1.2 (range 0-4), undergoing RFCA for symptomatic, drug-refractory AF, were enrolled in this study. There were 21 patients with persistent AF (i.e. >7 days in duration) and 15 with paroxysmal AF (i.e. <7 days in duration). The patient demographics and clinical characteristics are summarized in Table 1.

Esophageal Temperature Monitoring

In our clinical experience, an abrupt increase in LET above baseline was typically observed only when ablation was performed with the ablation electrode visually estimated to be within 10 mm from theCirca S-Cath™ temperature probe on the posterior wall of the LA. Thus, only ablations performed on the posterior LA wall, within a visually estimated 10 mm of the temperature probe where significant LET rises were typically observed, were included for analysis in this study. Using the Circa S-Cath™ temperature probe's maximum temperature reading function to adjust and limit power delivery during ablation, the average maximum LET observed in all patients was 37.8±1.42ºC (range 36.90-39.50ºC). During ablation, the average maximum power delivered was 31.08±8.02 watts and the average maximum ablation electrode temperature was 36.4±4.10ºC. Contact force was recorded in 29 patients when using a contact force measuring catheter (i.e. Thermocool Smart Touch™ or ST/SF™, Biosense Webster, Diamond Bar, CA, USA), and in these patients the average maximum contact force was 44.5±20.5 grams (average average contact force of 24±7.9 grams and minimum average contact force of 11.1±5.5 grams). Esophageal manipulation with the endoscope to move the esophagus away from the ablation electrode, was required in only two patients in this study (#12 and 20) in order to avoid study defined LET rises. In neither of these patients was any esophageal thermal or traumatic injury noted during esophagoscopy. These procedural data are summarized in Table 2.

Esophageal Evaluation

Among the36 patientsin this study,only 1lesion was observed in a region of the esophagus near where ablation may have been performed(i.e. described as a 3 mm edematous mucosal lesion at 32 cm from the incisors) that could possibly be related to thermal injury to theesophagus (Figure 2). Among the 18 patients undergoing esophagoscopy immediately after ablation, one had a small 3 mm linear erosion of the mucosa and one had a small area of linear erythema both thought to be possibly due to mechanical trauma. Among the 18 patients undergoing esophagoscopy one day after ablation two were observed to have small 3 mm superficial mucosal erosions also thought to be possibly due to mechanical trauma, and one had a 3 mm focus of edematous mucosa without erosion, which was thought to be possibly due to ablation (i.e. a thermal injury lesion). Although there were no statistically significant differences in average LET, catheter temperature, power or contact force between this patient with a possible esophageal thermal injury and those who did not have any thermal injury, this particular patient did have the highest maximum transient LET observed of any in either group at 39.5ºC. There were no ulcerations observed in any patients. Other incidental findings, also observed during esophagoscopy, includeda small inlet pouch in 2 patients, Barrett's esophagus in 3 patients, mild to moderate erosive esophagitis in 3patients, and a hiatal hernia in 2 patients. No patients in this study developed evidence of an atrio-esophageal fistula during follow-up.

Discussion

This study shows that when ablation power and duration of energy application are guided by the LET determined using an insulated multi-sensor esophageal temperature monitoring probe, there will be very little esophageal thermal injury during AF ablation, as confirmed by esophagoscopy in this study.

Limitation of Esophageal Injury during AF Ablation by LET Monitoring

Monitoring LET during AF ablation may limit esophageal thermal injury, especially when ablation is performed in close proximity (<1 cm) to the esophagus, by forcing the operator to reduce power delivery or duration of energy application, in order to maintain maximum LET at or below 39 ºC and average maximum LET below 38ºC. Previously reported data suggests thata correlation exists between LET and esophageal thermal injury[6,9,11,21], and that monitoring LET to guide ablation, including both power and duration of energy application, has been shown to reduce the risk ofesophageal ulceration[5,11]. Thus, an ablation strategy guided by LET temperature monitoring seems logical, but there may be some limitations in this approach too, considering that LET may underestimate the surface temperature of the esophagus during ablation, as noted in previous studies[22].

In this study, we used stringent limitations on power and duration of energy application guided by LET monitoring and demonstrated a near complete elimination of thermal esophageal injury (only 1 lesionswas observed in 1 patient in this study or 2.8% that might possibly have been related to thermal injury) during pulmonary vein isolation. Importantly, limitation of power and duration of energy application to prevent LET rises did not compromise the ability to isolate the pulmonary veins acutely, as all veins were successfully isolated based on standard current criteria for success.

The mere presence of a LET temperature monitoring probe during ablation or the type of LET monitoring probe used,are factors that

have been considered potential causes of increased risk of thermal injury with their use in the past[18,19,20].However, it appears that the use of uninsulated metallic electrodes on the esophageal temperature monitoring probe may produce the increased risk of thermal injury, rather than the presence of the monitoring probe itself producing displacement of the esophagus towards the left atrium[19,20,23]. The use of an insulated probe (Circa S-Cath™ LET monitoring probe), as done in this study, was not associated with an increased risk of esophageal thermal lesions, compared to that previously reported in the literature.

Study Limitations

Our study was not randomized but was prospective. For this study, esophagoscopy was performed by a single trained interventional endoscopist, who was also familiar with our techniques, which should have minimized the risk of missing significant esophageal lesions. In addition, several unrelated esophageal abnormalities were observed by the endoscopist, suggesting that it would be unlikely that thermal lesions would have also been missed. There was also no control group of patients undergoing ablation in this study using a standard single sensor temperature probe to compare the frequency of lesion detection during esophagoscopy, however this has been reported extensively in the literature and the development of potential thermal lesions was much higher than observed in this study. Another potential limitation of this study arises from the initial design of this study wherein the first 18 patients underwent EGD immediately after ablation and the second 18 patients underwent EGD approximately 24 hours after ablation. This could have allowed any potential thermal lesions to mature and become more visible to the endoscopist. Therefore, it is possible that the early EGD could have missed lesions that would have otherwise become evident if allowed to mature for 24 hours. Lastly, this study was not poweredto determine if ablation guided by esophageal temperature monitoring had any effect on long-term outcome of AF recurrence, after PV isolation.

Conclusions

Monitoring LET, as done in this study using an insulated multi-sensor temperature probe (Circa S-Cath™), allowed the operator performing AF ablation to adjust radiofrequency power output and energy application duration, to prevent LET rises above a critical level thought to be responsible for thermal esophageal injury, which may be related to subsequent development of atrio-esophageal fistula. In only rare cases, was adjustment of power and duration of energy delivery unsuccessful in minimizing LET rises within study limits, so as to avoid esophageal manipulation. Furthermore, this ablation strategy did not compromise success in achieving pulmonary vein isolation acutely.

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Chronic Obstructive Pulmonary Disease and Risk of Atrial Arrhythmias after ST-Segment Elevation Myocardial Infarction

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Abstract

Background ST-segment elevation myocardial infarction (STEMI) and cardiac arrhythmias frequently occur in patients with chronic obstructive pulmonary disease (COPD). However, little is known about the association of COPD with the occurrence of atrial arrhythmias after STEMI.

Methods This retrospective analysis consisted of 320 patients with first STEMI without a history of atrial arrhythmias, with available 24-hour holter-ECG at 3- and/or 6 months follow-up. In total, 80 COPD patients were compared with 240 non-COPD patients, matched by age and gender (mean age 67±10 years, 74% male). Atrial arrhythmias were defined as: atrial fibrillation/flutter, atrial tachycardia (≥3 consecutive premature atrial contractions (PAC's)) and excessive supraventricular ectopy activity (ESVEA, ≥30 PAC's/hour or runs of ≥20 PAC's).

Results Baseline characteristics were similar among COPD and non-COPD patients regarding infarct location, β-blocker use and cardiovascular risk profile except for smoking (69% vs. 49%, respectively, p=0.002). Additionally, atrial volumes, LVEF and TAPSE were comparable. During 1 year follow-up, a significantly higher prevalence of atrial tachycardia and ESVEA was observed in patients with COPD as compared to non-COPD patients (70% vs. 46%; p<0.001 and 21% vs. 11%; p=0.024, respectively). In multivariate analysis, COPD was independently associated with the occurrence of atrial arrhythmias (combined) during 1 year of follow-up (HR 3.59, 95% CI 1.78-7.22; p<0.001).

Conclusion COPD patients after STEMI have a significantly higher prevalence of atrial tachycardia and ESVEA within 1 year follow-up as compared to age- and gender matched patients without COPD. Moreover, COPD is independently associated with an increased prevalence of atrial arrhythmias after STEMI.

Introduction

Patients with chronic obstructive pulmonary disease (COPD)have an increased risk of cardiac arrhythmias.[1,2] In particular the association between impaired pulmonary function and the development of atrial fibrillation (AF) has been recognised in previous studies.[2,3] In the Atherosclerosis Risk in Communities (ARIC) study, the rate of incident AF increased along with decrease in pulmonary function (measured with forced expiratory volume in 1 second, FEV1).[3] Moreover, theindependent association between the presence and severity of COPD and the occurrence of AF/atrial flutter and non-sustained ventricular tachycardia (NSVT) has been demonstrated.[4]

COPD induces hemodynamic changes (pulmonary hypertension, diastolic dysfunction, atrial remodelling), autonomic imbalance, oxidative stress and inflammation that increase the risk of cardiac arrhythmias.[2] In addition, the presence of coronary artery disease is frequent in COPD patients and may influence the arrhythmogenic substrate, further increasing the risk of arrhythmias.[5] Up to one fifth of the patients with acute myocardial infarction develops AF in the acute setting or during follow-up, doubling the risk of all-cause mortality.[6,7]

Despite the known risk of atrial arrhythmias in patients with COPD or acute myocardial infarction, studies addressing a combination of both diseases are scarce. Therefore, the objective of the present study was to evaluate whether COPD is associated with an increased risk of atrial arrhythmias after ST-segment elevation myocardial infarction (STEMI).

Key Words

Chronic Obstructive Pulmonary Disease; Atrial Arrhythmias; STEMI

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Methods

Patient population

From an ongoing clinical registry of ST-segment elevation myocardial infarction (STEMI) patients treated with primary percutaneous coronary intervention (PCI) at the Leiden University Medical Center (Leiden, The Netherlands), patients admitted between 2006 and 2012 and with history of chronic obstructive pulmonary disease (COPD) were identified after thorough chart review.[8] The diagnosis of COPD

was confirmed with pulmonary function tests (if available).[8] A control group consisting of STEMI patients without COPD admitted during the same time period was selected. COPD and non-COPD patients were matched by age and gender on a 1:3 basis. All patients were treated according to the institutional STEMI protocol, based on the international STEMI guidelines.[9-11] During hospitalization (at least 48 hours), continuous electrocardiographic (ECG) monitoring and transthoracic echocardiography were performed. Guidelines-based medical therapy was initiated. Patients with a previous myocardial infarction, prior documented atrial arrhythmias and/or missing 24-hour Holter-ECG follow-up data were excluded from the present study.

Clinical and echocardiographic data were collected prospectively in the departmental cardiology information system (EPD-vision) and echocardiographic database, respectively. For retrospective analysis of clinically acquired data and anonymously handled, the institutional review board waived the need for patient written informed consent.

Clinical and echocardiographic data

Baseline clinical characteristics included demographic data, cardiovascular risk factors, infarct characteristics consisting of peak levels of creatine kinase (CK) and troponin T, and procedural variables such as culprit vessel and the presence of multi-vessel disease as defined by >50% luminal stenosis in more than one vessel. All echocardiographic data on right and left ventricular and atrial dimensions and function were prospectively measured and analysed (the present study does not concern mere tabulation of data included in clinical echocardiographic reports). Following current guidelines, left atrial volume was indexed to body surface area.[12] In addition, color-coded tissue Doppler imaging of the atria was used to assess total atrial conduction time (PA-TDI, time between the onset of the P-wave in the surface ECG and the peak of the A-wave on the TDI velocity recording, a marker of atrial fibrosis, as described before.[13] Left ventricular systolic function was evaluated using left ventricular ejection fraction (LVEF) and right ventricular systolic function was evaluated with tricuspid annular plane systolic excursion (TAPSE).[12]

Follow-up and definitions

Patients were followed-up at the outpatient clinic for a minimum of 1 year. The follow-up included a 24 hour Holter-ECG at 3 and 6 months follow-up. The 12-lead ECG performed at every outpatient clinic visit (within and after 1 year follow-up) was also included in the analysis. Finally, emergency department visits or hospital admissions for atrial arrhythmias were documented.

Three types of atrial arrhythmias were studied: 1) atrial fibrillation (AF) or flutter, 2) atrial tachycardia and 3) excessive supraventricular ectopy activity (ESVEA). Atrial fibrillation or flutter was defined according to current guidelines[14], lasting ≥ 30 seconds,either at 12-lead ECG or during 24-hour Holter-ECG monitoring. Atrial tachycardia was defined as a run of ≥3 premature atrial contractions (PACs).[15] Premature atrial contractions were characterized by a coupling interval of ≤70% to the preceding QRS complex, based on the mean RR interval of the basic rhythm.[15] Finally, ESVEA was defined according to previous literature, as ≥30 PAC per hour or any runs of ≥20 PAC.[15] An isolated run of ≥20 PAC's was considered ESVEA.

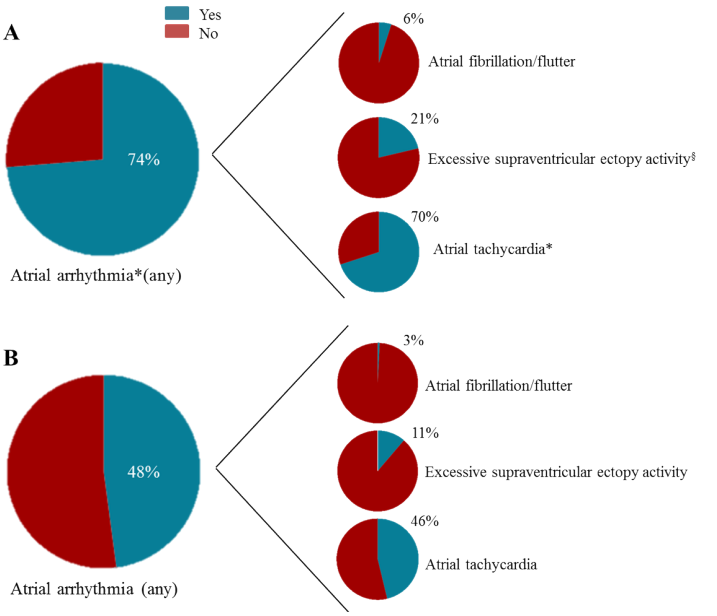

Figure 1: **Prevalence of atrial arrhythmias in patients with (A) and without (B) chronic obstructive pulmonary disease (COPD) after ST-segment elevation myocardial infarction during 1 year follow up.**

*p<0.001 and §p<0.05, respectively, compared to patients without COPD.

Study endpoint

The primary endpoint of this study was a composite endpoint of the occurrence of any predefined atrial arrhythmia, during 1year follow-up after STEMI. Second, the incidence of atrial fibrillation or flutter >1 year after STEMI was registered.

Statistical analysis

All statistical analyses were performed using SPSS software (version 24, IBM SPSS statistics for windows, Armonk, New York). Categorical data are presented as frequencies and percentages. Comparison of categorical variables between COPD and non-COPD patients was performed using chi-square ($\chi 2$) tests or Fisher's exact test, as appropriate. Continuous data are presented as mean ± standard deviation (SD) or median and interquartile range (IQR), in case of non-normal distribution. Subsequently, continuous data were compared between COPD and non-COPD patients using the unpaired Students-t-test or Mann-Whitney U test, as appropriate.

To identify independent factors associated with the primary endpoint,univariate and multivariate binary logistic regression analysis were performed. Variables with a p-value <0.2 in univariate logistic regression and considered of clinical relevance were included in a multivariate model. Variables with a substantial number of missing values were excluded from the multivariate analysis. The outcomes are presented as odds ratios and associated 95% confidence intervals (CIs). A two-sided p-value of ≤0.05 was considered of statistical significance.

Results

The total study population consisted of 320 STEMI patients (mean age 67±10 years, 74% male), including 80 patients withCOPD and 240 age- and sex-matched control patients without COPD. Echocardiography was available for 309 patients (97%). In 276 patients (83%) two 24-hour Holter-ECGs at 3 and 6 months follow-

Table 1: Baseline characteristics of patients with and without COPD.

