Correlates of Arrhythmia Recurrence After Hybrid Epi- and Endocardial Radiofrequency Ablation for Persistent Atrial Fibrillation

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Background—Long-term efficacy of catheter-based treatment of persistent atrial fibrillation is unsatisfactory. Minimally invasive surgical ablation techniques have been developed recently, but their efficacy has never been systematically tested.

Methods and Results—Seventy patients (median age, 63.5 years) with persistent atrial fibrillation underwent epicardial thoracoscopic radiofrequency pulmonary vein isolation, linear ablation, Marshal ligament disruption, and exclusion of the left atrial appendage. The procedure was followed by electroanatomic mapping and ablation (EAM) 2 to 3 months later. Only 76% of patients were in normal sinus rhythm at the beginning of EAM. All 4 pulmonary veins and the left atrium posterior wall were found isolated in 69% and 23% of patients, respectively. Arrhythmia-free survival off antiarrhythmic drugs 12 months after EAM was 77%. Using previously ineffective antiarrhythmic drugs and reablation procedures, arrhythmia free-survival increased to 97% during follow-up (mean, 936±432 days; range, 346–1509 days). The majority of arrhythmia recurrences occurred during the first 12 months after EAM. In a multivariable-adjusted estimates, left atrium volume >165 mL, absent normal sinus rhythm at admission for EAM, and inducibility of any sustained tachyarrhythmia at the end of EAM procedure were identified as independent correlates of atrial fibrillation recurrence.

Conclusions—Our report demonstrated that the majority of patients after epicardial ablation, using bipolar radiofrequency instruments, required endocardial catheter ablation to complete the linear ablation lesions and a significant proportion of patients required spot-ablations to complete electric pulmonary vein isolation. Noninducibility of any arrhythmia after a staged hybrid procedure seemed to be the strongest correlate of long-term arrhythmia-free survival.

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Catheter ablation (CA) of atrial fibrillation (AF) has become standard treatment for patients, especially when antiarrhythmic drugs (AADs) have failed to control arrhythmia recurrence.[1] While the cornerstone of CA of paroxysmal AF is pulmonary vein (PV) isolation, catheter-based treatment of persistent and long-standing persistent arrhythmia varies across centers and among electrophysiologists. Different schools of thought have proposed and tested various approaches: staged approach,[2] linear ablation lines,[3] ablations of fractionated potentials,[4] ganglionic plexi ablation,[5] elimination of low-voltage areas in the left atrium (LA),[6] ablation of focal impulses and rotors,[7] or different combinations, which were driven mainly by unsatisfactory results reported for ablations, in general. The multicenter randomized STAR-AF II trial (The Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial Part II) found no reduction in the rate of AF recurrence when PV isolation, in patients with persistent AF, was supplemented with linear ablations or ablations of complex fractionated electrograms.[8]

As with catheter-based AF ablations, surgical methods have been evolving during the last 20 years and have resulted in the development of minimally invasive methods that can be offered to patients without any other concomitant indication for cardiac surgery. The hybrid approach has been proposed as a technique that potentially overcomes the limitations of both endocardial- and epicardial-only ablations.[9] However, published data on the efficacy of epicardially created ablation lesions is scarce, and systematic evaluations of long-term efficacy have yet to be published. No data are available for predicting recurrence of AF after hybrid treatment. This type of data is essential for understanding both the mechanisms of

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WHAT IS KNOWN

- Optimal ablation strategy for the persistent and long-standing persistent atrial fibrillation is missing. Despite of different proposed methods, long-term arrhythmia-free survival after radiofrequency catheter ablation is disappointing.
- Minimally invasive surgical methods can be nowadays offered to patients without any other concomitant indication for cardiac surgery, and the hybrid approach has been proposed as a technique that potentially overcomes the limitations of both endocardial- and epicardial-only ablation.

WHAT THE STUDY ADDS

- The efficacy of epicardial radiofrequency ablations in creating transmural linear lesions is surprisingly low, resulting in low clinical effectiveness of the 1-stage surgical approach in the treatment of persistent or long-standing persistent atrial fibrillation.
- Adding delayed endocardial ablation on top of epicardial surgical ablation led to the extraordinarily successful arrhythmia control with extremely low number of late atrial fibrillation recurrences.
- Achieving arrhythmia noninducibility at the end of hybrid procedure seemed to be the critical end point for prediction of subsequent arrhythmia-free survival.

AF and residual atrial tachycardias (ATs) after surgery, so that future developments in AF treatment can be directed toward the most promising areas. Naturally, the information is also critical for cardiac surgeons and electrophysiologists involved in hybrid AF treatment programs.

Therefore, the goal of our study was (1) to analyze the effectiveness of epicardially created lesions, using bipolar radiofrequency energy, and describe any residual arrhythmogenic substrate after completion of both parts of a strictly-defined hybrid ablation protocol and (2) to define correlates for AF recurrence during long-term follow-up.

