Hybrid approach for the treatment of long-standing persistent atrial fibrillation: electrophysiological findings and clinical results†

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Abstract

OBJECTIVES: The sequential, staged hybrid approach has recently emerged as a novel strategy for the treatment of long-standing persistent atrial fibrillation (AF); nevertheless, the potential modifications in terms of electrophysiological findings and their correlation with mid-term results have not been fully elucidated so far.

METHODS: Forty-five patients with long-standing persistent AF underwent a hybrid procedure combining surgical closed-chest posterior left atrium (LA) and pulmonary veins (PV) isolation (box lesion) first, followed by transcatheter evaluation at least 1 month afterwards. Electrophysiological findings and their correlation with rhythm outcomes were assessed at different time points, i.e. following the surgical ablation (T1), during (T2) and at the end (T3) of the transcatheter evaluation and at 28-month follow-up (T4).

RESULTS: At T1, exit and entrance blocks were achieved in 100 and 91.1% (41 of 45) of patients, respectively. At T2, the percentage of conduction block was unchanged, while at T3 also entrance block was achieved in all instances. In terms of electrophysiological findings (at T2), PV reconnection occurred in 6.7% (3 of 45) of patients, fractionated electrograms were targeted in 44.4% (20 of 45) while right atrium isthmus lesion was performed in 24.4% (11 of 45) of patients. Sinus rhythm was restored in 75.6% (34 of 45) at T1, at T2 (with AF induction) in 68.9% (31 of 45), at T3 in 93.3% (42 of 45) and at T4 in 88.9% (40 of 45) of patients, respectively. In those patients with a bidirectional block at T1, sinus rhythm restoration steadily improved from 78 (32 of 41) at T1 to 82.9 (34 of 41) at T2 and finally 92.6% (38 of 41) at T4.

CONCLUSION: Complete posterior LA and PV isolation with the box lesion in a staged hybrid approach is associated with incremental benefits in terms of sinus rhythm maintenance in patients with long-standing persistent AF.

Keywords: Atrial fibrillation • Ablation • Minimally invasive surgery • Transcatheter

INTRODUCTION

During the past decade, there has been a steady evolution of minimally invasive surgical approaches for the treatment of stand-alone atrial fibrillation (AF) [1, 2]: in particular, technical implementations have allowed for a refined analysis of electrophysiological end-points also during the surgical ablation with the integration of transcatheter tools and validation techniques on a routine basis [3–5].

We recently introduced an interventional hybrid approach for the treatment of long-standing persistent AF merging fully endoscopic surgical and transcatheter techniques in a sequential, staged fashion: first, patients routinely undergo a closed-chest isolation of the pulmonary veins and the posterior left atrium (box lesion set) followed by a transcatheter evaluation and potential ablation if required [3, 6].

We therefore sought to further investigate and to define the type of electrophysiological findings during surgery and compare them with the evaluation at the time of the second step of the hybrid approach (electrophysiological procedure); finally, we analysed the potential correlation with the results in terms of sinus rhythm restoration over the post-procedural time course.

MATERIALS AND METHODS

Study population

Forty-five patients with stand-alone AF underwent a hybrid procedure combining a surgical closed-chest posterior left atrial and pulmonary-vein isolation (box lesion) first, followed by transcatheter evaluation at least 1 month afterwards. Demographic data are provided in detail in Table 1: in particular, all patients had long-standing persistent AF.

Electrophysiological end-points (i.e. entrance/exit block) and findings (i.e. potential gaps in the box lesion), and the correlation with rhythm outcomes, were assessed at different time points: at the completion of the surgical ablation (T1), during (T2) and at

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Patients (N = 45)

<table>
<thead>
<tr>
<th>Age</th>
<th>62.3 ± 9.8</th>
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</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>12 (26.7%)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>6 (13.3%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14 (31.1%)</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>17 (37.8%)</td>
</tr>
<tr>
<td>Obesity</td>
<td>17 (37.8%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>34 (75.6%)</td>
</tr>
<tr>
<td>Arteriopathy</td>
<td>9 (20.0%)</td>
</tr>
<tr>
<td>Previous thromboembolic events</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Log EuroSCORE II (%)</td>
<td>1.17 ± 0.5</td>
</tr>
<tr>
<td>Atrial fibrillation type</td>
<td>100%</td>
</tr>
<tr>
<td>Long-standing persistent</td>
<td>100%</td>
</tr>
<tr>
<td>Mean atrial fibrillation duration (months)</td>
<td>83.8 ± 69.1</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>56.3 ± 7.0%</td>
</tr>
<tr>
<td>Left atrium dimension (mm)</td>
<td>51.3 ± 9.7</td>
</tr>
</tbody>
</table>

the end (T3) of the transcatheter evaluation and at 28-month follow-up (T4).

