Catheter Ablation Versus Electrophysiological Guided Thoracoscopic Surgical Ablation in Long Standing Persistent Atrial Fibrillation - (CASA-AF)

Short title - Haldar CASA-AF Study

Shouvik K. Haldar MRCP, MD (Res)1, David G. Jones MRCP, MD (Res)1, Toufan Bahrami PhD, FRCS1, Anthony De Souza MD, FRCS1, Sandeep Panikker MBBS MRCP1, Charlie Butcher MRCP1, Habib Khan MRCP1, Rashmi Yahdev MD FRCS1, Julian Jarman MRCP, MD (Res)1, Lilian Mantziari MD PhD1, Eva Nyktari1, Raad Mohiaddin MD FRCP1, Wajid Hussain MBChB1, Vias Markides MD FRCP1, Tom Wong MD FRCP1

1Heart Rhythm Centre, NIHR Cardiovascular Biomedical Research Unit, Royal Brompton & Harefield NHS Foundation Trust, Imperial College London, London SW3 6NP, UK.

Address for Correspondence
Dr Tom Wong
Heart Rhythm Centre, NIHR Cardiovascular Biomedical Research Unit
The Royal Brompton and Harefield NHS Foundation Trust, Sydney Street, London, SW3 6NP United Kingdom
Email: tom.wong@imperial.ac.uk; Phone: +44 20 7351 8619; Fax: +44 20 7351 8629

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Abstract

Background: Catheter ablation (CA) outcomes for long standing persistent AF (LSPAF) remain suboptimal. Thoracoscopic surgical ablation (SA) provides an alternative approach in this difficult to treat cohort.

Objective: To compare electrophysiological (EP) guided thoracoscopic SA with percutaneous CA as the first line strategy in LSPAF.

Methods: Fifty-one patients with de-novo symptomatic LSPAF were recruited. Twenty-six patients underwent EP guided thoracoscopic SA. Conduction block was tested for all lesions intraoperatively by an independent electrophysiologist. In the CA group, 25 consecutive patients underwent stepwise left atrial (LA) ablation. The primary endpoint was single procedure freedom from atrial fibrillation (AF) and atrial tachycardia (AT) lasting > 30 seconds without anti-arrhythmic drugs (AAD) at 12 months.

Results: Single and multi-procedure freedom from AF/AT was higher in the SA group than in the CA group: 19/26 (73%) vs. 8/25 (32%); p=0.003 and 20/26 (77%) vs. 15/25 (60%); p=0.19 respectively. Testing of the SA lesion set by an electrophysiologist increased success rate in achieving acute conduction block by 19%. In the SA group the complication rate was 7/26 (27%) vs. 2/25 (8%) in the CA group (p=0.07).

Conclusion: In LSPAF, meticulous EP guided thoracoscopic SA as a first line strategy can provide excellent single procedure success rates as compared to CA, but there is an increased upfront risk of non-fatal complications

Clinical Trial Registration ClinicalTrials.gov Identifier: NCT01385358

Keywords: Arrhythmia; Electrophysiology; Atrial Fibrillation; Catheter ablation; Surgical ablation.
Introduction

Catheter ablation (CA) is well established for paroxysmal AF with a class 1A recommendation in the European AF guidelines.\(^1\) Persistent AF represents more progressive disease while long standing persistent AF (LSPAF), defined as those with continuous AF lasting greater than 12 months, represents the most advanced end of the disease spectrum. Unsurprisingly, CA outcomes for LSPAF are poor with single procedure success rates in the region of 30%.\(^2,3\)

Despite the clinical success of the open-heart Cox-Maze surgical procedure with freedom from AF of up to 90% at 10 years, it was seldom used to treat standalone AF due to its technical complexity and high morbidity.\(^4\) Nowadays it is reserved as an adjunct to open-heart surgery. The development of a minimally invasive, thoracoscopic SA technique renewed interest in SA with encouraging data in non-paroxysmal AF.\(^5,6\)

To date there has been no direct comparison between the outcomes of thoracoscopic SA versus CA in de-novo LSPAF patients. We hypothesised that thoracoscopic SA would confer superior outcomes compared with CA in LSPAF. This prospective, non-randomised study sought to compare the efficacy and safety of electrophysiological (EP) guided thoracoscopic SA with percutaneous CA as the first line strategy in LSPAF.

