Electrophysiological efficacy of Epicor high-intensity focused ultrasound†

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Abstract

OBJECTIVES: Clinical success of atrial fibrillation (AF) ablation depends on persistent blocking of electrical conduction across the ablation lines. Epicor high-intensity focused ultrasound (HIFU) ablation has been credited with a variable clinical efficacy. The aim of this work is to ascertain the electrophysiological (EP) efficacy of such lesions, by assessing pulmonary vein isolation (PVI) after open chest HIFU ablation, in the clinical setting.

METHODS: Ten consecutive mitral patients (mean age: 57 ± 10 years) with paroxysmal AF undergoing concomitant ablation with the Epicor ablation system (St. Jude Inc., Minneapolis, MN, USA) were enrolled for EP assessment. During surgery, pairs of additional temporary wires were positioned on the right PVs (RPVs) and on the roof of the left atrium (RLA), before epicardial ablation. Exit block (no capture during PV pacing) of RPV and of RLA was assessed before, after ablating and immediately after closure of the chest, in order to check the correct positioning of the wires. EP assessment was repeated before discharge and at 3 weeks.

RESULTS: Baseline RPV pacing threshold (PT) was 3.5 ± 2 mA (range 1.5–8), of RLA 1.73 ± 1.1 mA (range 0.7–4.3 mA). PVI was not reached any time after HIFU ablation. At the pre-discharge EP study, the absence of isolation was observed in all cases. At 3 weeks, the PTs were 6.8 ± 5.8 mA on RPV (range 2–16) and 6.4 ± 5.3 mA (range 1–19) on RLA. All patients were discharged in sinus rhythm.

CONCLUSIONS: PVI was not achieved after Epicor HIFU ablations, up to 3 weeks after surgery.

Keywords: Arrhythmia • High-intensity focused ultrasound • Conduction block • Atrial fibrillation • HIFU ablation

INTRODUCTION

Durable transmurality of the ablation lines is instrumental to the successful cure of atrial fibrillation (AF). One of the key aspects of AF treatment consists in ablating the pulmonary vein (PV) ostia, obtaining their electrical disconnection [1–3].

Despite the significant advances that characterized ablation technology during the past decade, linear uninterrupted lesions proved difficult to obtain epicardially with unipolar devices. In particular, only bipolar radiofrequency appears to be reproducibly transmural from the epicardium, on the beating heart [4, 5].

Epicor is a unipolar ablative platform that uses high-intensity focused ultrasound (HIFU) to create a box lesion around the four PVs and a mitral connecting line epicardially to the beating heart. Although the clinical value of HIFU has been investigated in a number of studies, with variable results [6–9], its electrophysiological (EP) efficacy has never been systematically studied.

We assessed the evolution of the conduction across the PV box ablation performed with HIFU, by pacing from additional strategically positioned atrial temporary wires.

MATERIALS AND METHODS

Patients

Ten patients underwent mitral valve surgery and concomitant AF treatment with HIFU, between April 2010 and July 2010.

In all patients, indication for ablation was paroxysmal AF, documented by means of EKG or 24-h Holter monitoring before hospital admission as self-terminating AF episodes.

Preoperative data are summarized in Table 1.

The study protocol was approved by our Institutional Review Board, and informed written consent was signed by each patient.
before surgery. All enrolled patients agreed to stay at our institution until completing the post-operative rehabilitation period.

Preoperative data performed in all patients were coronary angiography, transoesophageal echocardiography (also to rule out atrial appendage thrombi) and 24-h Holter monitoring. Eight patients were hospitalized under antiarrhythmic drugs (AADs): five patients under sotalol and three patients under flecaïnide. The patients under AADs stopped all the drugs a minimum of five half-lives before the 24-h Holter monitoring.

At follow-up, a 12-lead electrocardiogram, 24-h Holter monitoring and transthoracic echocardiography were performed at 3, 6 and 12 months after surgery.