Variable	Overall (n=320)	COPD Yes (n=80)	COPD No (n=240)	p-value
Age (years)	67 ± 10	70.5 [62 – 77]	67 [59 – 74]	0.05
Male (n %)	236 (74)	21 (26)	63 (26)	1.00
Body surface area (m^2)	1.94 ± 0.2	1.96 [1.80 – 2.08]	1.95 [1.83 – 2.06]	0.81
Systolic blood pressure (mmHg)	137 ± 29	140 [117 – 165]	130 [117 – 150]	0.21
Diastolic blood pressure (mmHg)	82 ± 18	83 [70 – 95]	80 [70 -90]	0.15
Heart rate at admission (bpm)	73 ± 18	73.5 [62 – 85]	70 [60 – 84]	0.54
Killip class ≥2 (n %)	12 (4)	6 (8)	6 (3)	0.08
β-blocker use at discharge (n %)	305 (95)	74 (93)	231 (96)	0.22
eGFR (ml/min/1.73m^2)	85 ± 26	88 [69 – 101]	83 [65 – 102]	0.41
Peak CK (U/l)	1298 [603 -2416]	1253 [551-2125]	1313 [611 – 2544]	0.46
Peak Troponin T (µg/l)	3.16 [1.30-6.47]	3.1 [1.26 – 5.82]	3.27 [1.34 – 6.81]	0.34
Culpritvessel (n %):				0.29
LAD RCA LCx	127 (40) 143 (45) 46 (15)	26 (33) 39 (49) 14 (18)	101 (43) 104 (44) 32 (14)	
Multi-vessel disease (n %)	181 (57)	42 (53)	139 (58)	0.40
Cardiovascular risk factors :				
Hypertension (n %)	132 (41)	32 (40)	100 (42)	0.79
Diabetes mellitus (n %)	33 (10)	6 (8)	11 (27)	0.34
Hypercholesterolemia (n %)	54 (17)	14 (18)	40 (17)	0.79
Family history of CVD (n %)	114 (36)	26 (34)	88 (37)	0.59
Current or previous smoking (n %)	170 (53)	55 (69)	115 (49)	0.002
Echocardiographic parameters:				
Right atrial area (cm2)	14.9 ± 3.7	14.3 [12 -18]	14.7 [12.6 – 17]	0.90
Left atrial volume index (ml/m2)	23.3 ± 8.3	22.5 [16.2 – 26.8]	22.2 [17.3 – 29.1]	0.44
PA-TDI duration (ms)*	109 ± 26	109 ± 25	108 ± 27	0.76
LV end-systolic volume (ml)	48 [37 – 59]	47 [38 – 55]	48 [37 – 62]	0.66
LV end-diastolic volume (ml)	93 [74 – 111]	91 [73 – 111]	94 [74 – 111]	0.58
LV ejection fraction (%)	47 ± 9	48 [42 – 53]	48 [42 – 54]	0.85
TAPSE (mm)	17.7 ± 3.7	18.3 ± 3.6	18.8 ± 3.7	0.31

CK, creatine phosphokinase; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; LAD, left anterior descending coronary artery; LV, left ventricular; RCA, right coronary artery; LCx, left circumflex coronary artery; TAPSE, tricuspid annular plane systolic excursion. *Analysis feasible in 302 patients.

up were available for assessment of atrial arrhythmias. The percentage of patients with two 24-hour Holter-ECGs was similar in COPD and non-COPD patients (86% vs. 83%, respectively, p=0.435). The remaining patients had only one 24-hour Holter-ECG at either 3 or 6 months follow-up.

Baseline characteristics

Table 1 presents the baseline characteristics of COPD and non-COPD patients. As per study design, no differences in age or gender were present between COPD and non-COPD patients. Furthermore, the distribution of culprit vessels and the presence of multi-vessel disease were similar. Regarding cardiovascular risk factors, patients with COPD were more frequently current or previous smokers (69% vs. 49%, respectively, p=0.002). On echocardiography, patients with COPD had similar atrial volumes, PA-TDI and left and right ventricular systolic function compared to their counterparts (Table 1).

Prevalence of atrial arrhythmias

Table 2 presents the occurrence of atrial arrhythmias at the different time points during follow-up in COPD and non-COPD patients.In particular atrial tachycardia was observed more frequently in patients with COPD at both 24-hour Holter-ECG monitoring time points, when compared to patients without COPD (58% vs 38%; p=0.001 and 57% vs 38%; p=0.005, at 3- and 6 months follow-up, respectively). Additionally, COPD patients had a significantly higher absolute number of PAC's, both at 3- and 6 months (Table 2). At 1year follow-up, atrial tachycardia and ESVEA had occurred more frequently in COPD patients as compared to patients without COPD (Figure 1). The rate of AF or flutter was low in the overall population (3.8%) and did not differ significantly between groups (Figure 1). At long-term follow-up (mean time 69.5 ± 39 months), only 5% of the total population had new onset AF, with no significant differences between patients with and without COPD (Table 2).When analysing the ECG data obtained at emergency room visits, hospital admissions or at the outpatient clinic, the frequency of atrial arrhythmias was similar in COPD and non-COPD patients (9 out of 240 patients without COPD (3.8%) vs. 3 out of 80 patients with COPD(3.8%), p=1.00). Most of these events (67%) were registered prior to the 3-months Holter monitoring (median time interval 3 [IQR 2 – 3,75] months).

Finally, 177 patients (55%) reached the composite endpoint of any atrial arrhythmia during 1 year follow-up. COPD patients reached more frequently the composite endpoint compared to their counterparts (74% vs 49%, respectively, p<0.001).

Determinants of atrial arrhythmias

Table 3 presents the clinical and echocardiographic variables with a p-value <0.20 in univariate regression analysis to identify associates of the composite endpoint. Age, male sex, the presence of COPD, kidney function, body surface area and LVEF were significantly associated withthe composite endpoint in the univariate analysis. On multivariate analysis, only age (odds ratio 1.13, 95% CI 1.09 – 1.17, p<0.001) and the presence of COPD (odds ratio 3.29, 95% CI 1.64 – 6.58, p=0.001) were independent associates of atrial arrhythmias in this STEMI population (Table 3).

Discussion

The present study demonstrates that patients with COPD have a significantly higher prevalence of atrial tachycardia and ESVEA during 1 year follow-up after STEMI, compared to matched patients without COPD. COPD and increasing age are independently associated with the occurrence of atrial arrhythmias during 1 year follow-up after STEMI.

Table 2: Occurrence of atrial arrhythmias in patients with and without COPD

	Overall (n=320)	COPD		P value
		Yes (n=80)	No (n=240)	
Atrial fibrillation < 48 hours (n %)	18 (6)	9 (11)	9 (4)	0.021
24-hour Holter-ECG at 3 months (n %)	316 (99)	79 (99)	237 (99)	1.000
Atrial fibrillation/flutter (n %)	5 (2)	3 (4)	2 (1)	0.103
Atrial tachycardia (n %)	135 (42)	46 (58)	89 (38)	0.001
Excessive supraventricular				
ectopy activity (n %)	32 (10)	13 (17)	19 (8)	0.032
Premature atrial complexes	44 [19 – 142]	65 [29 – 276]	34 [18 – 119]	0.017
24-hour Holter-ECG at 6 months (n %)	271 (85)	70 (88)	201 (84)	0.645
Atrial fibrillation/flutter (n %)	5 (2)	3 (4)	2 (1)	0.110
Atrial tachycardia (n %)	116 (36)	40 (57)	76 (38)	0.005
Excessive supraventricular				
ectopy activity (n %)	31 (10)	11 (16)	20 (10)	0.196
Premature atrial complexes	38 [17 – 141]	67 [22 – 269]	33 [15 – 127]	0.019
Atrial arrhythmia within 1 year (n %)	177 (55)	59 (74)	118 (49)	<0.001
Atrial fibrillation/flutter > 1 year (n %)	15 (5)	3 (4)	12 (5)	0.769

Continuous variables are presented as median [interquartile range]. COPD; chronic obstructive pulmonary disease, ECG; electrocardiogram

Cardiac arrhythmias in patients with COPD

Previous studies have shown an independent relationship between COPD and decreased pulmonary function and the occurrence of both supraventricular and ventricular arrhythmias.[3, 4] Among AF patients, the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation(ARISTOTLE) and EURObservational Research Programme Atrial Fibrillation (EORP-AF) registries, including 18,134 and 3,086 patients, respectively, reported an 11% prevalence of COPD in their study populations.[16,17] Among patients with COPD, the reported prevalence of cardiac arrhythmias ranges from 5% up to 29%.[18] Compared to patients without COPD, therisk of developing cardiac arrhythmias almost doubled in COPD patients (pooled OR 1.94, 95% CI 1.55 – 2.43; p<0.0001).[18] In the present study, the incidence of new-onset AF was low in both patient groups (6% vs. 3% for COPD and non-COPD patients, respectively) considering only 1 year follow-up and also at longer term follow-up. However, almost three-quarters of the COPD patients develop sometype of atrial arrhythmia during this short time period compared to onlyhalf of the non-COPD patients. The importance of increased atrial ectopic activity for future development of AF was demonstrated recently by Johnson et al.[19] A total of 383 patients who underwent 24-hour Holter-ECG recording were evaluated. Thenumber of atrial tachycardia episodes and the presence of ESVEA were independently associated with a1.99and2.66 times increased incidence of AF after a mean follow-up of 10.3 years, respectively.[19] The association between PAC count and incident AF was also demonstrated in a larger community-based cohort, analysing 1,260 participants aged 65 years or older.[20] The median PAC count of the study population was 2.5 beats/hour (IQR 0.8 – 9.5 beats/hour) and each doubling in PAC count per hour resulted in a 17% increased risk of incident AF during 10 year follow-up.[20] These studies accentuate the importance of recording atrial ectopic activity at 24-hour Holter-ECG to identify patients at risk for AF, since PAC's might be a modifiable risk factor for primary prevention of AF. Ablation of PAC or antiarrhythmic drugs could be initiated at an early stage toreduce the risk of future AF development.[21] Furthermore, detection of frequent PAC could lead to more frequent screening and early detection of AF, resulting in timely intervention with anticoagulants reducing the risk of stroke. Even beyond AF, excessive atrial ectopy is associated with an increased risk of ischemic stroke suggesting anticoagulant therapy might be needed even before AF diagnosis is established.[22] However, careful considerations should be taken sinceno evidence is currently available to support these theories.

Table 3: Univariate and multivariate determinants of the composite end point.

	Univariate			Multivariate		
	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
Age, per 1 year increase	1.14	1.11 – 1.17	<0.001	1.12	1.08 – 1.16	<0.001
Male sex yes/no	0.42	0.25 – 0.72	0.002	0.83	0.40 – 1.73	0.619
COPD yes/no	2.91	1.66 – 5.08	<0.001	3.29	1.64 – 6.58	0.001
Hypertension yes/no	1.52	0.97 – 2.39	0.07	1.32	0.75 – 2.35	0.339
Killip class ≥2 yes/no	2.52	0.67 – 9.47	0.173	1.00	0.22 – 4.59	0.998
Peak troponin level per 1 unit increase	1.03	0.99 – 1.08	0.189	1.01	0.95 – 1.07	0.815
eGFR per 1 unit increase	0.98	0.97 – 0.99	<0.001	0.99	0.98 – 1.01	0.357
BSA per 1 unit increase	0.13	0.04 – 0.44	0.001	1.46	0.27 – 8.05	0.662
β-blocker use yes/no	0.43	0.14 – 1.39	0.161	0.72	0.18 - 2.96	0.649
LVEF per 1 unit increase	0.97	0.94 – 0.99	0.010	0.98	0.95 – 1.01	0.160
LAVI per 1 unit increase	1.02	0.99 – 1.05	0.089	1.02	0.99 – 1.06	0.191

BSA, body surface area; CI, confidence interval; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction

Pathophysiologic factors responsible for the arrhythmogenic mechanisms in COPD patients are diverse. Both intrinsic factors of the disease itself (i.e. systemic inflammation, oxidative stress) as well as changes in physiology (i.e. hypercapnia, hypoxia, autonomic dysfunction, pulmonary hypertension) could explain this increased arrhythmogenicity. In addition, common concomitant cardiovascular diseases in patients with COPD such as heart failure and coronary artery disease also impact on the occurrence of arrhythmias.[2] These factorscould potentially lead to atrial structural remodelling or slowing of atrial conduction, increasing the risk of AF. Our results did not show any difference in atrial size or total atrial conduction time, however we did not assess the presence of atrial fibrosis for which cardiac magnetic

resonance imaging is the recommended imaging technique.[23] This could be of interest for future studies exploring the pathophysiologic mechanisms behind arrhythmias in these patients.

Atrial arrhythmias after acute myocardial infarction

Literature regarding atrial arrhythmias after or during acute myocardial infarction mainly focus on AF or atrial flutter. In the Global Utilization of Streptokinase and TPA (alteplase) for Occluded Coronary Arteries (GUSTO-I) trial, a total of 40,891 STEMI patients were included, with a 10.4% incidence of AF.(24) The strongest predictors for incidentAF (post-admission)were age, peak CK level, Killip class and heart rate.[24] This was later confirmed by the Global Use of Strategies To Open occluded coronary arteries (GUSTO-III) study, regarding only early onset AF <30 days after STEMI.[25] In this study, a total population of 13,858 STEMI patients with initial sinus rhythm were included, of whom 906 patients developed AF or atrial flutter during hospitalization (6.5%).[25] The independent predictors of new AF in the GUSTO-III study were similar to those described in the GUSTO-I trial, despite the different timing of AF onset in these studies.[25] In addition, diabetes, hypertension, prior heart failure and prior myocardial infarction are known to be important predictors of AF in the setting of acute myocardial infarction.[6] Although COPD is a recognised risk factor for AF in the general population, data on the influence of COPD as a risk factor for atrial arrhythmias after STEMI are scarce. In the present study, COPD emerges as a strong and independent correlate of the occurrence of atrial arrhythmias within 1 year after STEMI. Variables such as diabetes, hypertension and Killip class at admission were not independently associated with the endpoint in our study. These inconsistencies with the GUSTO-I(24) and GUSTO-III[25] trials and the review by Schmitt et al.[6] could be explained by the use of a combined atrial arrhythmia endpoint(as in the present study) instead of only AF.Also, the present study addressed atrial arrhythmias by 24-hour Holter monitoring several months after STEMI whereas most previous studies evaluated onset of arrhythmias only during hospitalisation.

Clinical implications

The insights we provide in our study might create awareness in physicians to consider COPD as a risk factor for atrial arrhythmias after STEMI. Subsequently, this could result in a regular screening program for these patients. The presence of new-onset AF during or shortly after STEMI is associated with higher rates of in-hospital complications (i.e. re-infarction, heart failure, cardiogenic shock), 30-day and 1-year mortality.[6, 24, 25] In addition,in 3,220 patients with acute myocardial infarctionJabre et al. demonstrated that patients with late development of AF after acute myocardial infarction (>30 days), have the highest risk of death as compared to patients without new-onset AF (HR 2.58, 95% CI 2.21 – 3.00; p<0.001). Our findings mainly represent arrhythmias at 3- and 6-months follow-up, detecting a substantial incidence of atrial tachycardia and ESVEA in patients with COPD after STEMI. These atrial arrhythmias could lead to incident AF during long-term follow-up, as described before.(19, 20)Long-term follow-up for AF/flutterin the present study showed only low prevalence of AF/flutter, although it should be noted that the current study was designed to assess atrial arrhythmias during1 year follow-up by standardized 24-hour Holter monitoring at regular intervals. Future prospective studies are necessary to provide additional data to support this hypothesis in COPD patients.

Study limitations

Several study limitations should be acknowledged. This is a retrospective study, therefore no causal relationships can be proven. Besides, the single center study design limits the generalizability of the results. Patients were excluded if they were known with atrial arrhythmias prior to the index event (although not all patients had 24-hour Holter monitoring). The presence of arrhythmias was based on 24-hour Holter-ECG monitoring or emergency department visits due to symptoms. Subclinical atrial arrhythmias might therefore be underreported. After 1 year follow-up patients were frequently referred back to their general practitioner or regional hospital for long-term follow-up and therefore, the long-term follow-up data presented may be an underestimation of the true incidence of AF at long-term follow-up. The risk of new-onset COPD with increasing age during follow-up was not considered in the multivariate analysis, although the relatively short follow-up limits the possibility of a significant increase in the incidence of COPD. Finally, pulmonary function tests were not available for all patients either in their medical history as well as during follow-up, accordingly COPD diagnosis was based on thorough chart review.

Conclusions

COPD patients after STEMI have a significantly higher prevalence of atrial tachycardia and ESVEA within 1 year of follow-up as compared to age- and gender matched patients without COPD. Moreover, COPD was independently associated with the occurrence of atrial arrhythmias 1 year after STEMI. These results indicate that close clinical monitoring might be appropriate in this patient population.

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Concealed Coronary Atherosclerosis in Idiopathic Paroxysmal Atrial Fibrillation is Associated with Imminent Cardiovascular Diseases

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Abstract

Background: Previous research showed a significant difference in the presence of subclinical coronary artery disease (CAD) on cardiac CT angiography (CTA) between patients with idiopathic paroxysmal atrial fibrillation (iAF) versus a matched sinus rhythm population (iSR). Here we present 5-year follow-up data and the consequences of subclinical CAD on baseline CTA on the development of cardiovascular disease in iAF.

Methods: In 99 iAF patients (who underwent CTA as part of work-up for pulmonary vein isolation) and 221 matched iSR controls (who underwent CTA for CAD assessment), the incidence of hypertension, diabetes and major cardiovascular events (MACCE) during follow-up was obtained. Multivariable Cox regression analysis was used to reveal predictors of incident cardiovascular disease in the iAF group.

Results: During a follow-up of 68±11 months, over one third of patients developed cardiovascular disease, with no difference between iAF and iSR (log-rank p=0.56), and comparable low rates of MACCE (4.0% vs 5.0%,p=0.71). Within the iAF group, age (HR1.12(1.03–1.20);p=0.006), left atrial diameter (HR1.16(1.03–1.31);p=0.01), Segment Involvement Score (total number of coronary segments with atherosclerotic plaque; HR1.43(1.09–1.89);p=0.01) and the number of calcified plaques on CTA (HR0.53(0.30–0.92);p=0.01) were independent predictors of incident cardiovascular disease.