Methods

Patients

Patients with symptomatic LSPAF refractory to either AAD and/or direct current (DC) cardioversion being considered for interventional management were eligible. Patients with previous cardiac surgery; previous CA for AF; left ventricular ejection fraction (LVEF) <
40%; contraindication to anticoagulation; active malignancy; and cerebrovascular accident within 6 months were excluded from the study.

The study protocol complies with the Declaration of Helsinki and was approved by the local ethics committee. All patients gave written informed consent. All definitions are in accordance to the 2012 HRS/EHRA/ECAS consensus document for catheter and surgical ablation of AF.7

Fifty-one patients were recruited between July 2011 and December 2013. All patients were potential candidates for either SA or CA and were given clinical information about both options without bias towards either modality. The final decision was based on patient preference. All patients that chose SA were discussed at an EP multi-disciplinary meeting and all were deemed appropriate to proceed. All patients underwent a 12-lead ECG, transthoracic echocardiogram, laboratory tests, symptom and quality of life assessments before their procedure.

**Catheter Ablation**

The procedure was performed under general anaesthesia on uninterrupted warfarin with on-table transoesophageal echo to exclude intracardiac thrombus. CA was guided by the EnSite Velocity™ 3D electroanatomical system (St Jude Medical, MN, USA), multi-electrode high-density (AFocus II™, St Jude Medical) mapping catheter and a 3.5mm irrigated-tip ablation catheter (Thermocool, Biosense Webster) limiting power to 30 W.

Circumferential pulmonary vein isolation (PVI), roof and mitral isthmus lines were conducted followed by ablation of LA complex fractionated electrograms (CFE). If AF persisted, patients were DC cardioverted to sinus rhythm (SR). If AT occurred, this was mapped and ablated. Cavotricuspid isthmus (CTI) ablation was only performed if there was documented evidence of CTI-dependent atrial flutter. After restoration of SR, PVs and linear
lesions were assessed for bi-directional block with further ablation conducted as required to achieve block.

**Surgical ablation**

SA patients stopped warfarin 5 days’ pre-procedure with low molecular weight heparin bridging until 24 hours prior to their procedure. Patients underwent video-assisted thoracoscopic SA under general anaesthesia. Double-lumen endotracheal tube intubation was used for selective lung ventilation, followed by transoesophageal echo to exclude intracardiac thrombus. Thoracoscopic access was gained bilaterally (Supplementary Figure S1) followed by pericardiotomy and then right-sided epicardial PVI using the bipolar radiofrequency ablation clamp (AtriCure Inc.) to deploy up to 8 overlapping lesions around the PV antrum. The bipolar radiofrequency ablation clamp (Atricure Inc.) delivered RF at a frequency of 460KHz with power ranging from 12-30 watts guided by an Ablation and Sensing Unit (ASU) (Atricure Inc.). This unit displayed tissue conductance between the jaws of the clamp versus time. Transmurality was deemed to be achieved when associated with a sharp drop in tissue conductance to a steady state within 5 seconds of RF application.

The next step was epicardial ganglionated plexi (GP) ablation. Most epicardial GP located at the PV antrum were abolished by PVI, however any remaining GP were identified using high-frequency stimulation (1200 bpm, 18 V output, 2 msec pulse width) to elicit a vagal response (increased R-R interval >50% and/or > 3 seconds of asystole). These sites were then ablated with confirmation of abolition by the absence of a vagal response.

Linear epicardial ablation then followed using the internally-irrigated bipolar radiofrequency Coolrail® linear pen (Atricure Inc.) to connect contralateral superior PVs (superior/roof line) and the inferior PVs (inferior line) in order to deploy a posterior box lesion. Lesions were overlapped to ensure a contiguous lesion was achieved (Figure 1).
Left-sided PVI was then undertaken in a similar manner to complete the posterior box lesion. If AF persisted, DC cardioversion was conducted to restore SR. The LAA was excluded in the latter 13 surgical patients using initially an amputating thoracoscopic surgical stapler device (n=7) (Endo GIA, Covidien) and then superceded by the AtriClip® LAA occlusion system (n=6) (Atricure Inc.).

