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Predictors of complete arrhythmia free survival in patients undergoing surgical ablation for atrial fibrillation. PRAGUE-12 randomized study sub-analysis ☆

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ABSTRACT

Background: Surgical ablation (SA) is commonly used in atrial fibrillation (AF) patients undergoing cardiac surgery. However, its effect has been established in few randomized studies. To assess the complete atrial fibrillation free (AF-free) survival in randomized study assessing the effects of additional concomitant SA of AF in patients primarily indicated for other cardiac surgery.
Methods: The PRAGUE-12 study was a prospective randomized study comparing the effect of adding SA to other cardiac surgery. We examined the data from the PRAGUE-12 trial and grouped patients according to complete AF-free survival. All patients had regular check-ups at 3, 6, 9 months, some of them with Holter recordings, and a final check-up at 12 months with Holter recording.
Results: One hundred ninety-four patients were analyzed; 104 originally randomized to surgery with adding SA (SA group) and 90 without it (non-SA group). Complete AF-free status was found in 46 patients from the SA group (44.2%) and 25 patients (27.8%) from the non-SA group ($p < 0.05$). In a multivariate logistic regression, the SA group was associated with a greater chance for complete AF-free survival (OR 1.87, $p < 0.05$). In the multivariate analysis of the SA group, history of myocardial infarction (OR 0.2, $p < 0.05$) and a higher EuroSCORE (OR 0.9, p 0.05) were independently associated with a lower probability of AF-free survival.
Conclusion: Complete AF-free survival following SA was present in almost one half of patients. Patients with a history of myocardial infarction and higher EuroSCOREs were less likely to benefit from an add-on SA procedure.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia affecting 1–2% of the general population [1]. Its incidence has been trending higher, and estimates suggest a rate of about 28 per 1000 person-years in the United States [2]. AF is associated with increased morbidity and mortality, its prevalence increases with age and with the presence of significant valve or ischemic heart disease [3].

The surgical procedure for the treatment of AF was introduced by James L. Cox [4] and for more than two decades, the Cox–Maze III procedure represented the standard for AF treatment.

In recent years, patients undergoing cardiac surgery and suffering from AF are more and more frequently indicated for some type of concomitant surgical ablation procedure, with variable lesion sets and energies. There has been an increased use of concomitant surgical ablation, and in some centers the use of ablation has become a standard concomitant procedure for almost all cardiac surgery candidates with a simultaneous history of AF; despite this increase use and acceptance, there have been very few randomized trials on this topic.

To the best of our knowledge, one of the largest or even the largest, multicenter randomized trial on this topic, the PRAGUE-12 study, was recently published [5]. This study compared, using a randomized design, the addition of SA in a non-selected cohort of patients indicated for common cardiac surgery procedures (coronary bypass surgery, mitral or aortic valve surgery). The end-point in the original PRAGUE-12 study was the absence of atrial fibrillation, based on 24-h Holter monitoring, one year after surgery. In a recent sub-analysis, we tried to assess the "complete arrhythmia free survival" of the PRAGUE -12 cohort during the entire study period, relative to concomitant SA and other important variables.

2. Methods

2.1. Patient population

In the present study, we analyzed the patients included in the recently published PRAGUE-12 study [5]. The PRAGUE-12 trial was a prospective, open, randomized, multicenter, clinical trial assessing the outcome of cardiac surgery with left atrial ablation vs. cardiac surgery alone (without ablation) in patients with coronary and/or valve disease and AF [6]. The primary hypothesis was that surgical ablation of the left atrium (LA)

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would result in a higher incidence of sinus rhythm (SR) in the treated group 1 year after surgery. The primary efficacy endpoint was the presence of SR (without any AF episodes) during a 24-h electrocardiogram (ECG) 1 year post-op. Currently, the 5-year extension of the study is being planned; the extension was a part of the original protocol [6].

