Benefit of ablation of first diagnosed paroxysmal atrial fibrillation during coronary artery bypass grafting: a pilot study†

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Received 5 August 2011; received in revised form 24 August 2011; accepted 5 September 2011

Abstract

OBJECTIVES: Whether patients with recent onset of paroxysmal atrial fibrillation (PAF) might benefit of epicardial atrial fibrillation (AF) ablation concomitant to coronary artery bypass graft (CABG) is not known. The aim of this prospective, randomized, single-centre pilot study is the comparison of patients with first diagnosed AF submitted to CABG and treated with and without epicardial pulmonary vein isolation (PVI).

METHODS: Patients with first diagnosed PAF and indication for CABG were enrolled in this prospective randomized pilot study. The primary endpoint was AF-free survival (AF burden <0.5%) between the two groups at 18-month follow-up. The secondary endpoints were the percentage of AF burden defined through continuous monitoring using an implantable loop recorder, thromboembolic events and procedural complications. All patients were implanted with a subcutaneous cardiac monitor to track the cardiac rhythm and measure the AF burden.

RESULTS: This study enrolled 35 patients (mean age 59 ± 7 years, 74% males), followed up for 18 months after CABG. The patients were randomly allocated to two groups, CABG alone (n = 17) and CABG with concomitant PVI (n = 18). At 18-month follow-up after surgery, 16 (89%) patients in the CABG + PVI group were AF-free (i.e. AF% < 0.5%) vs 8 (47%) in the CABG only group (log-rank test, P = 0.007). At the end of follow-up, the mean AF burden in the CABG and the CABG + PVI group was 7.8 ± 5.1 and 1.6 ± 1.8%, respectively (P < 0.001). Two (18.2%) of the 11 patients with AF recurrences were completely asymptomatic.

CONCLUSIONS: Patients with recent-onset AF submitted to CABG may benefit of concomitant ablation of the arrhythmia for preventing recurrences.

Keywords: Ischaemic heart disease • Atrial fibrillation ablation • Continuous subcutaneous monitoring • Coronary artery bypass grafting

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia occurring after coronary artery bypass graft (CABG) surgery and results in increased morbidity and prolonged post-operative hospital stay with a resultant increase in healthcare costs [1–7]. AF following minimally invasive coronary artery bypass surgery is analogous to AF after CABG, with a similar possibility for associated co-morbidities and increases in healthcare costs [8].

In patients with a long-term history of paroxysmal AF (PAF), a decision can be made to go for concomitant CABG and epicardial AF ablation procedures [9]. This approach has recently been proposed by our group for the patients with a long-term history of AF in combination with continuous AF monitoring performed by an implanted device [9]. The results are promising with ~70% responders at 1-year follow-up after the procedure. Whether patients with recent onset of PAF might benefit of epicardial AF ablation concomitant to CABG is not known.

The aim of this prospective, randomized, single-centre pilot study is the comparison of patients with first detected AF submitted to CABG and treated with and without epicardial pulmonary vein isolation (PVI).

MATERIALS AND METHODS

Patient populations

Patients with first diagnosed PAF were enrolled in this prospective randomized study.

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Inclusion criteria
(i) First diagnosed PAF.
(ii) Indication for CABG according to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for CABG surgery.

Exclusion criteria
(i) Previous treatment with IC or class III antiarrhythmic drugs (AAD)
(ii) Previous heart surgery and AF ablation procedure
(iii) Requiring concomitant valve surgery
(iv) Left ventricle ejection fraction <35%
(v) Left atrial diameter >55 mm
(vi) Unwillingness to participate.

Definition of the first diagnosed paroxysmal atrial fibrillation
Documented AF episodes ≥1 h in duration with ≥2 episodes over 4 months with ECG documentation of one episode.

The baseline assessment included clinical evaluation, standard laboratory tests, 12-lead ECG, transthoracic, transoesophageal echocardiography and coronary angiography.

This study was approved by the local Ethic Committee and conducted in compliance with the protocol and in accordance with the standard operating procedures of the study. All patients signed the informed consent form for participation in the study.

The study was a prospective, randomized and single blind study designed to compare the two treatment methods: (i) CABG only (n = 17) and (ii) CABG with concomitant PVI (n = 18).

Clinical characteristics of the patients are presented in Table 1.

The primary endpoint was AF-free survival (AF burden <0.5%) between the two groups at 18-month follow-up. The secondary endpoint was the percentage of AF burden defined through continuous monitoring using an implantable loop recorder (ILR), thromboembolic events and procedural complications.