**EP guided testing of SA conduction block**

An electrophysiologist independent of the cardiac surgeon undertook 2-step conduction block testing in all patients. Step 1 involved conventional surgical testing using the multifunctional (ablation and pacing) surgical pen and the Micropace OR lab intraoperative testing unit (AtriCure Inc.). The surgical pen was placed on the superior and inferior aspect of the PV antrum to sense and prove entrance block post PVI. After SR restoration, the pen was used to pace the PV side of the PVI lesions and within the posterior box lesion to confirm exit block (Figure 2).

The limitations of using the surgical pen is that it may miss regional sleeves of electrical connection post PVI. Therefore, we developed an adjunct EP mapping strategy which we used as step 2 in all SA patients. Using a 20-pole multielectrode EP catheter (Bard RADIA™ Bidirectional Diagnostic Catheter) and a mobile EnSite Velocity™ mapping system (St Jude Medical) the EP catheter was introduced through a thoracoscopic port and positioned around the entire circumference of each of the ipsilateral pairs of PVs (Figure 2). PVs were mapped at multiple locations to provide detailed confirmation of entrance block, akin to circular catheters used endocardially in CA (Supplementary Figure S2). After completion of the box lesion and restoration of SR, the circular catheter was positioned within the box to test for entrance block and pacing manoeuvres conducted to verify box lesion exit block.
Post-ablation rhythm management

Class I and III AADs were stopped at or before the index procedure. If persistent AF/AT recurred during the pre-specified 3-month blanking period, the patient was treated by DC cardioversion. When symptomatic AF/AT recurred outside of the blanking period, a second ablation procedure was offered to the patient. The redo procedure was always CA irrespective of index procedure modality.

Follow-up

Patients were followed up at 3, 6, 9 and 12 months and assessed for any symptomatic arrhythmia episodes reported between follow-ups. At each visit, patients underwent clinical evaluation, the SF36 Quality of Life Questionnaire; and 7-day continuous ambulatory rhythm monitoring (R-Test Evolution 4, Novacor, UK). Two experienced cardiac physiologists independent and blinded to the study interpreted the results. If there was ambiguity, there was a consensus opinion of an independent blinded electrophysiologist.

Endpoints

The primary endpoint was single procedure freedom from AF/AT lasting ≥ 30 seconds off AAD. Secondary endpoints included: multi-procedure success off AADs at 12 months; clinical (partial) success - defined as 75% or greater reduction in either the number or the duration of AF/AT episodes in the presence or absence of previously ineffective AAD; serious adverse event rates (stroke, MI, emergency surgery, death); major procedural complication rates (complications that result in permanent injury or death or that require emergency treatment or prolongs / requires hospitalisation for more than 48 hours); change in quality of life scores. Quality of life was assessed at each visit using the SF-36 v2
questionnaire which provides psychometrically based physical and mental health summary measures.⁹

**Statistical analysis**

Categorical data were presented as proportions and comparisons made using the chi-squared test or Fisher’s exact test. Normally distributed continuous variables were presented as mean±SD and comparisons made using the 2-sample t-test. Skewed continuous data were presented as the median (interquartile range) with comparisons made using Mann-Whitney test and visually represented using box plots. Linear regression was performed to assess factors associated with change in SF 36 scores (mode of ablation and freedom from atrial arrhythmia) with variables that had p < 0.10 included in the multivariable model.

Outcomes analysis was performed as per intention to treat (ITT) and by independent comparison of absolute change from baseline where appropriate. Arrhythmia-free survival was analysed by Kaplan-Meier survival curves with log-rank comparisons. Statistical significance was defined as p < 0.05. Data were analysed using GraphPad Prism version 6.00 for Mac (GraphPad Software, San Diego California, USA).

**Results**

Fifty-one patients with LSPAF were recruited (65±10 years, 67% male). Baseline characteristics (Table 1) were similar between the two groups, except for greater duration of continuous AF in the SA group (24 vs. 18 months, p=0.04), and more hypertensive patients in the CA group (20 vs. 13%, p=0.03).

**Catheter ablation group**

Twenty-five patients chose CA and all 25 (100%) patients had bi-directional block of the
LPV, RPV, roof and mitral isthmus lines at the end of the procedure. Intra-procedural termination of AF (termination to SR without DC cardioversion) occurred in 5/25 (20%) patients (2 during roof line and 3 via AT during CFE ablation).