**Surgical technique**

The surgical procedure has been previously described in detail [6, 7]: briefly, a thoracoscopic, monolateral, right-sided, closed-chest approach was utilized in order to deliver a continuous lesion encircling the origin of all pulmonary veins (‘box’ lesions set) by means of a temperature-controlled, internally cooled radiofrequency monopolar device with suction adherence (COBRA ADHERE XL, Estech, San Ramon, CA, USA).

At the completion of the surgical ablation, an intraoperative evaluation of conventional electrophysiological end-points was performed in order to demonstrate entrance and/or exit block across the box lesion. In case of the absence of spontaneous recovery of sinus rhythm, an electrical cardioversion was performed. As per the recommendations from the 2012 Heart rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society (HRS/EHRA/ECAS) expert consensus paper [8], potential PV reconnection was tested at least 20 min following the PV isolation: at a minimum, at least unidirectional block had to be reached through the box lesion; if such an end-point was unmet, additional ablations were delivered until either entry or entry block (or both) were obtained.

From the technical standpoint, electrophysiological assessment was performed as follows: before the surgical procedure, a 6-Fr decapolar endocardial catheter (P-SUPRA CS, Webster, Diamond bar, CA, USA) was positioned in the electrophysiological lab at the level of the coronary sinus and connected to an electrophysiological workstation. Once the surgical ablation had been completed, a tetrapolar catheter (Avail, Josephson Curve, Type A, Webster, USA) was introduced through a port and advanced epicardially within the box lesion (at the level of the right pulmonary veins and the roof of the left atrium) and connected to the electrophysiological workstation as well: therefore, one catheter was within (at the level of the posterior LA), and the other outside (in the coronary sinus), the box lesion. To test for exit block, pacing was performed from the catheter within the box lesion while sensing with the one in the coronary sinus or vice versa to confirm the presence of entrance block; in either instances, the maximum pacing output was 20 mA.

**Transcatheter technique**

All patients underwent an additional transcatheter evaluation within a timeframe of 30–45 days following the surgical ablation: the maintenance of an effective pulmonary-vein isolation was assessed and if required, additional transcatheter ablations were performed.

In particular, a decapolar endocardial catheter (P-SUPRA CS) was positioned at the level of the coronary sinus and an octopolar one at the level of the His bundle (Parahisian, Webster, USA); then, following a trans-septal puncture, a Navistar-Thermocool catheter (Webster, USA) was advanced into the left atrium, which was evaluated by means of non-contact mapping (CARTO-Merge, Webster, USA).

In case of evidence of PV reconnections, the presence of complex atrial fractionated electrograms (CAFÉs), or if patients had a history of typical atrial flutter (requiring a cavo-tricuspid isthmus ablation), tailored additional transcatheter ablations were delivered.

Non-inducibility of AF and flutter was confirmed by means of atrial rapid pacing.

**Follow-up**

All patients were implanted with an implantable loop recorder (Reveal XT, Medtronic, MN, USA) at the time of surgery and continuously monitored up to the latest follow-up. The data from the Reveal XT were remotely retrieved via the CareLink Network (Medtronic) on a monthly basis, in order to rule out AF recurrences and relative burden. As previously reported, stable sinus rhythm was considered as the absence of AF episodes duration <5 min and an overall burden of 0.5% of time spent in AF on a monthly basis [6, 9, 10].

**RESULTS**

**Perioperative outcomes**

Endoscopic surgical ablation was successfully performed in all cases and no intraoperative complications occurred. Mean ablation and overall procedural times were 33 ± 6 and 85 ± 9 min, respectively. All patients were extubated in the operating room at the completion of the procedure without any need for intensive care unit stay; and the postoperative course was uneventful in all cases, with a mean hospital stay of 3.9 ± 1.4 days. Hospital mortality was 0%.