System description and surgical technique

All ablations were carried out using the Epicor Medical HIFU Ablation System (Epicor Medical, Inc., St Jude Medical Company), which consists in an array of transducers (UltraCinch; Epicor) positioned on the epicardium after proper sizing around the four PVs, over the antral portion of the left atrium (LA). HIFUs are deployed sequentially by the single transducers across three phases, focussing different depths of the LA wall (deep, intermediate and surface). The device creates a circumferential box lesion around the four PVs in ≏ 10 min. Such a lesion pattern was completed in all patients by making a linear ablation extending from the lower PV orifice to the region of the mitral valve annulus with an additional linear tool (UltraWand; Epicor), employing the same ultrasonic acoustic energy. The apex of the heart was lifted and the handheld UltraWand was placed in position to create the linear lesion from the box line to the atrioventricular groove, in the coronary-free area, as identified by coronary angiography and direct inspection. After HIFU ablation, cardiopulmonary bypass was instituted. The ostium of the left appendage was sutured from the inside in all patients and the mitral disease was then addressed.

Table 1: Preoperative data

<table>
<thead>
<tr>
<th>Variables</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>10</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57 ± 10</td>
</tr>
<tr>
<td>Female gender</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>II</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Duration of atrial fibrillation (year)</td>
<td>3.3 ± 4.5</td>
</tr>
<tr>
<td>Atrial fibrillation type</td>
<td></td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>Persistent</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td></td>
</tr>
<tr>
<td>Mitral</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>Tricuspid</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>46 ± 6</td>
</tr>
<tr>
<td>Left atrial volume (mm)</td>
<td>108 ± 44</td>
</tr>
<tr>
<td>Telediastolic left ventricular diameter (mm)</td>
<td>62 ± 7</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>63 ± 4</td>
</tr>
</tbody>
</table>

Values are expressed as number (percentage) for discreet variables and as mean ± standard deviation for continuous variables.

EP and clinical assessment

Pairs of additional temporary wires (6494F, Medtronic Inc., Minneapolis, USA) were transfixed both on the right PVs (RPVs), close to their atrial ostium (Fig. 1) and on the roof of the LA (RLA), in the proximity of the Bachmann bundle, during surgery. We chose to test both the RPV and the RLA in order to have a more reliable EP validation of the circumferential ablation around the four PVs.

Pacing thresholds (PTs) from all atrial wires were assessed at baseline and after the circumferential ablation around the PV, using an external temporary pulse generator (5833, Medtronic Inc.).

Further, the same assessment was repeated after chest closure and after the removal of chest drains, to rule out possible dislodgement of the wires, before discharge from the division and 3 weeks after surgery, before leaving the rehabilitation unit of our hospital.

By definition, the exit block was considered significant when no capture was obtained at 20 mA, the maximum output of our pulse generator [10, 11].

After completing the 3-week control, the wires were removed and a transthoracic echocardiogram was performed the following day in order to rule out pericardial collection, before discharge.

HRV analysis

A 24-h Holter recorder (Mortara™ Instrument Inc., USA) was used for a 10-lead ECG recording before the intervention and 12 months after.

The calculation of the heart rate variability (HRV) parameters of the resulting N–N series was carried out on KUBIOS (The Biomedical Signal and Medical Imaging Analysis Group,
Department of Applied Physics, University of Kuopio, Finland, also based on Matlab v.2008a.

Following the standard recommendation on HRV analysis, the following parameters were calculated [12]:

(i) SDNN (standard deviation of the N–N intervals in the portion of signal considered),
(ii) RMSSD (squared root of the mean-squared differences between successive N–N intervals): higher values are correlated with higher vagal activity,
(iii) pNN50 (percentage of difference between two adjacent intervals that is longer than 50 ms): higher values are correlated with higher vagal activity,
(iv) LF [power spectrum estimate for the low-frequency band (0.01–0.04 Hz)], accounting for the sympathetic activity and
(v) HF [power spectrum estimate for the low-frequency band (0.04–0.15 Hz)], accounting for the vagal activity.

Both frequency and time domain-related parameters were calculated over a time span of 24 h and also two intervals of 3 h during day-time and night-time, respectively.

All results of HRV analysis were presented as percentage variations from the preoperative baseline to the 1-year follow-up (Table 2).

Data analysis

No formal sample size calculation was performed. The study was designed as a pilot study as no previous data were available. Statistical analysis was conducted using the JMP 8.0 package (SAS Institute, Inc., Cary, NC, USA). The PTs, grouped for the site of measurement, were compared with a Friedman test. The variations in the HRV parameters were tested with a Wilcoxon signed-rank test. All results are presented as median (first quartile; third quartile) for continuous variables and as proportion (%) for categorical variables; P-values of <0.05 were considered statistically significant.