Operation technique
The ablation procedure was performed using an irrigated bipolar RF ablation system [Cardioblate BP, Model 60821 (Medtronic Inc., Minneapolis, MN, USA)] as described previously [9]. Briefly, after onset of cardiopulmonary bypass, when the heart was still beating, the dissection of pericardial reflections and eventually the interatrial groove were performed and the bipolar device was clamped around the atrial cuff containing the inflow of the right pulmonary veins. Radiofrequency energy was delivered to create the encircling ablation. On the left side, after the heart was lifted, the encircling ablation was created in a similar manner. The patients received at least two encircling lesions on the left side and on the right side. No further connecting lines to the mitral annulus or the left atrial appendage were made. To ensure the left atrial appendage was untouched. The assessment of intra-operative conduction block was performed in all patients.

The implanted device
The ILR (Reveal XT, Medtronic Inc.) for continuous monitoring was implanted in the parasternal area of the chest at the end of the surgical operation [9]. The trend of more than 500 ventricular beats preceding the detection marker of the most recent AF episode.

Definition of atrial fibrillation-free (responders)
Patients with an AF% <0.5% were considered AF-free (responders). The cut-off of 0.5% corresponds to a maximum cumulative time in AF of 3.6 h in 1 month and to more than 99.5% of the time spent in sinus rhythm during the overall follow-up period. Patients with AF%≥0.5% were classified as non-responders: AF was visually confirmed by investigators through the analysis of the stored ECGs.

Post-operative management and follow-up
All patients were free from AAD therapy before and after surgery at least until the end of the follow-up, but all of them (100%) were taking β-blockers. All patients received oral anticoagulation therapy for a minimum of 6 months. At 6-month follow-up, all patients with a CHADS2 score = 0 and all responders with a CHADS2 score = 1 discontinued oral anticoagulation.

The data stored by the ILR were collected every month during the 12-month follow-up. In patients with recurrences, the telemetric data and the stored ECGs were used to tailor the antiarrhythmic therapy and/or to guide a percutaneous ablation procedure.

Table 1: Baseline characteristics of the patient population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CABG + PVI (n = 18)</th>
<th>CABG only (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59 ± 6</td>
<td>60 ± 8</td>
</tr>
<tr>
<td>Sex (M/F) (n)</td>
<td>14/4</td>
<td>12/5</td>
</tr>
<tr>
<td>Mean NYHA FC</td>
<td>2.4 ± 0.8</td>
<td>2.2 ± 0.5</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>59 ± 4</td>
<td>58 ± 5</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>45 ± 5</td>
<td>46 ± 5</td>
</tr>
<tr>
<td>Type 2 diabetes melitus [n (%)]</td>
<td>2 (11.1)</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Hypertension [n (%)]</td>
<td>3 (16.6)</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Prior stroke, [n (%)]</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Number of IM (n)</td>
<td>2.0 ± 0.3</td>
<td>1.9 ± 0.5</td>
</tr>
</tbody>
</table>

LVEF, left ventricular ejection fraction; LAD, left atrial diameter; AF, atrial fibrillation.
Statistical analysis

The sample size calculation was driven by the primary endpoint. A study sample of 17 patients in each group was estimated to detect a 30% difference in the clinical outcome with a statistical power of 0.80 and a two-tailed \( \alpha \) of 0.05. The clinical and statistical hypotheses came from our prior experience on ablation and continuous monitoring. Results are expressed as the mean values ± SD or as numbers and percentages, as appropriate. Continuous variables were compared by one-way ANOVA. The Mann–Whitney test was used if normal distribution criteria were not met. \( \chi^2 \) analysis for categorical variables was used for comparisons between characteristics of patients (Table 1). The Kaplan–Meier analysis with the log-rank test was performed to determine the probability of success, estimated as the percentage of responders. For the success rate, all patients experiencing a recurrence from 3 to 18 months were considered to have failed. All reported \( P \)-values were based on two-sided tests and a \( P \)-value of <0.05 was considered significant. All statistical calculations were performed using the SPSS version 13.0 software (SPSS Inc., Chicago, IL, USA).

The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

RESULTS

Study population

This study enrolled 35 patients (mean age 62 ± 5 years, 58 males) and followed up for 18 months after CABG. The patients were randomly allocated to two groups, CABG alone (n = 17) and CABG with concomitant PVI (n = 18; Table 1). All the patients (100%) had ischaemic heart disease and first diagnosed PAF.

