Fatal End of a Safety Algorithm for Pulmonary Vein Isolation

with Use of High-Intensity Focused Ultrasound

Short Title: Neven et al.; Fatal End for High-Intensity Focused Ultrasound

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ABSTRACT

Background: High-intensity focused ultrasound (HIFU) can achieve pulmonary vein isolation (PVI), but there are safety concerns after severe complications. Therefore we evaluated an esophageal temperature (ET) guided safety algorithm in order to apply HIFU safely.

Methods and Results: After standard left atrial access HIFU was repeatedly applied until complete PVI. Safety algorithm: ≤3 complete ablations per pulmonary vein (PV), early abortion when no effect after 50% of programmed time or when ET ≥40.0°C, use of Power Modulation (PM) at ET 39.0°C: to reduce ablation temperature in surrounding tissue, acoustic power is switched on/off at 1 Hz, in all first ablations use of PM after 50% of programmed time. Touch-up radiofrequency ablation when PVI failed. ET monitoring and endoscopy 2 days after ablation. Twenty-eight patients (18 male, mean age at enrollment 63), with paroxysmal atrial fibrillation (AF) (n=19) & persistent AF (n=9). In 84/109 PV (9/25 patients) PVI was achieved using HIFU only. In 9/109 PV HIFU was aborted due to high ET. Mean ET at the end of the ablations with and without use of PM were 38.1 ± 2.0°C and 37.4 ± 1.0°C (p=0.0002). During endoscopy in 2/26 patients a small thermal lesion was found. Other complications: 2 persistent phrenic nerve palsies, 1 ischemic stroke, 1 pericardial effusion 48 days after ablation, 1 unexplained death 49 days after ablation, 1 lethal atrial-to-esophageal fistula 31 days after ablation.

Conclusions: The safety algorithm failed to prevent lethal complications. Currently HIFU does not meet the safety standards required for treatment of AF.

Key words: Atrial fibrillation, catheter ablation, complications
Introduction

Catheter ablation has been implemented in the latest guidelines as curative treatment of atrial fibrillation (AF)\(^1\). In recent years a novel balloon-based ablation system has been introduced and has demonstrated the potential to achieve complete electrical pulmonary vein isolation (PVI) using high-intensity focused ultrasound (HIFU) (ProRhythm, Inc, Ronkonkoma, NY, USA)\(^2,3\). However, there have been safety issues due to occurrence of severe and even lethal complications\(^2,4\). Several parameters (defocused energy zone, reduced outer sheath diameter of 12 French (F), esophageal temperature (ET) measurement and use of an oversized balloon) were suggested that could possibly identify and prevent complications\(^5\).

Our primary objective was to develop an ET guided safety algorithm in order to apply HIFU in a safe and effective way.

METHODS

INCLUSION AND EXCLUSION CRITERIA

This was the first study conducted with HIFU in which there was no preprocedural patient selection or imaging. Patients were considered to be not eligible for PVI when one or more of the following criteria were met: long-standing persistent AF (continuous AF for >1 year), a left atrial (LA) diameter >55 mm, markedly reduced left ventricular (LV) ejection fraction of <45%, severe LV hypertrophy (LV wall thickness >15 mm), LA thrombus, uncontrolled heart failure or inability to adhere to the follow-up scheme. All patients gave a written informed consent.

PRE-ABLATION INVESTIGATIONS
One day before PVI all patients underwent transesophageal echocardiography to determine LA diameter and LV ejection fraction, to exclude LA thrombus, to evaluate presence of a shunt through the interatrial septum and valve patency.

STEERABLE HIFU BALLOON CATHETER

The steerable HIFU balloon catheter (BC) consists of a non-compliant distal balloon, which is filled with a mixture of water and contrast medium and an integrated 9 Megahertz ultrasound crystal. Proximal, a second non-compliant balloon, filled with carbon dioxide, forms a parabolic surface at the base of the distal balloon. Thereby, ultrasound waves are reflected in forward direction, focusing a ring of ultrasound energy (sonicating ring) approximately 2-6 mm to the balloon surface. The HIFU BC is steerable through a pull wire mechanism integrated in the handle of the catheter and is available in balloons with a sonication ring diameter of 20 mm, 25 mm and 30 mm, respectively. The catheter has a central lumen used for insertion of a hexapolar spiral mapping catheter (ProMap™, ProRhythm, Inc.) for real-time assessment of pulmonary vein (PV) potentials.

