Atrial remodeling and subsequent atrial tachyarrhythmias

Summary of PhD Thesis

by

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Introduction

Treatment of atrial tachycardias has changed a lot in the last decade; catheter ablation has emerged as the curative therapy. In order to achive the better outcome, clinical arrhythmologists are paying more attention to the anatomy and function of the heart. Being familiar with atrial anatomy and structure is particularly important to treat patients with atrial tachycardias. Atrial fibrillation (AF) is the most common arrhythmia in clinical practice and associated with several important adverse clinical outcomes, including impairment of quility of life, embolic events and congestive heart failure. Pulmonary vein isolation (PVI) using radiofrequency catheter ablation (RFA) is an important and effective therapeutic option for AF. However despite several technical improvements and advances in the implementation of ablation, AF recurrences are common and significant number of p tients require repeated procedures. Despite the numerous available data in the literature, the association between the clinical and atrial diastolic parameters and recurrence after catheter ablation in atrial fibrillation is not fully described. Atrial flutter often

coexists with atrial fibrillation but probably the most common atrial arrhythmia in patients who undergo open heart surgery. Surgery procedures for acquired valvular and ischemic heart disease involves incisions applied to the right and/or left atrium either for establishing extracorporal circulation or creating an access to intracardiac structures. Together with structural and hemodynamic changes resulting from the underlying heart disease, these atriotomies create an ideal substrate for developing atrial tachycardias (AT) even months or years after surgery. AT mechanisms can be different depending on underlying heart disease and after different operations, specifically, different atrial incisions applied at the time of heart surgery.

Aims

1. We sought to evaluate atrial diastolic parameters including two-dimensional (2D), pulsed-wave Doppler (PWD) and tissue Doppler imaging (TDI) parameters, and the directly measured left atrial pressure (LAP) values for associations with AF recurrence after RFA in a large cohort of patients with persistent and longstanding persistent AF.

2. We shought to perform a long-term follow-up study of patients with AF recurrence after catheter ablation to determine whether the time to recurrence of AF affects AF characterisctics, response to therapy and clinical outcome.

3. We shought to have a deeper insight into the association between organic heart disease, atrial incisions and the mechanism of AT developing late after open heart surgery in a routinely encountered patient population with acquired or simple congenital heart disease.

Methods 1.

Study Population

A total of 125 patients were enrolled in the retrospective study. Clinical data were obtained from medical records.

Echocardiography

All patients underwent routine clinical transthoracic echocardiogram (TTE) examinations including M-mode, 2D, PWD, and TDI on the first postprocedural day following PVI. Left atrial diameter was obtained in the parasternal long axis view. Left atrial area (LAA) and left atrial length were measured in the apical 4-chamber (4C) view and apical 2-chamber (2C) view. LAV was derived using the biplane area-length method. Both LAA and LAV were measured at LV endsystole (LA maximum volume, LAV_{max}; LA maximum area, LAA_{max}) and at LV end-diastole (LA minimum volume, LAV_{min}; LA minimum area, LAA_{min}). LAV index (LAV_i) was calculated based on the body surface area. Mitral inflow measurements using PWD included peak early diastolic velocity (E) and deceleration time (DT) of early diastolic velocity. Pulmonary venous flows using PWD were

characterized by peak systolic velocity (PVS), peak diastolic velocity (PVD), and the ratio of PVS to PVD (PVSD). TDI obtained from the 4C view included early velocities from the septal and lateral mitral annulus (E_{septal} and $E_{lateral}$, respectively). The ratio of early diastolic transmitral flow velocity to annular motion velocity was calculated for both lateral and septal annular sites ($E/E_{lateral}$ and E/E_{septal}, respectively) and was also calculated for the average between the two sites ($E/E_{average}$).

The left atrial pressure was transduced through the transseptal needle during the procedure, immediately after the transseptal puncture.