**Surgical ablation group**

Twenty-six patients chose SA but the procedure was abandoned (anatomical difficulties) in 2 patients who crossed over to the CA arm but were analysed in the assigned group as per ITT (Supplementary Figure S3). Entrance block for both RPV and LPV was demonstrated in 24/26 (92%). Intra-procedural termination of AF occurred in 1 patient terminating directly to SR during superior (roof) line ablation.

**Procedural results**

There were no procedural deaths, strokes or conversion to sternotomy in either group. Hospital stay for surgical patients was higher at 7.4±3 vs. 4.1±3 days in the CA group (p<0.001). Within the blanking period, 5/26 (19%) SA patients vs. 4/25 (16%) CA patients underwent DC cardioversion (p=0.76).

**EP guided testing of SA conduction block**

To ensure robust assessment of conduction block for SA lesions, 2-step testing was used as described earlier. Of the 24 patients who completed SA, technical challenges in positioning precluded the use of the EP catheter testing in 2 patients. Of the 22 patients who had both surgical and EP catheter testing, 3 patients were found to have PV connections (entrance) on the EP catheter post PVI and 2 patients had conduction into the box lesion on the EP catheter (entrance) – all of which were deemed isolated on surgical pen testing. Therefore, EP catheter testing prompted further ablation to achieve conduction block in 23% (5/22) of patients over
and above that of conventional surgical testing. If including those in whom it was not possible to use the EP catheter this still represents 19% (5/26) where EP catheter testing improved the success rate in achieving acute conduction block in the SA arm.

**Primary and secondary end-point results**

**Primary end-point**

Single procedure freedom from atrial arrhythmia, off AADs occurred in 19/26 (73%) of patients in the SA group versus 8/25 (32%) patients in the CA group (p=0.003). Kaplan-Meier survival curves are shown in Figure 4.

**Secondary end-points**

**Multi-procedure success**

Multi-procedure success off AADs occurred in 20/26 (77%) patients in SA versus 15/25 (60%) patients in the CA group (p=0.19) with mean number of procedures 1.23±0.43, and 1.48±0.51 respectively. Kaplan-Meier survival curves are shown in Figure 5.

**Serious adverse events**

Only one serious adverse event (stroke, MI, emergency surgery or death) occurred in the study. This was a primary intra-cerebral haemorrhage in a patient 60 days post CA. It was unrelated to the index procedure and therefore not included in the MACE analysis.

**Major complications**

In the SA group, eight major complications occurred in 7/26 patients (27%) post-operatively, compared with two in 2/25 (8%) patients in the CA group (p=0.07) (Table 2).

In the SA group, one patient had a pleural effusion requiring drainage and one had a pneumonia. Another patient had both pneumonia and symptomatic, left upper and lower PV stenosis (≥ 70%) necessitating angioplasty which fully resolved symptoms. Two further
patients had significant PV stenosis of the left lower PV, but neither were symptomatic and hence did not require intervention whilst two patients had phrenic nerve paralysis. In the CA group, one patient had asymptomatic left lower PV stenosis which was managed conservatively. Another patient had acute pulmonary oedema within 48 hours of discharge. ITT Kaplan-Meier MACE free survival curves were not significantly different between the two groups; log-rank p=0.19 (Supplementary Figure S4).

The 3 phrenic nerve dysfunctions were not due to direct trauma, as the pericardiotomy was deliberately performed 4-5cm anterior to the nerve’s course but postulated to be indirect trauma via the tension from the pericardial retraction sutures. In latter cases, this tension was relaxed without further phrenic nerve dysfunction.

The 4 cases of severe (>70%) PV stenosis (1 in CA group, 3 in SA group) were surprising given that in both groups, PVI was undertaken at the PV antrum. Only one of the patients (in SA group) was symptomatic, requiring PV angioplasty. In this case, both the LUPV and LLPV had stenosed (Figure 6), with two possible reasons for this occurrence. First, technical difficulty getting good contact with the ablation pen at the (epicardial) junction of the left PVI line and superior line resulting in several overlapping lesions at this site which may have breached the PV ostium. Second, seven RF clamp applications on the PV antrum may have been excessive for this patient. In the other two patients, a possible explanation was again the number of RF clamp applications (8 and 7) which led to a change in the target number of applications at the PV antrum to 5 after which no further PV stenosis occurred.