The trial was approved by the Institutional Ethics Committee of each participating center and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. Consecutive patients older than 18 years, who were indicated for cardiac surgery (CABG, valve replacement or repair, others, or combinations) and with a history of AF (paroxysmal, persistent, or long-standing persistent; documented at least twice in the 6 months prior to surgery) were enrolled in the study. The only exclusion criterion was emergency surgery. Randomization was done using the envelope method: after informed consent was obtained, an envelope containing either "SA" or "non-SA" was opened [6]. The number of envelopes corresponded to the estimated number of patients which was based on study recruitment. Patient pre-operative, intra-operative, and early post-operative data were prospectively recorded. After discharge from the cardiac unit, all follow-up data were prospectively recorded in anti-arrhythmic units of participating cardiology departments.

2.2. Surgical strategy and medication

For details of the SA protocol, see the original publication [5]. Except for anticoagulation and antiplatelet therapy, which was either discontinued 5 days prior to surgery or switched to heparin, all other patient medication was continued until the day of surgery. Post-operative care was identical for both groups. Unless contraindicated, all patients received anti-arrhythmic drugs (AADs) post-operatively, starting on the day of surgery; amiodarone was the first choice, with propafenone or sotalol as second choices. All patients were put on warfarin with a target international normalized ratio of 2–2.5. Other medication, including beta-blockers, was adjusted routinely, according to the patient comorbidities. It was recommended that AADs be discontinued 3 months after surgery if the patient appeared to be AF-free. Unless otherwise contraindicated, it was recommended that warfarin can be discontinued 6 months after surgery (i.e. 3 months after discontinuation of AADs) if patients remained in stable sinus rhythm (SR). Direct current cardioversion was strongly recommended if AF was present at the 30-day follow-up. The actual treatment strategy was left to the discretion of the treating cardiologists (and was based mainly on patient risk assessed by $CHADS_2$ scores and other characteristics).

2.3. Follow-up

Post-operative follow-ups were performed at 3, 6, and 9 months and 1 year after surgery. All of the follow-ups were performed at the participating cardiology centers. The first three follow-ups included a clinical examination (with detailed patient history) and an ECG; the 1-year follow-up also included a 24-h Holter-ECG and ECHO. Additional ECG Holter recordings were approved by participating cardiologists as needed (e.g. for verification of arrhythmia if some symptoms occurred, or verification of the absence of AF in patients in SR, in whom the discontinuation of p.o. anticoagulation was planned). Patients were asked to bring complete documentation from their cardiologists to each of the scheduled study follow-up visits. At each follow-up, data regarding current medications, recent complications, or hospitalizations were recorded.

2.4. Data analysis

For the present analysis, the primary endpoint was arrhythmia-free survival (e.g. the complete absence of AF or other atrial arrhythmias during the entire study period (excluding the first three months post-surgery), not only during the one scheduled 24-h Holter monitoring at the one year follow-up. AF-free patients were considered patients who had had SR on all visits, had no documentation from another physician indicating AF and, were symptoms-free with SR at the one year Holter monitoring. If a single episode of AF occurred after the blanking period of the first three months, the patient was assessed as "treatment failure"(non AF-free).

The first three months after surgery were considered to be a blanking period, and if AF occurred during this period, it was not evaluate. Patients who died during the first three months from any reason and those for who a rhythm could not be evaluated after the 3-month blanking period were excluded from analysis.

2.5. Statistical analysis

Continuous data are presented as means plus SD for normally distributed variables or as medians with percentiles for log-normally distributed variables. Normality was tested using the Shapiro–Wilk test. Categorical data are given as absolute and relative frequencies (percentages). Comparison of groups was based on Student's two-sample *t*-test and the Mann–Whitney test. The differences in proportions between groups were analyzed using Fisher's exact test and its generalization.