Methods

Patients with symptomatic drug refractory persistent or long-standing AF were included in the trial. The definitions of paroxysmal, persistent, and long-standing persistent AF were based on recent guidelines.[1] All patients underwent the surgical part of the hybrid arrhythmia treatment, which followed a standardized protocol. Two to 3 months later, patients were admitted for the transvenous catheter part of the procedure. Exclusion criteria included previous CA for AF, presence of severe coronary artery disease (>60% stenosis of the main coronary arteries), moderate or severe heart valve disease, a history of stroke, previous pulmonary surgery or cardiac surgery, inability to use anticoagulant drugs, or the presence of a thrombus in the left atrial appendage.

All patients underwent transesophageal echocardiography, cardiac computed tomography with contrast, and pulmonary function tests. Patients >50 years or with symptoms of angina pectoris also underwent coronary angiography. Transesophageal echocardiography and computed tomography scans were repeated in all patients before radiofrequency CA. Oral anticoagulation therapy was discontinued 7 days before the procedure, and low molecular weight heparin was administered twice a day until the evening before the procedure. The study was approved by the local institutional ethics committee. All patients signed informed consents, and the data were recorded prospectively in a web-based database.

Surgical Technique

The surgical phase was in details described elsewhere.[10] Briefly, the procedure started on the right side with placement of endoscopic tools and after right lung deflation, the pericardium was opened anterior to the phrenic nerve from the superior vena cava to the diaphragm and gently separated and secured with 3 stitches. The oblique sinus was accessed between the inferior vena cava and the right lower PV. An articulating and illuminating dissector (LumiTip Dissector; AtriCure, OH) was used to surround the right PVs to guide insertion of an ablation clamp (Isolator Synergy; AtriCure, OH). A series of ablations (usually 5–10) around the right PVs was performed followed by verification of an entry block. If any electric activity was recorded inside the veins, further radiofrequency energy applications were administered until electric isolation was confirmed. A roof line (connecting the superior right-side and left-side PVs) and an inferior line (connecting the inferior right-side and left-side PVs) were created using a linear pen device (Bipolar Linear Pen; AtriCure, OH). Completeness of the box lesion was verified by demonstrating entry block, in cases of continuous AF, and both entry and exit blocks in cases where AF was converted to normal sinus rhythm (SR). According to the protocol, a trigone line on the roof of the LA extending from the right superior PV to the left fibrous trigonum was made. No verification of completeness of this line was performed during surgery. Ganglionated plexi were also ablated, guided by high-frequency stimulation and the vagal response. The left-side approach was similar to the right side. On top, the ligament of Marshall was dissected using scissors, and both ends were burned using a linear pen. At this point, if the patient was in AF, an electric cardioversion was performed, and the epicardial bidirectional block was confirmed for the PVs and for the box lesion. The left atrial appendage was excluded using an AtriClip device (AtriCure, OH). Low molecular weight heparin was administered 6 hours after surgery, and warfarin was commenced after removal of both pleural drains.

Catheter-Based Part of Procedure

All electroanatomic mapping (EAM) studies were performed 2 to 3 months after surgery. Cavotricuspid isthmus ablation was performed first in patients with SR, and a bidirectional block was confirmed using standard criteria. After a double transseptal puncture, a virtual 3D reconstruction and a detailed bipolar voltage LA map (minimum 300 points) was constructed using the CARTO3 mapping system. Areas with voltages <0.05 mV were considered electrically isolated. A circular mapping catheter (LASSO; Biosense Webster, Inc) was positioned in all PVs and also on the posterior LA wall to confirm isolation or electric reconnection by demonstrating the presence of both entry and exit blocks. Radiofrequency energy was applied using a 3.5-mm irrigated-tip ThermoCool Smart Touch catheter (Biosense Webster, Inc, Diamond Bar, CA). Electric reconnection sites (gaps) between the LA and PVs were mapped and targeted to achieve complete PV isolation. Similarly, both the superior and inferior connecting lines were meticulously mapped to look for gaps using stimulation maneuvers. After this step, the anterior mitral isthmus line was completed. Additionally, incremental atrial pacing, ≤300 beats per minute, was performed at the end of the procedure. If any AT was induced, the mechanism of the arrhythmia was elucidated and tachycardia sources eliminated with radiofrequency ablation using noninducibility of any arrhythmia as an end point. Mapping and ablation of ATs was performed first when it was recorded at the beginning of the procedure.

Postoperative Care and Follow-Up

After completion of the catheter phase of the procedure, all patients underwent continuous telemetric monitoring until discharge from the hospital. No AADs were prescribed at the time of discharge. Patients had follow-up visits at 3, 6, 9, and 12 months after the completed hybrid procedure and thereafter every 6 months. A 7-day ECG Holter was performed before each follow-up visit. In addition, if patients complained of palpitations and no arrhythmia was detected during Holter monitoring, they were equipped with an ECG event recorder and were instructed to record their ECG whenever they felt palpitations. Success was defined as the absence of AF or any other supraventricular arrhythmias lasting >30 seconds on any of the 7-day Holter recordings or self-recorded ECGs during the entire follow-up.