RESULTS

Clinical

Before the operation, no patients documented episodes of AF during the 24-h Holter monitoring. Nine patients underwent mitral valve repair (positioning of neochordae in six patients, in five cases posteriorly and in one patient on the anterior leaflet) with implantation of a partial flexible ring; in two patients, concomitant tricuspid annuloplasty was associated.

One patient required mitral mechanical prosthesis valve replacement, due to extensive calcific degenerations of the posterior segment of the mitral annulus, involving the leaflet.

The mean cardiopulmonary bypass duration was 60 ± 12 min.

All patients survived, without any complication. Post-operative length of stay was 6 ± 2 days and all patients were discharged in sinus rhythm.

After a mean follow-up of 12 ± 1 months, the latest control at our institution showed sinus rhythm in all patients, with five (50%) patients free from antiarrhythmic medications. In fact, five patients were under AADs because one patient experienced episodes of AF due to thyroid dysfunction caused by amiodarone treatment and after atrial tachycardia requiring flecainide; one patient experienced atrial flutter 4 months after the operation, treated with DC shock and after sotalol treatment was maintained; another patient had symptomatic tachycardias, requiring sotalol prophylaxis. Another two patients maintained AADs after surgery because of the preventive policy of their local cardiologists.

The patients under AADs stopped all the drugs a minimum of five half-lives before the 24-h Holter monitoring. All the patients (100%) were in sinus rhythm.

EP study

During surgery, the median of the PTs considered as baseline was 3.3 (2.0; 4.5) mA (range 1.5–8 mA) on the RPV and 1.3 (1.1; 2.0) mA (range 0.7–4.3 mA) on the RLA.

The absence of isolation persisted in all patients at chest closure and after the removal of chest drains (Fig. 2).

At pre-discharge EP study, the median of the RPV PTs was 6.8 (3.0; 7.6) mA (range 1–7.8 mA), and the median of the RLA PTs was 5.0 (3.3; 7.6) mA (range 1.5–17 mA).

At 3 weeks, the median of the PTs was 4.0 (2.4; 11.6) mA from the RPV and 5.5 (3.3; 7.4) from the RLA (range 2–16 and 1–19 mA, respectively).

Complete isolation, as identified by the simultaneous absence of capture from both the RPVs and the RLA leads in the same patients, was never obtained.

Friedman statistics showed a significant difference in the average PT values over time (P < 0.05).
Heart rate variability

The 24-h Holter recordings for HRV analysis were available for eight patients at a mean follow-up of 12 ± 1 months. The comparison of the R-R series with the preoperative baseline showed a statistically significant decrease (P < 0.05) in all the HRV parameters for all the time periods considered, as shown in detail in Table 2.

The variations in the time domain parameters correlated with vagal influence (SDNN, RMSSD and pNN50) showed comparable results both at night-time and at day-time, with a slightly (<10%) larger reduction during the night-time with respect to the day-time.

On the side of the frequency domain parameters (LF and HF, indicating, respectively, the sympathetic and the vagal tone), over the 24 h, the power spectral density (PSD) in the HF band reduced by −80.0 (−89.5; −68.4) %, whereas in the LF band, the reduction was −84.7 (−92.0; −45.9) %, showing close relative variations for both the frequency bands (Fig. 3). In particular, HF reduced mostly during the night [−83.4 (−90.1; −78.2) % against a reduction of −78.0 (−94.4; −58.9) % during the day] with absolute values of HF lower during the night-time than the day-time.

The mean heart rate over the 24 h was 74 ± 8 bpm, 11% higher than the preoperative level.

DISCUSSION

Electrical isolation of the PVs was not reached at any time up to 3 weeks after HIFU ablation. This is the first study to systematically assess the EP properties of HIFU ablation in the surgical setting.

Conversely, clinical results have been described in a number of reports, in which the success rate has a wide variation [6-9]. Groh et al. [7] reported an overall freedom from AF or left-sided flutter of 86.2% (in which 51% were patients with concomitant permanent forms) at 18 months, whereas in the European experience published by Ninet et al. [6], the overall success at 6 months was 85% (80% in patients with permanent AF, which constituted 74% of the enrolled patients). Instead, results reported by Klinkenberg et al. [8] at 1-year follow-up showed an extremely low efficacy of the ablative platform, with freedom from AF of 27% (only lone AF forms).