Conclusion: Subclinical coronary disease on CTA may be useful to identify the subset of patients with iAF that harbour concealed cardiovascular risk factors and need intensive clinical follow-up to ensure timely initiation of appropriate therapy once CV disease develops, including anticoagulation and vascular prophylactic therapy.

Introduction

Idiopathic atrial fibrillation (iAF) is defined as the presence of this arrhythmia in which none of the predisposing factors are present, such as hypertension, diabetes mellitus, heart failure, structural abnormalities on echocardiography, pulmonary disease, thyroid disease, and renal disease. A number of underlying pathophysiologic mechanisms have been proposed for iAF, including increased atrial stretch, autonomic imbalance, systemic inflammation, oxidative stress, and structural and electrophysiological alterations. These mechanisms may reflect a shared underlying pathophysiology between iAF, atherosclerosis and other forms of cardiovascular disease (CVD)[1], and it may thus be hypothesized that iAF is the first overt expression of the underlying pathophysiological processes that lead to various forms of CVD[2,3]

In a previous study, Weijs et al.[4] showed that patients originally diagnosed with paroxysmal iAF more often show subclinical atherosclerosis on cardiac computed tomographic angiography (CTA) than a matched sinus rhythm (iSR) control group. Here we present 5-year follow-up data on both the iAF group and the iSR group to assess the development of CVD in this previously presumed healthy population. Furthermore, we studied the role of CTA in distinguishing between patients that will or will not develop CVD after the initial diagnosis of i AF.

Key Words

Atrial Fibrillation, Coronary Artery Disease, Computed Tomography Angiography, Hypertension

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Material and methods

Study population

The patients in this cohort were described previously[4]. In short, 390 consecutive patients (mean age 55±10 years, 67.7% male), who underwent CTA at the Maastricht University Medical Centre between January 2008 and March 2011 were included: 115 patients with paroxysmal iAF as part of work-up for pulmonary vein isolation (PVI) or for exclusion of coronary artery disease (CAD) before initiation of anti-arrhythmic drugs, and 275 healthy patients in sinus rhythm (SR) who were referred by their treating physician for CTA to assess the presence of CAD. iAF and iSR were defined as the absence of any form of CVD, including hypertension (defined as antihypertensive drug use, systolic blood pressure ≥140mmHg, or diastolic blood pressure ≥90mmHg on CTA visit, or left ventricular hypertrophy (LVH)), diabetes, or hypercholesterolemia. All patients had no history of CAD, renal dysfunction, stroke, malignancy, obstructive sleep apnea, thyroid or pulmonary disease, and no evidence of structural CVD on echocardiogram, including valvular heart disease. Angina or abnormal stress test were never an indication for CTA. iAF and iSR patients were matched on sex, age at time of CTA (±1 year), and PROCAM risk score[5]. All patients underwent transthoracic echocardiography. This study was approved by the Institutional Review Board and complies with the ethical principles of the Declaration of Helsinki. All patients gave written informed consent.

CTA data acquisition and analysis

At baseline, a prospective unenhanced coronary scan was performed in all patients as described previously[4]. The Agatston score was calculated using a 3-mm CT slice thickness and detection threshold ≥130 Hounsfield units involving ≥1mm2 area/lesion (3 pixels). Coronary arteries were evaluated according to the 16-segment classification scheme. Coronary plaques were defined as structures >1 mm2 within and/or adjacent to the coronary artery lumen, which could be clearly distinguished from the vessel lumen and the surrounding pericardial tissue. Plaques were categorized as soft, mixed or calcified plaques, based on visual judgment of plaque composition. The Segment Involvement Score (SIS), the sum of segments in which a plaque was found, was calculated as a measure of the extent of CAD[6].

Follow-up

Development of hypertension, diabetes and major cardiovascular and cerebrovascular events (MACCE) during follow-up (between the date of CTA and July 2016) were obtained and cross-checked by two independent observers. Data were derived from the patient records as kept by the (referring) hospital and general practitioner. MACCE was defined as cardiovascular death, acute coronary syndrome, percutaneous coronary intervention, coronary bypass grafting, congestive heart failure, transient ischemic attack or stroke. Development of CVD was defined as the occurrence of MACCE, the development of hypertension (blood pressure repeatedly ≥140mmHg systolic and/or ≥90mmHg diastolic, prescription of anti-hypertensive drugs or development of LVH on echocardiography) and diabetes mellitus.

Statistical analysis

Statistical analysis was performed using SPSS statistical software (SPSS statistics 23.0, IBM Corporation, Armonk, NY). Categorical variables are reported as number (percentage) of patients and compared using Chi-square testing. Continuous variables are presented as mean±SD or as median[interquartile range], depending on distribution, and were compared with an independent T-test and Mann–Whitney test respectively. All demographic, echocardiographic and CT parameters showing a significant univariable relation with the development of CVD during follow-up - using Cox regression - were included as covariates in a multivariable Cox regression model. Proportional hazards were checked. Manual backwards elimination was used to construct the final models (retention level set at 0.10), yielding hazard ratios and 95% confidence intervals. Results were checked for collinearity and interaction among covariates. P<0.05 was considered statistically significant.

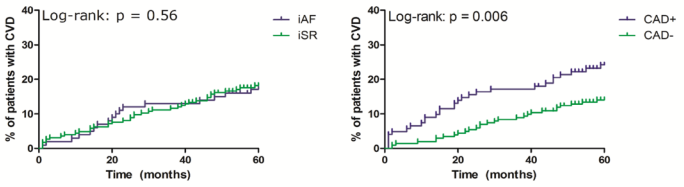

Figure 1: Kaplan-Meier curves for the cumulative incidence of cardiovascular risk factors.

There is no difference in the cumulative incidence in the idiopathic atrial fibrillation (iAF) versus the sinus rhythm control group (iSR; Log-rank p=0.56; Panel 1). However, there is a highly significant difference in development of risk factors in iAF patients with coronary artery disease on CT (CAD+) when compared to those without (CAD-; Log-rank p=0.006; Panel 2). All iAF patients developing cardiovascular risk factors receive one (hypertension, diabetes, vascular disease, heart failure) or two (TIA/stroke) extra points on the CHA2DS2-VASc-score, leading to an indication for the use of anti-coagulant therapy

Results

Incidence of cardiovascular disease during follow-up

Follow-up was complete in 99 iAF (13.9% lost to follow-up; median AF history 29 months) and 221 iSR patients (19.6% lost to follow-up). Patients in whom follow-up was not complete did not differ significantly from the study patients at baseline characteristics and number and type of plaques on CT. During a follow-up duration of 68±11 months, one third of patients developed CVD, with no

Table 1: Incidence of MACCE and cardiovascular diseases during 5 years of follow-up for patients with idiopathic atrial fibrillation (iAF) compared to sinus rhythm controls (iSR).

	iAF (N=99)	iSR (N=221)	p
Death	0	0	-
ACS	0 (0)	3 (1.4)	0.40
PCI	0 (0)	4 (1.8)	0.18
CABG	1 (1)	0 (0)	0.14
CHF	0 (0)	1 (0.5)	0.50
TIA	4 (4.0)	5 (2.3)	0.37
Stroke	0 (0)	2 (0.9)	0.34
Any MACCE	4 (4.0)	11 (5.0)	0.71
Hypertension	24 (24.2)	67 (30.3)	0.27
DM2	4 (4.0)	9 (4.1)	0.99
Any cardiovascular disease	32 (32.3)	82 (37.1)	0.41

Shown is n (%). ACS=Acute Coronary Syndrome; CABG=Coronary Artery Bypass Grafting; CHF=Congestive Heart Failure; DM2=Type 2 Diabetes Mellitus; iAF = idiopathic AF; iSR=idiopathic Sinus Rhythm control group; MACCE=Major Adverse Cardiac and Cerebrovascular Events; PCI=Percutaneous Coronary Intervention; TIA=Transient Ischemic Attack

Table 2: Baseline characteristics of idiopathic AF (iAF) patients who do and do not develop cardiovascular disease during follow-up.

		No CVD (n=67)	CVD development (n=32)	p
Sex (female)		22(32.8)	7(21.9)	0.26
Age (years)		52.9±10.4	59.2±8.7	0.004
BMI		25.9±3.3	26.9±3.0	0.20
BSA		2.01±0.26	2.03±0.16	0.70
Family history of CAD		8(11.9)	5(15.6)	0.61
Smoking		8(11.9)	6(18.8)	0.36
CHA_2DS_2-VASc score	0	37(55.2)	20(62.5)	0.02
	1	28(41.8)	7(21.9)	
	2	2(3.0)	5(15.6)	
Systolic blood pressure (mmHg)		125±13	128±14	0.21
Fasting glucose (mM)		5.4±0.6	5.5±0.6	0.23
LDL (mM)		3.7±0.8	3.3±0.9	0.09
HDL (mM)		1.3±0.4	1.2±0.3	0.25
Total cholesterol (mM)		5.6±0.9	5.2±1.0	0.07
Triglycerides (mM)		1.7±1.1	1.5±0.6	0.35
eGFR (MDRD; ml/min/1.73m²)		81±13	82±17	0.73
VKA		22(32.8)	11(34.4)	0.88
Aspirin		33(49.3)	19(63.3)	0.19
Beta blocker		22(32.8)	15(50.0)	0.11
Non-dihydropyridine CCB		6(9.0)	4(13.3)	0.51
ACE inhibitor		0(0.0)	0(0.0)	-
ARB		0(0.0)	0(0.0)	-
Dihydropyridine CCB		0(0.0)	0(0.0)	-
Statin		4(6.0)	6(18.8)	0.048
Echocardiography				
Aorta diameter (mm)		34.2±3.1	34.3±3.2	0.89
LA diameter (mm)		39.3±4.8	41.5±5.2	0.04
LVEF (%)		61.4±5.8	60.1±5.2	0.28
IVSd (mm)		8.4±0.8	8.7±0.9	0.16
LVPWd (mm)		8.3±0.6	8.6±0.8	0.04
CT angiography				
Agatston score >0		22(32.8)	18(56.3)	0.03
Agatston score		0.0[22]	11.1[140]	0.017
Any soft plaque		7(10.4)	14(43.8)	< 0.001
Number of soft plaques		0[0]	0[1]	< 0.001
Any mixed plaque		18(26.9)	9(28.1)	0.90
Number of mixed plaques		0[1]	0[1]	0.66
Any calcified plaque		16(23.9)	14(43.8)	0.04
Number of calcified plaques		0[0.75]	0[3]	0.03
Any plaque		28(41.8)	22(68.8)	0.01
Segment Involvement Score		0[2]	1[8]	< 0.01

Shown is n(%) or mean±SD. ACE=angiotensin-converting-enzyme; ARB=Angiotensin II receptor blocker; BMI=Body Mass Index; BSA=Body Surface Area; CAD=Coronary Artery Disease; CCB=Calcium Channel Blocker; CT=Computed Tomography; CVD=Cardiovascular Disease; eGFR=estimated Glomerular Filtration Rate; HDL=High Density Lipoprotein; IVSd=Interventricular Septum thickness at end diastole; LA=left atrium; LDL=Low Density Lipoprotein; LVEF=Left Ventricular Ejection Fraction; LVPWd=left ventricular posterior wall thickness at end diastole; VKA=Vitamin K Antagonist.

significant differences between the iAF and iSR group (32.3% vs 37.1%, p=0.41; Table 1). The occurrence of MACCE did not differ between groups (4.0% vs 5.0%, p=0.71). Patients developed hypertension most frequently (24.2% and 30.3% respectively). The Kaplan–Meier curve for the cumulative incidence of CVD is not different for both groups (Log-rank p=0.56; Fig 1, Panel 1).

Characteristics of iAF patients who develop cardiovascular disease

As the development of risk factors has effects on the necessity to initiate anti-coagulation therapy, we studied factors associated with CVD development in the iAF patients. Patients who developed CVD during follow-up were on average older than patients who did not (59.2±8.7 vs 52.9±10.4, p=0.004), and more often used a statin at baseline (18.8% vs 6.0%; p=0.048; Table 2). The percentage of smokers and patients with a family history of CAD did not differ significantly between patients that developed CVD and those who did not. Echocardiography showed a larger left atrial diameter (41.5±5.2 vs 39.3±4.8 mm, p=0.04) and higher left ventricular posterior wall thicknessat end diastole (LVPWd; 8.6±0.8 vs 8.3±0.6 mm, p=0.04) in patients who developed CVD. At the end of follow-up, in patients who did not develop CVD, 14.9% used VKA and 4.5% NOAC, while in those who developed CVD, 46.9% used VKA and 16.2% used NOAC.

On the coronary calcium scan, patients who developed CVD more often had an Agatston score greater than zero (56.3% vs 32.8%, p=0.03) and a higher median coronary Agatston score (11.1[140] vs 0.0[22], p=0.02). CTA showed a higher median SIS (iAF 1[8] vs 0[2], p<0.01), with a higher number of soft plaques (43.8% vs 10.4%, p<0.001) and calcified plaques (43.8% vs 23.9%, p=0.04; Table 2). The presence of any form of CAD on CT was associated with a higher cumulative incidence of CVD (Log-rank p = 0.006; Fig 1, Panel 2).

Prediction of CVD development in iAF

Univariable Cox regression analysis showed a relation with CVD development for the following parameters (Table 3): age (HR1.12(1.05–1.20),p=0.001), statin use (HR3.10(1.01–9.40),p=0.048), LA diameter (HR1.17(1.05–1.30),p=0.005), LVPWd (HR1.87(1.01–3.50),p=0.047), Agatston score>0 (HR3.13(1.22–8.02),p=0.017), Agatston score continuous (HR/10 units 1.02(1.004–1.04),p=0.01), presence of any soft plaque (HR4.56(1.79–11.60),p=0.001), number of soft plaques (HR2.91(1.55–5.47),p=0.001), any calcified plaque (HR2.50(1.02–6.19),p=0.05), number of calcified plaques (HR1.37(1.02–1.83),p=0.03), any plaque (HR2.89(1.09–7.71),p=0.03), and SIS (HR1.34(1.17–1.59),p=0.001). Multivariable Cox analysis regression in which only clinical and echocardiographic parameters were tested, revealed that from these parameters only age (HR1.12(1.04–1.21),p=0.004) and LA-diameter (HR1.12(1.01–1.24),p=0.03) were independently associated with CVD development. Addition of CT parameters to this model, showed that the SIS (HR1.43(1.09–1.89),p=0.01) and number of calcified plaques (HR0.53(0.30–0.92),p=0.01) were independently associated with incident CVD on top of age (HR1.12(1.03–1.20),p=0.006) and LA diameter (HR1.16(1.03–1.31),p=0.01).

Discussion

This study shows that a significant proportion of clinically healthy iAF patients - over one third - develops cardiovascular disease within 5 years of follow-up, most frequently hypertension. Independent predictors of CVD development include age, LA diameter, and the

Table 3: Univariable and multivariable Cox-regression analysis of factors associated with development of cardiovascular disease in idiopathic AF patients.

	Univariable		Model 1		Model 2	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age	1.12 (1.05–1.20)	0.001	1.12 (1.04–1.21)	0.004	1.12 (1.03–1.20)	0.006
Statin	3.1 (1.01–9.4)	0.048				
Left atrial diameter (per mm)	1.17 (1.05–1.30)	0.005	1.12 (1.01–1.24)	0.03	1.16 (1.03–1.31)	0.01
Left ventricular posterior wall thickness at end diastole (per mm)	1.87 (1.01–3.5)	0.047				
Coronary Agatston>0	3.13 (1.22–8.02)	0.017				
Coronary Agatston (per 10)	1.02 (1.004–1.04)	0.01				
Soft plaque	4.56 (1.79–11.60)	0.001				
Number of soft plaques	2.91 (1.55–5.47)	0.001				
Calcified plaque	2.50 (1.02–6.19)	0.05				
Number of calcified plaques	1.37 (1.02–1.83)	0.03			0.53 (0.30–0.92)	0.01
Any plaque	2.89 (1.09–7.71)	0.03				
Segment Involvement Score	1.34 (1.17–1.59)	0.001			1.43 (1.09–1.89)	0.01

Model 1 included clinical parameters only, Model 2 includes parameters derived from CT angiography.

extent of CAD on CTA expressed as a higher SIS, mainly when caused by non-calcified plaques. This study therefore suggests that CTA in combination with clinical measures may enhance identification of iAF patients - currently considered to have a low CV risk - who are prone to develop CVD. This allows timely initiation of individualized follow-up programs as well as the start of adequate cardiovascular preventive therapy. This includes repeated thromboembolic risk assessment over time as iAF patients, once they emerge with hypertension, are in need of anticoagulation on top of other prevention measures[7,8].

The natural course of risk factor development in AF patients may best be studied in those patients originally diagnosed with idiopathic AF. The definition of iAF used in this study was very strict, which, based on the Euro Heart Survey on Atrial Fibrillation, corresponds to a prevalence of 3% of all AF patients[9]. Notwithstanding this strict definition of iAF, a significant proportion of the patients developed CVD. In the first study on this subject, Katritsis et al.[10] found an incidence of hypertension of 44% within 3 years of follow-up, which is higher than the 24.2% in 5 years in our study, which may be attributed to the inclusion of patients with persistent iAF instead of paroxysmal iAF in the study by Katritsis et al. Potpara et al.[11] found a lower incidence of CVD in patients with iAF, which may be related to the younger age at inclusion. Also, Weijs et al.[12,13] previously showed an incidence of CVD of almost 50% in patients with first detected iAF during the same duration of follow-up of 5 years – which is higher than the 32.3% in 5 years found in this study. This might be explained by the observation that patients with first detected AF harbour a high short term risk of CVD development[14]. Patients in our study had gone through a median of 29 months of AF without developing CVD at inclusion, which may have selected those patients who went through the initial phase of AF - in which they may have had the highest propensity of developing CVD - without developing CVD.