Statistics

Continuous variables are expressed as mean±SD. Shapiro–Wilk test was used to assess normality in distribution of continuous variables. Categorical variables are presented as absolute numbers and percentages. Comparisons between categorical variables were made using the McNemar test; comparisons between continuous variables were made using the Wilcoxon signed-rank test. A P value <0.05 was considered statistically significant. Arrhythmia-free survival was estimated using the Kaplan–Meier method. Correlates of arrhythmia occurrence during the first year of follow-up were assessed using univariable and multivariable-adjusted estimates of hazard ratio (estimated using Cox proportional hazard regression model). The cut-off values were determined using receiver operating characteristic curve analysis. Statistical analyses were performed using SPSS Statistics, for Windows, version 24.0 (IBM Corp, Armonk, NY).

Results

Seventy patients (49 men; median age, 63.5 years) were included in the study. Basic clinical characteristics are listed in Table 1. Basic procedural characteristics of both epicardial and endocardial procedures are listed in Table 2.

Overall, 9 (13%) major complications were recorded during the surgical part of the hybrid procedure. Two patients required conversion of the thoracoscopic procedure to a sternotomy approach because of persistent bleeding (both complications occurred among the first 10 patients), 1 patient needed a pericardial drain insertion for cardiac tamponade because of a coumarin derivate overdose (international normalized ratio, 8.0), 2 diabetic women with body mass index >35 developed an infection requiring IV antibiotic therapy, and 1 patient had a hemodynamically significant, but clinically silent, stenosis of both left-sided PVs. The most serious complications were phrenic nerve palsies, which were observed in 7 (10%) patients. Two of these patients had complete regression and full recovery of diaphragm function. The remaining 5 patients did not experience spontaneous recovery within 12 months after the procedure. One patient underwent surgical plication of the diaphragm because of severe symptoms, 2 patients were totally asymptomatic and did not require any intervention. The remaining 2 symptomatic patients had intensive physiotherapy and their symptoms had dramatically improved by the subsequent follow-up.

EAM was conducted on average 94±30 days (median, 87 days; range, 56–167 days) after the index surgical procedure. Fifty-three (76%) patients presented with a normal SR, all other patients had documented sustained supraventricular arrhythmias on a 12-lead surface ECG (Figure 1). All spontaneously running ATs were successfully eliminated using radiofrequency CA. No major complications were noted during EAM and CA. All groin hematomas were treated conservatively, and an arteriovenous fistula was successfully treated using noninvasive compression with an ultrasound probe.

Table 1. Basic Clinical Characteristics of Patients Undergoing Epicardial Ablation

Parameter	N (%) or average±SD	Median (range)
No. of patients, %	70 (100)	
Men, %	49 (70)	
Age, y	62.4±7.9	63.5 (42–75)
Body mass index, kg/m^2	30.8±4.6	30.6 (22.5–41.5)
Left atrial diameter in PLAX, mm	49.1±4.9	49 (40–59)
Left atrial volume, mL	150±34	148 (89–257)
Ejection fraction, %	64±8	65 (36–77)
Atrial fibrillation duration, mo	41.8±35	32 (9–200)
Failed electric cardioversion, %	48 (69)	
Failed antiarrhythmic drugs	1.7±0.6	2 (1–3)
Arterial hypertension, %	55 (79)	
Diabetes mellitus, %	20 (29)	
Previous stroke or transitory ischemic attack, %	9 (13)	
Hypolipoproteinemia, %	18 (26)	

PLAX indicates parasternal long axis.

Table 2. Procedural Characteristics and Complications of Hybrid Approach

	Epicardial Surgery	Endocardial Ablation
Total procedural time, min	222±48	131±38*
Fluoroscopy time, min	NA	7.2±3.9
RF time, min	NA	29.8±16
In-hospital stay, d	8.2±6.2	3.2±0.8*
Major complications (total no.), %	9 (13)	0 (0)*
Conversion to sternotomy	2 (3)	0 (0)
Permanent phrenic nerve injury (>12 mo)	5 (7)	0 (0)
Clinically significant PV narrowing†	1 (1)	0 (0)
Tamponade	1 (1)	0 (0)
Minor complications (total no.), %	11 (16)	6 (9)*
Clinically insignificant PV narrowing‡, %	7 (10)	0 (0)
Temporary phrenic nerve injury, %	2 (3)	0 (0)
Wound infection treated conservatively, %	2 (3)	0 (0)
Groin hematoma§, %	NA	5 (7)
Arteriovenous fistula, %	0 (0)	1 (1)

NA indicates not applicable; PV, pulmonary vein; and RF, radiofrequency. *P<0.001, †narrowing ≥50%, ‡narrowing <50%, §defined as colorization of the skin covering an area larger than a clenched fist.