Procedural and follow-up data

In the CABG and CABG + PVI groups, the average conduits number was 2.9 ± 1.1 and 2.7 ± 1, respectively (\( P = 0.81 \)). The average duration of aorta cross-clamping in the CABG group and the CABG + PVI group was 56 ± 9 and 59 ± 11 min, respectively (\( P = 0.42 \)). The mean cardiopulmonary bypass duration in the CABG and CABG + PVI groups was 108 ± 7.8 and 111 ± 9.2 min, respectively (\( P = 0.36 \)). At the end of the surgical procedure, the ILR was implanted in the parasternal area, which required 9.8 ± 8.4 min on average.

In the CABG + PVI group, the ablation procedure was done during on-pump, while the heart was beating. The mean time of ablation was 3.2 ± 0.8 min. At least two applications of the clamp were performed per lesion. The mean number of applications was 2.9 ± 0.4 and 3.1 ± 0.7 for left and right PVI, respectively. Complete disconnection of the PVS from the left atrium [the absence of atrial capture (conduction block) during pacing from PV] was successfully achieved in all patients.

No ablation or monitoring device implantation-related complications occurred.

All patients were discharged in sinus rhythm. No patients were excluded during ILR implantation and follow-up due to sensing issues, and all data were analysed by the investigators. Each patient had 1-, 3-, 6-, 9-, 12- and 18-month follow-up ILR data collection. There were no thromboembolic events during the 18-month follow-up.

Atrial fibrillation freedom at 18-month follow-up

At 18-month follow-up after surgery, 16 (88.9%) of the 18 patients were AF-free (i.e. AF% < 0.5%) at 18-month post-ablation follow-up examination (the CABG + PVI group) and 8 (47.1%) of the 17 patients were AF-free (the CABG only group; log-rank test, \( P = 0.007 \), Fig. 1). None of these patients were treated with antiarrhythmic medication. No significant associations were observed between baseline patient characteristics and AF recurrence.

AF% burden at 18-months follow-up

At the end of the follow-up, the mean AF burden in the CABG and the CABG + PVI group was 7.8 ± 5.1 and 1.6 ± 1.8%, respectively (\( P < 0.001 \)). Two (18.2%; from both the groups) of the 11 patients with AF recurrences were completely asymptomatic.

DISCUSSION

The main finding of this pilot study is that surgical AF ablation concomitant to CABG may prevent AF recurrences in patients with recent-onset AF. In a previous study [9], we showed that surgical AF ablation can have a positive impact on recurrences in patients with a long-term history of the arrhythmia. A similar benefit seems achievable also in patients with a short-term history of AF. These findings are clinically relevant because we used an implanted AF monitoring device able to continuously track the cardiac rhythm independently of the patient’s symptoms.

The XPECT study [11] first validated the diagnostic features of Reveal XT (Medtronic Inc.), the device we used in our trial. The study showed that the overall accuracy of the leadless cardiac monitor in measuring AF burden was 98.5%, with a Pearson correlation coefficient of \( r = 0.976 \). We used AF% at follow-up to identify responders and non-responders to ablation. In accordance with prior experiences by our group [9, ...
we choose an AF% ≥ 0.5% to classify patients as non-responders. All patients with an AF% < 0.5% were considered responders.

The cut-off of 0.5% corresponds to 7 min AF per day and to a maximum cumulative time in AF of 3.6 h in 1 month and to 99.5% of time spent in sinus rhythm during the follow-up period. We decided this cut-off based on the results of the TRENDS study [12]: this study defined the minimum amount of AF that doubles the thromboembolic risk compared with patients without AF or with a lower burden. This threshold was 5.5 h on 1 day.

The majority of studies regarding concomitant AF ablation during surgery estimated the efficacy of ablation through 24 or 48-h Holter monitoring [13–16]. Even if such methods are currently used, there may be an increase in asymptomatic events after AF ablation [17, 18], which could potentially increase the risk of stroke due to undetected silent AF. Moreover, the correction of the ischaemia also minimizes the patients' complaints and can mask AF events. That is why it is very important to use continuous monitoring, especially regarding the discontinuation of anticoagulation therapy.

Recently, Hanke et al. [19] confirmed that continuous heart rhythm surveillance most accurately identifies AF recurrence after surgical ablation therapy. In addition, his study provided strong evidence that commonly used intermittent follow-up strategy is significantly inferior to full disclosure heart rhythm observation with respect to AF recurrence detection.

The significantly lower AF recurrence in patients treated with ablation supports the hypothesis that patients with recent-onset AF may benefit from the concomitant procedure once CAGB has been planned. Whether the benefit is maintained in the long term was not the objective of this pilot study. Larger scale and prospective studies should be designed to evaluate the long-term clinical impact of ablation vs no-ablation in this patient population.