The iAF and iSR patients included in this study were matched on future vascular risk, yet as reported before, the iAF patients had a significantly higher prevalence of subclinical CAD on CTA[4] and associated biomarker profiles[15,16]. Surprisingly, in this report we show that – in contrast to our hypothesis – this higher prevalence of subclinical CAD is not associated with a higher incidence of CVD in the iAF patients as compared to the iSR patients. Apparently, in iAF patients, there are processes that lead to the development of AF and to progression of plaque burden, but are not associated with the development of hypertension. Results from the Bruneck Study have shown that there are distinct processes leading to initiation and to progression of atherosclerosis[17]: risk factors for initiation of atherosclerosis lie in traditional risk factors, such as hypertension, hyperlipidemia, and cigarette smoking – factors that are comparable between the iAF and iSR group. In contrast, risk factors for progression of atherosclerosis lie in markers of a hypercoagulable state. A prothrombotic state is already present very early in AF patients as compared to controls without AF[18], or may even be the reason AF has developed[19]. From these observations, it may be hypothesized that atherosclerosis is initiated to the same extent in both iAF and iSR, yet early plaques in iAF patients progress more rapidly to forms that are detected by CTA due to the prothrombotic state, while this prothrombotic state does not yet increase the incidence of other forms of early CVD.

Interestingly, multivariable analysis within the group of iAF patients showed that a greater burden of CAD, and especially soft not fully calcified plaques, associates with imminent CVD. In general, soft plaques are an early form of atherosclerosis[20] which fits with the notion that iAF associates with early subclinical vascular disease and imminent overt CVD. Based on the present study design, one cannot tell whether early coronary abnormalities – subclinical - CVD leads to subclinical angiographic abnormalities or vice versa, or that they share a common pathophysiological mechanism. Furthermore, it is of interest to note that the presence of plaques on CT was shown to associate with incident CVD on top of LA size. LA enlargement has been shown previously to be an early marker of vascular disease[21], as it is a sign of atrial remodelling, reflecting a state of pressure and volume overload[22], endothelial dysfunction[23], inflammation, and oxidative stress[24]. Although coronary artery calcification is a well-established risk factor for MACCE[25,26], and decreased systemic vascular compliance enhances the development of hypertension, this is to our knowledge for the first time that the association between plaques on CT angiography and development of CVD in apparently healthy AF patients is shown.

Clinical implications of this study

Patients scheduled for AF ablation frequently undergo a diagnostic CT-angiography. This study suggests to use this CTA not only for pulmonary vein anatomy to guide the ablation, but also for triggering more intense follow-up to detect CVD and timely instalment of appropriate prophylactic vascular therapy, including antithrombotic

treatment[27]. All iAF patients in this study who are under 65 years of age at inclusion, have by definition a CHA_2DS_2-VASc-score of 0 (males) or 1 (females) and are thus considered low-risk and to have no indication for anticoagulation[28], yet all patients developing the endpoint of CVD in this study receive one (hypertension, diabetes, ACS/PCI/CABG, CHF) or two (TIA/CVA) extra points on the CHA_2DS_2-VASc-score, leading to an indication for the use of anticoagulant therapy, with a NOAC and in selected cases in combination with antithrombotics [29, 30]. Whether CTA could help fine tune risk scores – for example whether CAD or aortic calfication[31] on CT should be scored as a CHA_2DS_2-VASc-point for vascular disease – remains to be determined. CTA will help to broaden the focus of clinical electrophysiologists to also include an integrated vascular approach in addition to rhythm control, and timely initiation of anticoagulation – or continuation after PVI. Furthermore, patients without abnormalities on CTA may be discharged with and taken off anticoagulation after PVI with more confidence.

Study limitations

Firstly, these results were obtained in a selected population as it only includes patients with iAF referred for PVI and iSR patients that were referred for screening purposes. Due to the strict definition of idiopathic AF, during the first 5 years of follow-up mainly early forms of vascular disease occurred, and very low rates of MACCE. Longer follow-up may reveal the use of CTA in predicting MACCE. Lastly, since follow-up was not predefined and thus 24-hour blood pressure monitoring was not used consistently, subclinical forms of hypertension may have been missed.

Conclusion

One third of idiopathic AF patients develop cardiovascular disease within 5 years of follow-up. Independent predictors of cardiovascular disease development in iAF patients include age, LA-diameter, and the extent of CAD on CTA expressed as higher SIS, mainly when caused by non-calcified plaques. CTA may be used to identify those patients with idiopathic AF that harbour concealed cardiovascular risk factors and thus need close surveillance.

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Clinical and Echocardiographic Predictors of Atrial Fibrillation after Coronary Artery Bypass Grafting

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Abstract

Objectives: to detect the clinical and echocardiographic parameters that predict AF in coronary artery disease (CAD) patients after coronary artery bypass surgery (CABG).

Methods: one hundred CAD patients scheduled for CABG were included. Standard 2D, PW Doppler and 2D speckle tracking echocardiography were performed to assess left atrial (LA) and ventricular (LV) function and their role in predicting post-operative atrial fibrillation (POAF).

Results: twenty-two percent of patients developed POAF. POAF patients were significantly older (P= 0.001) with increased heart rate (P= 0.001). POAF patients had increased LA diameters and volumes (P < 0.001). Left ventricular ejection fraction (LVEF) was significantly lower in POAF patients (P < 0.004). POAF patients had significantly lower LA and LV global longitudinal strain (LVGLS) (p < 0.001). Clinical predictors of POAF were age and heart rate (P < 0.001). While, echocardiographic measures associated with POAF were LA and LV global longitudinal strain (P <0.001). LA longitudinal strain ≤ 23.1 (85% sensitivity and 66% specificity) and LVGLS ≤ -14.4 (70% sensitivity and 85% specificity) predicted POAF.

Conclusion: Preoperative LA and LV global longitudinal strain predicts POAF in CABG patients. Echocardiographic deformation measures can enhance clinical profile to identify patients at high risk for POAF.

Introduction

After cardiac surgery, postoperative atrial fibrillation (POAF) is the most common type of arrhythmia with an incidence ranging from 33% to 49% [1]. Patients with POAF had higher morbidity and mortality post-cardiac surgery [2]. Preventive measures may be possible if patients at high risk for POAF were identified early. Preoperative heart rate and rhythm control can be effective in preventing POAF [3]. However, the use of prophylactic treatment does not outweigh the risk and thus, medical prophylaxis is not routinely used.

Unfortunately, clinical variables only are not sufficient to identify patients at risk of developing POAF. Therefore, it is still not possible to depend on clinical data only to guide POAF prophylaxis. Impaired left ventricular ejection fraction was associated with POAF [4]. However, the role of subclinical LV mechanical dysfunction detected by 2D speckle tracking is less clear. Reduced LV global longitudinal strain, measured by speckle tracking echocardiography (STE), was associated with POAF in patients with aortic stenosis [5] and after mitral valve replacement [6].

Our study aimed at detecting the clinical and echocardiographic measures that can predict POAF in CAD patients undergoing coronary artery bypass graft (CABG).

Key Words

Atrial fibrillation; Coronary artery bypass graft; LA longitudinal strain; LV global longitudinal strain

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2. Patients and methods:

2.1. Study design:

It is a single center, prospective, observational study that included patients with CAD undergoing CABG at National Heart Institute, Egypt. Exclusion criteria were history of paroxysmal or permanent AF, reduced LV ejection fraction (LVEF < 40%), associated aortic or mitral valve disease requiring aortic or mitral valve replacement, co morbidities precluding cardiac surgery, congenital heart diseases, prior cardiac surgery, and patients refusal. The local ethics committee approved this study, and the patients provided an informed consent.

2.2. Study endpoint:

The primary study endpoint was occurrence of post-operative AF. It was diagnosed by the presence of irregular ventricular rhythm with absence of P wave lasting for at least 30 seconds. Continuous ECG

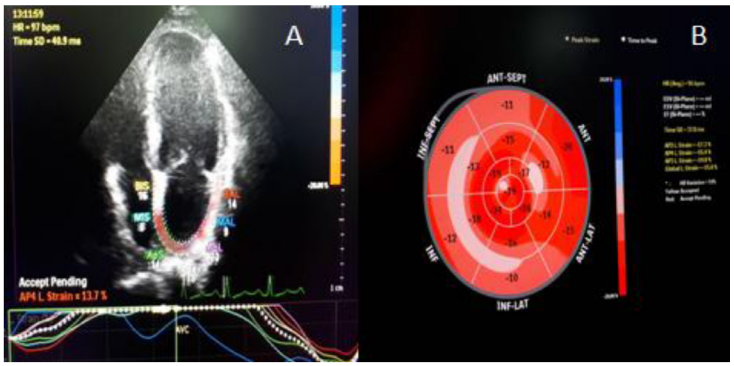

Figure 1: A 60 years old male developed AF 2 days postoperative. (A) LA strain = 13.7%, (B) LVGLS = -15.8%.

monitoring was performed in the intensive care unit. Daily ECG was performed until discharge from the hospital, and then it was performed on regular weekly visits during the first post-operative 30 days. 12 lead ECG was performed immediately if there was a clinical suspicion of cardiac arrhythmia (palpitation, dyspnea, or chest pain). In patients with new onset post-operative AF, amiodarone was used to regain sinus rhythm. In patients with persistent AF and controlled heart rate, warfarin was started before discharge. Hemodynamically unstable patients or with failure of antiarrhythmic therapy to control heart rate underwent cardioversion.

2.3. Echocardiography:

Echocardiographic examination was performed using Philips iE33 xMatrix – DS Ultrasound Machine with a multi frequency transducer equipped with DTI software and conducted to a single-lead ECG. All measurements were done from the standard views, according to the guidelines of the American Society of Echocardiography and were digitally stored for offline analysis.

LA dimensions were measured during end-ventricular systole. Antero-posterior diameter was measured in the parasternal long-axis view while, longitudinal and transverse diameters were measured in the apical 4-chamber view. Minimal LA volume (Vmin) was measured in end-diastole just before the mitral valve closure. Maximal LA volume (Vmax) was measured in end-systole just before the mitral valve opening. Atrial emptying fraction is the difference between maximum and minimum LA volume divided by the maximum LA volume [7].

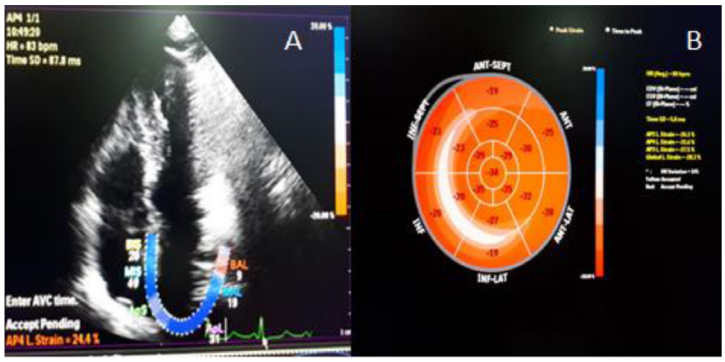

Figure 2: A 46 years old male remained in sinus rhythm. (A) LA strain = 24.4%, (B) LVGLS = -28.3%.

LV volumes and ejection fraction were measured from the apical 2- & 4-chamber views, by modified Simpson's method [8]. Color Doppler jet area was used to assess the severity of MR: severe MR (jet area of > 8 cm^2), moderate MR (4-8 cm^2) and mild MR (< 4 cm^2) [9]. Tissue Doppler mitral annular velocities "systolic (S), early diastolic (E'), and late diastolic (A')" were assessed in the apical views (apical four- and two-chamber views) [10].

LV global longitudinal strain was measured by 2D speckle tracking echocardiography in the apical 4-, 2-chamber and long axis views with frame rates ranging from 50 to 90 frames/second. The endocardial border was manually traced and the region of interest was adjusted manually to track the entire myocardium. Each left ventricular image was divided into six segments for analysis of segmental strain; global peak systolic longitudinal strain is the average of peak systolic values of the eighteen segments from the three apical views [11]. LA strain was also measured by 2D speckle tracking of the apical 4-chamber view. The ECG reference point was set at the onset of the QRS complex, and the region of interest was adjusted to the thickness of the LA wall [12] (figure 1 and 2).

2.4. Coronary angiography: All patients had preoperative coronary angiography. Significant coronary artery stenosis was defined by decreased luminal diameter by by ≥ 50% for left main coronary artery and 70% for the left anterior descending, circumflex, and right coronary arteries. Multivessel coronary artery disease was considered if there is significant stenosis in ≥ 2 vessels [13].

2.5. STS score: The risk of mortality and morbidity were calculated pre-operatively using STS score for coronary artery bypass graft [14]. Parameters for STS score included age, gender, body surface area,

Table 1: Baseline demographic & clinical data of the studied groups

Variable	Overall patients	POAF (n=22)	No POAF (n=78)	P value
Age (Mean ± SD)	56.9 ±7.8	65.3 ±5.3	54.5 ±6.7	<0.001
Gender:				
Male	68 (68%)	16 (72.72%)	52 (66.66%)	0.59
Female	32 (32%)	6 (27.27%)	26 (33.33%)	
Cardiac risk factors:				
Diabetes mellitus	56 (56%)	12 (54.54%)	44 (56.41%)	0.876
Hypertension	69 (69%)	17 (77.27%)	52 (66.66%)	0.342
Dyslipidemia	80 (80%)	17 (77.27%)	63 (80.76%)	0.717
Smoking	66 (66%)	11 (50%)	55 (70.51%)	0.613
Family history of CAD	23 (23%)	6 (27.27%)	17 (21.79%)	0.59
Patients' clinical data:				
Heart rate (bpm)	81.8 ±11.7	90.1 ±7.5	79.4 ±11.7	<0.001
Systolic blood pressure(mmHg)	115.4±14.4	115.7 ±13.7	115.3 ±14.7	0.895
Diastolic blood pressure(mmHg)	70.8 ±9.8	72.7 ±9.5	70.3 ±9.9	0.232
BMI (kg/m^2)	28.8 ±0.93	28.8 ±0.83	28.8 ±0.97	0.92
Patients' presentation:				
STEMI	23 (23%)	6 (27.27%)	17 (21.79)	0.925
NSTEMI	28 (28%)	7 (31.81%)	21 (26.92%)	0.452
Unstable angina	27 (27%)	3 (13.63%)	24 (30.76%)	0.11
Stable angina	22 (22%)	6 (27.27%)	16 (20.51%)	0.499
Medications:				
Beta-blockers	53 (53%)	9 (40.90%)	44 (56.41%)	0.198
ACE inhibitors	66 (66%)	14 (63.63%)	52 (66.66%)	0.791
Angiotensin receptor blockers	10 (10%)	4 (18.18%)	6 (7.69%)	0.148
Statins	100 (100%)	22 (100%)	78 (100%)	NA
Aspirin	100 (100%)	22 (100%)	78 (100%)	NA
Clopidogrel	100 (100%)	22 (100%)	78 (100%)	NA

CAD: coronary artery disease; BMI: body mass index; STEMI: ST elevation myocardial infarction; NSTEMI: non ST elevation myocardial infarction; ACE: angiotensin converting enzyme.

Table 2: Echocardiographic and angiographic parameters of the studied groups

Variable	Group I (n=22)	Group II (n=78)	P value
Echocardiography:			
LA antero-posterior diameter	4.9±0.3cm	4.43±0.2cm	< 0.001
LA longitudinal diameter	6.3±0.4cm	5.6±0.4cm	< 0.001
LA transverse diameter	4.6±0.2cm	4.4±0.2cm	< 0.001
LA maximal volume	102±5ml	96±7ml	< 0.001
LA minimal volume	63±7ml	58±9ml	< 0.001
LA emptying fraction	40±10%	43±11%	0.143
LVESV	38.57±14.11ml	28.4±1.12ml	0.063
LVEDV	75±20ml	72±13ml	0.563
LV EF	56±7%	60±6%	0.004
MR severity:			
No	10 (45.45%)	42 (53.84)	
Mild	6 (27.27%)	33 (42.3%)	0.437
Moderate	2 (9.09%)	6 (8.97%)	
TDI:			
S	0.07±0.08 m/s	0.08±0.02 m/s	0.609
E'	0.12±0.05m/s	0.12±0.03m/s	0.22
A'	0.7±0.2m/s	0.8±0.2	0.274
E/E' ratio	9.84±2.15	7.4±2.3	<0.001
LA strain	20.4±1.7%	22.1±1.9%	<0.001
LV GLS	-14±2.2 %	-18±3.2%	< 0.001
Number of diseased vessels:			
Single	1 (4.54%)	12 (15.38%)	0.072
2 vessel	12 (54.54%)	40 (51.28%)	0.071
Multi-vessel	9 (40.9%)	26 (33.33%)	0.09
Affected vessel:			
Left main	11 (50%)	18 (23.07%)	0.014
LAD	22 (100%)	78 (100%)	NA
LCX	15 (68.18%)	53 (67.94%)	0.983
RCA	15 (68.18%)	39 (50%)	0.131

LVESV: left ventricular end systolic volume; LVEDV: left ventricular end diastolic volume; LV GLS: left ventricular global longitudinal strain; LAD: left anterior descending; LCX: left circumflex; RCA: right coronary artery.