Results of Endocardial Mapping After Epicardial Radiofrequency Ablation

Right PVs were found isolated in a significantly higher proportion of patients compared with left-sided PVs (64 [91%] versus 53 [76%] patients; P=0.006). All PVs were found isolated in 48 patients (69%). Complete isolation of the posterior

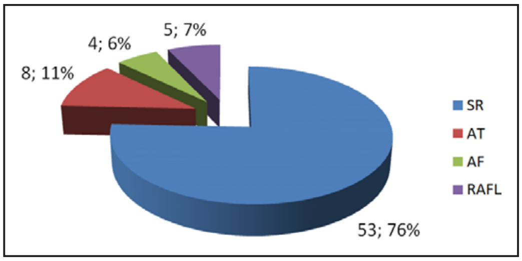

Figure 1. Cardiac rhythm in patients after epicardial surgical ablation at the beginning of electrophysiological examination. Included perimitral flutter (n=4), roof-dependent left atrial tachycardia (n=1), focal atrial tachycardia arising from the coronary sinus ostium (n=1), and right sided atrial tachycardias (n=2). AF indicates atrial fibrillation; AT, atrial tachycardia; RAFL, typical right atrial flutter; and SR, normal sinus rhythm.

LA wall was achieved in only 16 (23%) patients. The conduction block across the inferior line connecting both inferior PVs was more successful (ie, complete) compared with the roof line connecting both superior PVs (41 [59%] versus 11 [24%] patients; P<0.001). A conduction block across the trigone lesion (line connecting right superior PV to the mitral annulus) was found in only 6 (9%) patients. The AtriClip had been placed on the left atrial appendage in 62 (89%) patients. The results of AtriClip placement were published elsewhere.[11]

The majority of patients, who were not in SR, were also not in AF and presented either with ATs or typical right atrial flutter. Two of four patients presenting with AF had all PVs isolated, while in another 2 patients, reconduction was found only to the left PVs. Posterior LA wall isolation (ie, box lesion) and trigone line were not accomplished in any of these 4 patients.

All incomplete PV isolations were successfully finalized using endocardial radiofrequency applications. Creation of a conduction block along the superior (roof) connecting line was unsuccessful in 5 (10%) of 51 patients who presented with reconduction along this line after epicardial surgical ablation. Creation of a conduction block along the inferior connecting line was unsuccessful in only 1 (3%) of 29 patients who presented with reconduction along this line after surgery. In all remaining patients, complete posterior left ventricular wall isolation was achieved using endocardial ablations. A bidirectional conduction block across the anterior mitral isthmus line was ultimately successful, via endocardial ablation, in all but 2 (6%) of 64 patients who presented with reconduction. Thus, a full intended lesion set (PV isolation, box lesion, anterior mitral line, and cavotricuspid isthmus line) was accomplished in 62 of 70 patients (88.6%).

Results of Incremental Atrial Pacing

After completion of PV isolation and all linear lesions, incremental atrial pacing was conducted to test arrhythmia inducibility. In 58 (83%) patients, no sustained arrhythmia (lasting >30 seconds) was induced. Sustained AF was induced in 5 (7%) patients: in 2 patients, AF terminated spontaneously after 40 seconds in one and after 5 minutes in the other. In 3 patients, AF termination required external electric cardioversion. Eleven sustained ATs were induced in 8 patients (11%). Radiofrequency CA led to successful elimination and further noninducibility in 6 (55%) of these 11 ATs. Thus, in total, 64 patients (91%) with previously persistent and long-standing persistent AF had no inducible supraventricular arrhythmia lasting >30 seconds at the end of the procedure (Table 3).

Arrhythmia-Free Survival and Correlates of Arrhythmia Recurrence

Twelve-month follow-up was accomplished by all 70 patients, and arrhythmia-free survival, off AADs, during this period reached 77%. If we included reintroduction of AADs in 5 patients and a reablation procedure in another patient, arrhythmia free-survival at the 12-month follow-up increased to 86%. During the whole follow-up period (mean duration, 936±432 days; range, 346–1509 days), estimates of arrhythmia-free survival off AADs, according to Kaplan–Meier analysis, reached 75%, and after reintroduction of the previously ineffective AADs, our hybrid procedure success

Table 3. Spectrum of Inducible ATs After Completion of the Hybrid Procedure and Their Mechanisms

Patient	N	Localization	Ablation Success	Other Way of Termination
1	3	RA: below SVC (reentry AT)	Yes	NA
		RA: CS ostium (focal or μ-reentry AT)	Yes	NA
		RA: other multireentry ATs	No	External cardioversion
2	1	RA: appendage base (focal AT)	Yes	NA
	1	LA: interatrial septum (μ-reentry AT)	No	External cardioversion
3	1	LA: roof-dependent reentry	No	External cardioversion
4	1	LA: roof-dependent reentry	Yes	NA
5	1	RA: interatrial septum (reentry)	Yes	NA
6	1	LA: interatrial septum (reentry)	No	External cardioversion
7	1	LA: interatrial septum (reentry)	Yes	NA
8	1	LA: multireentry AT	No	Overdrive pacing

AT indicates atrial tachycardia; CS, coronary sinus; LA, left atrium; N, number of inducible atrial tachycardias; NA, not applicable; RA, right atrium; SVC, superior vena cava; and μ-reentry, microreentry atrial tachycardia.