HIFU ABLATION PROCEDURE

Vital parameters were continuously monitored through the entire electrophysiological procedure. The procedure was performed under deep sedation using boluses of midazolam (0.15 mg/kg, premedication) and fentanyl (0.02 mg every 45 minutes, during ablation) as well as continuous infusion of propofol (10 mg/ml, infusion rate continuously adjusted according to level of consciousness).

After placing 6F decapolar catheters (D-type, Biosense Webster, Inc., Diamond Bar, CA, USA) into the coronary sinus and to the His bundle region, 2 transseptal punctures were
performed using a modified Brockenbrough technique to introduce 2 8.5F sheaths (Fast-Cath™ SL1, St. Jude Medical, Minnetonka, MN, USA) into the LA. Thereafter, heparin boluses were repeatedly administered to maintain the activated clotting time between 250 and 300 seconds. Selective PV angiographies were performed to identify PV ostia. A spiral catheter (Lasso™, Biosense Webster, Inc., Diamond Bar, CA, USA) was placed at the PV ostium to record PV potentials using a conventional computerized electrophysiology system (AXIOM Sensis™, Siemens, Erlangen, Germany). Then pacing from the superior vena cava was performed with maximal output (10 volts, 2.9 milliseconds) in an attempt to capture the phrenic nerve (PN).

In all study patients, a 8.5F sheath was exchanged for a steerable 12F transseptal sheath (CryoFlex™, CryoCath, Montreal, Canada) in order to introduce the HIFU BC into the LA. After optimal ostial placement and perfect alignment with PV axis the proximal balloon was inflated with carbon dioxide and HIFU energy (acoustic power 45 Watt) was applied for 40, 60 or 90 seconds for the balloon with the 20, 25 or 30 mm sonication ring, respectively.

PVI was evaluated online using the ProMap™ spiral catheter. Persistent acute PVI was defined as intraprocedural absence of PV potentials in the targeted PV, assessed by the Lasso™ spiral catheter, without evidence of reconnection by the end of the procedure. If the PV was not isolated, the HIFU BC was repositioned or exchanged for a different balloon size. Endpoint for ablation was the absence of PV potentials assessed by the Lasso™ spiral catheter.

**ESOPHAGEAL TEMPERATURE MONITORING**
Under fluoroscopic guidance, a temperature probe with 3 sensors (Esotherm, FIAB SpA, Vicchio, Italy) was trans-orally advanced in the esophagus. Its position was adjusted for each ablation in order to position the sensors as close as possible to the ablation site.

**POWER MODULATION MODE**

Analogous to radiofrequency current ablation catheter, where the physician has the option to lower the delivered power, a similar capability is incorporated in the HIFU ablation system. It intends to reduce temperature elevation in adjacent tissue due to conductive heat transfer. Normally, the current cycles of the HIFU ablation system deliver constant electrical power resulting in constant acoustic power output from the HIFU balloon throughout the preset ablation time. To reduce ablation temperature acoustic power is being switched on and off with a frequency of 1 Hertz (Power Modulation).

**SAFETY ALGORITHM**

In order to decrease potential periprocedural complications due to excessive heating of adjacent tissue a safety algorithm was developed:

1. if during HIFU ablation ET increased above 39.0 degrees Celsius (°C) or if after 20-30 seconds no change in PV electrograms was seen Power Modulation was switched on. Previous experience with HIFU has shown that if after 20-30 seconds no change in PV electrograms is observed, it is less likely that the PV will be isolated during that particular sonication. In order to prevent excessive heating of adjacent tissue Power Modulation mode was switched on;

2. HIFU ablation was aborted when ET reached 40°C, also in order to prevent excessive heating of adjacent tissue;
3. a maximum number of 3 complete HIFU ablations per PV. PVI is rarely completed with HIFU only if 3 full sonications failed to achieve PVI.

