Damage to the esophagus following atrial fibrillation ablation – just the tip of the iceberg? High prevalence of mediastinal changes diagnosed by endosonography

Short title: Esophageal and mediastinal changes following atrial fibrillation ablation

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ABSTRACT:

Background: Radiofrequency (RF) catheter ablation is increasingly used in the treatment of atrial fibrillation (AF). Esophageal wall changes varying from erythema to ulcers have been described by endoscopy in up to 47% of the patients following pulmonary vein isolation (PVI). Although esophageal changes are frequently reported, the development of a left atrial-esophageal (LA-eso) fistula is fortunately rare. Nevertheless, mucosal changes may just represent “the tip of the iceberg”. The aim of this study was therefore to investigate the more subtle changes of and injuries to the posterior wall of the LA, the periesophageal and mediastinal connective tissue and the whole wall of the esophagus including mucosal changes by esophago-gastro-duodenoscopy (EGD) combined with radial endosonography (EUS).

Methods and Results: Twenty-nine patients (pts, 7 females, mean age 57.7±10.5 years, range 23-75 years) underwent EGD and EUS prior to and following PVI within 48 hours. PVI was performed as a circumferential antral isolation of the septal and lateral...
pulmonary veins guided by a decapolar circular mapping catheter using a 3-dimensional mapping system with the integration of a pre-procedurally acquired CT-scan of the left atrium. The maximum power applied was 30 watts with an open-irrigated catheter using a maximum flow-rate of 30 ml/min. In all pts, the esophagus was reconstructed using the same CT-scan and displayed during the ablation procedure. In case of newly detected periesophageal changes, EGD and EUS were repeated one week after the PVI. In all pts, a regular contact area between the LA and the esophagus could be demonstrated prior to PVI. The mean vertical contact length was 4.4±1.5 cm (range 2 - 10 cm), the mean distance between the anterior wall of the esophagus and the endocardium was 2.6±0.8 mm (range 1.4 – 4.0 mm). After PVI, morphological changes of the periesophageal connective tissue and the posterior wall of the LA were diagnosed by endosonography in eight pts (27%, 95% CI 12.73 to 47.24). No mucosal changes of the esophagus in terms of erythema or ulcers were found. In all but one patient (who refused the control), all periesophageal and atrial changes had resolved within one week. No atrio-esophageal fistula occurred during follow-up (mean follow-up 294±110 days, range 36 – 431 days).

Conclusions: Mucosal changes of the esophagus after PVI like ulcers or erythema could not be demonstrated, yet structural changes of the mediastinum, that were only visible by endosonography, occurred in 27% of the pts in the present study. This may indicate a higher than expected periesophageal injury due to PV ablation. Endosonography might prove to be a sensitive and reliable tool in the follow-up after PVI.

**Key words:** atrial fibrillation, catheter ablation, esophageal injury, mediastinal injury, fistula, endosonography
INTRODUCTION

Radiofrequency (RF) catheter ablation has evolved to a possibly curative treatment of atrial fibrillation (AF) in recent years giving rise to increasing procedural numbers throughout the world.\textsuperscript{1} Most procedures target the pulmonary veins by placing RF lesions around their ostia to isolate AF triggers from the left atrium.\textsuperscript{2} Collateral damage to adjacent structures\textsuperscript{3} has been described, in particular to the esophagus caused by its vicinity to the posterior wall of the left atrium.\textsuperscript{4-6} In rare cases this may lead to formation of left atrial-esophageal (LA-eso) fistula with disastrous consequences.\textsuperscript{7-9} Some few studies investigated mucosal changes of the esophagus after atrial fibrillation ablation.\textsuperscript{10-12} However, these mucosal lesions may represent just “the tip of the iceberg”, as a dramatic swelling of the posterior LA wall due to RF application has been described.\textsuperscript{13} The variability of the thickness of the posterior LA wall and the esophageal wall may play an important role in esophageal heating and development of thermal damages. Mediastinal and submucosal esophageal thermal injuries cannot be diagnosed by conventional EGD while endosonography (EUS) may be useful to detect these mediastinal and submucosal esophageal changes following pulmonary vein isolation (PVI). EUS was developed as a diagnostic tool in diseases of the esophagus and the mediastinum, the gastric wall and the pancreas. Furthermore, EUS enables aiming biopsies of mediastinal and pancreatic lesions and plays also a role as a therapeutic modality guiding drainage of pancreatic pseudocysts or abscesses.\textsuperscript{14, 15} Compared to other imaging modalities like computed tomography, EUS is superior in staging of esophageal tumors due to its higher spatial resolution which allows to differentiate the esophageal wall layers.\textsuperscript{16, 17} Using EUS, the aim of this study was therefore to investigate the more subtle changes of and injuries to the posterior wall of the left atrium, the periesophageal connective tissue and the whole wall of the esophagus including mucosal alterations.
METHODS