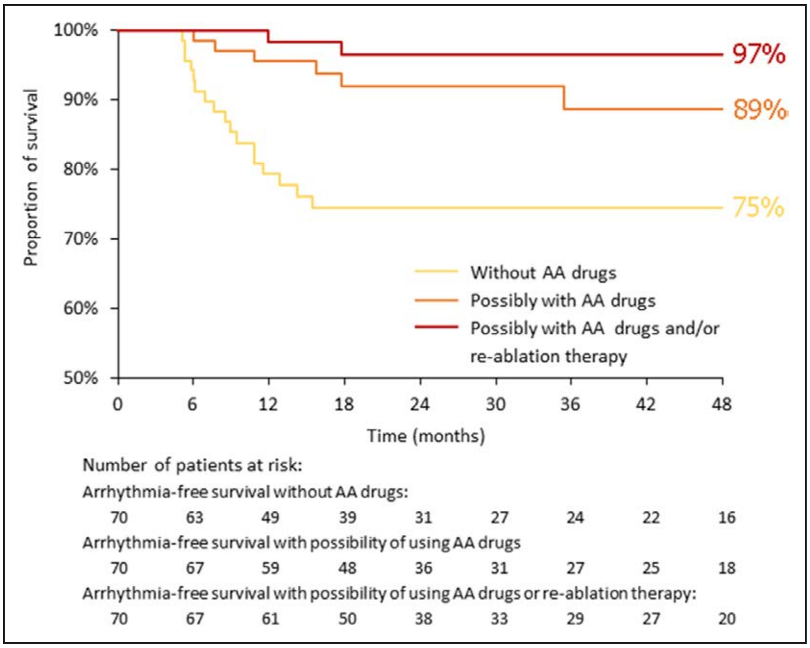

Figure 2. Kaplan–Meier estimate of arrhythmia-free survival after hybrid ablation. AA indicates antiarrhythmic.

rate increased to 89%. When repeat ablations were also included (n=3), arrhythmia control was achieved in 97% of patients (Figure 2). Interestingly, the majority of arrhythmia recurrences occurred during the first 12 months following the ablation procedure. Recurrences beyond 18 months were extremely rare.

In a univariable Cox regression, age >65 years, LA volume >165 mL, absence of SR at admission for the catheter part of hybrid procedure, and inducibility of any sustained atrial tachyarrhythmia at the end of EAM were found to be significant correlates of arrhythmia-free survival after hybrid ablation during the first year of follow-up (Table 4). The cut-off values used were determined according to results of receiver operating characteristic curve analysis.

In a multivariable-adjusted calculation, LA volume >165 mL, other than SR at admission for the catheter part of hybrid

Table 4. Correlates of Arrhythmia-Free Survival After Hybrid Ablation Considering Complete Follow-Up (Univariable Cox Proportional Hazard Regression Model)

		Univariable Cox Regression Model	
Predictor	Cut-Off	HR (95% CI)	*P* Value
Age, y	>65	3.748 (1.319–10.650)	0.013
Men		0.719 (0.266–1.945)	0.516
Body mass index, kg/m^2	<30	1.749 (0.666–4.599)	0.257
LA diameter, mm	>50	1.601 (0.617–4.155)	0.333
LA volume, mL	>165	2.584 (1.011–6.774)	0.046
Ejection fraction, %	<50	1.788 (0.409–7.822)	0.440
AF duration, mo	>48	2.241 (0.864–5.812)	0.097
Other than SR at admission		4.409 (1.698–11.448)	0.002
Both left PVs isolated		0.608 (0.225–1.645)	0.328
Both right PVs isolated		0.775 (0.177–3.392)	0.736
All PVs isolated		0.698 (0.266–1.834)	0.465
Box lesion done		1.461 (0.514–4.153)	0.477
LAA clip		0.368 (0.120–1.131)	0.081
Testing: no inducible AF or inducible AF lasting <30 s		0.269 (0.099–0.728)	0.010
Testing: induced AF lasting ≥30 s but with spontaneous termination		4.118 (1.339–12.660)	0.014
Testing: sustained AF (DCCV needed)		2.150 (0.491–9.418)	0.310

AF indicates atrial fibrillation; CI, confidence interval; DCCV, direct current external electric cardioversion; HR, hazard ratio; LA, left atrium; LAA, left atrial appendage; PV, pulmonary vein; and SR, sinus rhythm.