DM, HTN, smoking status, chronic lung disease, peripheral vascular disease, cerebrovascular disease, preoperative renal failure, preoperative creatinine level, CHF, prior revascularization procedure, MI timing (hours since MI), preoperative angina, LVEF, left main disease, urgency of operation (status), and preoperative use of an intraaortic balloon pump. The patients were limited to those without previous valve surgery, preoperative endocarditis, or a ventricular assist device.

2.6. Statistical analysis: Statistical analysis was performed using STATA/SE version 11.2 for Windows (STATA corporation, College Station, Texas). Numerical data were summarized in terms of mean± standard deviation (SD). Categorical data were summarized as numbers and percentages. Numerical data were compared using Student t-test (t), or Mann-Whitney test (z). Categorical data were compared using Chi-square test ($\chi 2$) and Fisher Exact test (FET) (as appropriate). Receiver operating characteristics (ROC) analysis was used to detect the diagnostic performance of LV and LA global longitudinal strain for POAF. The best cutoff value and its corresponding sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under the curve (AUC) were calculated. Stepwise logistic regression analysis was carried out to predict POAF and the results were presented as OR and 95% CI. Comparisons between the models based on the corresponding log likelihood (the smaller the better) and AUC (the greater the better). P-value <0.05 was considered significant, P value <0.001 was considered highly significant while a P value >0.05 was considered non-significant.

3. Results:

One hundred ten CAD patients scheduled for CABG were assessed. Four patients with aortic valve disease requiring aortic valve replacement and six patients with mitral valve disease requiring mitral valve replacement were excluded. Finally, 100 patients were included. Baseline clinical data are summarized in Table 1.

During the follow up period (1 month after surgery), 22 patients (22%) had new onset AF (group I) who were compared with the remaining 78 patients (78%) with sinus rhythm (group II). Group I had 8 patients (36.36%) with paroxysmal AF, 6 patients (27.27%) with persistent AF who regained sinus rhythm on pharmacological cardioversion (amiodaron infusion) and 8 patients (36.36%) required DC shock to regain sinus rhythm.

Patients of group I were significantly older (65.3 ± 5.3 vs. 54.5 ± 6.7, p =0.001) with significantly greater heart rate (90.1±7.5 vs. 79.4±11.7, P <0.001).

3.1. Conventional Echocardiographic parameters:

Group I had significantly increased LA diameters (antero-posterior, transverse and longitudinal) (4.9±0.3 vs. 4.43±0.2 cm, 4.6±0.2 vs. 4.4±0.2 cm and 6.3±0.4 vs. 5.6±0.4 cm, respectively; p <0.001) and LA volumes (maximal and minimal) (102±5 vs. 96±7 ml and 63 ±7 vs. 58±9 ml, respectively; p <0.001).

LVEF was significantly lower in group I (56±7 vs. 60±6%; p = 0.004). Data were comparable as regard LV end-systolic volume (38.57±14.11 vs. 28.4±1.12 ml; p =0.063), LV end diastolic volume (75±20 vs. 72±13ml; p =0.563) and the severity of mitral regurgitation (table 2). E /E` ratio was significantly higher in group I (9.84 ± 2.15 vs. 7.4±2.3; p <0.001). Data were comparable as regard S, E`, and A`.

3.2. Speckle tracking echocardiography: LA and LV global longitudinal strain (LVGLS %) were lower in group I (20.4 ± 1.7 vs. 22.1 ± 1.9 % and -14± 2.2 vs. -18 ± 3.2 %; p < 0.001).

3.3. Coronary angiography: Left main coronary artery involvement was more prevalent in patients of group I (11 patients "50%" vs.18 patients "23.07%", p =0.014). The data regarding the number of diseased vessels did not differ (table 2). The risk of mortality and morbidity, cardio-pulmonary bypass time, cross clamping time, ventilator time, ICU time, inotropic support (dopamine and adrenaline), type of cardioplegia (cold or warm), and post-operative complications were similar in both groups (table 3).

3.4. Predictors of POAF

Multivariate logistic regression analysis revealed that age (OR 0.005, 95% CI 0- 0.22, p =0.001), heart rate (OR 1.43, 95% CI 1.09- 1.89, p =0.009), LA strain (OR 1.111, 95% CI 1.003- 1.23, p <0.001), and LVGLS (OR 0.643, 95% CI 0.488- 0.846, p <0.001) were significant predictors of POAF.

ROC analysis showed that LA strain cut-off value ≤ 23.1 predicted AF post CABG with a sensitivity of 85% and specificity of 66% (AUC 0.761; 95% CI 0.648 - 0.873; p < 0.001). LVGLS cut-off value ≤ -14.4 can predict AF post CABG with a sensitivity of 70% and specificity of 85% (AUC 0.84; 95% CI 0.742 - 0.935; p < 0.001) (figure 3).

Table 3: Operative data and postoperative complications of the studied groups

Variable	Group I (n=22)	Group II (n=78)	P value
STS score:			
Risk of mortality	1.1±0.5%	1.5±0.14%	0.82
Risk of morbidity	13.8±6.36	17.1±6.8%	0.14
Cardio-pulmonary bypass time	127±14 min	130±9 min	0.054
Cross-clamping time	78±8 min	78±5 min	0.287
Ventilator time	8.3±2.1 hr	10.6±5.9 hr	0.079
ICU duration	36.95±15.07 hr	28.1±1.9 hr	0.518
Dopamine use	12 (54.54%)	49 (62.82%)	0.482
Adrenaline use	6 (27.27%)	38 (48.71%)	0.074
Cold cardioplegia	22 (100%)	71 (91.02%)	0.145
Warm cardioplegia	0 (0%)	7 (8.97%)	0.766
Postoperative complications:			
Graft failure	0 (0%)	2 (2.6%)	NA
Pericardial effusion	0 (0%)	2 (2.6%)	NA
Post-operative VT	0 (0%)	3 (3.84%)	NA
Post-operative MI	0 (0%)	6 (7.69%)	0.334
Number of diseased vessels:			
Single	1 (4.54%)	12 (15.38%)	0.072
2 vessel	12 (54.54%)	40 (51.28%)	0.071
Multi-vessel	9 (40.9%)	26 (33.33%)	0.09
Affected vessel:			
Left main	11 (50%)	18 (23.07%)	0.014
LAD	22 (100%)	78 (100%)	NA
LCX	15 (68.18%)	53 (67.94%)	0.983
RCA	15 (68.18%)	39 (50%)	0.131

VT: ventricular tachycardia; MI: myocardial infarction.

4. Discussion:

Our study aimed at determining the clinical and echocardiographic predictors of POAF in patients with CAD and scheduled for CABG as early detection and management of this group of patients may improve their outcome.

We found that 22% of patients developed AF. Folla et al., [15] also, reported a 19% prevalence of AF post CABG. POAF patients were older in age, which is consistent with Perrier et al., [16]. We did not find any significant statistical difference between the 2 groups regarding coronary risk factors and preoperative medications, a finding consistent with Parsaee et al., [17].

Left atrial size is a parameter that reflects structural changes in LA. However, LAVI is more accurate for assessment of LA size. LAVI is a predictor of AF in the general population and post cardiac surgery [18].

In the present study, POAF patients had increased LA diameters and volumes. Ozben et al., [19] reported that LAVI was an independent predictor of POAF and LAVI >36 ml/m^2 had 84.6% sensitivity and 68.6% specificity in predicting POAF.

In the current study, POAF patients had reduced left ventricular ejection fraction (LVEF %). However, the data were comparable regarding both left ventricular end diastolic and end-systolic volumes. This was similar to Ismail et al., [20] who reported lower left ventricular ejection fraction in patients with POAF.

Impaired atrial systolic dysfunction is usually associated with increased atrial pressure. This may induce electrical remodeling with increased tendency of developing POAF. E/e' is associated with LV filling pressures and increased E/e' ratio is associated with new onset AF [21]. In our study, POAF patients had significantly higher E/e', a finding consistent with Ozben et al., [19].

In the present study, LA global longitudinal strain assessed by 2D STE was significantly reduced in patients with POAF. Similarly, a systematic review of 6 papers by Bigdelu et al., [22] considered strain and strain rate as an independent predictors of POAF after CABG. Global peak atrial longitudinal strain reflects passive stretching of LA during LV systole and is an accurate measurement of LA reservoir function [23].

In the present study, LV global longitudinal strain was significantly decreased in POAF patients (p <0.001). This was similar to Mansour et al., [6] who found that LV global longitudinal strain was significantly reduced in POAF patients after mitral valve replacement. While, This is in contrast to Başaran et al., [24] who reported that the left ventricular global longitudinal strain value was not different between the 2 groups (p >0.005). This could be related to the different group of patients they evaluated who had preserved LV function (the mean LVEF= 62.5%) with spared subenocardial fiber function.

In the present study, left main coronary artery involvement was higher in patients with POAF, but there was no statistical difference regarding the number of diseased vessels. Ismail et al., [20] found no statistical difference between both groups regarding neither diseased vessels nor the number of grafts performed.

There was no significant statistical difference between the 2 groups regarding the risk of mortality and morbidity, cardio-pulmonary bypass time, cross clamping time, ventilator time, ICU time, inotropic support (dopamine and adrenaline), type of cardioplegia (cold or warm) or the post-operative complications. This was similar to Perrier et al., [16] who found no difference between both groups regarding the EuroSCORE. While, Parsaee et al., [17] reported longer cardio-pulmonary bypass time, hospital and ICU stays in patients with POAF as they evaluated patients with impaired preoperative LV systolic function (the mean LVEF = 42.63 ± 9.7%), while in our study, patients had better LV systolic function (the mean LVEF = 52 ± 9%).

In the present study, multivariate logistic regression of the preoperative clinical and echocardiographic data revealed that age and heart rate significantly predicted POAF (P =0.001). While, the echocardiographic parameters were LA longitudinal strain (P <0.001) and LVGLS% (P =0.001). The area under the curve (AUC) was 0.761 and 0.84, respectively.

These results were consistent with Verdejo et al., [11] who reported

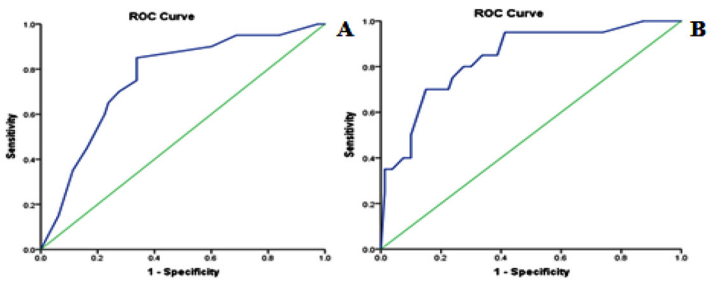

Figure 3: Roc curve of LA systolic strain (A) and LV global longitudinal strain (B).

Table 4: Logistic regression analysis including pre-operative clinical and echocardiographic data

Variable	OR	95% CI	P
Age	0.005	0.00 - 0.22	0.001
Heart rate	1.43	1.09 - 1.89	0.009
LVGLS	0.643	0.488 - 0.846	<0.001
LA strain	1.111	1.003 - 1.23	<0.001

LVGLS: left ventricular global longitudinal strain; LA: left atrial; CI: confidence interval; OR: odds ratio.

that age (OR 1.09, 95% CI, 1.01–1.16) and LASs (OR1.63, 95% CI, 1.19–2.22) were both independent predictors of POAF, suggesting that atrial function assessed by echocardiographic deformation may enhance the clinical profile for identifying patients at high risk for developing POAF.

ROC curve identified that LA strain ≤ 23.1 has diagnostic accuracy of 76% in detection of AF post CABG (sensitivity = 85% and specificity = 66%) with an AUC of 0.761 (95%CI "0.648 - 0.873 "). LVGLS ≤ -14.4 has an accuracy of 84% in detection of AF post CABG (sensitivity = 70% and specificity =85%) with an AUC of 0.84 (95%CI "0.742 - 0.935"). This is in agreement with Sabry et al., [6] who reported that LVGLS < -14.9 (sensitivity = 63.6%; specificity = 100.0%) and Tissue Doppler LA systolic strain < 23 (sensitivity = 90.91%; specificity = 93.33%) are the best cut off for the prediction of POAF after mitral valve replacement.

Conclusion:

POAF patients were older with greater heart rate. Multivariate regression analysis identified age, heart rate, lower LA, and LV global longitudinal strain as significant predictors of POAF. LA strain cut-off value of ≤ 23.1% and LVGLS ≤ -14.4 can predict new onset AF after CABG.

Limitations:

Firstly, the relatively small size of the patient population and it was a single center study. Secondly, AF was considered only when objectively documented but could be transient, and all episodes may not be detected. Additionally, our observations are limited to the first month after CABG; we could not draw conclusions regarding long-term outcomes. In addition, we included only patients with LVEF > 40%.

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Guest Editorial

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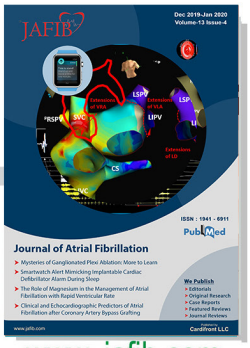

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Mysteries of Ganglionated Plexi Ablation: More to Learn

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Myocardial sleeves of the pulmonary veins (PVs) act as

Myocardial sleeves of the pulmonary veins (PVs) act as triggering foci for the great majority of patients with paroxysmal atrial fibrillation (AF)[1]. Although the exact mechanisms are not completely understood, studies have focused on electrophysiological properties of PVs and the adjacent left atrial myocardium. As a potential explanation, PV myocytes are more prone to autonomicnervous system (ANS) stimulation and associated shortening of action potential duration, early after depolarization formation and triggered firing compared to myocytes of the adjacent left atrium (LA)[2].

Autonomic control of the heart is regulated in a couple of feed back loops at different levels with a balance of sympathetic and parasympathetic signals between the heart and the central nervous systems [3]. While extrinsic part of ANS access the epicardial area as extensions of extracardiac nerves such as the left and right vagus nerves and both sympathetic trunks, the great majority of neurons of the intrinsic part of ANS reside inside epicardic ganglia that are interconnected by epicardial nerves on the human atria and ventricles [4, 5]. Based onhistologic studies, theseepicardiac ganglia are localized preferentially at certain epicardial sites adjacent to the left and right atriaand called as ganglionated plexi (GPs) [5]. Although earlier reports suggest that only the postsynaptic neuronal bodies of parasympathetic system exist in the ganglia, according to recently published reports, the nervous system in the mammalian heart contains populations of different neurons consisting of both efferent parasympathetic and sympathetic neurons, local circuit neurons/interneurons, and sensory neurons [6-9]. Although the density of sympathetic nerves was lowerthan that of parasympathetic ones in the cardiac tissue, the intracardiac nervous system of the heart possesses not only an extensive system of intrinsic parasympathetic postganglionic nerves but also a significant population of intracardiac ganglion cells possessing sympathetic activity. As an emerging technique, neuromodulation via ablation of GPs might be a potentially effective way at reducing afferent, efferent, or local circuit neuronal activity in epicardiac ganglia. Previous studies demonstrated that targeting the GPs endocardially with catheter ablation may alter cardiac autonomic activity and decrease the recurrence of atrial arrhythmias in patients with AF [11-14].

In this issue of the journal, Sohinki et al [15] present the results of GP ablation in addition to PV isolation in patients with AF and hypertension. The authors delivered high-frequency stimulation from endocardial locations corresponding to the epicardialLA GPs. Locations with a positive response (defined as > 3 seconds ofasystole noted on the arterial pressure waveform) were marked as GP on themap. A total 53 patients undergoing catheter ablation for AF were divided into 2 groups based on the LA size: normal LA size (n=16) and patients with LA enlargement (n=37).At the end of 12 months follow-up, systolic blood pressure (SBP) and number of used anti-hypertensive drugs were lowerin patients with normal LA size. While mean SBP did not change significantly in the LAenlargement group(increase of 3.72± 3.15 mmHg, CI-10.08 – 2.65 mmHg, p = 0.25), mean SBP decreased by 10.33 ± 5.1 mmHg, (CI 0.06 – 20.60 mmHg, p =0.04) in the normal LA size group. Authors concluded that in patients with AF and concomitant hypertension, normal LA size predictsimprovement in blood pressure control after PV isolation +GP ablation. We would like to congratulate Sohinki et al [15] for their contribution which allows a better understanding about additional effects of GP ablation in patients with AF. Previous studies proposed that ablation of GPs may decrease the parasympathetic control of the heart, and indirectly promote the sympathetic nerve sprouting. Considering the heterogeneous nature of GPs including both parasympathetic and sympathetic efferent neurons,similar and durable denervation on the sympathetic system as well as on the parasympathetic system might be possible after GP ablation.The concept of "cardiogenic" or "autonomically-mediated" hypertension which is driven by sympathetic tone was suggested by Dustan et al [16]. Thus, if sympathetic overactivity is playing a significant role in hypertension in a subset of patients, GP ablation would be expected to have a beneficial effect by modulating sympathetic output via GP ablation. As a supporting finding of this hypothesis, we found a significant and durable shortening of QTc after GP ablation

Key Words
Atrial Fibrillation, Catheter Ablation, Ganglionic Plexus, Autonomic Nervous System

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in patients with normal corrected QT interval range and long QT syndrome [17, 18]. Shortening of QTc was attributed to the additional sympatholytic effect of GP ablation. In a recently published study, Pachon et al [19] studied whether the amount of parasympathetic and sympathetic denervation persists after one- and two-year after GP ablation. Isolation of PVs in addition to GP ablation was performed in 70% of cases. A significant and durable decrease was not only seen in the high-frequency band demonstrating parasympathetic tone but also seen in the low-frequency as an indicator of sympathetic tone after GP ablation. In the current study, blood pressure lowering effect was significantly higher in patients with normal LA size. This may be due to the fact thatlarger left atrial diameter might imply more extensive structural disease which may change electrophysiological response to ablation.