**Electrophysiological end-points**

At the completion of surgical ablation (T1), spontaneous restoration of sinus rhythm occurred in 66.7% of patients (30 of 45), while in the remaining, an electrical cardioversion was successfully performed (15 of 45, 33.3%). At this time point, exit and entrance blocks were assessed as described above in the Materials and Methods section: in particular, exit block was achieved in 100% and entrance block in 91.1% (41 of 45) of patients, respectively. Therefore, all patients could reach at least a unidirectional block (exit block in our series), whereas the bidirectional block was achieved in above 90% of cases.
One-month postoperatively, during the electrophysiological evaluation (T2), conduction block (either entrance or exit) was maintained unchanged (Fig. 1): therefore, in 4 patients, only exit block was present. Interestingly, among those 4 patients with an unidirectional block, in 3 (3 of 45, 6.7%), a PV reconnection could be identified and was therefore targeted by a transcatheter approach; CAFEs could be identified in the remaining patient with the unidirectional block. Figure 2 outlines a breakdown of the additional transcatheter ablations, namely targeted at PV reconnections (6.7%, 3 of 45 patients), CAFEs (44.4%, 20 of 45 patients) or cavo-tricuspid isthmus ablation (24.4%, 11 of 45). No lesion to the mitral annulus was created at the time of the electrophysiological evaluation.

At the end of the transcatheter procedure (T3), the presence of a bidirectional block could be documented in all cases (Fig. 1).

Rhythm outcome

The overall trend in terms of sinus rhythm restoration is depicted in Fig. 3: after the first 6 months, the conversion to sinus rhythm was maintained almost stable in the study population up to a mean follow-up of 28.4 ± 1.7 months, with 88.9% (40 of 45) of patients free from AF.

A more detailed breakdown of rhythm outcome with respect to the type of conduction block achieved (i.e. either unidirectional or bidirectional) is provided in Fig. 4: in particular, in those patients with the bidirectional block, sinus rhythm restoration improved steadily from 78 (32 of 41 patients) at the end of the surgical procedure (T1) to 82.9 (34 of 41 patients) at the beginning of the staged electrophysiological evaluation (T2) and finally 92.6% (38 of 41 patients) at the end of the follow-up time (T4).

DISCUSSION

The interventional treatment for long-standing persistent AF represents a major clinical challenge: from the surgical standpoint, the Cox-maze procedure represented the gold-standard option so far [11], albeit the significant degree of invasiveness and its technical complexity having hampered a wide diffusion in clinical practice; similarly, percutaneous techniques have demonstrated poor results in the long term even after several repeated procedures [12].
The possibility of merging both approaches, i.e. minimally invasive surgical and percutaneous, has recently emerged as an additional option in the treatment of persistent AF: in particular, preliminary reports have been providing encouraging results with a reduced rate of potential complications [3–6, 13]. In particular, our group recently reported the benefits of a sequential, staged procedure combining a surgical wide isolation of the posterior left atrium and the pulmonary veins by means of a box lesion set (via an endoscopic approach) followed by a transcatheter evaluation and additional ablation (if required), one-month postoperatively [3, 6].

Nevertheless, the potential modifications in terms of electrophysiological findings during the surgical ablation and the subsequent transcatheter procedure and finally the correlation with mid-term results have not been fully elucidated so far: we therefore investigated the potential changes occurring to electrophysiological findings and endpoints during surgery and compared them with the evaluation at the time of the second step of the hybrid approach (electrophysiological procedure); finally, we analysed the potential correlation with the results in terms of conversion to sinus rhythm over the follow-up period.

The main goal of any successful linear ablation is the possibility of achieving electrical isolation [HRS guidelines]: the possibility of having electrophysiological tools available in the surgical theatre allowed for a more refined assessment of the surgical ablation, rather than evaluating only the restoration of sinus rhythm per se. The first electrophysiological end-point we analysed was the possibility of reaching conduction block: as outlined above in the Materials and Methods section, our protocol implied reaching at least unidirectional block (either entrance or exit) through the box lesion; if such an end-point was unmet, additional ablations were delivered until either unidirectional or bidirectional block was obtained. At the end of the surgical ablation (T1), we could achieve exit block in all instances, while a concomitant entrance block was observed in above 90% of patients (91.1%, 41 of 45), but not in all cases: the first relevant finding at the time of the second step—transcatheter evaluation (T2) was that the same results were maintained one-month postoperatively. Therefore, the surgical ablation device utilized in the current series was able not only to acutely achieve bidirectional block in the majority of patients (or at least exit block in all of them), but such results were maintained unchanged also in the ‘chronic’ setting (i.e. one-month postoperatively). Moreover, at the end of the second step—transcatheter evaluation (T3), all patients had reached the optimal end-point for an electrical isolation following ablation, i.e. bidirectional block (Fig. 1).