Patient characteristics and PV-Isolation

Twenty-nine patients (pts, 7 females, mean age 57.7±10.5 years, range 23-75 years) underwent PVI for paroxysmal (n=12) or persistent (n=17) symptomatic atrial fibrillation refractory to antiarrhythmic drugs (AAD). The clinical demographics of the study are shown in Table 1. All patients received intravenous piritramide and midazolam to achieve conscious sedation. After venous access, a decapolar catheter was placed into the coronary sinus via the left femoral vein. Double transseptal puncture was accomplished by utilizing fluoroscopic imaging and pressure monitoring. Ablation was performed as a circumferential antral isolation of the septal and lateral pulmonary veins guided by a decapolar circular mapping catheter (Inquiry Optima®, St. Jude Medical, St. Paul, MN, USA) using a 3-dimensional mapping system (CARTO XP®, Biosense Webster, Diamond Bar, CA, USA, or NavX®, St. Jude Medical, St. Paul, MN, USA) with the integration of a pre-procedurally acquired CT-scan of the left atrium. In all patients, the esophagus was reconstructed using the same CT-scan and displayed during the ablation procedure. The maximum power applied was 30 watts with a 3.5 mm (ThermoCool®, Biosense Webster, Diamond Bar, CA, USA) or 4.0 mm (Therapy CoolPath®, St. Jude Medical, St. Paul, MN, USA) open-irrigated tip catheter using a maximum irrigation rate of 30 ml/min. The ablation catheter was moved around the pulmonary veins in a dragging fashion rather than a point by point ablation, with 48° Celsius maximum catheter tip temperature. Energy delivery was adjusted to 20 watts when ablation was performed in close proximity to the esophagus and ablation was prematurely stopped in response to pain. The end point of the PVI technique was the local elimination of all the pulmonary vein potentials with an electrical disconnection between the LA and the pulmonary veins. No additional lines in the left or right atrium were drawn. PVI and endoscopic examinations were only performed after extensive...
information of the patient and after receiving written informed consent regarding the PVI itself as well as the endoscopic examinations.

**Esophago-gastro-duodenoscopy (EGD) and endosonography (EUS)**

Endoscopic examinations were performed by two highly experienced EUS-endoscopists (H.U. and T.M.). All examinations were done in a standardized way. Patient preparation consisted of a fasting period of at least 6 hours before the examination. Sedation was performed by intravenous administration of 50 mg pethidine once and propofol in a dosage as needed for adequate sedation. Patients were monitored by continuous measurement of oxygen saturation and pulse rate as well as intermittent measurement of blood pressure.

EGD and EUS were performed prior to and following PVI within 48 hours. Due to the stiffness of EUS-endoscopes the fundic region of the stomach could not precisely be evaluated in retroflexion. Therefore, we performed EGD with a standard video-gastroscope (GIF-Q160 or GIF-Q160Z, Olympus, Tokyo, Japan) previous to EUS to detect endoluminal changes of the esophagus and stomach. EUS was performed with a 7.5 MHz radial scanner (EUB 8500, Hitachi, Tokyo, Japan). With deflated EUS-balloon the minimal distance between the esophageal lumen and the endocardium of the left atrium as well as the vertical contact length between the left atrium and the esophagus were determined. Careful examination of the mediastinum and the esophageal wall was performed using a moderately inflated EUS-balloon before ablation to document preexisting esophageal and mediastinal alterations. Within 48 hours after ablation, a follow-up endoscopic examination was performed assessing mucosal and periesophageal/mediastinal lesions. In cases of newly detected structural changes, a second follow-up examination including EGD and EUS was performed one week after PVI.
Statistical analysis

Categorical variables were compared using the Fisher’s exact test. Continuous variables are presented as the mean plus or minus one standard deviation and were compared using an unpaired Student t-test. Statistical significance was reached at a $P$ level $\leq 0.05$.

RESULTS

Topographic anatomy

In all pts, a regular contact area between the LA and the esophagus could be demonstrated prior to PVI. The mean vertical contact length was 4.4±1.5 cm (range 2 - 10 cm), the mean distance between the anterior wall of the esophagus and the endocardium was 2.6±0.8 mm (range 1.4 – 4.0 mm).