Several questions remain about the GP detection modality in the present study: were the GP sites located at only certain left atrial regions?; why were right atrial sites not tested?; and what about the autonomic effects of used general anesthesia on the reliability of GP identification? The mean heart rates and heart rate variability results of patients after the procedure were not provided by the authors. It might have demonstrated how effective ablation was in terms of neuromodulation. As another important limitation, AF free survival was not provided and compared between groups in the present study. Finally, classical lesion set of PV isolationmight be expected to partially ablate some of epicardial GPs, the relative importanceof PV isolation itself vs. the addition of HFS-based GP ablation remains unclear from the current study.

It is not yet clear which is the best way to modulate intrinsic cardiac ANS and what are the long-term consequences of these therapies. Based on experimental evidence, there might be a paradoxical interaction between neuromodulation and AF [19]. In a group ofdogs, ablation on the major GP swere compared with sham control group. In the ablated group, although the acute studiesshowed a significant prolongation of effective refractory period and a significant decrease in AF inducibility in the intervention group,eight weeksafter ablation, the effective refractory period was significantly shorter and AF inducibility was significantly greater than the sham control group. Further more, immunohistochemical staining demonstrated a higher parasympathetic and sympatheticnerve density in the ablation group but not in the sham group. Hopefully, larger randomized studies in the future would answer some of these questions.

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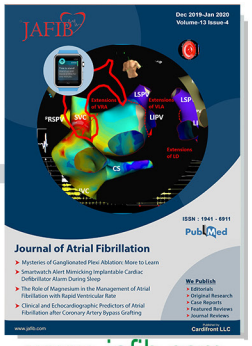

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Recurrent Takostsubo Cardiomyopathy During Cryoablation Procedure for Atrial Fibrillation: A Case Report

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Abstract

We report a case of 72-year-old female with prior history of takotsubo cardiomyopathy (TSC) who had recurrence of TSC during cryoablation of pulmonary veins for atrial fibrillation (AF) ablation. This case is unique because this is the first report of TSC detected during cryoablation and the procedure being stressor for recurrent TSC. We discuss possible mechanism of TSC and management of this case. Readers would have higher alertness of detecting TSC during AF ablation and therefore would be able to manage this serious condition properly.

Introduction

We present a case of a 72-year-old Caucasian female with a previous history of hypertension, coronary artery disease, resolved takotsubo cardiomyopathy (TSC) and symptomatic paroxysmal atrial fibrillation (AF), who underwent cryoablation of pulmonary veins (PV) for AF. She developed recurrent TSC following cryoablation of left inferior pulmonary vein. Intense vagal response to cryoablation was followed by epinephrine injection to restore circulation. Epinephrine injection or possible ganglionic plexus response could be implicated as trigger for TSC recurrence. This reports increases awareness of ganglionic plexus (GP) response and management considerations associated with cryoablation of pulmonary veins for AF.

Case Description:

A 72-year Caucasian female with history of stable coronary artery disease, right coronary artery stenting for abnormal stress test and preserved ejection fraction (EF) had episode ofcervical discitis in year 2011. She had fever and neck stiffness which resolved with antibiotic therapy. During this episode she had chest pain and electrocardiogram (EKG) showing anterior T wave inversions. Her left ventricular (LV) ejection fraction (EF) was 45% (previously 65%). The entire apex was severely hypokinetic to akinetic. She had coronary angiogram, which revealed mild diffuse stenosis of all three coronary vessels with patent stent in the right coronary artery. Apical wall motion extended beyond one coronary artery territory, a typical finding for TSC. Repeat echocardiogram after 5 weeks showed resolution of apical wall motion abnormality and normalization of EF confirming diagnosis of TSC.

Key Words

Atrial Fibrillation, Ablation, Takotsubo Cardiomyopathy, Cryoablation, Recurrent Takotsubo Cardiomyopathy

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In July 2012, she started noticing palpitations and dyspnea. An event monitor was placed, which revealed paroxysmal AF. She was started on warfarin, amiodarone and metoprolol. Amiodarone was later discontinued due to lethargy and intolerance. Event monitoring revealed frequent premature atrial contractions, premature ventricular contractions and brief nonsustained ventricular tachycardia (VT). In May 2018, she was put on dofetilide for rhythm control.

She continued to have increasing burden of symptomatic paroxysmal AF despite being on antiarrhythmic therapy. In October 2019, she underwent ablation for atrial fibrillation. Preproceduretransesophagealechocardiography showed normal LV function and absence of intracardiac thrombus. Patient underwentcryoablation (28 mm 2nd generation Arctic Front cryoballoon, Medtronic) of pulmonary veins to control AF. Procedure was performed under general anesthesia. She was in sinus rhythm at baseline.Patient had normal pulmonary venous anatomy. Firstly, left superior pulmonary vein was isolated then left inferior pulmonary vein (LIPV) was isolated. Baseline esophageal temperature (measured via single sensor, ES400-18) was 34.2 degree Celsius. During LIPV isolation, esophageal temperature declined to 30.1 degree Celsius. Lowest recorded cryoballoon temperature was -47 degree Celsius. After 63 seconds of application freezing was stopped due to drop in esophageal temperature. There was concern for close proximity of esophagus to left veins and successive/cumulative freezing effect on esophagus. During thawing period patients heart rate decreased to 40 beats per minute (sinus bradycardia) and systolic blood pressure dropped down to 29 mm Hg (baseline of 109 mm Hg). Due to profound and rapid hypotension anesthesiologist used intravenous

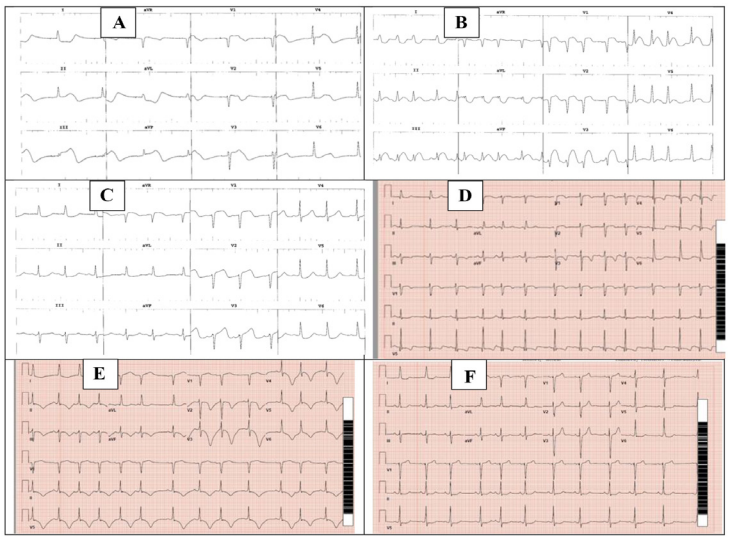

Figure 1A,B,C,D,E,F: Figure 1A- EKG showsprominent ST elevation in inferior and V1 to V3 as well as ST depression in I and aVL followed by biphasic T-wave changes in inferior leads and precordial leads.
Figure 1B- EKG show prominent tomblike ST elevation in inferior leads and V1-V4, ST depression in I, aVL. This EKG is 8 minutes after figure 1A EKG and 2 minute after nonsustained VT.
Figure 1C- EKG show significant resolution ST elevation in inferior and precordial leads (taken 10 minutes after figure 1A EKG).
Figure 1D- EKG done in post-procedure recovery area revealed only borderline ST depression in inferior and high lateral leads, T wave inversion in precordial leads.
Figure 1E- EKG (done 24 hours later) at this time showed classical generalized wide T wave inversions in precordial lead and QT prolongation associated with TSC.
Figure IF- EKG done at 4 months show resolution of ST-T changes.

epinephrine upto 200 mcg. Her heart rate increased to 120 bpm and systolic pressure transiently increased to 220 mm Hg before normalizing. EKG (prior to epinephrine injection) revealed prominent ST elevation in inferior and V1 to V3 as well as ST depression in I and aVL followed by biphasic T-wave changes in inferior leads and precordial leads (figure 1A). About 2 minutes after epinephrine, she had brief (<5 seconds) ventricular tachycardia (VT) which terminated by itself. EKG following VT termination showed more prominent (tombstone like) ST elevation in inferior and precordial leads (figure 1B). By 10 minutes ST segments show significant resolution (figure 1C). Subsequent ECG showed continued improvement ST segments with mild ST depression in inferior, lateral and high lateral leads with T wave inversion in precordial leads. Immediate transthoracic echocardiogram showed mild global hypokinesis with moderate hypokinesis of apex and no pericardial effusion.Left ventricular (LV) functionwas mildly reduced at 45%-50%. We continued with right sided pulmonary veinsablation, which was uneventful. Following ablation, bidirectional block was confirmed in all pulmonary veins.

Post procedure EKG was done which revealed only borderline ST depression in inferior and high lateral leads, T wave inversion in precordial leads (figure 1D). Patient denied chest pain, pressure or shortness of breath. Left heart catheterization was done within 24 hours revealed mild obstruction in the coronaries without any significant lesion and patent RCA stent. EKG at this time showed classical generalized wide T wave inversions in precordial lead and QT prolongation associated with TSC (figure 1E). Echocardiogram revealed LVEF of 55% with hypokinetic distal apex (Figure 2A-2D). These finding were consistent with recurrent TSC.

After the procedure, she stayed in sinus rhythmand her dofetilide was discontinued. She was continued on metoprolol, losartan, spironolactone and rivaroxaban. She had an echocardiogram 6 weeks after her cardiac ablation procedure which revealed an EF of 60% without any apical hypokinesis. Her ECG over next few days shows resolution of T wave inversion but continue to show biphasic T waves in precordial leads. T wave changes also resolved within 4 months (figure 1F).

Discussion:

This case report shows that TSC can recur with stress of cryoablation for AF. TSC is often precipitated by emotional or physical stress. Recent reports have shown that TSC can also be associated with ablation procedure for arrhythmia, however only two reports of TSC related to cryoablation of AF are available.[1, 2] One case reported on asymptomatic detection of EKG changes next day following pulmonary vein cryoablation for AF and cavotricuspid isthmus ablation. Second case describes TSC associated with pericardial tamponade and coronary artery injury. Our case is unique in multiple aspects. First, our report is the first care of recurrent TSC associated with cryoablation. Second, the detection of TSC followed immediately after pulmonary vein ablation and was not associated with coronary artery injury or tamponade. Third, this case report brings forth additionalside effect of cryoablation when compared to radiofrequency, which in general is considered more potent in tissue damage. We also demonstrated the dramatic ECG changes in earlier stages of TSC. More importantly, our report allows readers to develop higher alertness for detection and management of TSC which can cause serious morbidity including death.[3]

Cryoablation has been shown to preserve endothelial integrity and extracellular matrix.[4] Cryoablation has also been shown to decrease procedure timeand lower risk of moderate pulmonary vein stenosis compared to radiofrequency ablation.[5-7] Despite relative safety of cryoablation, our case reveals possible complication of TSC arising from pulmonary vein ablation.

As to mechanism of TSC, two possible contenders are epinephrine use and autonomic dysfunction from ganglionic plexus (GP). Both alone or in combination could cause TSC. We hypothesize that GP ablation during cryoapplication precipitated significant bradycardia and hypotension to cause relative myocardial ischemia. Rapid use of intravenous epinephrine could have caused additional direct myocardial stunning or microvascular dysfunction. Focal ballooning is attributed to effect of catecholamine surge on LV myocardial wall segments with varyingβ-receptordensities;however, this theory is not supported by reports of different recurrent ballooning patterns.[8] In our case, epinephrine use was followed by brief tachycardia, hypertension but its sole contribution to development of TSC remains suspect. Few reports of TSC associated with intravenous epinephrine are available.[9-11] However, in all reports, five times higher dose of epinephrine compared to our patient (1000 mcg vs 200 mcg) was used. Additionally, a recent in-depth analysis of literature has questioned the direct causal relationship of epinephrine and TSC.[12]

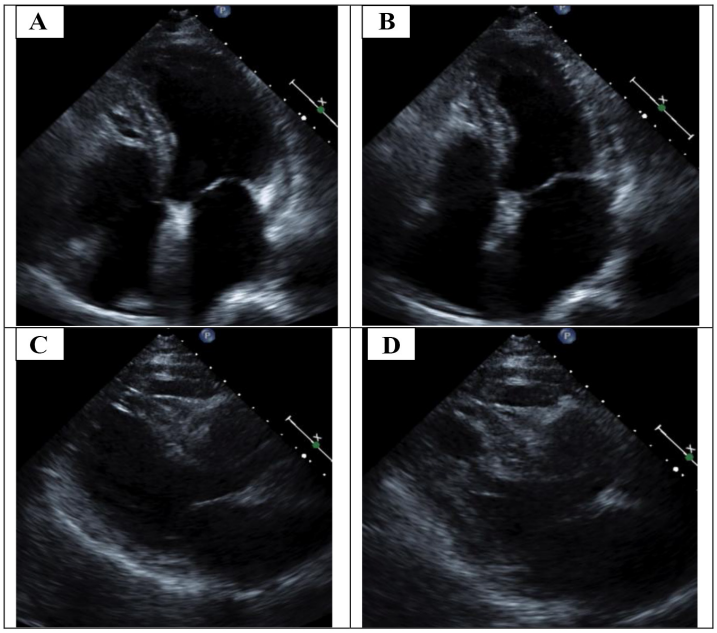

Figure 1A,B,C,D: Figure 2A- End diastolic frame of 4-chamber view
Figure 2B- End systolic frame of 4-chamber view shows relative hypokinesis of LV apex
Figure 2C- End diastolic frame of parasternal long axis view
Figure 2D- End diastolic frame of parasternal long axis view (shortened) show apical ballooning and basal segment's normal contractility

An interesting angle as to possible development of TSC is role of GP ablation. Autonomic nervous system plays a significant role in initiating AF and atrial autonomic remodeling. GP are located close to pulmonary veins promote AF by predominantly parasympathetic action.[13] Ablation of pulmonary veins via radiofrequency or cryoapplication can lead to at least partial GP ablation and therefore can have preventive effect on AF recurrence.[14] Additionally, GP ablation can result into parasympathetic withdrawal or vagal denervation and therefore enhanced adrenergic tone.[15,16] However, cryoablation seem to have no greater effect than radiofrequency in terms of GP ablation.[17] In our case, an intense hypotensive and bradycardic response was noted with LIPV cryoablation. If this response was followed by an intense sympathetic response from GP ablation which led to TSC, cannot be ascertained because patient also received a low dose intravenous epinephrine.

Other interesting fact of our case is recurrence of TSC. Recurrent TSC has been reported in upto 10% of cases with index TSC. Why some develop recurrent TSC while others develop possible immunity, is not well understood. Microcirculation dysfunction in addition to endothelial dysfunction is suspected to underlie the mechanism of recurrent TSC.[18] Of note, cryoablation lesions cause almost no disruption of endothelial surface despite having acute effect of local myocardial necrosis.[4]

Our patient was treated with beta-blocker and angiotensin converting enzyme inhibitor along with her LV dysfunction and CAD therapy. Although, most patients are treated with beta-blockers and ACE inhibitors due to coexisting myocardial dysfunction, no randomized data is available showing efficacy of above therapy in preventing recurrent TSC.[19]

Limitations:

This case report suggests but does not prove conclusively that GP ablation related to pulmonary vein cryoablation lead to recurrence of TSC. A significant bradycardia and hypotension temporally related to thawing of cryoballoon and EKG changes suggest that excessive autonomic effect could have precipitated TSC as has been suggested by two reports.[16, 20] Patient also received epinephrine to raise blood pressure and patient had brief self-terminating VT that could be a significant stressor for development of TSC. However, in this case relatively low dose (200 microgram) of epinephrine was used and VT lasted <5 seconds. It is possible that a relative low dose can result in significant myocardial tissue level and produce effects (BP and heart rate) as demonstrated in our patient. In our experience, use of vasopressor is very common in patients undergoing ablation under general anesthesia. Rare nature of TSC following ablation reduces likelihood of vasopressor as possible etiologic agent but does not exclude it. Transient ST elevation during ablation has also been attributed to possible parasympathetic nerve damage during transseptal puncture, air embolism or coronary artery spasm. In this case, ST changes happened at least 20 minutes after transseptal puncture. We use continuous intravenous flushing of sheaths and take due diligence in avoiding air embolism. Air embolism often affects right coronary artery and is associated with AV block. Generalized ST-T changes in ECG and absence of AV block reduces possibility of air embolism as an etiology. Coronary artery spasm is also unlikely because of posterior nature of left inferior pulmonary vein and absence of abnormal anatomy in this patient.

Conclusion:

This case report describes recurrence of TSC associated with pulmonary vein cryoablation for AF. Readers should also appreciate that recurrent TSC could be associated with serious morbidity including death. Therefore, recognition and management of recurrent TSC is warranted.