The multivariate analysis used a stepwise backward logistic regression model. Initially, a univariate logistic regression analysis was performed using various clinical and other potentially important variables. Clinical variables used in the model were age, gender, BMI, type of AF, AF duration, history of MI, hypertension, renal insufficiency, diabetes, thyropathy, COPD, type of surgery (valve, CABG) and randomization to SA or not. For other variables, the logistic EuroSCORE, ejection fraction, and left atrial dimensions were entered. All univariate predictors with p values less than 0.1 were included in the multiple logistic regression model with the goal of identifying those that were independently related to complete AF-free survival. Statistical analysis was performed using statistical software Stata, release 9.2 (Stata Corp LP, College Station, TX, USA) and SPSS v. 12 (SPSS, College Station, TX).

3. Results

3.1. All patients

One hundred and ninety-four (86.6%) patients from 224 originally enrolled patients from the PRAGUE-12 study were included in the present analysis. The remaining 27 patients were excluded because of death within the first three months or because they were lost in follow-up (3 patients). Out of the entire population, 104 patients underwent SA and 90 did not.

3.2. Logistic regression

In the univariate logistic regression model, the following variables were significantly (or almost significantly, $p < 0.1$) associated with AF-free survival: randomization to the SA group (OR 2.06, $p = 0.018$), age (OR 0.97, $p = 0.062$), BMI (OR 0.94, $p = 0.068$), long-standing persistent AF before surgery (OR 0.30, $p = 0.001$), history of MI (OR 0.55, $p = 0.093$), renal insufficiency (OR 0.21, $p = 0.041$), additive EuroSCORE (OR 0.85, $p = 0.011$), logistic Euroscore (OR 0.92, $p = 0.007$), and AF duration (OR 0.98, $p = 0.003$). All these parameters were next tested using multiple logistic regression models. Variables, which were independently associated with AF-free survival were SA group randomization (OR 2.07 (95%CI 1.06–4.05, $p = 0.032$), logistic EuroSCORE (OR 0.92 (95%CI 0.86–0.98, $p = 0.013$), BMI (OR 0.91 (95%CI 0.85–0.99, $p = 0.025$) and persistent AF before surgery (OR 0.28 (95%CI 0.13–0.62, $p = 0.002$).

3.3. Surgical ablation subgroup analysis

One hundred and four patients underwent concomitant surgical ablation. In the univariate logistic regression model, the following variables were significantly (or almost significantly, $p < 0.1$) associated with AF-free survival: BMI (OR 0.92, $p = 0.058$), history of MI (OR 0.22, $p = 0.014$), additive EuroSCORE (OR 0.83, $p = 0.044$), logistic EuroSCORE (OR 0.89, $p = 0.016$), and AF duration (OR 0.98, $p = 0.009$). These parameters were next tested in multiple logistic regression models. Variables, which were independently associated with AF-free survival were history of MI (OR 0.27 (95%CI 0.08–0.92, $p = 0.036$) and logistic Euroscore (OR 0.89 (95%CI 0.80–0.98, $p = 0.015$).

If the SA patients were divided into quartiles according to the EuroSCORE (Fig. 1), the odds ratio for having an AF recurrence in the 4th quartile (EuroSCORE 9.69–25.87) compared to the 1st quartile (EuroSCORE 1.51–3.07) was 3.35 (95%CI 0.99–11.38, $p = 0.052$). The characteristics of subgroup of patients which underwent surgical ablation (Tables 1 and 2).

4. Discussion

The main finding of the sub-analysis was that surgical ablation independently increases the chances for sinus rhythm maintenance. Furthermore, among SA patients, the highest chance for sinus rhythm restoration and maintenance was for patients without a history of MI and a low EuroSCORE.

The European System for Cardiac Operative Risk Evaluation (EuroSCORE) was developed in 1999 to assess the risk for cardiac surgery candidates. The original score parameters included age, female gender, serum creatinine, extracardiac arteriopathy, chronic pulmonary disease, severe neurological dysfunction, previous cardiac surgery, recent myocardial infarction, left ventricular ejection fraction, congestive heart failure, pulmonary hypertension, active endocarditis,