RADIOFREQUENCY CURRENT TOUCH-UP ABLATION

If PV potentials persisted after 3 ablations per PV it was left to the discretion of the operator to change from HIFU to irrigated radiofrequency current ablation (RFC). An irrigated tip catheter (Celsius Thermocool, Biosense Webster, Inc.) was used with a power of 30-40 watt, a temperature limit of 43°C and a flow-rate of 17-25 ml/minute. Gap location and assessment of PVI were performed with a Lasso™ spiral catheter positioned at the respective PV ostium.

POST-ABLATION TREATMENT

After the end of the procedure pericardial effusion was excluded by transthoracic echocardiogram. On readmission to the ward, patients were treated with intravenous heparin. Oral anticoagulation was started the following day. All patients received phenprocoumon targeting an international normalized ratio (INR) range of 2 to 3 for at least 3 months. Two days after the ablation an endoscopy was performed to evaluate possible presence of thermal lesions in the esophagus. In case of presence of a thermal lesion the endoscopy was repeated after 2 weeks. Irrespective of the maximal ET all patients received proton pump inhibitors (pantoprazol 40 mg twice daily) for 4 weeks following the ablation. Antiarrhythmic therapy was continued for 1 month.

STATISTICAL ANALYSIS

Data mean ± standard deviation (SD) was used to describe continuous variables with normal distribution, otherwise median and range were used. For diagnostic parameters the absolute and relative frequencies were counted. The effect of Power Modulation on the success of the
ablation and on the esophageal temperatures was assessed using a generalized mixed model under consideration of repeated measures taken of each patient. All statistical analyses (concerning mixed modelling) were performed with Statistical Analysis System (SAS) 9.2 using the MIXED and GLIMMIX procedures.

RESULTS

From July to December 2008 a total of 28 patients (18 male) with a mean age at enrollment of 63 ± 7 years and a mean of 1 ± 1 antiarrhythmic drugs used were enrolled. Nineteen patients had paroxysmal AF and nine patients had persistent AF. The mean AF duration was 6 ± 4 years, the median duration of the last episode of persistent AF before ablation was 4 (range 1-72) months (Table 1).

PROCEDURAL PARAMETERS

The mean procedure time was 158 ± 42 minutes, of which the HIFU BC remained in the LA for a mean of 71 ± 23 minutes. The mean fluoroscopy time was 29 ± 10 minutes.

ACUTE PVI

In 28 patients 109/111 PVs (1 patient had a left common PV) were ablated with HIFU. In 2 right inferior PVs (RIPV) no ablation was attempted due to PN palsy that had occurred during earlier ablation of the right superior PV (RSPV). In 84/109 PVs (77%) persistent acute PVI was achieved exclusively using HIFU.

In 25/28 patients (89%) all PVs were isolated at the end of the procedure. In 3/28 patients (11%) 1 PV could not be isolated because of failure to isolate the RIPV with touch-up RFC, due to high ETs seen during HIFU application at the RIPV or due to abortion of the ablation
procedure following aspiration. In 9/28 patients (32%) all PVs were isolated exclusively using HIFU (Figure 1).

The mean time to PVI using HIFU was 9 ± 5, 8 ± 7, 13 ± 8 and 14 ± 12 seconds for the RSPV, RIPV, left superior PV (LSPV) and left inferior PV (LIPV), respectively.

For the isolation of 13/84 PVs (15%) >3 HIFU ablations were required, because 11/13 HIFU ablations (85%) were aborted prematurely due to high ET or BC dislodgement. In 2/13 PVs (15%) there was reconduction after initial isolation with HIFU, these PVs were reisolated with HIFU. Maximal ET in these 13 PVs was 41.2°C. Table 2 summarizes the number of HIFU applications needed to achieve PVI.

After PVI had been achieved, a bonus application was delivered empirically in 47 of 84 PVs isolated with HIFU only (56%) to ascertain the permanency of the transmural lesion.

TOUCH-UP RADIOFREQUENCY CURRENT CATHETER ABLATION

In a total of 25/111 PVs (23%) in 16/28 patients (57%) persistent acute PVI was achieved only after additional touch-up with RFC. Isolation failure using HIFU occurred at all PVs (5 RSPVs, 7 RIPVs, 8 LIPVs and 5 LSPVs). Figure 2 shows the location of the conduction gaps.