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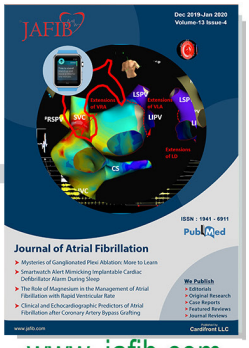

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Comparison of Fragmented Electrogram Based Strategy and High Frequency Stimulation for Detection of Ganglionated Plexi

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Abstract

Ganglionated plexus (GP) ablation is an emerging technique in patients with cardioinhibitory vasovagal syncope and vagally mediated atrial fibrillation. Localization of GPs can be impacted by the technique used. A reproduciblemethodology for GP detectionis needed to account for individual variations during electrophysiologic study.In this article, we aim to compare and contrast high-frequency stimulation vs. a fragmented electrogram guided strategy for GP localization.

Introduction

As the most common form of syncope, vasovagal syncope (VVS) is caused by intermittent impairment of cardiovascular reflexes eliciting sympathetic withdrawal-mediated hypotension and/or parasympathetic hyperactivity-based bradycardia.1Those who have recurrent VVS with a predominant cardioinhibitory response can benefit from cardiac pacing. However, alternative therapies that avoid pacing is desirable in this predominantly young population.[1,2] Similarly, the autonomicnervoussystem (ANS) plays an important role in both initiation and maintainance of atrial fibrillation (AF).[3] Structurally, the ANS of any visceral organ is represented by a complex neural plexus formed by extrinsic and intrinsic parts.[4] According to previous reports, large numbers of neurons of the intrinsic cardiac ANS are associated with ganglionated plexuses (GPs) in human atrial tissue.5In recent years, catheter based GP ablation has emerged as a promising therapy, when compared with pharmacological therapies, for VVS and vagallymediated AF.[6] Because the full extent of the distribution of GPs in the human heart remain insufficiently known, reasonable GP detection methods are needed to account individual variation during electrophysiologic study. Herein, we aimed to discuss potential role of 2 previously used GP localization techniques.

Key Words

Ablation, Bradycardia, Syncope, Atrial Fibrillation

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Case report

A 27-year-old female was referred for recurrent cardioinhibitory type vasovagal syncope and paroxysmal AF episodes. The frequency of syncope episodes was about three per month since the age of 16. The patient reported several AF episodes with vagal triggers such as sleeping and resting. One of those episodes was documented by 12-lead electrocardiography.

We decided to perform ganglionated plexus (GP) ablation. GP sites were detected by using our fractionated electrograms (FEG) based strategy and compared with high-frequency stimulation (HFS) data.[7,8] During HFS (continuous 2-5s at 10V, 20Hz), the sites showing positive vagal response (VR) and inducing AF were indicated with blue and orange dots in the 3D electroanatomic map, respectively (Figure 1).A positive VR was defined as transient ventricular asystole, atrioventricular block, orR-R interval increased by 50%. The response to HFS was reproducible at each site. During baseline electrophysiological study, AA interval was calculated as 976 msec (Figure 2A). Ablation points were selected based on our previously defined FEG based strategy. [4,9] According to FEG based strategy, bipolar electrograms demonstrating greater or equal to four deflections in both atria were tagged and ablated (Figure 2B).[4,9] Fragmented electrograms demonstrated a high consistency with HFS regardless of the response characteristics except on the posterior wall. All fragmented electrograms were ablated. After ablation of GPs, final AA interval decreased to 648 msec (Figure 2B). All positive vagal response sites using HFS were retested. No vagal response was seen with repeat HFSs. There was no further spontaneous AF which had occurred frequently prior to ablation during mapping.

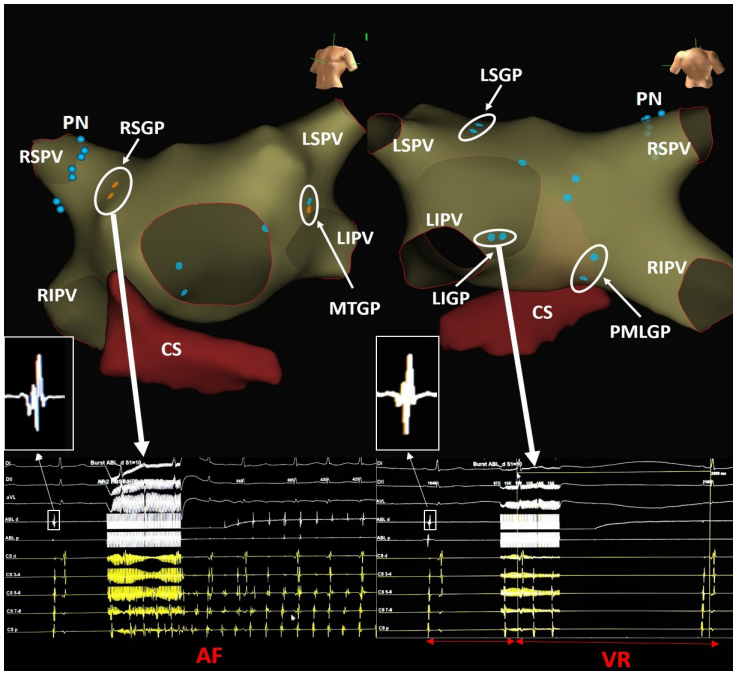

Figure 1: **The schematic view of ganglionated plexuses according to high-frequency stimulation-evoked response characteristics. According to Armour's anatomical definition (ref 4), following 5 major and 1 minor atrial location are consistently identified and called ganglionated plexuses(GPs)**

1) The superior right atrial GP (RSGP) located on the posterior superior surface of the right atrium adjacent to the junction of the superior vena cava (SVC) and right atrium; 2) the superior left atrial GP(LSGP)isidentified on the posteriorsurface of the left atrium between the pulmonary veins; 3) theposterior right atrial GPor the right inferior GP(RIGP)located on the posterior surface ofthe right atrium adjacent to the interatrial groove; 4) theposteromedial left atrial GP(PMLGP) settled on the posterior medial surface of the left atrium; and 5) theinteratrial septal GPconsists of fusion and extensions of theRIGPand theposteromedial left atrial GP (PMLGP).The posterolateral left atrial GP or the left inferior GP (LIGP) isa relatively small atrial GPwhich is identified on the posterior lateralsurface of the left atrial base on the atrial side of theatrioventricular groove. Except for these atrial GPs, theobtuse marginal GP or the Marshall tract GP(MTGP),which is a ventricular GP,located adjacent to the origin of the left obtusemarginal coronary artery. Panels in below demonstrate intracardiac electrograms during high frequency stimulation (HFS). While orange dots demonstrate GPs causing induction of atrial fibrillation (AF), blue dots reveal (+) vagal response sites during HFS. Blue spheres demonstrate the course of the phrenic nerve.

Considering clear vagal nature of AF and younger age of the patient, pulmonary vein isolation was not performed. All pulmonary veins remained electrically connected at the end of the procedure.

Follow-up 72-hour Holter recordings at months 1 and 6 showed no AF recurrence. No syncope was noted.

Discussion

As a definition, a ganglion is a cluster of neuron cell bodies in the peripheral nervous system.The distribution, size, and anatomic relationships of intrinsic cardiac ganglia were studied by Armour et al.[4] They proposed a terminology that identifies cardiac sites with the aim to locate these neural structures for functional studies. Following 5 major and 1 minor atrial locations were consistently identified and called GPs:1) The right superior GP located on the posterior superior surface of the right atrium adjacent to the junction of the superior vena cava and right atrium; 2) the left superior GP is identified on the supero-posterior surface of the left atrium; 3) the right posterior (inferior) GP located on the posterior surface of the right atrium adjacent to the interatrial groove; 4) the posteromedial left atrial GP ison the posterior medial surface of the left atrium; and 5) the interatrial septal GP consists of fusion and extensions of the right inferior GP and the posteromedial left atrial GP. A relatively small atrial GP that was identified on the posterior lateral surface of the left atrial base on the atrial side of the atrioventricular groove has been named the posterolateral left atrial GP (the left inferior GP). However, these ganglia may be very densely packed one over another, their sizes may vary extremely and range from those that are just observable with a microscope to those that are easily discernible with the naked eye.[10] In these ganglia areas, there is a close relation between the atrial myocytes and the cardiac innervation interface due to the incursion of the nervous fibres into the myocardium. This cellular blend causes an electrical heterogeneity resulting in a fragmented electrograms.

Theoretically, HFS application detects GP sites by checking existence of (+) VR which is defined as a significant prolongation of the PR or RR intervals. Thus, in the previous protocols, the places only demonstrating (+) VR during HFS were targeted.[3] However, induction of AF during HFS should also be accepted as a clue for GP because HFS induces AF by causing a shortening of action potential duration, an early afterdepolarization formation, and a triggered firing in the adjacent

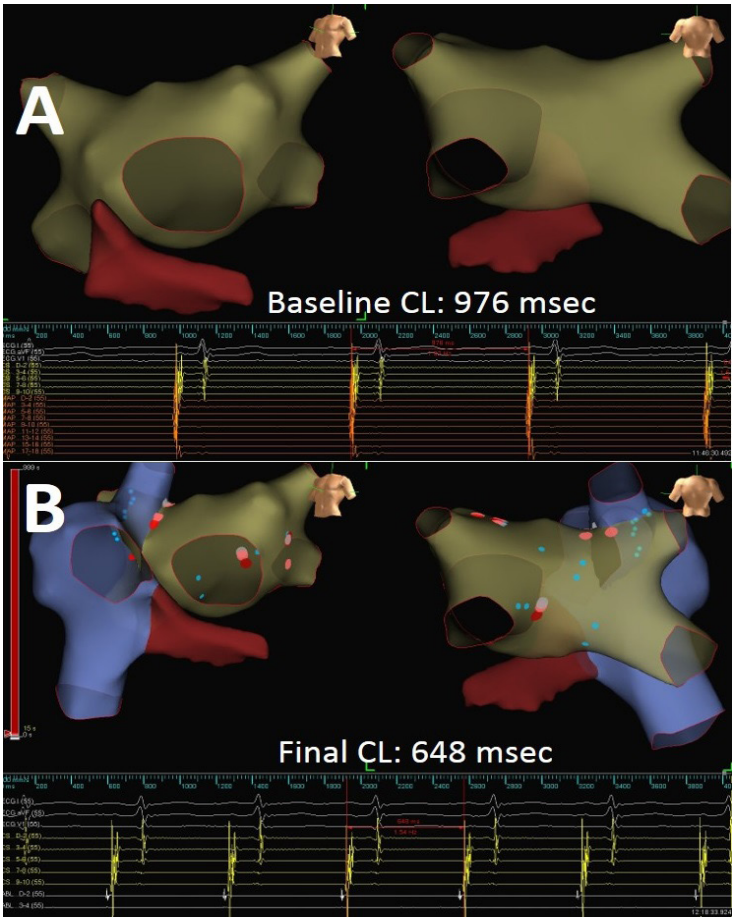

Figure 2: **A. Baseline cycle length of 976 msec is seen at the baseline situation before HFS application and ablation.B. Correlation between locationsof fractionated atrial electrograms andHFS-evoked response sites regardless of the response characteristics is seen except the posterior wall of the left atrium.Pink and red dots demonstrate ablation points based on fragmented electrogram characteristics. Blue dots demonstrate the phrenic nerve.**

CS, coronary sinus; LIPV, the left inferior pulmonary vein; LSPV, the left superior pulmonary vein; RIPV, the right inferior pulmonary vein; RSPV, the right superior pulmonary vein.

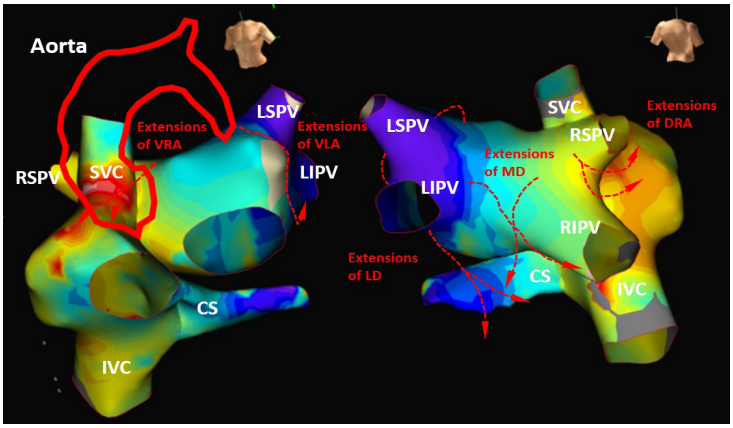

Figure 3: **The schematic view of distribution of ganglionated subplexuses According to Pauza's anatomical definition (ref 10), following 5 atrial location are consistently identified and called ganglionated subplexuses.**

1) The ventral right atrial ganglionated subplexus occupies the following regions: ventral superior right atrial region, ventral side of the root of the superior vena cava, and ventral inferior right atrial region. The postganglionated nerves of this ganglionated subplexus extended mostly into the ventral atrial regions and some of these nerves may innervate the sinoatrial node, as well as penetrate the lower part of the interatrial septum.
2) The ventral left atrial ganglionated subplexus occupies essentially the ventral superior left atrial region. Postganglionated nerves of this ganglionated subplexus may be observed to extend to the ventral inferior left atrial region, where they merged with the postganglionated nerves of the ventral right atrial ganglionated subplexus.
3) The left dorsal ganglionated subplexus distributes across the left coronary sulcus, region of dorsal left coronary sulcus, and middle left atrial region and contains abundant ganglia. The greatest portion of the postganglionated nerves of this ganglionated subplexus passes through the left dorsal coronary sulcus and spread onto the dorsal surface of the left ventricle.
4) The middle dorsal ganglionated subplexus occupies the dorsal superior left atrial region and around the crux cordis. While a part of the postganglionated nerves traverses the coronary sulcus and spreads onto the dorsal surface of both ventricles, part of the nerves passes superficially to the zone of the crux cordis along the coronary sulcus and approaches the postganglionated nerves of the dorsal right atrial ganglionated subplexus.
5) The dorsal right atrial ganglionated subplexus occupies mainly the dorsal superior right atrial region, dorsal side of the root of the superior vena cava, and region over the interatrial septum. The postganglionated nerves of this ganglionated subplexus spread widely into the dorsal and lateral right atrium, including the sinoatrial nodal region and superior surface of the right atrial appendage.

pulmonary vein.[3] This unique phenomenon might be an explanation for conflicting results of previous studies investigating potential role of GP ablation in addition to pulmonary vein isolationusing HFS-evoked VR to define location of GPs.[3]

Duration of HFS may affect the response type because each GP contains both parasympathetic and sympathetic neural fibers; stimulation of the former typically causes an immediate response (within 2–4 seconds), while stimulation of the latter may produce a delayed response (8–10 seconds).[11] Therefore, HFS should be applied at each site for only 2–5 seconds to avoid provoking a sympathetic response that may also induce AF due to sympathetic over-activity or mitigate the parasympathetic response.[9]

In the present case, fractionated potentials were used as primary ablation target. Lellouche et al 9 defined three different endocardial electrograms during sinus rhythm in the patients with paroxysmal AF: normal, low-amplitude fractionated electrograms, and high-amplitude fractionated electrograms. They found that the fractionated pattern was associated with a higher VR during ablation. Then, we retrospectively analyzed our radiofrequency ablation points for electrogram characteristics which were detected by using a combination ofspectral analysis and HFS.[12] All the electrograms on the ablation sites demonstrated either a high or low-amplitude fractionated pattern. Therefore, in our next work, we only targeted fractionated sites to detect GPs.[7] Compared with the previous combined approach strategy, this new FEG based strategy demonstrated shorter procedure and fluoroscopy times and achieved an identical success rate in preventing prodromal symptoms.

What was the cause of positive VR to HFS without fragmented potentials in posterior wall of the left atrium?

Although the terminology of Armour[4] is suggested to provide an overview of the distribution, and the sizes of intrinsic cardiac ganglia, the real number of these ganglia was identified a bit later by Pauza et al 13counting these ganglia on the whole heart preparations. It has been disclosed that the number of ganglia in the human heart varies from heart to heart and ranges from 706 up to 1,560. According to Pauza, staining of intrinsic cardiac neural plexus on the whole (non-sectioned) human heart demonstrated that the heart is under neuronal control through one intrinsic epicardiac neural plexus, nerves of which extend to distinct cardiac regions by five atrial and 2 ventricular pathways (routes) that were named as epicardiac sub plexuses.Since epicardial ganglia are persistently distributed along those subplexal nerves they were termed as ganglionated subplexuses. All five atrial ganglionated subplexuses are densely interconnected by nerves but their ganglionated areas (Figure 3). Despite use of different terminology, the superior and posterolateral left atrial GPs indicated by Armour et al 4 are properly ganglia from the same left dorsal subplexus, as well as that the posteromedial left atrial and posterior descending GPs in Armour et al 4 are only a part of the wide ganglionated field of the middle dorsal subplexus.

We believe that positive VR to HFS demonstrates not only ganglia cluster areas but also demontratesthe postganglionated neural fibers ofganglionated subplexuses. This is why we see (+) VR to HFS in some irrelevant left atrial sites. In contrary, fragmented electrograms may demonstrate cluster of neuron cell bodies. To understand this unique phenomenon, electrophysiologists should keep in mind routes of nerve fibers relatedganglionated subplexuses and potential location of GPs.