Table 5. Correlates of Arrhythmia-Free Survival After Hybrid Ablation Considering Complete Follow-Up (Multivariable Cox Proportional Hazard Regression Model)

Predictors	Cut-Off	Multivariable-Adjusted Estimates of HR (Forward Stepwise)	
		HR (95% CI)	*P* Value
Left atrial volume, mL	>165	3.505 (1.093–11.237)	0.035
Other than SR at admission		5.426 (1.874–15.709)	0.002
Positive testing*		7.278 (2.189–24.197)	0.001

CI indicates confidence interval; HR, hazard ratio; and SR, sinus rhythm.

*Induced atrial fibrillation or atrial tachycardia lasting ≥30 s during incremental atrial pacing, either with spontaneous termination or requiring direct current electric cardioversion.

procedure, and positive testing with inducibility of any sustained tachyarrhythmia at the end of procedure were found to be mutually independent correlates of arrhythmia recurrence after hybrid ablation during the first year of follow-up (Table 5). Kaplan–Meier arrhythmia-free survival estimate for the strongest predictor, that is, inducibility of sustained AF, is drawn in Figure 3.

Discussion

Our study highlights several important findings:

1. the surprisingly low efficacy of epicardial radiofrequency ablations in creating transmural linear lesions and the underwhelming efficacy in creating PV isolation, resulting in low clinical effectiveness of the 1-stage surgical approach in the treatment of persistent or long-standing persistent AF,
2. extraordinarily high success rate in terms of arrhythmia control using the staged hybrid approach (ie, combined epi- and endocardial ablation) as seen during long-term follow-up with an extremely low number of late AF recurrences,
3. the importance of achieving arrhythmia noninducibility as the critical end point of the hybrid procedure for prediction of subsequent AF-free survival.

We consider this information to be of utmost importance, serving both as helpful feed-back for cardiac surgeons and for electrophysiologists involved in hybrid AF treatment.

Effectiveness of Epicardial Radiofrequency Ablation

The number of surgical ablation procedures has been continuously rising because it follows the technological and methodological developments associated with mini-invasive techniques complimented by their relatively low complication rates. However, the technique of epicardially deployed radiofrequency energy using commercially available bipolar radiofrequency instruments has never been fully validated, with only a few studies assessing the effectiveness of epicardial ablations.[12–15] To our knowledge, no studies have systematically addressed both the persistence of PV isolation and linear lines after thoracoscopi epicardial radiofrequency ablation, using bipolar AtriCure clamps and linear pen, in a large series of patients with persistent and long-standing persistent AF undergoing staged hybrid ablation with a predefined time frame of a minimum of 2 months between stages. A meaningful assessment of the long-term durability of lesions created during an epicardial ablation can only be done after sufficient time has elapsed for edema resorption and lesion consolidation with coagulation necrosis. Pison et al[13] showed that after the creation of an epicardial box lesion, complete isolation of the posterior LA wall was found in only 50 (64%) of 78 patients. However, both procedures were performed simultaneously, which prevented a definite conclusion on whether the conduction block was permanent or only transient, that is, the block was caused by tissue stunning or edema. All patients included in our study had a confirmed entry block to the posterior wall based on perioperative mapping at the time of surgery. In spite of this, we were able to find electric conduction to the posterior LA wall in >3 quarters of patients during the deferred EAM procedure. These data suggest that in the majority of patients, acutely measured conduction blocks are possibly only transient and

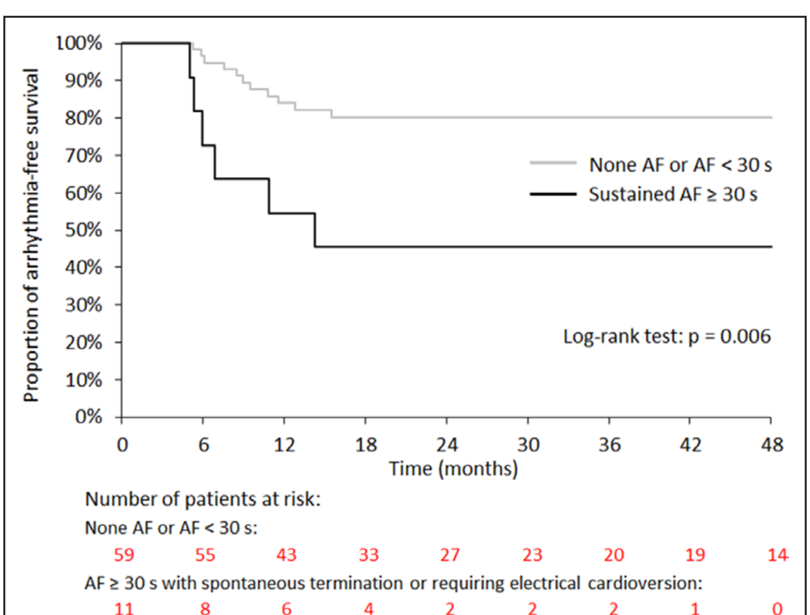

Figure 3. Kaplan–Meier estimate of arrhythmia-free survival off antiarrhythmic drugs after hybrid ablation by inducibility of atrial fibrillation (AF) during testing at the end of hybrid procedure.

definite conclusions unreliable. Also, Osmancik et al[12] confirmed that when electrophysiological mapping was deferred for 2 to 3 months following the index epicardial procedure, only ≈50% of patients with acutely confirmed conduction block on the posterior wall were found to have permanent blocks. A noteworthy difference between our study and that of Osmancik et al was that they used different instruments (ie, COBRA ablation system), which simultaneously encircles both PV antra and the posterior LA during radiofrequency energy application.