Finally, pulmonary complications are often a by-product of the double lumen endotracheal intubation technique used for selective lung ventilation. Post-operative pneumonia and atelectasis can be minimised with prophylactic antibiotics and post-operative pain management (facilitating deep inspiration) and early mobilisation.
DISCUSSION

This is the first prospective head-to-head study to examine these two ablation strategies in LSPAF alone. The principle finding was that a thoracoscopic SA strategy with meticulous electrophysiological validation of conduction block was superior to CA, although this was offset by a trend towards a higher rate of major (non-fatal) complications.

LSPAF is the least studied category of AF and also the hardest to treat. The suboptimal efficacy of CA in LSPAF was the driver for our study. Given the promising results from early thoracoscopic SA series we felt this technique warranted evaluation as a first line strategy to see if the increased invasiveness could be justified by better outcomes and fewer procedures as compared to CA. It is widely accepted that PVI is not enough for non-paroxysmal AF, especially LSPAF, therefore when designing the SA lesion set we felt it necessary to ensure it was not too technically demanding, was reproducible and provided substrate modification. By simplifying the SA lesion set to PVI plus posterior wall box lesion (e.g. omitting complex lesions such as the trigone lesion) our aim was for broader real-world applicability whilst providing a degree of parity with the CA lesion set facilitating comparison.

Achieving such a high success rate off AADs in LSPAF patients despite the mean duration of continuous AF being longer than in the CA group (24 vs. 18 months; p=0.04) shows the promise of this technique. The fact that this was achieved with a single procedure also indicates the potential cost-effectiveness benefits in the longer term which warrants future investigation. Our results corroborate previous surgical series in LSPAF from Edgerton, Sirak, and Krul where the unifying theme with our data is thorough electrophysiological validation of conduction block. Our CA results are also in keeping with previous reports in LSPAF. More recently, the first multi-centre randomised
controlled trial, the FAST study, comparing SA with CA in predominantly paroxysmal AF patients (67%) showed significant AF-free survival at 12 months without AADs (65% vs. 36.5%) although the adverse event rate was also higher (34% vs 16%). This was an important study albeit with limitations such as: mixed population (paroxysmal and persistent); heterogeneity in lesion sets; and inconsistent verification of conduction block which made comparison between the two groups difficult. A subsequent systematic review documented freedom from AF post SA of 67-80% in persistent AF based on 3 small studies with less rigorous follow-up than our study.

The superior efficacy of SA is likely to be multifactorial but we believe our robust electrophysiological assessment of conduction block is a major factor. Other reasons include:

1. Epicardial SA lesions applied under direct vision provide more contiguous, transmural and long-lasting lesions than those created by standard point-by-point CA, particularly if validated conduction block is demonstrated;
2. GP ablation may impact the substrate and hence outcome but a recent study comparing SA groups with and without GP ablation would not support this as a likely mechanism.
3. Thirdly, LAA exclusion may have improved outcomes, supported by recent data showing better outcomes when the LAA is electrically isolated in addition to a conventional AF ablation strategy in LSPAF. However, as the first ten surgical patients did not have LAA exclusion, it was possible to perform sub-analysis of the SA group with and without LAA exclusion which showed no significant difference in primary outcome at 12 months [75% (9/12) vs. 71% 10/14); p= 0.84].

The rate of recurrence in the CA group combined with the fact that SA lesion sets were mostly intact in those that required a restudy, further supports the superiority of
epicardial surgical lesions in terms of producing lasting transmural lesions. Animal and clinical studies have previously shown that the bipolar radiofrequency clamp and the linear ablation device can create robust transmural lesions.\textsuperscript{17} The fact that EP testing increased the SA acute conduction block success rate by 19\% highlights the importance of robust conduction testing.

**Multi-procedure success**

Multi-procedure success in CA improved outcomes from 32\% to 60\%. ‘Touch-up’ ablation was required to correct PV reconnections and gaps in linear lesions reinforcing the shortcomings of CA lesions in terms of durability. Contact force sensing catheters were not available at the time of study design but may have reduced recurrences by achieving optimal and consistent CF during lesion formation which likely translates into more durable RF lesions.\textsuperscript{18} In the SA group, multi-procedure success improved outcomes only marginally with 2/4 SA patients that had redo CA still failing the primary endpoint because of inability to restore SR despite two procedures.