In a very thorough analysis of their experience at the Northwestern Memorial Hospital, McCarthy et al. described a 43% of freedom from AF at 1 year (in which 75% of the patients were affected by paroxysmal AF forms and the majority performed a standalone procedure). Nine patients with relapsing AF (out of 24) underwent EP analysis and reablation after the procedure: mapping disclosed an absent isolation of the PVs [9].

There is considerable evidence supporting the correlation between complete electrical isolation and clinical efficacy of ablation, since the major predictor of arrhythmia recurrence after catheter ablations is the absence of PVI, indicating restored PV conduction or ineffective PV disconnection [2]. Furthermore, recorrection of failed PVI through repeat ablation leads to improved clinical control of AF [13]. Such a direct cause-effect relationship between PVI and cure rate supports the central role of durable transmurality of the ablations in AF treatment [13, 14].

This notwithstanding, despite the penetration properties of HIFU ablations being extensively studied at histology, there is no evidence of any relationship between HIFU ablation and electrical block even in the animal model [15, 16].

Perioperative EP assessment through the pacing wires is a convenient way to gain information of the post-ablation block due to its simplicity and safety profile. In a similar study setting, multiple ablations with bipolar irrigated radiofrequency (RF) around the RPV couple yielded complete acute block in 100% of the patients which persisted at 3 weeks in 62% of the patients [11].

It has been hypothesized that HIFU lesions might ‘mature’ with time and that, based on this, post-ablation immediate

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**Table 2:** Results of the HRV analysis. The values are expressed as per cent variation of the HRV parameters from baseline to 1 year after monitoring

<table>
<thead>
<tr>
<th>%change 24 h</th>
<th>Day</th>
<th>Night</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN</td>
<td>−29.63, −43.0, −18.8 (P = 0.0078)</td>
<td>−42.8, −55.6, −29.2 (P = 0.0156)</td>
</tr>
<tr>
<td>RMSSD</td>
<td>−43.02, −61.8, −21.4 (P = 0.0391)</td>
<td>−43.4, −70.5, −27.4 (P = 0.0078)</td>
</tr>
<tr>
<td>pNN50</td>
<td>−70.3, −97.0, −55.1 (P = 0.0078)</td>
<td>−47.2, −97.3, −18.3 (P = 0.0156)</td>
</tr>
<tr>
<td>LF</td>
<td>−84.7, −91.9, −45.9 (P = 0.0078)</td>
<td>−91.0, −95.3, −69.8 (P = 0.0078)</td>
</tr>
<tr>
<td>HF</td>
<td>−80.0, −89.5, −68.4 (P = 0.0078)</td>
<td>−78.0, −94.4, −58.9 (P = 0.0078)</td>
</tr>
</tbody>
</table>

All Wilcoxon signed-rank tests showed a double-tailed P < 0.05.
testing to assess effective electrical isolation in the operating room could be avoidable, due to the scarce prediction of late clinical success [7]. In our opinion, this attitude is simplistic. Apart from the fact that the increase in PTs recorded from within the HIFU ablation around the four PVs along the first 3 weeks was similar to that occurring in the unablated right atrial leads, this can be consistent with a normal foreign body reaction around the electrodes.

Our findings might well explain the unsatisfactory clinical results reported by other authors with HIFU. Despite absent PVI, our clinical results were consistent with a fair freedom from arrhythmia in most patients. This topic must be pondered considering the small size of our study group and that all of our patients had paroxysmal AF, which may be easier to cure.

Furthermore, the correction of the mitral valve disease and the modulation of the autonomic nervous system (ANS) induced by the HIFU ablation on the epicardium of the LA might have played a role in abating the AF burden. In our study, we also investigated the HRV changes, comparing the results at 1 year to the preoperative status. The significant reduction in HRV parameters in the time domain is related to a comprehensive reduction in sympathovagal modulation of the heart activity. All these parameters appear to be reduced one year after the operation, but no clear unbalance is evident toward vagal or sympathetic modulation, despite the HIFU ablation on the epicardial side of the posterior LA being able to theoretically account for a higher depression of the vagal activity.

It must be said that some degree of modulation of the ANS can also be observed after the standard open heart surgery without concomitant ablation [19, 20].

Finally, it has been observed that incomplete conduction block could slow the electrical conduction and lessen the inducibility of AF, but only complete electrical block could completely eliminate the arrhythmia [21]. Today, other technologies which grant a more reproducible PVs isolation like bipolar RF or endocardial cryoenergy seem more appealing [5]. It is worth adding that incomplete ablations may also enhance drug resistant iatrogenic arrhythmias [22, 23]. In our series, one patient had a typical flutter 4 months after the operation and one reported undocumented symptomatic ‘tachycardias’ requiring sotalol prophylaxis.