In case of a unidirectional block, it could be debatable whether entrance or exit block should be the goal: the 2012 HRS/EHRA/ECAS expert consensus paper states that there is no univocal opinion about the optimal electrical end-point (either entrance or exit block), albeit the vast majority of studies tending to favour the achievement of entrance block [8]. In our series, we could observe that the presence of acute bidirectional block at the end of the surgical ablation was, in general, associated with the absence of early pulmonary-vein reconnections as well as improved rhythm outcomes throughout the postoperative course (Fig. 4). If confirmed by further evaluations on larger series of patients, such an observation may potentially impact clinical practice: in fact, currently, the only tools available in the surgical armamentarium allow only for the assessment of exit block that could represent a suboptimal end-point for electrical isolation; therefore, rather than relying on such tools, the majority of surgeons should integrate more sophisticated techniques and devices such as as those routinely utilized by any electrophysiological lab.

Furthermore, another advantage of a sequential, staged transcatheter procedure was the achievement of the optimal end-point in terms of electrical isolation (bidirectional block) in all cases: therefore, if the surgical ablation fails to reach such an end-point in the first instance, the delayed transcatheter ablation could ‘fill the gap’ and account for the relevant rates of success at mid-term. In particular, as outlined in Fig. 3, the high success rates were maintained at a mean follow-up of 28 months: therefore, it could be likely that the combination of the surgical and transcatheter approaches could overcome the poor results of electrophysiological ablation alone as recently reported [12].

In the current series, around one-third of patients (28.9%, 13 of 45) did not receive any additional ‘touch-up’ during the sequential, staged electrophysiological evaluation: therefore, it is likely that such subgroup of patients may have undergone unnecessary electrophysiological procedures following the surgical ablation. However, we believe that a larger series of patients is warranted in order to further confirm our preliminary results and potentially lead to a more tailored approach: for example, we foresee that a patient may not undergo a second electrophysiological step based on the electrophysiological findings during surgical ablation (i.e. confirmation of entrance or bidirectional block) and the absence of AF recurrences (assessed with an implantable loop recorder).

In conclusion, a surgical box lesion set by means of an epicardial ablation can achieve bidirectional block in the majority of cases, which can be maintained afterwards and can lead to incremental benefits in terms of sinus rhythm maintenance in patients with long-standing, persistent AF.

Conflict of interest: Claudio Muneretto and Gianluigi Bisleri disclose a financial interest with Estech, San Ramon, CA, USA.

REFERENCES


Dr. C. Kik (Rotterdam, Netherlands): The patients you chose were those with long-standing persistence, not the easiest group. We all know that the complete Maze procedure is the best procedure for this. You chose to perform an elegant other Maze, let me call it this. I think it is nice; it is left and right. Can you tell me why you chose this procedure? Is it because that it is possible with minimally invasive surgery or was your decision based on other factors? Dr. Muneretto: Yes. Your question obviously addresses the issue of why the Maze operation, a perfect operation, was not applied over the years, and was done only in very few patients around the world. The answer is very simple. It is much too invasive, and obviously there were no patients in whom cardiologists advised such a procedure. And for that reason, during the past years, many people have tried to develop a minimally invasive approach for the treatment of atrial fibrillation. We definitely chose that kind of approach for persistent AF in developing this hybrid procedure. Hybrid means that you take the best from surgery, and you take the best from the transcatheter approach, trying to eliminate the worst aspects of any single procedure. We take the best of the surgical lesion, represented by isolation of the posterior wall of the left atrium and of all the pulmonary veins, and we tried to eliminate the worst, which is obviously its invasiveness. Same thing for the transcatheter approach. We take the best which is the right side lesion. If required, we consider the possibility of treating fragmented potentials, which may have additional value for very long-standing disease. Therefore, the hybrid approach combines the best from both techniques, and this is the reason why we chose this type of approach.

Dr. Kik: Secondly, can you comment on what the electrophysiologists found? Where were the gaps? Where were the difficulties? Were they on left side, the right side, or were they all over the place?

Dr. Muneretto: Gaps have been found in approximately 6% of the entire population, very dependent on the anatomy of the patients and especially the amount of fat pad all around the left atrium. Fat pad is a barrier for any type of energy source, including radiofrequency, laser, whatever, because obviously it is a type of insulation that God invented to protect us from thermal exchange and is very effective for such a purpose. Fat pad is located especially close to the Waterston’s groove, to the superior right pulmonary vein and to the superior left pulmonary vein. Sometimes we have some gaps that are unresponsive to any type of device, including the bipolar clamp. This fat pad did not allow thermal transmission, and in such patients you will have a gap in those areas.

