Long-term clinical outcome following pulmonary vein isolation with high-intensity focused ultrasound balloon catheters in patients with paroxysmal atrial fibrillation

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Aims

High-intensity focused ultrasound (HIFU) applied via a balloon catheter is a novel technology for pulmonary vein isolation (PVI) in patients with paroxysmal atrial fibrillation (PAF). The long-term success rate is unknown.

Methods and results

Thirty-two patients (22 male, age 60 ± 9 years) with a long history [5 (4;9) years] of drug refractory [3 ± 1 anti-arrhythmic drugs (AADs)], symptomatic PAF were included into the analysis. Pulmonary vein isolation was performed using the first- and second-generation HIFU balloon catheters (ProRhythm®, Ronkonkoma, NY, USA). Follow-up (F/U) included regular telephonic interviews, trans-telephonic Holter ECG, and event recording. Recurrence was defined as a documented or symptomatic AF episode ≥ 30 s without a blanking period. In total 101/116 targeted PVs (87%) were acutely isolated exclusively using HIFU. During a median F/U of 1400 (930;1568) days, 18 patients (56%) were free of AF without AAD after a single HIFU procedure. In nine patients with AF recurrence, 20 PVs exhibited electrical reconduction and re-isolation was performed using irrigated radiofrequency current (RFC) ablation.

Conclusion

Patients treated with the first- and second-generation HIFU balloon catheters due to symptomatic PAF show long-term success rates similar to RFC-based PVI procedures. The major determinant of AF recurrence after HIFU treatment seems to be reconduction of previously isolated PVs. However, the favourable effectiveness is offset by the severe complications reported following HIFU treatment. This led to a halt of its clinical use.

Keywords

Atrial fibrillation • Pulmonary vein isolation • HIFU balloon catheter • Long-term follow-up

Introduction

The procedural endpoint for catheter ablation of atrial fibrillation (AF) is complete electrical pulmonary vein isolation (PVI) as implemented in the latest guidelines for AF treatment.1,2 Commonly, radiofrequency current (RFC) point-by-point lesions are deployed to achieve PVI by complete circumferential linear lesions.3,4 Long-term success rates after RFC-based PVI for patients suffering from paroxysmal AF lie in the range of 29—89%.5–8

The major determinant of clinical AF recurrences is PV to left atrial (LA) reconduction, and it remains a challenge to achieve permanent continuous transmural lesions using RFC.9

In addition, RFC-based PVI may be associated with serious complications such as PV stenosis, stroke, and atrial-to-oesophageal fistula.10,11,26
The mentioned limitations of RFC kindled the interest in the development and investigation of new energy sources as well as new catheter designs. Novel balloon-based ablation systems have been introduced and the potential to achieve complete electrical PVI with a single application using different energy sources such as high-intensity focused ultrasound (HIFU) or cryothermal energy has been demonstrated. First mid-term follow-up (F/U) results after HIFU ablation in patients with AF have shown promising results. However, long-term success rates are still unknown.

Methods

Inclusion and exclusion criteria

Between August 2003 and December 2007, 32 consecutive patients with highly symptomatic, drug-refractory PAF were admitted for PVI and were eligible for HIFU balloon ablation. Exclusion criteria for HIFU ablation were persistent AF, previous PVI attempt, LA diameter ≥ 55 mm, severe valvular disease, and contraindication for post-interventional oral anticoagulation.

Pre-interventional magnetic resonance imaging (MRI) was performed to investigate the individual LA and PV anatomy. Left ventricular hypertrophy >15 mm and a diameter of one PV >30 mm were additional exclusion criteria. Transesophageal echocardiography was performed in each patient prior to PVI to assess the LA diameter and to rule out intracardiac thrombi. Each patient gave written informed consent for HIFU balloon-based PVI. The studies were approved by the local ethics committee (study number 2783, Ethics Committee of Hamburg).