Esophageal, mediastinal, and atrial findings

The course of the esophagus was left-sided in the majority of patients (n=17), a right-sided and middle course could be demonstrated by CT in one and ten pts, respectively. One patient with a history of achalasia and myotomy presented with a dilated esophagus covering the whole posterior wall of the left atrium. After PVI, morphological changes in the periesophageal connective tissue and the posterior wall of the LA were diagnosed by endosonography in eight pts (27%, 95% CI 12.73 to 47.24), including abolition of the regular esophageal mucosal layer pattern with edema and periesophageal accumulation of liquid, swelling of the posterior wall of the LA also beyond the site of ablation and mediastinal adenopathy (Table 2, Figure 1). The observed changes did neither correlate with the vertical contact length nor with the distance between the anterior wall of the esophagus and the endocardium. No mucosal changes of the esophagus in terms of erythema or ulcers were found. The patient with achalasia presented no lesions...
detectable by EGD/EUS. Two of the eight pts (25%) with documented lesions complained about mild chest pain, yet three of the remaining twenty-one pts without esophageal and mediastinal alterations also reported such symptoms (14%). Clinical characteristics of the two groups were not different (Table 3).

Follow-up

In all but one patient (who refused the control), the above-mentioned changes were checked again one week after the first post-PVI endoscopy: All changes had resolved within this period of time. No atrio-esophageal fistula occurred during follow-up (mean follow-up 294±110 days, range 36 – 431 days).

DISCUSSION

Thermal injury is likely to play the crucial role in the development of atrio-esophageal fistula. Consequently, limiting the magnitude of power (20 - 30W) and duration of RF application is used in the clinical setting to avoid esophageal damage. Additionally, the course of the esophagus in relation to the left atrium is monitored by numerous investigators. The exact position of the esophagus and its relation to the posterior wall may be different at the time of the ablation procedure compared to the pre-procedurally acquired CT-scan, perhaps due to the fasting state and the resulting fluid changes. Yet, Piorkowski et al. showed a high concordance between the esophageal–LA relationship on an electroanatomic reconstruction and a CT-scan in a similar setting. The mobility of the esophagus, however, cannot be monitored by this approach. Apart from a probe inside the esophagus and tagging its course in the 3D mapping system, this may be accomplished by ingestion of barium paste at the beginning of the ablation. However, there is conflicting data concerning the mobility of the esophagus in the segments relevant to the ablation procedure. Piorkowski et al. described a degree of
mobility of the esophagus toward the roof of the LA using an in-vivo 3D tagging of the esophagus and a stable anatomical relationship at the midportion and the inferior LA. In contrast to this, Good et al.\textsuperscript{23} demonstrated a significant mobility of the esophagus also in these segments visualizing the esophagus by a barium swallow. A significant discord between CT-defined and esophagram-defined borders of the esophagus was also reported by Daoud et al.\textsuperscript{24} Luminal esophageal temperature monitoring during ablation at the posterior LA wall is utilized to guide the ablation procedure and possibly reduce esophageal injury.\textsuperscript{25-27} All periesophageal and mediastinal lesions described here are directly related to the ablation procedure given the regular index examination prior to ablation. The absence of mucosal changes in the present study is possibly due to a different ablation strategy and the use of conscious sedation rather than general anesthesia or deep sedation. Schmidt et al.\textsuperscript{11} reported esophageal wall changes in 47\% of their patients using either 8mm solid tip ablation catheter or 3.5mm tip open irrigated catheter with a maximum power setting of 50 watts. This high power, compared to our study, may lead to deeper ablation lesions affecting also the esophageal mucosa. Mediastinal changes were not investigated in that study. Recently, a US wide survey reported six fistulae in 20425 patients undergoing AF ablation.\textsuperscript{28} The development of an atrio-esophageal fistula was associated with the use of 8mm tip catheters and high power settings, further supporting the above hypothesis. Recently, an increased risk of esophageal damage due to ablation of atrial fibrillation in patients undergoing general anesthesia has been described.\textsuperscript{12} Mucosal lesions of the esophagus occurred in a much higher proportion in this subgroup than in patients undergoing conscious sedation. Several mechanisms may explain the higher incidence of esophageal lesions in the general anesthesia group. The esophageal motility may be reduced, leading to a prolonged exposure of the same area of the esophagus to thermal energy during ablation. Moreover, the lack of swallowing might reduce the physiologic cooling effect
and lead to thermal injury. In general, ischemia by thermal damage to the anterior esophageal arteries is likely to play a crucial role in the development of esophageal lesions. Whether a reduced or changed perfusion under general anesthesia might aggravate this during PVI, is not known. Stopping ablation secondary to pain may not be specific concerning esophageal injuries. Yet, Aryana et al.\textsuperscript{29} found an association with pain and esophageal temperature rise and a lack of pain with an absence of temperature rise in patients undergoing PVI during monitoring the esophageal temperature with a probe. Hence, not being able to detect pain during ablation under general anesthesia as a surrogate for imminent tissue injury might also add to the likelihood of esophageal injury. In the study by di Biase et al.\textsuperscript{12}, endoscopic evaluation was performed using capsule video endoscopy, which is unable to provide information concerning esophageal wall and mediastinal changes. Moreover, cost-efficiency strongly favors standard endoscopic evaluation.