Dr. S. Benussi (Milan, Italy): I have a couple of questions. First of all, a comment regarding entrance block and exit block. I totally disagree with Professor Muneretto’s position on this because actually the most practical electrophysiological assessment during surgery is exit block validation. And transmurality results show there are some patients in whom exit block is not achieved while you have entrance block. But I cannot figure any instance in which you might see it the other way around. So if all the exit blocks mean total bidirectional isolation and some of the entrance blocks are not bidirectional, my point is that exit block is the strongest predictor of a good job. Therefore I disagree with your assumption that entrance block is the optimal predictor of ablation success (as opposed to exit block); I think it is exactly the other way around. What the electrophysiological cardiologists state in the guidelines relates mainly to catheter ablation in the electrophysiological lab. It is probably not targeted to the surgical arena.

Then my first question is: you are the only one to report this 100% isolation, or over 90% isolation rate, with unipolar radiofrequency on the epicardial surface, while everybody else is leaving unipolar radiofrequency due to unsatisfactory transmurality results. Are you doing something different in the operating theatre? Are you doing double ablations? Are you overburning, or are you testing in a different way?

And my last question is, why do you that very original burning in the side of the right atrium? The few times in which I happened to ablate that area with bipolar radiofrequency, it actually turned into a high rate of sinus node dysfunction. The sinus node is very close, actually, in that triangle you nicely portrayed in the lateral side of the right atrium. I wonder why you do it?

Dr. Muneretto: I am sorry that there has been such a consistent misunderstanding from your side about our presentation, especially with respect to the achievement of an exit or entrance block. We achieved exit block in all patients while entrance block was achieved in 91% of patients. I did not invent the HRS guidelines; they were developed to define isolation of the left atrium by our colleagues, the electrophysiologists. Whenever we address the issue of atrial fibrillation, we should use and we should have common end points with the electrophysiologists. I do not know if you believe that you personally could be better than an electrophysiologist in establishing a new definition and new end points, but definitely from this point of view, I do not. I do follow the HRS guidelines, and I adopt also the end points of the electrophysiologists.

There are important differences between the achievement of exit and entrance block. The main difference is related to the conduction velocity. Any kind of ablation introduces a considerable delay in conduction velocity through the ablation line. This considerable delay particularly influences the exit block, and this is the reason why sometimes the exit block is a false sign of isolation. In other words, when you measure the entrance block, especially with a decapolar catheter in the coronary sinus, we would be able to reach any electrical signal coming from the outside. This is the best evaluation that we can perform so far. In any case, I did not choose this evaluation myself. I had several EP consultants, including the most important ones in Europe, trying to establish the best end point for the surgical EP activity, and this is the reason why we chose these end points.

This study addressed the issue of how the surgical community is evaluating the AF ablation results. And my personal point of view, even if you could disagree, is that we should respect the work of people that are working in this field, the electrophysiologists, and we should share with them the same - I have to stress again - the same end points without trying to introduce anything new in such a field.

The last issue is the same every time and concerns the use of monopolar technology and how monopolar could be effective in reaching isolation. This is a never-ending debate that divided the surgical community. I do not want to spend any more time discussing this issue. The only thing that I can say is that the EP community acts as a unique entity. They try to support each other and defend their activities.

There is a funny tendency within the surgical community in which surgeons divide themselves, trying to oppose one technique or device in favour of another. And this tendency, until now, has destroyed our reputation as a community and destroyed our possibility to impact seriously from the clinical point of view on the issue of atrial fibrillation. I would disagree with you in relation to almost all of your comments.

Dr. Benussi: Yes, but you did not reply to my second and third questions. How come all of your 41 patients leave the operating theatre with a total exit block? Is it something in the ablation procedure that you do differently from other surgeons, or is this something you do differently in the electrophysiological assessment of the pulmonary veins?

Dr. Muneretto: No. It is very simple. We try to reach the end point in all cases. Most surgeons are simply doing the ablation, supposing that this is enough to create an effective isolation. This is true even if you use a bipolar clamp or any kind of device. We do the ablation with the idea in our minds to reach the end points, and the end point for us is at least the exit block. By doing that and prolonging the duration of ablation from the standard of 5–8 min to even 15 or 20 min, you should be able to achieve isolation and exit block in almost all patients. This is the end point of the procedure, and we believe that this procedure should reach some end points. Once you select your endpoints, usually you should reach them. We are not the only group able to achieve isolation and exit block in all patients. This is a matter of how you perform the ablation.