Surgical ablation of atrial fibrillation after the PRAGUE-12 study: more questions than answers

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This editorial refers to ‘Comparison of cardiac surgery with left atrial surgical ablation vs. cardiac surgery without atrial ablation in patients with coronary and/or valvular heart disease plus atrial fibrillation: final results of the PRAGUE-12 randomized multicentre study’†, by P. Budera et al., on page 2644

No doubt surgical research has paved the way to curative treatment of cardiac arrhythmias. Long before the idea of catheter ablation was born, accessory atrioventricular pathways were interrupted by surgical knives, ventricular tachycardia was successfully treated by endocardial resection or scar circumcision, and even the first successful approaches to cure atrioventricular nodal re-entrant tachycardia were done in the surgical operating theatre. However, for these types of arrhythmias, surgical procedures are nowadays performed very rarely, mainly because of the tremendous success of catheter ablation. In atrial fibrillation (AF), current interventional treatment concepts and strategies would have been impossible without the milestone work of James Cox and colleagues who established the Maze operation, the first curative treatment option for AF patients.1 In an attempt to replicate the Maze procedure with percutaneous catheter ablators, John Schwarz initiated the development of catheter ablation procedures for AF in the early 1990s. Subsequently, and step by step, techniques and technologies were improved, and today catheter ablation is established as a leading treatment strategy for symptomatic patients with AF. The most important contribution came from the PRAGUE-12 randomized multicentre, prospective evaluation of surgical ablation of AF in patients with an indication for cardiac surgery.2 A total of 224 patients were randomized to no ablation (n = 107) or surgical ablation (n = 117) concomitant with various other surgical procedures, mainly coronary artery bypass graft (CABG) and/or valvular surgery. Most importantly, patients were included regardless of AF-related symptoms or any other AF-specific selection criteria. The primary efficacy outcome parameter was freedom from AF during a single 24 h Holter electrocardiogram (ECG) recorded 1 year after ablation. The primary safety outcome parameter included 30 day perioperative complications. In the overall patient population, the authors observed a significantly higher sinus rhythm rate in the ablation group, while perioperative complications were similar in both groups. In addition, secondary outcome parameters such as total mortality, stroke rate, and the incidence of heart failure were not different between both groups.

The PRAGUE-12 study addresses a very interesting and clinically highly relevant issue: does it make sense to perform surgical ablation of AF in an unselected patient cohort with an indication for cardiac surgery? Indeed, the unselected patient population included in the study seems to reflect closely routine clinical application of surgical AF ablation concomitant with other surgical interventions in Europe. The authors have to be congratulated for their efforts to investigate this patient population within the frame of a prospective, randomized, multicentre study. However, does the PRAGUE-12 study really help to better understand the outcome of surgical ablation in an unselected population? Does the...
present study help to improve the selection process to better identify patients most likely to benefit from surgical ablation? Lastly: what may be the benefit of surgical ablation of AF in unselected patients?

Budera and co-workers studied a cohort quite representative of today’s patient population undergoing cardiac surgery: relatively old (mean age 70 years) with significant co-morbidities and a high proportion of patients requiring multiple surgical interventions during a single operation. Thus, the mortality and morbidity rates observed in both study arms are not really surprising. It is important to learn from their study that additional surgical ablation, although prolonging cardiopulmonary bypass time, cross clamp time, and operation time, obviously did not add significant periprocedural risks. However, is the procedure effective? The methods applied in the PRAGUE-12 study as well as the outcome data as reported deserve detailed review for correct interpretation. The primary efficiency outcome parameter was the sinus rhythm rate 12 months after ablation measured in a single 24 h Holter ECG. For a clinical study with a rhythm-based primary outcome parameter, this follow-up regimen is by far not enough to generate reliable and solid results. Indeed, according to current knowledge and a huge set of valid scientific data, it must be expected that with such weak follow-up ~ 70% of all AF recurrences may have been missed. Thus, the true AF recurrence rate certainly was significantly higher than reported. The main reason for this is the well documented and extremely high incidence of asymptomatic AF episodes. In this light, the rhythm outcome data reported in the PRAGUE-12 study are of very limited value. The only solid observation on rhythm outcome may be that some patients with longstanding persistent AF before surgery may no longer have longstanding persistent AF after surgical ablation. Unfortunately, any conclusion on rhythm outcome beyond this is impossible to be drawn from this study. No episodes of atrial flutter or atrial macro-re-entrant tachycardia were reported during the follow-up period. This would be very uncommon in a patient population that underwent surgical pulmonary vein isolation plus linear lesion ablation. Based on current knowledge, the incidence of these arrhythmias during 1-year follow should exceed 10%. However, ECGs need to be recorded to document these arrhythmias.