EFFECT OF POWER MODULATION ON ACUTE SUCCESS OF HIFU

In 191/311 ablations (61%) (temporary) PVI could be achieved using HIFU only. In 57/191 successful ablations (30%) Power Modulation was used, however in 26/57 isolated PVs (46%) reconduction occurred during or after ablation with Power Modulation switched on. The remaining 134/191 successful ablations were performed without use of Power
Modulation, in this group 49/134 PVs (37%) showed reconduction after the end of the ablation. This difference is statistically not significant (p=0.61).

**EFFECT OF POWER MODULATION ON ESOPHAGEAL TEMPERATURE**

In 77 of 311 (25%) HIFU ablations Power Modulation was switched on after a median of 27 ± 9 seconds. Mean ET at start of Power Modulation was 37.6 ± 1.2°C. Mean ET at the end of the ablations with use of Power Modulation was 38.1 ± 2.0°C. In contrast, mean ET at the end of the ablations without use of Power Modulation was 37.4 ± 1.0°C (p=0.0002).

When ET at start of Power Modulation was <39.0°C mean change in ET at the end of the ablation was +0.1 ± 0.3°C, but when ET at start of Power Modulation was ≥39.0°C mean change in ET at the end of the ablation was +1.7 ± 1.1°C (p<0.0001).

**ENDOSCOPY**

Endoscopy was performed in 26/28 patients (93%). Two out of 28 patients refused to undergo endoscopy but remained asymptomatic during follow-up. In 2/26 patients (8%) a small thermal lesion was found in the anterior part of the esophagus. Maximal ETs were 37.3°C and 41.9°C, respectively. At repeat endoscopy after 2 weeks all thermal lesions were healed. No complaints occurred during follow-up.

**COMPLICATIONS**

Using the new 12F transseptal sheath no major bleeding or hematoma were seen.

In 6/28 patients (21%) transient (n=4) or persistent (n=2) PN palsy occurred during ablation at the RSPV.
Several hours after ablation one patient developed a reversible ischemic neurologic deficit, confirmed by magnetic resonance imaging. Symptoms resolved completely within 48 hours.

One patient developed progressive dyspnea due to pericardial effusion 7 weeks after ablation. After pericardial puncture and evacuation of 1500 ml bloody fluid the patient’s condition improved significantly. Pathologic and histologic analysis, transesophageal echocardiography and computed tomography did not reveal any cause for the pericardial effusion.

One 79-year old patient was found dead in bed 49 days after ablation. Her previous medical history revealed hypertension, diabetes mellitus, obesity (BMI: 30.9 kg/m²) and non-significant coronary artery disease with a good LV function. The ablation procedure was uncomplicated, with a maximal ET of 36.5°C. The patient had remained asymptomatic during follow-up. No autopsy was done. No clear cause of death could be established.

LETHAL ATRIAL-TO-ESOPHAGEAL FISTULA

A 69-year old patient died suddenly after 31 days of follow-up. His previous medical history revealed chronic obstructive pulmonary disease, obesity (Body Mass Index: 39.4 kg/m²), non-significant coronary artery disease, hypertension with secondary LV hypertrophy and a good LV function. During ablation of the RSPV persistent PN palsy occurred. The procedure was completed with touch-up RFC of an anteroinferior gap in the RSPV and an anterior gap in the LSPV. Maximal ET was 39.1°C. Routine echocardiogram and endoscopy did not show any abnormalities. The further clinical course was uneventful. Thirty-one days after ablation the patient collapsed and was admitted to another hospital, a pneumonia was diagnosed. After several hours the patient suddenly developed general seizures and severe hematemesis.
Despite resuscitation the patient died. On autopsy an atrial-to-esophageal fistula (AEF) of 11x7 mm from the posterolateral part of the LA to the distal third of the esophagus was found (Figure 3). The pericardial fat tissue around the AEF showed extensive necrosis (Figure 4). In the stomach and jejunum there was 2500 ml of fresh blood. The esophagus showed no thermal or Barrett lesions. Besides the AEF there were also signs of beginning septicemia and multiple fresh cerebral infarcts.

**DISCUSSION**

We report on the largest unselected, prospective series of patients treated with HIFU for AF. Earlier studies have demonstrated high acute success rates, but serious complications were also reported. Therefore we attempted to develop a safety algorithm following a distinct protocol.