There are many plausible reasons for the failure of epicardial PV isolation. First of all, the presence of epicardial fat is a significant predictor of epicardial radiofrequency ablation failure in experimental settings. Hong et al[16] showed that bipolar radiofrequency energy can produce reliable lesions only in the absence of epicardial fat, and no transmural lesions can ever be created when fat thickness is ≥3 mm. Second, the most distant parts of the PVs encompassed by the AtriCure clamp device—for example, roof portions of the PVs—were most likely exposed to lesser compression by the device claws, especially if there was an abundance of proximally clamped tissue. A theoretical reason might be that the most distal part of the branches of the clamp device was unable to reach the superior portion of the PVs because of the overall length of the compressed tissue, although the surgeons were aware of this limitation and took meticulous care to fully encircle the PVs before clamping and application of radiofrequency energy. Epicardial fat is also more abundant along the roof line compared with the inferior line,[12] which may explain the better overall success in creating conduction blocks across the inferior line with epicardial ablation and may also theoretically explain failure to create bidirectional conduction blocks through the roof line in almost 10% of patients, despite a combined epi- and endocardial radiofrequency energy application, despite of using latest version of ablation catheters equipped with contact force sensors. Another potential explanation may be linked to the excessive thickness of myocardial tissue, which can be sometimes observed using periprocedural intracardiac echocardiography imaging.

Hybrid Approach in AF Treatment—Clinical Utility and Complications

Our study suggests that a single-stage epicardial surgical ablation cannot completely overcome the current limitations of endocardial catheter-based procedures in terms of reduced effectiveness in patients with persistent and long-standing persistent AF. However, the majority of patients returning for EAM, who were not in SR, were also not in AF and presented with regular arrhythmias. Apparently, right atrial flutter and perimitral or roof-dependent ATs were related to either incomplete epicardially created linear lesions or epicardially unreachable substrate, that is, cavotricuspid isthmus. On the contrary, ATs arising from the right atrium or coronary sinus likely represented residual arrhythmogenic substrate that could not be targeted during surgery anyway. This is also likely the case for the majority of inducible ATs. Interestingly, epicardial thoracoscopic ablation was unable to convert AF into either SR or regular tachycardias in only 6% of patients. Unsurprisingly, posterior box lesions and trigone lines were unsuccessful in all of these patients, and isolation of all PVs was only successful in half of these patients. Incomplete linear ablations or microreentrant ATs from atrial scarring were thought to be the main culprit for AT/AF recurrence, which may also explain the poor results in the STAR-AF II trial.[8]

Our findings justify the adoption of the hybrid ablation approach in patients with persistent and long-standing persistent AF, that is, surgical treatment should be supplemented by subsequent, but deferred, EAM and CA, by at least 2 to 3 months. Consistent with our results, Richardson et al[15] clearly supports the staged compared with the simultaneous hybrid approach, not only because of lower bleeding risks but also because of a significantly higher percentage of late PV reconnections found during staged procedures, which can be subsequently addressed by endocardial ablation. In their study, however, the staged compared with simultaneous hybrid approach led to similar clinical results, most likely because of short interval between the stages of the hybrid procedure, differences between ablation protocol and less-strict end points compared with our trial, and use of less-effective technology for endocardial ablation, that is, catheters without contact force sensors.

A significant drawback preventing hybrid AF treatment from having wider clinical use is the relatively high number of complications compared with CAs. In our study, major complications occurred in almost 13% of patients. Two conversions to sternotomy and one significant PV narrowing, as well as all other nonsignificant PV narrowings occurred during the initial phase of our study and involved the first 10 patients. One tamponade was linked to Warfarin overdose (international normalized ratio, 8.0) and, thus, was not related directly to the surgical procedure. Further complications included 2 wound infections, both occurring in diabetic patients with a body mass index >35. Today, such patients are excluded from undergoing hybrid AF treatment in our center. Right phrenic nerve palsy was the most often encountered surgical complication. After changing the surgical technique of securing the incised pericardium with stitches with significantly reduced tension on the phrenic nerve, no further phrenic nerve injuries were observed in the final 30 patients. Interestingly, the complication rates in the earlier surgical series of patients were reported between 0% to 39%,[17] suggestive of underestimation of both early and late surgical complications at least in some studies. A recent meta-analysis of thoracoscopic epicardial ablations revealed the overall incidence of ≈3% for major complications, with phrenic nerve paralysis occurring only in 0.7% of patients.[18] However, the majority of articles included in this meta-analysis did not state explicitly, whether or not they routinely screened all patients for diaphragmatic motion using sciascopy. We are convinced that phrenic nerve palsies are underreported in the surgical literature, mainly because severe symptoms only appear in a small percentage of patients or symptoms may disappear once the phrenic nerve regains its functionality, even before the appropriate reason for dyspnea on exertion is medically explained.