In younger patients without structural heart disease, a spectrum of vagal triggers such as VVS, after ingestion of a meal, at night, or during the recovery phase of exercise, can bring about a paroxysm of AF.[13] Further studies are needed to determine whether FEG based GP ablation without pulmonary vein isolation is enough to prevent vagally mediated AF episodes.

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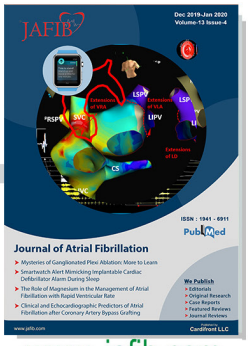

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Smartwatch Alert Mimicking Implantable Cardiac Defibrillator Alarm During Sleep

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Introduction

Consumers are now able to purchase mobile devices with built in arrhythmias alerts and other activities. Two devices (AliveCorKardiaBand and Apple Watch Series 4) are currently cleared by the FDA for single lead electrocardiographic detection of atrial fibrillation (AF) in those who do not have a history of diagnosed arrhythmia, based on feasibility studies shown over 99% specificity [1,2]. Therefore, it is likely these devices will lead to increased healthcare utilization due to both true-positive and false-positive diagnostic alerts. Here we present the case of atypical healthcare presentation due to over-monitoring with consumer devices.

Case report

A 71-year-old male with a history of anxiety and chronic lymphocytic leukemia (CLL) on ibrutinib was diagnosed with new onset AF and nonischemic cardiomyopathy. Given the complexity of his medical management and increased risk of bleeding due to underlying CLL with thrombocytopenia, AF management was challenging and led to significant stress and anxiety of the patient. Maintenance of sinus rhythm was unsuccessful owing to recurrent AF triggers in the setting of ongoing ibrutinib therapy, as well as baseline bradycardia, and a conservative rate-only control strategy was pursued. Despite goal directed medical therapy for heart failure, stress cardiac MRI revealed a persistently reduced ejection fraction of 30-35%, without evidence of ischemia or infarction. The patient expressed escalating fears about dying from his newly diagnosed cardiac disease rather than his hematologic malignancy. He underwent placement of a dual chamber implantable cardioverter defibrillator (ICD) for primary prevention of sudden cardiac death and to support antiarrhythmic drug therapy. He subsequently underwent dofetilide loading and cardioversion for rhythm control of AF. Due to significant stress and anxiety around his worsening medical condition, he purchased an Apple Watch to, "monitor his heart rhythm", despite the presence of continuous cardiac rhythm monitoring by ICD. One month after ICD placement, our patient awoke to recurrent vibratory sensations in the area of his ICD; an Abbott device capable of vibration alerts. He called the electrophysiology team the next morning, with great anxiety, to report his concern that this was a sign of ICD dysfunction or a low-battery alarm. Review of his remote ICD alerts did not reveal any sign of device malfunction or alarms; however, the vibratory alert feature was confirmed to be active. On further questioning, patient reports his recently-purchased Apple Watch (Apple, Inc., Cupertino, CA), has a variety of alert settings that were set to vibratory alert. On review of the watch alerts, he reported prior alerts at the time of vibratory sensation prompted by inactivity (Example demonstrated in Figure 1). In the left lateral decubitus position, these alerts were likely confused as originating from his ICD.

Key Words

Smartwatch, Arrhythmia, Surveillance, Atrial Fibrillation

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Discussion

AF and heart failure are associated with significant anxiety and stress [3, 4]. Post-traumatic stress disorder among patients with inappropriate ICD shocks has been well described [5]. As consumer grade devices capable of rhythm detection become more accessible, usage of these devices will become more widespread with varying levels of user technological literacy and health literacy. While these devices may provide reassurance to patients, our case highlights that they can also lead to additional distress and reduced health-related quality of life. Individuals may present with alerts/alarms that may be true positives consistent with new diagnoses of arrhythmias, or false positives requiring clinician assessment and reassurance. Both may be associated with increased stress and anxiety. Despite promising performance of AF detection by the Apple Watch Study, it remains unclear if clinical encounters triggered by consumer-wearables lead to improved outcomes. As this case demonstrates, more healthcare is not necessarily better healthcare. Consumer arrhythmia monitoring devices will inevitably lead to increased healthcare encounters, with unclear benefit. This case also highlights one harm noted in the Apple Watch Study, in that some patients that wear an Apple Watch with frequent feedback experience higher levels of anxiety. As appropriate, targeted deployment and implementation of these technologies remains to be determined.

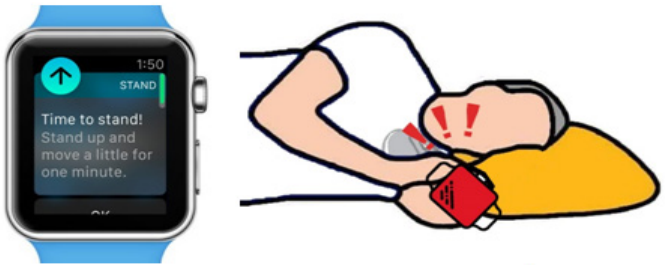

Figure 1: On the left: Apple watch time to stand notification6. On the right: diagram demonstrating patient's smartwatch alert in proximity to patient's ICD while sleeping in a left lateral decubitus position.

To our knowledge, this is the first case reported of a smartwatch alert erroneously mimicking as a pacemaker/ICD alert in a patient with an implanted device. We also recognize that increased vigilance due to the novel coronavirus infection may have contributed to our patient's excess caution in his self-care. No direct clinical adverse event resulted. The alert resulted in undue stress and anxiety by the patient, and required additional healthcare resources during a period of extreme resource scarcity.

Conclusion

Consumer grade wearable / mobile devices are becoming more prevalent in the cardiology patient population. Our patient, despite having remote monitoring capabilities and a continuously-recording ICD, felt compelled to also self-monitor with a consumer-based, wearable device. This may have been prompted by baseline anxiety, legitimate concern of his cardiac and hematologic comorbidities, and perceived benefit in a FDA-cleared wearable device with arrhythmia detection capabilities. Wearable external devices such as a smartwatch may mimic alarms originating from an implanted pacemaker or defibrillator, resulting in unnecessary healthcare encounters and furthering patient anxiety. While consumer-based, wearable arrhythmia monitoring technology has the potential to improve care while reducing healthcare resource utilization, careful deployment and management will be required.

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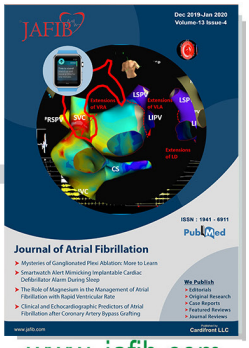

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Unexpected detection of Floating Thrombi in Left Atrium After Left Atrial Appendage Ligation With Atriclip Device: A Case Report

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Abstract

AtriClip device has demonstrated an excellent efficacy, long-term durability and safety of left atrium appendage (LAA) closure. We report, the unexpected postoperative transesophageal echocardiography (TEE) finding of thrombi in left atrium (LA)after deployment of an AtriClip in a 73-year-old man with chronic atrial fibrillation and 3-vessel-coronary artery disease undergoing coronary artery bypass grafting (CABG) surgery and LA appendage ligation. The heart was re-arrested and thrombi were retrieve successfully through a left atriotomy. This case emphasizes the unanticipated role of AtriClip in dislodging the thrombus from LAA, in addition to the importance of sufficient and well-founded imaging (Transesophageal Echocardiogram/Multidetector Computed Tomography) before and after the deployment of AtriClip device.

Introduction

The left atrial appendage (LAA) is the primary source of thromboembolic events in patients with non-valvular(90%) and valvular (60%) atrial fibrillation (AF)[1]. As the standard-of-care with oral anticoagulants (OAC) has limited applicability to selected patients, novel interventional and surgical approaches have emerged for LAA occlusion [2]. While LAA occlusion with percutaneous approaches fail to provide 100% solution due to inherent limitations[3], the use of AtriClip has shown near 100% occlusion rates in comparison to previous surgical techniques[4], in addition to excellent efficacyand safety[3,4]. To date, no randomized studies or societal guidelines have been published regarding AtriClip use in patients with AF undergoing cardiac surgery.

Herein, we present a case of thrombi in left atrium (LA) after deployment of AtriClipdevice on LAA in a patient undergoing coronary artery bypass grafting (CABG) surgery.

Case Description

A 73-year-old man with a history of hypertension, vascular claudication, chronic atrial fibrillation (AF) and 3-vessel-coronary artery disease, presented for coronary artery bypass graft (CABG) surgery and left atrium appendage (LAA) ligation using the AtriClip device. He was anticoagulated with Pradaxa(New Oral Anticoagulant (NOAC), 150mg twice daily) for nine years, which was discontinued four days before the surgery as per institutional guidelines. Unfortunately, on the scheduled day of CABG surgery, the procedure was postponed due to emergency operations. The patient was discharged to home on the same day without re-commencement of Pradaxa as the surgery was re-scheduled only four days later.

The procedure was performed via median sternotomy. Baseline cardiac rhythm was AF. A complete 2-dimensional (2D) intraoperative transesophageal echocardiogram (TEE)before cardiopulmonary bypass (CPB) demonstrated severely depressed left ventricle function (Ejection Fraction (EF) 30%) and dilation of both atriums and appendages. Mitral – and aortic valves were found to be normal, while the tricuspid valve was noted to have a mild insufficiency. The interrogation of LA and LAA showed no evidence of thrombus. The CPB was commenced after achieving an activated clotting time (ACT) > 480 seconds, which was maintained throughout the surgery.Before the cardioplegic arrest, the surgical manipulation of LAA was performed to size the appendage. Subsequently, an AtriClip device was deployed uneventfully across the base of the LA appendage, isolating it from the LA. The heart was then arrested to perform the CABG surgery. A post-procedural TEE unexpectedly revealed echo-dense object in the LA, suspected to be a thrombus (Figure 1).

A decision was made to re-arrest the heart and retrieve the suspected thrombus in the LA via the right atrium (RA) and through fossa ovalis. Four objects with the consistency of thrombus were removed from the LA with the largest one located free floating close to the right

Key Words

Atrial fibrillation, AtriClip, Cardiac surgery, TEE, LA/LAA thrombus

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pulmonary veins, while the other three were trapped in the clamp of the AtriClip and could easily be detached from the device (Figure 2).

All chambers in the heart were inspected meticulously with no further findings of thrombus. The incisions of fossa ovalis and RA were closed and the patient was weaned off from the CPB followed by de-heparinization. The follow-up TEE revealed no more thrombus in the LA. The patient had an uneventful postoperative course except anticipated AF for which digoxin and warfarin was commenced. Patient was discharged home after five days of surgery.

Discussion

Most updated guidelines from European Society of Cardiology (ESC - 2016) [5] and AHA/ACC/HRS (2019) [6] on AF management recommend surgical LAA occlusion/excision in patients undergoing open-heart surgery (Class IIb; Evidence Level B). Surgical methods of LAA exclusion such as running sutures, purse-string or external ligation, have failed to provide reproducible and durable LAA occlusion [7]. However, a few non-randomized studies have shown that the AtriClip has excellent efficacy for stroke prevention and long-term durability of LAA closure [3,4]. In addition, the device has been deemed as a safe procedure with some reporting no device-related complications post-procedural or in follow-up period [3], while others revealed minimal anticipated adverse events such as pericardial effusions with or without pericarditis, tachyarrhythmias and respiratory dysfunction mostly related to atelectasis after thoracoscopic application [4].

In our case, the AtriClip device may have broken an undetected thrombus free from the LAA after the manipulation of the LAA for sizing and subsequent deployment of the device, leading the thrombus to be broken down into multiple small fragments pushed into the LA. Thus, AtriClip application could have resulted in a serious and unanticipated complication, which, however, was avoided by timely discovery and rescue of the thrombi. Another possible way of thrombus dislodgement could be during positioning of the heart for CABG. However, in our case CABG was performed after the AtriClip placement suggesting that the force needed to break the thrombus free from the LAA, was already applied by the AtriClip. In addition, some of the thrombi were extracted from the clamped AtriClip during the thrombi evacuation from the LA. Thus, in our case AtriClip was most likely the source of dislodging the undetected thrombus, which also is in line with a previous study[8].

Two-dimensional (2D) TEE has been proved to be an accurate tool in identifying LA/LAA thrombus, thus consensually; it is used as a gold standard procedure for detection of thrombus[9]. However, three-dimensional (3D) TEE has shown to further improve differentiation of thrombi from pectinate muscle and other surrounding structures [9]. In our case, an experienced echocardiographer was not able to detect a thrombus in LA or LAA despite using multiplanar 2D TEE. Given the exceptional higher risk of thrombus development in our patient due to chronic AF and preoperative discontinuation of anticoagulation, 3D TEE may have assisted further in identifying the thrombus. Nevertheless, considering the challenging LAA morphology and in result complex anatomic features of thrombi, it can be difficult to detect them by TEE modalities [9]. Multidetector computed tomography (MDCT) provides more accurate assessment of LAA anatomy and thereby findings of thrombi [9]. In our high-risk patient, MDCT may also have been an ideal pre-procedural approach in visualizing the thrombus.

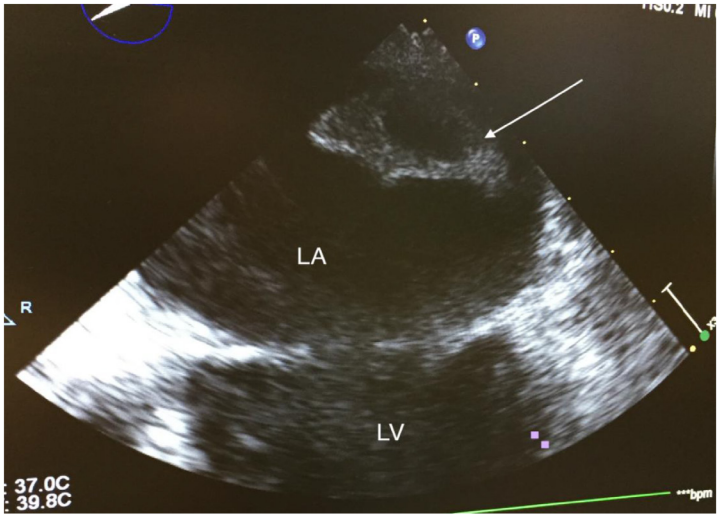

Figure 1: Two-dimensional transesophageal echocardiogram (TEE) after deployment of AtriClip, showing the largest thrombus in the left atrium (LA) indicated by the arrow.

LV; Left Ventricle

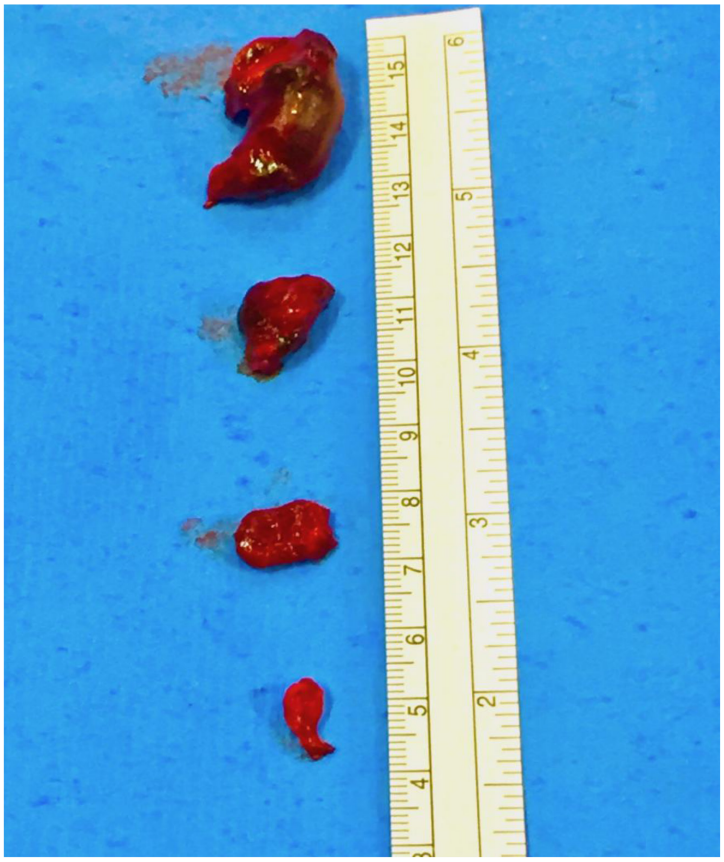

Figure 2: Evacuated thrombi with the largest thrombus found free floating in the left atrium (LA) close to the right pulmonary veins, while three smaller thrombi were seen trapped in the AtriClip.

Conclusions

AtriClip may aggravate thromboembolic event if LAA thrombus is undetected.Patients with high risk of thrombus formation should undergo an extensive pre-operative TEE examination, in some complicated cases perhaps MDCT, to confidently exclude a thrombus in LAA before AtriClip application. A post-AtriClip deployment TEE during the operation is a must in all patients.

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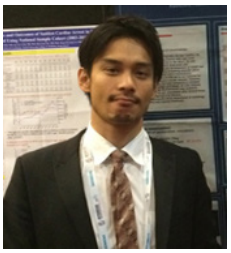

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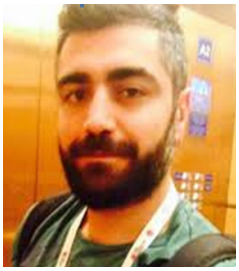

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