**Complication rates**

The outcome benefits from thoracoscopic SA are offset by the higher complication rate. This is in line with previous reports, including a systematic review highlighting the commonest complications as pulmonary issues, phrenic nerve dysfunction and bleeding.\textsuperscript{13} Future refinement in surgical tools and technique is needed to reduce these complication rates in order to be comparable to CA.

**EP guided intraoperative testing of conduction block**

The addition of EP catheter testing for conduction block of the PVs and the box lesion increased the pick-up rate of acute non-isolated lesions. An additional 5/26 patients required further ablation to isolate lesions deemed blocked by the multifunctional surgical pen. This is
important, as without it these 5 patients (19%) may have failed the primary endpoint reducing SA success to 54%. In this hypothetical scenario and under ITT analysis the SA success rate would have been 54% (14/26) vs. 32% (8/25); p=0.12.

**Limitations**

This study has several limitations. It is a non-randomised study with patients choosing the modality which may result in unmeasured systematic differences between patient groups. The sample size was small but nonetheless able to show a significant difference between the two groups in terms of primary outcome. It is possible that an implantable loop recorder would provide more accurate rhythm assessment by capturing asymptomatic AF episodes that may not have been captured with our follow-up schedule. Finally, contact force sensing catheters became available after study commencement and are felt to increase the permanency of PVI. Not using these catheters in the CA arm may have contributed to the difference in outcomes between the two groups. In addition, the skills and experience of all operators will have increased over the span of the study resulting in potentially better results for those patients enrolled towards the end of the study.

**Conclusion**

EP guided thoracoscopic SA as a first line-strategy in LSPAF is more effective than CA but this efficacy comes at the cost of a higher complication rate. Thorough intraoperative electrophysiological testing during SA is crucial in achieving a high success rate. Further evaluation in randomised control trials including robust cost-effectiveness analysis will be important to determine the position of thoracoscopic SA in AF management.
Acknowledgements

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Disclosures

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References


16. Panikker S, Jarman JWE, Virmani R, et al. Left atrial appendage electrical isolation and concomitant device occlusion to treat persistent atrial fibrillation: a first-in-human safety,


Legends

Figure 1 Intraoperative image showing surgical linear (roof) line of ablation

Key: LSPV = left superior pulmonary vein, LAA = left atrial appendage, SVC = superior vena cava, LA = left atrium.

Figure 2 PA view illustration of 2-step conduction testing for SA lesion set

Right and Left PVI lesions and posterior wall box lesion are shown. Sites of testing by the Surgical pen are denoted by the red star (upper PVs, lower PVs and box lesion). EP catheter is also shown at 3 sites of testing 1) Right PVI 2) Left PVI 3) Box lesion.

Key: SVC = superior vena cavae; IVC = inferior vena cavae

Figure 3 Number and mode of recurrences and findings at redo procedures

Key: PV = pulmonary vein; LL = linear lesions

Figure 4 Single procedure freedom from AF/AT at 12 months

SA versus CA groups, single procedure Kaplan-Meier curves of AF/AT free survival off AAD (censored at 365 days). Success is defined as freedom from AF/AT after a 3-month blanking period.

Figure 5 Multi-procedure freedom from AF/AT at 12 months

SA versus CA groups, multi-procedure Kaplan-Meier curves of AF/AT free survival off AAD (censored at 365 days). Success is defined as freedom from AF/AT after a 3-month blanking period.

Figure 6 Example of left pulmonary vein stenosis post thoracoscopic SA

Pre- and post-ablation MRI images showing normal calibre left upper (LUPV) and lower (LLPV) pulmonary veins pre-ablation, followed by occlusion of the LUPV and severe (>70%) stenosis of the LLPV.
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<th>Surgical Ablation (n=26)</th>
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<td>Age (y) Mean ± standard deviation</td>
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<td>Left atrial volume - index BSA (ml/m²) Mean ± standard deviation</td>
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<td>Left ventricular ejection fraction (%) Mean ± standard deviation</td>
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Table 2 Major Complications

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