The present study demonstrates that using the safety algorithm acute PVI with HIFU ablation only could be achieved in only 77% of PVs. Eight percent of PVs could not be isolated with HIFU due to excessive esophageal heating or BC dislodgement. In only 32% of patients all PVs could be isolated using HIFU ablation only.

Although Power Modulation did not negatively influence acute success rates of PVI, it also did not prevent ET to exceed levels above 40.0 °C at end of the ablation.

Right PN palsy has been reported to occur in >0.1% of ostial PV isolations using RFC catheter ablation and may rise up to >10% using balloon-mounted technologies. This is due to the close proximity of the PN to the anterior part of the RSPV close to its ostium. PN injury with balloon technologies may stem from anatomic distortion of the PV orifice/PN
relationship, through increasing contact or shortening the relative distance between the ablation site and the PN, even without displacement of the balloon into the PV\(^9\).

Despite use of the safety algorithm and continuous PN pacing transient and persistent PN palsy occurred in 14% and 7% of patients, respectively. Even worse, use of the safety algorithm could not prevent occurrence of esophageal thermal lesions and lethal AEF.

Esophageal injury with AEF formation was observed after RFC and HIFU ablation in the LA for the treatment of AF\(^4,10\). Unfortunately, to date no effective strategy has been developed to avoid esophageal injury. Although peri-procedural real-time monitoring of ET is feasible\(^11\), recent experimental studies have demonstrated that esophageal injury can occur without detectable increase in ET\(^12\). In our analysis there was no relationship between maximal ET and occurrence of complications. Also, recent clinical studies showed no correlation between ET and occurrence of esophageal ulcers\(^13\). In fact, in 1 of the patients who developed an ulcer ET never increased above 37.3°C. We did not find a clear explanation for this finding. One can only speculate that there might be poor contact of the ET probe with the esophageal wall or that the mechanism of esophageal ulcer formation in patients treated with HIFU is independent of temperature. Significant differences between luminal ET and external esophageal tissue temperature during radiofrequency ablation of the LA have been reported\(^14\).

Furthermore, all cases of AEF were observed at 5 to 16 days after the surgical or catheter-based procedures, suggesting that progressive tissue necrosis with lesion expansion contributed to the fistula formation. However, there are no data on the chronic changes of esophageal lesions after RFC.
The same holds true for endoscopy. During endoscopy the luminal part of the esophagus is being inspected, the presence or absence of luminal thermal lesions is however no indicator for possible presence or absence of thermal damage in the outer layers of the esophagus. Also, the optimal waiting period before endoscopy should be performed is unclear. In our study we performed endoscopy after 2 days, whereas others state that most esophageal lesions are seen at day 4\textsuperscript{15}. This diagnostic issue thus remains unresolved. After the ablation procedure all patients received proton pump inhibitor therapy for minimally 30 days, nevertheless this did not prevent formation of ulcers as suggested by Yokoyama et al and Nakagawa et al\textsuperscript{16,17}.

In 1 patient lethal AEF occurred. Endoscopy performed 2 days after the procedure revealed no thermal lesions. Histological examination of the fatty tissue between LA and esophagus showed extensive necrosis. The development of AEF without demonstration of early endothelial injury is again raising questions about the exact pathophysiology of this complication. It could be speculated that extensive fat tissue necrosis caused and/or sustained fistula formation. Our current efforts to prevent this complication are still quite unsatisfactory.

PVI with HIFU has proven to be successful, but is not yet safe for everyday clinical use. As long as we do not understand the pathophysiology of AEF formation using HIFU we will not be able to develop an appropriate safety algorithm. Therefore, application of HIFU energy for PVI in humans can not be advised at this point in time. Still, the concept of the energy source and mode of energy delivery may be very interesting for future treatment of AF. With mean PVI times of less than 15 seconds and a high number of complications it is evident that the present energy source is too powerful in some patients. Furthermore, energy delivery is not titratable enough.
CONCLUSIONS

Implementation of a safety algorithm with ET guided use of Power Modulation for HIFU based PVI failed to decrease complication rates. A cut-off ET of 40.0°C does not prevent thermal damage. The problem of PN palsy and AEF occurrence remains unresolved. This issue has to be resolved before HIFU can meet the safety standards required for the treatment of AF.