Ablation procedure

Venous access was achieved through the right femoral vein, the left femoral vein, and the left subclavian vein. Prior to transseptal puncture (TP) diagnostic catheters were placed in the coronary sinus (7 F, WebsterTM, Biosense Webster®, Diamond Bar, CA, USA) and at the His-bundle region (6 F, ParahisianTM, Biosense Webster). Double TP was performed under fluoroscopic guidance with a modified Brockenbrough technique using two 8 F sheaths (Fast-CathTM, St Jude Medical®). One 8 F sheath was exchanged over the wire for a non-steerable 16.5 F sheath (ProRhythm®, Ronkonkoma, NY, USA). In addition to the HIFU balloon catheter, a spiral catheter (LassoTM, Biosense Webster®) was positioned in the PV to assess the presence or absence of PV potentials. Transseptal sheaths were constantly flushed with heparinized saline.

HIFU balloon size was selected depending on the measured PV diameter. Three different balloon sizes were available: a 24 mm diameter balloon (20 mm sonication ring diameter), a 27 mm diameter balloon (25 mm sonication ring diameter), and a 32 mm diameter balloon (30 mm sonication ring diameter). The first-generation HIFU balloon was a non-steerable device. The second-generation HIFU balloon catheter was deflectable over a pull-wire mechanism integrated in the handle of the catheter. HIFU application time was 40–90 s depending on the selected balloon size (24 mm diameter balloon 40 s, 27 mm diameter balloon 60 s, 32 mm diameter balloon 90 s).

The optimal balloon position was determined by a very ostial location of the balloon based on the initially performed selective biplane PV angiograms. Moreover, the position of the HIFU balloon was considered optimal if the vertical balloon axis and the longitudinal pulmonary vein axis were in perfect alignment.

To prevent phrenic nerve (PN) palsy, the PN was constantly paced (10 V, 2.9 ms) via a catheter placed in the superior vena cava while applying energy to the right PVs. In the case of loss of PN capture, the energy application was stopped immediately.

After each HIFU application, analysis of the treated PV was performed using a spiral catheter. HIFU application was repeated until complete electrical PVI was achieved.

If we failed to target or to isolate a PV by using the HIFU balloon catheter, the PV was left unisolated. No additional RFC touch-up was performed. The activated clotting time was kept between 250 and 300 s until sheath removal.

Post-ablation treatment

In all patients, transthoracic echocardiography and chest X-ray were performed 1 day post-ablation to rule out pericardial effusion and/or pneumothorax. After ablation, all patients were treated with intravenous heparin, until an INR value of 2–3 was reached and maintained for at least 3 months. Anti-arrhythmic drug (AAD) treatment was discharged 4 weeks post-ablation. All patients underwent MRI of the LA and the PVs to exclude PV stenosis 3 months post-ablation.

Repeat procedure

In patients admitted for a repeat procedure, venous access and TP were performed as previously described. The presence or absence of electrical activity inside the PVs was assessed using a spiral catheter. An electroanatomical LA map (CartoTM, Biosense Webster) was generated and the PV ostia were tagged. Identified gaps within the previously performed ablation lines were closed by irrigated RFC ablation using a 3.5 mm irrigated tip catheter (Biosense Webster, Navi-StarTM, Thermo-Cool®). The ablation power was set to 30–40 W with a flow rate of 17–25 mL/min and a maximal temperature of 43°C.

Follow-up

Follow-up included weekly telephonic interviews for 6 months after the index procedure, trans-telephonic Holter ECG, and event recording for 2 months. Outpatient clinic visits at 1, 3, 6, and 12 months after PVI including 48 h Holter ECGs were performed. Afterwards, telephonic interviews and Holter ECGs were repeated in 3 months periods. Additional outpatient clinic visits, Holter ECG, and event monitoring were immediately initiated in the case of symptoms suggestive for a recurred arrhythmia.

Endpoints

The primary endpoint was defined as recurrence of any symptomatic episode suggestive of AF or documented episode of AF >30 s after the index ablation procedure without a blanking period. Secondary endpoints were defined as procedure-related
symptoms and complications such as cerebral or cardiac embolism, PN palsy, PV stenosis, or atrial-to-esophageal fistula.

**Statistical analysis**

All continuous variables are expressed as means ± SD or median and quartiles where appropriate. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

**Results**

**Demographics**

Thirty-two consecutive patients (22 male, age 60 ± 9 years) with a long history [5 (4;9) years] of drug refractory (3 ± 1 AADs), symptomatic PAF were treated with the HIFU balloon system and included in the analysis. Median LA diameter was 43 (38:46) mm (Table 1).