Radiofrequency CA, on the contrary, represented the relatively safe part of hybrid procedure with only minor vascular complications observed. However, hematomas after vascular access in highly anticoagulated patients appear in ≈5% of patients. Observed arterio-venous fistula could have been prevented by ultrasound-guided vascular access. Recent reports show that this technique may limit the vascular complication rate to below that of nonanticoagulated patients.[19]

Long-Term Efficacy and Predictors of Recurrence

Compared with CA procedures, the staged hybrid approach in the treatment of persistent and long-standing persistent AF has an amazingly high success rate. Kaplan–Meier estimates of midterm survival indicate that strict arrhythmia control can be achieved in 3 quarters of patients without the use of AADs. However, when previously ineffective AADs were reintroduced in patients with an AF recurrence, arrhythmia control was further improved. This acceptable level of arrhythmia control can be achieved in almost 90% of patients, which would otherwise be difficult to treat because of considerably enlarged atria and long-term arrhythmia duration, such as that seen in our study population. CA of persistent AF is considered to be difficult, and many techniques have been introduced during the past 10 years, yielding various but mostly disappointing results, especially when used by operators other than the proponents of the technique.[2–7] Fiala et al,[20] using an extensive ablation approach (procedural time, 321±54 minutes with some ablations reaching 430 minutes) demonstrated long-term efficacy only between 20% to 30% after a single CA procedure. Additionally, reports from other renowned European centers have found similarly low (≈20%) success rates after a single CA procedure.[21,22]

In patients with persistent AF, prior studies have identified smaller atrial size,[23,24] shorter AF duration,[22,24–26] younger age[27] and male sex,[25] absence of hypertension,[28] and increased systolic LA strain and wall velocity[23] as predictors of better outcomes after CA. In our study, LA volume >165 mL, age >65 years, SR after epicardial surgery lasting until the endocardial part of the hybrid procedure, and noninducibility of any sustained atrial arrhythmia at the end of the endocardial procedure were identified as correlates of AF recurrence in a univariable analysis in patients with advanced atrial arrhythmogenic substrate. In multivariable-adjusted estimates, arrhythmia noninducibility overpowered all other baseline clinical factors and turned out to be the strongest independent correlate of arrhythmia recurrence: patients with inducible arrhythmias had >7× higher risk of AF recurrence. Our conclusion is in agreement with other published data derived from catheter-based procedures dealing with structurally remodeled atria.[20,23,29,30] However, in contrast to CA techniques, the staged hybrid approach allows testing of arrhythmia inducibility during the first CA procedure and allows to meaningfully target all clinically relevant atrial arrhythmias, something which is considered largely unrealistic because of time constraints and technical demands associated with a catheter-only approach. As a result, >90% of patients had been rendered noninducible by the end of our hybrid procedure. Moreover, compared with catheter-based procedures, a staged hybrid approach seems to ultimately eliminate complex atrial arrhythmogenic substrate in a majority of patients because late AF recurrences (ie, beyond 12 months) were extremely rare.

Limitations

Because only 7-day ECG Holters were performed in our patients, we cannot exclude that real-life occurrence of AF >30 seconds affecting reported arrhythmia-free survival could happen. However, if subjective symptoms of arrhythmia were felt, patients were motivated to record arrhythmia using event recorder, and the results were reflected in the analysis. Thus, we strongly think that we might have missed only asymptomatic and short-lived AF episodes.

Another limitation for wide-spread application of the hybrid procedure may be a relatively high incidence of complications observed during surgical part of hybrid procedure, especially concerning phrenic nerve palsy. Although we think that appropriate patient selection and modified technique using reduced tension on pericardial sac with the securing stiches significantly affected the absence of further phrenic nerve injury, we cannot completely exclude such an effect as fortuitous.

Conclusions

Our report found that the majority of patients after epicardial ablation, using bipolar radiofrequency instruments, required endocardial CA to complete the linear ablation lesions, and a significant proportion of patients required spot-ablations to complete electric PV isolation. Noninducibility of any AT at the end of a hybrid procedure turned out to be the strongest correlate of a long-term, stable SR, suggesting that an extensive epicardial and endocardial atrial ablation should be performed in a staged manner, and all potentially relevant atrial arrhythmias should be targeted to maximize arrhythmia-free survival.

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Disclosures

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