CONFLICT OF INTEREST DISCLOSURES: Boris Schmidt and Karl-Heinz Kuck are consultants to the manufacturer of the HIFU hardware (ProRhythm, Inc.).

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**Table 1. Patient Characteristics** - Data are mean ± standard deviation, median [plus range] or absolute number (plus percentage), SR: sinus rhythm, AF: atrial fibrillation

<table>
<thead>
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<td>Age at enrollment (years)</td>
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<tr>
<td>Men/women</td>
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<tr>
<td>Body Mass Index (kg/m²)</td>
<td>27.4 ± 4.1</td>
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<tr>
<td>Paroxysmal/persistent atrial fibrillation</td>
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<tr>
<td>Atrial fibrillation duration (years)</td>
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<tr>
<td>Median duration of last episode of persistent AF (months)</td>
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<td>Heart rhythm at start of procedure (SR/AF)</td>
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<td>Left atrial diameter (mm)</td>
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<tr>
<td>Left ventricular ejection fraction (%)</td>
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<tr>
<td>Arterial hypertension (%)</td>
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<tr>
<td>Coronary artery disease (%)</td>
<td>7 (25)</td>
</tr>
<tr>
<td>Failed anti-arrhythmic drugs</td>
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</table>
TABLE 2. NUMBER OF ABLATIONS NEEDED TO ISOLATE A PULMONARY VEIN USING EXCLUSIVELY HIFU - There were differences in the number of ablations needed to isolate a PV using exclusively HIFU. The majority of PVs needed 1 or 2 ablations to be isolated. For example: 8 LSPVs were isolated using only 1 HIFU ablation, and 6 LSPVs needed 2 ablations to become isolated. HIFU: high-intensity focused ultrasound, PV: pulmonary vein, LSPV: left superior pulmonary vein, LIPV: left inferior pulmonary vein, RSPV: right superior pulmonary vein, RIPV: right inferior pulmonary vein

<table>
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<tr>
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<td>2</td>
</tr>
<tr>
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</tr>
<tr>
<td>RIPV</td>
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<td>5</td>
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FIGURE LEGENDS

Figure 1: ACUTE PULMONARY VEIN ISOLATION - Flow chart showing patients who underwent HIFU ablation and the PVs treated. PV: pulmonary vein, HIFU: high-intensity focused ultrasound, RFC: radiofrequency current catheter ablation

Figure 2: LOCATION OF GAPS - Schematic view of the pulmonary vein ostia indicating the locations of the gaps that were closed with RFC when PVI with HIFU was not successful. If there were gaps on identical locations in different patients these gaps are marked only once in the figure. RSPV: right superior pulmonary vein, RIPV: right inferior pulmonary vein, LSPV: left superior pulmonary vein, LIPV: left inferior pulmonary vein, RFC: radiofrequency current catheter ablation, PVI: pulmonary vein isolation

Figure 3: ATRIAL-TO-ESOPHAGEAL FISTULA - Macroscopic posterior-anterior view of the esophagus and the exit of the atrial-to-esophageal fistula in the distal third of the anterior wall of the esophagus. The aorta shows extensive calcification and deposition of fatty streaks.

Figure 4: FATTY TISSUE NECROSIS WITH CHRONIC INFLAMMATION BETWEEN ESOPHAGUS AND LEFT ATRIUM - Histological sample of the border between left atrium and esophagus, showing fatty tissue in between. Hematoxylin and eosin staining with identification of lymfocytes in the fatty tissue, indicating fatty tissue necrosis. Figure is photographed with 10x magnification.
28 patients → in 3 patients (11%) 1 PV could not be isolated

in 25 patients (89%) all PVs were isolated by the end of the procedure

↓

in 16 patients (57%) all PVs were isolated using HIFU + RFC

↓

in 9 patients (32%) all PVs were isolated using HIFU only

↓

111 PVs → in 2 PVs (2%) no ablation was attempted due to phrenic nerve palsy

↓

109 PVs (98%) were ablated with HIFU → 25 PVs (23%) needed touch-up RFC

↓

in 84 PVs (77%) persistent acute PVI was achieved using HIFU only
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