Routine Follow-Up

All patients underwent a TTE on the first day after the procedure. Patients had 6-10 week and 6 month follow-up visits, and the majority of patients had 1 year follow-up from the date of the ablation procedure. Patients routinely underwent a 4-week transtelephonic monitoring immediately after ablation and at least once again at 3–12 months to assess for asymptomatic AF recurrence. At

each outpatient visit, patient symptoms were assessed and a 12-lead electrocardiogram (ECG) was recorded. Beyond the 1-year period, the patients were followed from our center.

Methods 2.

Study population

We identified patients who underwent first catheter ablation for AF between 2004 and 2008, had recurrent AF after procerudure and had a minimum of 18-month follow-up after recurrence. Patients were divided into an early (E) recurrence group, with recurrences occurring 3–6 months of ablation, a late (L) group, with recurrences occurring between 6 and 12 months, and a very late (VL) group, with recurrences occurring> 1 year after ablation.

Ablation strategy and routine follow-up

PVI and routine follow-up was performed as previously described.

Methods 3.

Study population

One hundred consecutive patients undergoing electrophysiology study for documented AT at least 3 months after open heart surgery for acquired or simple congenital heart disease were enrolled.

Surgical technique

Surgical procedures were grouped according to the incisions applied to the atria. In some cases, only a right atrial (RA) incision was placed: either for venous cannulation for cardiopulmonary bypass via a small incision on the RA appendage or a long incision on the RA free wall for the placement and fixation of a cardioplegic cannula inside the coronary sinus (open technique for retrograde cardioplegia) or to perform surgery at the right side of the heart. Venous cannulas for cardiopulmonary bypass in the latter cases were placed through incisions on the superior caval vein and the inferior vena cava-RA junction. In some patients, both RA and left atrial (LA) incisions were placed: The RA free wall atriotomy was prolonged superiorly and onto

the interatrial septum to access the left atrium (transseptal LA atriotomy). The remaining patients had only LA operation using direct LA atriotomy.

Electrophysiology study

The mechanism of atrial arrhythmia had been identified during electrophysiology (EP) study in accordance with standardised methods after tachycardia induction or during ongoing tachycardia. Conventional activation mapping and/or electroanatomical mapping had been used. Patients were classified into having focal or macro-reentrant arrhythmias based on the results of the EP study.

Results 1.

Procedural Outcomes

A total of 125 patients were included in the study. At the end of the follow-up period, 83 patients remained in SR (66.4%) and 42 (33.6%) had AF recurrence.

Baseline Clinical Characteristics

The patients' mean age was 61.3 ± 8.9 years (range 36–78 years), 81% of them were men. Seventy-seven percent of patients had persistent AF, whereas 23% had longstanding persistent AF. All patients had preserved LVEF (>50%).

Clinical Parameters Associated with Recurrence

Patients with AF recurrences were more likely to have longer duration of AF prior to RFA (9.0 ± 9.4 months vs. 19.3 ± 30.6 months, P = 0.02). According to the logistic regression analysis, the duration of AF prior to RFA (P = 0.04, odds ratio [OR]: 1.03, 95% confidence interval [CI] 1.0–1.1) was statistically significant for AF recurrence.

Echocardiographic and Atrial Pressure Parameters

All the LA size measurement at the 4C view, including both maximum and minimum lengths, area, and volume measurements, were significantly correlated with outcome. None of the TDI parameters or direct measured LAP was significantly different. Among the 2D parameters, LAV_{imin} of $26cm^3/m^2$ (P=0.033, OR: 2.5,

95% CI 1.08–5.9) and LAV_{imax} of 42 cm^3/m^2 (P = 0.015, OR 2.7, 95% CI 1.2–5.95) were the best single parameters of AF recurrence after PVI. When entered into multiple logistic regression analysis, LAV_{imin} of 26 cm^3/m^2 (P = 0.009, OR: 4.9, 95% CI 1.5–16.2) and duration of AF prior to RFA (P = 0.05, OR: 1.03, 95% CI 0.99–1.07) were the independent parameters for AF recurrence.

Results 2.