Another surprising finding from the PRAGUE-12 study is that patients with paroxysmal and persistent AF obviously did not profit from the intraoperative ablation procedure: at 1-year follow-up there was no statistically relevant difference in the sinus rhythm rate between both groups. This finding contradicts all previous reports on catheter ablation or surgical ablation of AF. It is generally accepted that the treatment outcome of patients with paroxysmal AF is superior to that of patients with persistent AF and that a less favourable outcome can be expected for patients with longstanding persistent AF. In addition, in the current study the overall benefit for surgical ablation was due solely to the higher sinus rhythm rate observed in patients with longstanding AF. The authors’ explanation that rhythm monitoring issues may be responsible for this finding is not convincing. Indeed, it is more likely to miss recurrences of paroxysmal AF as compared with longstanding persistent AF especially when only intermittent, low intensity ECG monitoring is applied. As very recently shown by Charitos et al., it is particularly difficult to document paroxysmal AF in patients with a low AF burden but high AF density. However, it remains speculative as to why patients with paroxysmal and persistent AF obviously did not profit from surgical ablation. The most likely explanation may be that the pulmonary veins have not been effectively isolated in a significant number of patients. In almost all patients who underwent surgical ablation, a cryo technique was applied, with a significant number of patients treated with epicardial energy application. As shown by Doll and co-workers, this technique is lacking lesion transmurality and may not be feasible to isolate the pulmonary veins.

According to the study protocol, post-operative treatment with antiarrhythmic drugs was foreseen for all patients for a period of at least 3 months. Afterwards withdrawal of antiarrhythmic drugs was recommended ‘if the patient appeared to be AF free’—which is difficult to judge in the absence of any rhythm monitoring. In addition, it is surprising to see that although the sinus rhythm rate after patient discharge was consistently lower in the control group, the use of antiarrhythmic drugs was roughly the same compared with the ablation group. It seems that the intensity of the rhythm control strategy with electrical cardioversion and comprehensive use of antiarrhythmic drugs may not have been the same in both groups—a typical indicator for treatment bias. It would have been interesting to see more detailed data on the number of cardioversions and the use of antiarrhythmic drugs. Another critical issue regarding the study of Budera et al. relates to the use of oral anticoagulation. First, the correct target international normalized ratio (INR) for most of the patients included should have been 2.0–3.0 and not 2.0–2.5 as outlined in the Methods section of the manuscript. In addition, it is not in line with numerous AF guidelines or AF consensus statements published so far to recommend withdrawal of oral anticoagulation in patients with a CHADS2 score of ≥ 2 even after successful ablation of AF. However, the protocol of the PRAGUE-12 study recommended stopping anticoagulation after 6 months when the patients apparently were in sinus rhythm. Looking at the patient population with respect to age and co-morbidities and considering the fact that no rhythm monitoring was applied during the study, this recommendation in the study protocol is difficult to understand. Indeed, > 40% of patients in both groups (!) were off oral anticoagulation at 12-month follow-up. There is another interesting aspect of the study: in all patients randomized to surgical ablation, excision of the left atrial appendage was recommended and obviously performed. Despite the fact that oral anticoagulation was continued in 60% of these patients the stroke rate at 12-month follow-up was not significantly lower compared with patients without appendage exclusion. This observation adds to other arguments that surgical excision of the left atrial appendage may not result in a significant reduction of stroke risk.

What are the benefits of surgical ablation in this study? There were no differences in left atrial size, left ventricular ejection fraction, or New York Heart Association class between both groups. This means that no reverse remodelling was observed in the ablation group, even in patients with sinus rhythm at 1 year. Again, this finding contradicts previous reports that successful ablation results in measurable reversed remodelling especially in patients with heart failure and reduced left ventricular ejection fraction.
The most likely explanation for the lack of reversed remodelling is that the efficiency of surgical ablation simply was too low and that persistent sinus rhythm could not be achieved in most patients. Unfortunately, quality of life was not systematically assessed in the PRAGUE-12 study. Thus, any potential benefit of this soft outcome parameter is speculative. At the end, no measurable benefit in any of the secondary outcome parameters could be achieved by surgical ablation.

Does it make sense to perform surgical ablation in unselected patients undergoing cardiac surgery? The 2010 ESC guidelines for management of AF recommend surgical ablation in asymptomatic patients undergoing cardiac surgery as a class IIb recommendation (‘may be considered’) with a level of evidence C (based on expert consensus only).13 Now we have data from a randomized, prospective study indicating that there are no benefits gained by the procedure. This should give rise to care being taken with the indication for surgical ablation in unselected and asymptomatic patients undergoing cardiac surgery. However, as discussed above, the PRAGUE-12 study has significant methodological limitations and leaves many questions on surgical ablation of AF unanswered. We encourage our colleagues from cardiac surgery to intensify cooperative clinical research in order to answer these important questions and further improve the quality of care for patients with AF.

Conflict of interest: none declared.

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