In considering an optimal ablation device to treat patients with concomitant AF, proarrhythmic complications must be considered, also in light of the HRS guidelines suggesting that ablation in asymptomatic patients should be considered provided the procedure has a ‘negligible risk’ [24]. Like for other energy sources, the risk of collateral damage of HIFU entails oesophageal perforation [25] and, when the mitral isthmus line is performed, potentially also a coronary obstruction.

This study has some limitations. First of all, a small cohort of patients was enrolled. Further, the EP analysis was performed only up to 3 weeks after HIFU ablation; hence, we are unaware of any further changes in the EP conduction possibly occurring beyond this period. Another limitation is the difficulty of directly correlating the HRV changes with the clinical efficacy of HIFU ablation, because of the absence of a control group (without ablation) with the HRV and ANS function studied in the same way to determine the real effect of the ablation.

In conclusion, the EP assessment through the pacing leads showed that an effective PVI does not occur after Epicor HIFU ablations, up to 3 weeks after surgery.

ACKNOWLEDGEMENTS
This work would not have been the same without the contribution of Leonardo Mandile and Gijs Eduard de Maat to whom we owe thanks for their ardent support and valuable suggestions. We are also grateful to Andrea Pozzoli for contributing the artwork and to Giliola Calori for the valuable statistics suggestions.

Conflict of interest: none declared.

REFERENCES
APPENDIX. CONFERENCE DISCUSSION

Dr. F. Wagner (Hamburg, Germany): I think this is very interesting work. To begin with, it is very unusual that a group reports a so-called negative result, because actually HiFU failed to obtain what we all think is necessary to achieve a cure of AF, and that is exit block of true pulmonary vein isolation. So this is somewhat unusual. Still, in your paper at least you describe that you had three time points where you measured the Holter ECG, at 3, 6 and 12 months. The first question is, to put it simply, in your paper you reported that all patients were in sinus rhythm at 12 months – correct?

Dr Pozzoli: Yes.

Dr Wagner: You described in the manuscript that you saw these patients three times; were they also always in sinus rhythm at the other time points?

Dr Pozzoli: The problem was that at follow-up, the patients were in sinus rhythm, but this is a cohort of patients suffering from paroxysmal atrial fibrillation. And so our EP studies are not so easy to correlate with, or to make inferences between clinical results and the efficacy of HiFU. We had patients in sinus rhythm on antiarrhythmic drugs, 50% were on antiarrhythmic drugs, but in the same 1-year time period one patient reported atrial flutter and other patients atrial flutter of the left-atrial source. And so, yes, you are right, this is an open point of our work. It was a limitation of the study.

Dr Wagner: The second very short question is, what kind of approach do you use to get to the mitral valve? Do you go through Waterston’s groove transecting the fat pad to go directly into the left atrium or do you have a trans-septal approach?

Dr Pozzoli: No, through the Waterston’s groove.

Dr Wagner: Then you might destroy simply by this access the more important ganglia at that point, and that might also be one of the reasons why you see those changes in your heart frequency variability.

Dr Pozzoli: Through the Waterston’s groove, yes.

Dr M. Castellá (Barcelona, Spain): I understood that you were pretty effective in isolating from the autonomic nervous system, and this is kind of important, because these are paroxysmal cases in which you suppose that the ganglionic plexi are going to be more important. Nevertheless, the results were not good, so it looks as though the ganglionic plexus, a fashion of 2 or 3 years ago when they appeared to be very important, and we were searching for them and burning them one by one, are apparently not so important. What do you think?

Dr Pozzoli: This is an epicardial approach, and we reported 1-year analysis, and it has also been reported that ablation of ganglionic plexi could have a transient-like efficacy. It is possible to imagine re-nerivation during time, and it was also for this reason, I think, a good point to put as a study limitation the mid-term clinical results, because, honestly, if you want to also do another comparison with the clinical results, we must wait for longer follow-up.

Dr S. Benussi (Milan, Italy): If I may add, my personal impression is that even if ganglionic plexi ablation can possibly play an important role in curing paroxysmal A-fib, pulmonary vein isolation must be obtained in order to have maximum clinical efficacy.