Patient characteristics

Four hundred and thirty nine consecutive patients with AF recurrence were included in the study. The first recurrence after catheter ablation occurred early (E group) in 245 patients, late (L group) in 118 patients, and very late (VL group) in 76 patients. Patient characteristics among the 3 groups categorized according to the time of recurrence after AF ablation were similar in terms of age, type of AF, prevalence of risk factors, and the presence of structural heart disease.

Recurrences during the 3-month blanking period

During the blanking period, 306 study patients (70%) had arrhythmia episodes. Patients with early recurrences were more likely to have had AF during the blanking period compared with patients with late and very late recurrences (201 patients [82%] in the E group vs 64 patients [54%] in the L group and 41 [54%] in the VL group; P< 0.001 for comparison across groups). DCCV was performed during the blanking period in 79 patients (39%) in the E group, 28 patients (40%) in the L group, and 22 patients (54%) in the VL group (P = 0.2).

AF recurrences after the blanking period

At the time of recurrence after the blanking period, 144 (59%) patients in the E group were on an anti-arrhythmic drug (AAD) in comparison to 37 (31%) patients in the L group and 5 (7%) patients in the VL group (P< 0.001). A total of 159 patients underwent at least 1 DCCV (81 patients [33%] in the E group, 45 patients [38%] in the L group, and 33 patients [43%] in the VL group; P = 0.2). The presence of only subsequent rare AF recurrences was significantly higher in L and VL groups than in the E

group. Only 23 of 245 [9%] patients in the E group had no or rare AF in comparison to 50 (47%) patients in the L group and 52 patients (68%) in the VL group *(*P< 0.001 for comparison across groups and for comparison between L and VL groups). In multivariate analysis, the strongest independent predictors of rare AF after the initial AF recurrence were late and very late time of recurrence after the procedure.

Efficacy of antiarrhythmic drug therapy after recurrence

Patients in the VL group were more likely to respond to AADs than patients with early and late recurrences (23 patients [72%] showed positive response in the VL group vs. 21 patients [19%] in the E group and 38 patients [58%] in the L group; P <0.001). In a multivariate model, baseline paroxysmal AF, the time to AF recurrence after ablation, and rare AF prior to initiating or changing AADs were independent predictors of a positive response to AAD therapy after the initial recurrence.

Repeat ablation and outcome

In this study cohort, 290 patients underwent repeat ablation (185 of 245 [75%] in the E group, 70 of 118 [59%] in the L group, and 35 of 76 [46%] in the VL group; $P< 0.001$) Patients in the VL group had the highest rate of AF control after repeat ablation (24 of 27 [89%] vs 38 of 54 [72%] in the L group and 78 of 160 [49%] in the E group; $P< 0.001$). In multivariate analysis, the type of AF, LA size, the duration of AF history prior to ablation, and the time to recurrence after ablation independently predicted AF control after repeat ablation.

Outcome of patients without repeat AF ablation

In multivariate analysis, the time to recurrence after ablation was the only independent predictor of no or rare arrhythmia episodes and patients in L and VL groups had more favorable outcome than did patients in the E recurrence group.

Results 3.

Mechanism of postoperative atrial tachycardias

One hundred patients had 151 atrial tachycardias (ATs) during 127 procedures— 88 (58%) cavotricuspid isthmus (CTI) dependent flutters, 34 (22.5%) RA incisional tachycardias, 12 (8%) perimitral flutters, 4 (3%) LA roof dependent flutters, 1 (0.7%) upper loop reentry and 11 (7%) focal ATs.