**High-intensity focused ultrasound ablation**

In 3 and 29 patients, PVI was performed with the first- and second-generation HIFU balloon device, respectively. Out of 126 (92%) PVs, 116 were targeted. In 10 patients, the right inferior PV (RIPV) was not treated due to limited navigation properties.

Out of 116 (87%) targeted PVs, 101 were successfully isolated exclusively using the HIFU balloon (Figure 1). However, in only 16/32 patients (50%), isolation of all PVs could be achieved with HIFU.

Mean procedure and fluoroscopy time was 349 ± 108 and 68 ± 28 min, respectively.

**Long-term follow-up**

During a median F/U of 1400 (930;1568) days, 18/32 patients (56%) remained free of any symptomatic or documented AF episode without AAD after a single HIFU procedure. Among this group were 6/10 (60%) patients in whom the RIPV was not targeted.

A tachyarrhythmia recurrence was observed in 14/32 (44%) patients. Twelve (86%) patients presented with PAF, one (7%) with persistent AF and one (7%) with PAF and atrial tachycardia (AT), respectively (Figure 2).

Eleven of 14 patients with tachyarrhythmia recurrence developed their first symptomatic and/or documented episode within the first 3-month period post-ablation, 1/14 patients after 10 months, 1/14 patients after 14 months, and 1/14 patients after 18 months (Figure 3).

Ten out of 16 patients (63%) in whom all PVs were successfully isolated during the initial procedure were free of AF recurrence during F/U. Conversely, only 8/16 patients (50%) in whom at least one PV could not be isolated during the initial procedure remained in stable SR during F/U.

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**Table 1** Demographics

| Patients (n) | 32 |
| Male gender, n (%) | 22 (69) |
| Age, mean ± SD (years) | 60 ± 9 |
| Prior anti-arrhythmic drugs, mean ± SD (n) | 3 ± 1 |
| PAF duration, median, and quartiles (years) | 5 (4.9) |
| LA size, median, and quartiles (mm) | 43 (38:46) |
| Arterial hypertension, n (%) | 9 (28) |
| Coronary artery disease, n (%) | 5 (16) |

Demographic data: gender, age, prior anti-arrhythmic drugs, history of arterial hypertension, and coronary artery disease given as mean and standard deviation (SD); PAF duration and LA size given as median and 25% and 75% quartiles, respectively. PAF, paroxysmal atrial fibrillation; LA, left atrium.
Repeat procedures

Nine patients underwent RFC-based PV re-isolation 147 (97;354) days after the index HIFU-based PVI. LA to PV re-conduction was found in 20/25 initially isolated PVs (6/6 RSPVs, 4/4 RIPVs, 3/7 LSPVs, 6/7 LIPVs, 1/1 LCPV) which were successfully re-isolated using RFC. The location of the conduction gaps at the respective PVs was randomly distributed (Figure 4).

Mean repeat-procedure time was 184 ± 52 min with a mean fluoroscopy time of 19 ± 6 min.

Complications

PN palsy occurred in two patients during HIFU application to the RSPV. None of the PN palsies recovered during F/U. No PV stenosis was detected. No atrial-to-esophageal fistula occurred.

Discussion

Balloon-based ablation devices using different energy sources (e.g. cryothermal energy, hot balloon, HIFU) are increasingly used for the treatment of PAF. Several studies demonstrated convincing acute and mid-term results.

HIFU offered the potential benefit to perform PVI with a single device without the need for 3D mapping systems. The technology was not critically dependent on balloon-to-tissue contact and should have facilitated PVI by a circumferential lesion design instead of point-by-point ablation.

However, the long-term success rate and risk profile remain to be determined. This analysis provides, for the first time, long-term F/U data after HIFU balloon-based PVI in patients with PAF.

Recently, 3-year-F/U data after RFC-based PVI in patients suffering from PAF were published, reporting success rates of 29 to 89% after a single PVI procedure. The long-term success rates after HIFU balloon-based PVI are comparable to RFC-based PVI. However, it has to be taken into consideration that only HIFU balloon catheters of the first and second generation were used. The limited navigation properties precluded complete PVI of all PVs in 50% of the patients. Therefore, it might be speculated that a technically improved HIFU balloon that enabled PVI of all PVs might even have ameliorated the long-term results.