More recently, Badger et al.\textsuperscript{30} demonstrated the feasibility of using delayed-enhancement MRI to assess the extent and progression of esophageal wall injury after PVI in 41 patients. Endoscopic evaluation, however, was performed in only three of the five patients exhibiting esophageal delayed-enhancement following ablation. In these patients, mucosal lesions in terms of erosions and erythema were observed. However, in contrast to our study EUS was not performed routinely but only in one patient. This patient was reported to have a preserved esophageal wall architecture with no mediastinal or periesophageal adenopathy, despite a more aggressive ablation strategy, which targeted also the posterior wall of the LA. Thus, it is tempting to speculate that MRI is less sensitive than EUS in detecting periesophageal lesions following PVI.

The present study clearly shows that endosonographic evaluation is a safe and reliable method to identify mediastinal changes after catheter ablation of AF. This tool might prove to be a valuable diagnostic option in symptomatic patients after pulmonary vein
isolation concerning the possible development of left atrial-esophageal fistula. Patients with mediastinal lesions identified by endosonography might be selected for a closer clinical and endosonographic follow-up than those with no lesions. In our patients, all mediastinal changes resolved completely within one week after PVI. Persisting mediastinal changes might herald the later development of a left atrial-esophageal fistula and should be monitored even more closely.

LIMITATIONS
An esophageal temperature probe was not routinely used in all patients to detect temperature rise during power delivery with radiofrequency energy applications, therefore a possible beneficial effect on esophageal damage as described elsewhere was not evaluated.

CONCLUSIONS
Mucosal changes of the esophagus after PVI like ulcers or erythema, as recently published, could not be demonstrated in this study, yet structural changes in the mediastinum, that were only visible by endosonography, occurred in 27% of pts in the present investigation. This may indicate a higher than expected periesophageal injury rate due to PV ablation. Endosonography might extend the range of tools at hand in the follow-up of patients after PVI considering the presumably higher sensitivity of EUS compared to MRI.

CONFLICT OF INTEREST DISCLOSURES: None
REFERENCES


for atrial fibrillation: observations about esophageal heating during ablation at the pulmonary vein ostia and posterior left atrium. *J Cardiovasc Electrophysiol.* 2006;17:166-170.


## TABLES

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<th>Total patients</th>
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<td>Female</td>
<td>7</td>
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<tr>
<td>Male</td>
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| Age (years)    | 57.7 ± 10.5 |

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<tr>
<td>Diabetes mellitus</td>
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<td>History of stroke</td>
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<tr>
<td>Hypertension</td>
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**Table 1:** Clinical demographics (CAD = coronary artery disease, CHF = congestive heart failure)
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<th>Type of lesion / patient</th>
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<th>#2</th>
<th>#3</th>
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<td>Alteration of the interface between LA and esophagus</td>
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**Table 2:** Postprocedural changes following PVI

<table>
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<th>Pts with lesions (n = 8)</th>
<th>Pts without lesions (n = 21)</th>
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<tr>
<td>Age (years)</td>
<td>56 ± 6</td>
<td>58 ± 12</td>
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<tr>
<td>Gender</td>
<td>2 females, 6 males</td>
<td>5 females, 16 males</td>
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<tr>
<td>LA diameter (cm)</td>
<td>4.5 ± 0.6</td>
<td>4.7 ± 0.7</td>
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<td>Distance LA-eso (mm)</td>
<td>2.7 ± 0.7</td>
<td>2.5 ± 0.8</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>29 ± 3.7</td>
<td>28 ± 4.7</td>
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<tr>
<td>Total RF duration (min)</td>
<td>44 ± 15</td>
<td>49 ± 15</td>
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</table>

**Table 3:** Characteristics of patients with and without newly detected lesions following PVI (p = ns for all variables)
Figure Legends:

**Figure 1 A and B:** EUS showing periesophageal edema and swelling of the posterior wall of the left atrium;

**Figure 1 C:** EUS showing preserved esophageal, mediastinal and left atrial anatomy in another patient (PV = pulmonary vein, AV = azygos vein)
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Supplemental figure 1: Normal endosonography prior to ablation

Supplemental video 1: Endosonography in the same patient showing mediastinal and esophageal changes after ablation