Distribution of atrial tachycardias between surgical groups

Of the 20 patients with RA appendage cannulation, 19 (95%) had CTI-dependent flutter, three (15%) had a non-CTI-dependent AFL, and none had focal AT. All non-CTI dependent AFLs in this group were RA incisional tachycardias related to the cannulation site of the RA. In patients with RA free wall atriotomy, a CTI-dependent AFL was seen in 30 of 32 (94%) patients, a non-CTI dependent AFL in 13 (41%) and focal AT in four (13%). Eleven of the 13 (85%) non-CTI dependent AFLs were RA incisional tachycardias related to the right atriotomy; there was one (8%) perimitral AFL and one upper loop

reentry in this group. Among patients with transseptal LA atriotomy the frequency of CTI-dependent flutter was 83% (34 of 41 patients), while at least one non-CTI-dependent AFL was seen in 30 patients (73%). One patient (2%) had two non-CTI-dependent circuits. Focal AT occurred in six (15%) patients. The most frequently encountered non-CTI dependent AFL was again RA incisional tachycardia— 20 of 31 circuits (65%), while seven (23%) perimitral and three (10%) LA roof-dependent AFLs were mapped in this group. Five of seven (71%) patients had CTI-dependent AFL in the direct LA atriotomy group and four patients (57%) had non-CTI-dependent AFLs. One patient (14%) had two non-CTI dependent circuits and one had focal AT. Perimitral was the most common non-CTI-dependent AFL— 4 of 5 (80%) circuits, while one (20%) LA roof-dependent AFL was diagnosed in this group.

Comparison of AT mechanisms between surgical groups

The frequency of CTI-dependent AFL was not different between groups (P = 0.195). A non-CTI-dependent AFL, on the other hand, was seen progressively more

frequently with more extensive atrial incisions (P <0.001)—15% of patients who had simple venous cannula insertion, 41% and 57% after RA and LA atriotomy, respectively, and 73% of patients after biatrial access (transseptal left atriotomy). After operations involving the RA, the most common non-CTI dependent circuit was that of a RA incisional tachycardia, seen more commonly in patients who had RA atriotomy as opposed to those who had only RA appendage cannulation (43% vs. 15%, P = 0.024). Perimitral AFL was seen more frequently in cases where the LA was opened compared with operations involving only the RA—22% versus 2%, respectively (P = 0.002), and the same was true for LA roof-dependent AFL (8% vs. 0% P =0.041).

Multivariate analysis

With non-CTI-dependent AFL, surgical group and larger LA diameter showed significant correlation, but only surgical group proved to be an independent predictor in multivariate analysis (P <0.001). With multivariate analysis surgical group and end-systolic diameter remained independent predictors of perimitral AFL

(P=0.019 and P=0.036, respectively). Left atrial atriotomy was the only predictor for LA roof-dependent AFL (P =0.041).

New observations

1. Our results draw the attention to the association of the longer duration of AF, larger indexed LAV and AF recurrence following PVI. These parameters and should be incorporated into the recurrence stratification in patients with persistent and longstanding persistent AF.
2. In patients with AF recurrence after catheter ablation, the time to recurrence is a significant predictor of subsequent clinical outcome. Patients with later recurrences are more likely to have sporadic AF episodes, can be better managed with AADs, and have better results after repeat ablation.
3. For the electrophysiologists treating operated patients with AT, it is very important to review surgical records and clarify the specific atriotomy used. The various surgical incisions result relatively well defined late formation of arrhythmias, which might influence the future design of the ablation procedure.

Publications related to the subject of the thesis

1. **Kohári M.,** Zado E.S., Marchlinski F.E., Callans D.J., Han Y., Left Atrial Volume Best Predicts Recurrence after Catheter Ablation in Patients with Persistent and Longstanding Persistent Atrial Fibrillation, PACE 2014; 37:422–429

2. Gaztanãga L., Frankel D.S.,**Kohari M.,** Kondapalli L.,Zado E.S.,Marchlinski F.E., Time to recurrence of atrial fibrillation influences outcome following catheter ablation, Heart Rhythm 2013;10:2–9

3. Pap R., **Kohári M.,** Makai A., Bencsik G., Traykov B.V., Gallardo R., Klausz G., Kis Zs., Forster T., Sághy L. Surgical technique and the mechanism of atrial tachycardia late after open heart surgery, J Interv Card Electrophysiol, 2012