The low number of patients treated with the first-generation HIFU balloon catheter (n = 3) precluded a meaningful statistical comparison between the patients treated with first and second generation HIFU balloon (n = 29), respectively.

During repeat procedures, it became evident that electrical re-conduction of previously isolated PVs was the major determinant of clinical recurrences. This corresponds to the experience with circumferential RFC ablations and might indicate the failure to achieve permanent transmural ablation lesions.

The type of arrhythmia recurrence is dependent on the ablation design during the index PVI procedure. Although after circumferential RFC-based PVI the predominant arrhythmia is AT due to PV tachycardia conducting to the LA via single or multiple conduction gaps, almost all patients presenting with arrhythmia recurrences after HIFU balloon-based PVI suffered from PAF and not AT. A potential explanation for this difference may be the level of PVI achieved with the respective technology. While circumferential ablation lesions include the antral region and up to 30% of the LA tissue, balloon-induced ablation lesions are located rather ostial without encircling the antral part of the PVs allowing for propagation of multiple electrical wavefronts initiating and sustaining AF.
Safety

The initial enthusiasm for this single-shot device was dampened by severe complications in terms of persistent PN palsy and an atrial-to-esophageal fistula.\textsuperscript{12,23} Despite 3D reconstruction of the PN anatomical course using electroanatomical mapping and PN pacing during HIFU sonication, persistent PN palsy occurred in two patients who did not recover during F/U.\textsuperscript{13} PN palsies have also been reported during cryo-balloon-based PVI but were always transient.\textsuperscript{16,24} However, to date, strategies beyond continuous PN pacing during sonication at the septal PVs to prevent PN palsy do not exist.

An atrial-to-esophageal fistula or oesophageal laceration did not occur in this patient population. However, the HIFU programme was stopped due to four severe esophageal complications including one lethal atrial-to-esophageal fistula in another series of patients.\textsuperscript{23}

A major limitation of the HIFU device is the ‘all-or-nothing-principle’ with regard to energy delivery. The manufacturer failed to implement a tool to titrate HIFU energy in order to avoid collateral damage and increase clinical safety.

Limitations

The data presented were collected during a single-centre feasibility study. The study cohort was selected and limited to patients with PAF and PVs amenable to HIFU balloon-based PVI as assessed by a pre-procedural MRI. Therefore, the general applicability of the results is limited. However, since pre-procedural imaging is frequently used, patient selection for this technology can easily be performed in the clinical setting.

Its usefulness in patients with persistent AF remains also debatable. Results from RFC-based trials for AF ablation suggested that PVI alone may not be sufficient to obtain a favourable long-term outcome.\textsuperscript{5,7} This is supported by the observation that cryothermal balloon-based PVI is associated with poor results in patients with persistent AF.\textsuperscript{24}

In our series, patients were treated with the first- and second-generation HIFU balloons. While the former was a non-steerable over the wire device, the second-generation HIFU balloon catheter was steerable but used in combination with a non-steerable trans-septal sheath. Both balloon catheters displayed limited navigation properties precluding to target and to isolate all PVs. Recently, it was demonstrated that the use of a steerable sheath in conjunction with a steerable balloon significantly improved acute success rates and shortened procedure times.\textsuperscript{25}

A mean procedure time of $349 \pm 108$ min and a fluoroscopy time of $68 \pm 28$ min have to be considered rather long compared with the conventional RFC-based PVI\textsuperscript{1} and limited its clinical use. However, the first- and second-generation HIFU balloon systems have to be considered as investigational devices and one could speculate that further technological refinement might have overcome this issue.

Conclusion

Patients treated with the first- and second-generation HIFU balloon catheters due to symptomatic PAF show long-term success rates similar to RFC-based PVI procedures. The major determinant of AF recurrence after HIFU treatment seems to be reconnection of previously isolated PVs. However, the favourable effectiveness is offset by the severe complications reported following HIFU treatment. This led to a halt of its clinical use.

Conflict of interest: none declared.

References