Study limitations

The study enrolled a limited number of patients in accordance with its pilot nature, so we cannot extrapolate our results to the general population of patients submitted to CAGB. There are factors which could hamper easy interpretation of results: (i) the data are fairly limited, rather a small number of events, making results not robust enough to draw meaningful conclusions out of it, and (ii) the data were taken from one single centre. Larger scale trials are needed on the same topic. In this study, we did not use the usual definition for failures (>30 s of AF): it is possible that we might get a different result. On the other hand, intermittent office ECG analysis or the Holter recordings are much less accurate than continuous monitoring [11].

CONCLUSIONS

Patients with recent-onset AF submitted to CAGB may benefit of the concomitant ablation of the arrhythmia for preventing recurrences.

Conflict of interest: G.C. is an employee of Medtronic Inc. Other co-authors have no conflict of interests to disclose.

References

APPENDIX. CONFERENCE DISCUSSION

Dr R.J.M. Klautz (Leiden, Netherlands): This paper gives a tsunami of new data; we come then to the relevance of all this data about atrial fibrillation. You defined freedom from AF as an AF burden less than 0.5% of the time per month. This means less than 3.6 hours of AF in any given period of 30 days for 18 months. This is much more liberal than the period of 30 seconds to define therapy failure stated in the guidelines.

To defend your choice for this cut-off value, you refer to the TRENDS study which found that the risk of thromboembolic events doubled in patients who have more than 5.5 hours of AF on any given day, or more than 10.8 hours in any 30-day period. However, in that study comprising almost 2,500 patients, the twofold increase in thromboembolic events was not statistically significant; the patients were at higher risk for thromboembolic events, the CHADS2 score was at least 1, and monitoring was performed using pacemakers or ICD’s.

In your study, which includes patients with lower thromboembolic risk, the CABG-only group has a mean duration of 5.6 hours per month, which is only almost half of the cut-off value of 10.8 hours that was identified in the higher risk patient group that constituted the TRENDS study. Let me be clear that nobody knows exactly how to define failure of AF ablation therapy. My question to you, however, is, are you sure that the cut-off value you used (which deviates from the guidelines and the TRENDS study) will have any clinical relevance for these patients?

Dr Romanov: Can you please repeat the question.

Dr Klautz: In other words, you do show a big difference in the two groups, but are you sure that there is also clinical relevance with the cut-off value you used? What happens if you use another cut-off value, and does it really mean that the patients are better? I know that they have less AF, but what does it mean? Do you have a more specific end point?

Dr Romanov: It is a good question, and you mentioned that we didn’t use the strict criterion of 30 seconds as in the guidelines. We used our criterion of 0.5%. Of course, it is a discussable value. But we used this criterion based on our previous experience, as well as on the TRENDS trial and some studies published by Botto. You also mentioned that 0.5% means that the patient can possibly have 3.6 hours of atrial fibrillation per month, and this has a low association with stroke risk.

Dr Klautz: But you have so much data in your institution. Could you link the cut-off value to a clinical outcome, like neurological outcome?

Dr Romanov: Unfortunately in this particular study we cannot do it because there are not enough patients. But now in our EP department we can actually do it. We can perform a correlation between the percentage of AF burden and a cardiovascular event. This data is now being collected and we will plan to publish it at the end of this year, because we now have experience with more than 1,000 ILR’s, and almost 300 patients who had ILR during three years of follow-up, and I think it will be interesting.

Dr Klautz: It is going to be very interesting. A very brief last question: have you considered implanting these loop recorders a couple of weeks before surgery?

Dr Romanov: That is a very interesting question, but, of course, we do not have the possibility of doing it.

Dr Klautz: Why not?

Dr Romanov: Before the surgery you mean?

Dr Klautz: Yes. Let your EP guys put it in.

Dr Romanov: We don’t have this possibility due to financial reasons. The patients come to our clinic just for surgery, that’s it, and we cannot implant such devices in advance.

Dr M. Castellá (Barcelona, Spain): I have a minor question. Is this definition of less than 5% due to the fact that you are using the Reveal device, and that maybe the Reveal cannot check differences of 30 seconds of AF? Therefore, you chose this definition because of the Reveal perhaps?

Dr Romanov: Yes, you are absolutely right that the Reveal device cannot detect an episode of 30 seconds. I mean, Reveal cannot detect an episode lasting more than two minutes. But we use this definition based on the previous work such as in the TRENDS trial.

Dr Castellá: Well, I think you proved very nicely that even in coronary cases, atrial fibrillation, when it is paroxysmal, in terms of pulmonary vein ablation is very useful, and since the other cases didn’t have the ablation, most of them continued to have atrial fibrillation. That has also already been shown in different papers.