Ph.D. Thesis

NEW ASPECTS OF ABLATION TREATMENT FOR ATRIAL FIBRILLATION

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Publications related to the thesis:

I. **Bencsik** G, Martinek M, Hassanein S, Aichinger J, Nesser HJ, Purerfellner H. Acute effects of complex fractionated atrial electrogram ablation on dominant frequency and regulatory index for the fibrillatory process. Europace. 2009 Aug;11(8):1011-7. IF: 1.871

II. **Bencsik** G. Automatikus szoftverek alkalmazása komplex frakcionált pitvari elektrogramok ablációja során. Cardiologia Hungarica. 2009; 39 : 58–61.

III. Martinek M, **Bencsik** G, Aichinger J, Hassanein S, Schoefl R, Kuchinka P, Nesser HJ, Purerfellner H. Esophageal damage during radiofrequency ablation of atrial fibrillation: impact of energy settings, lesion sets, and esophageal visualization. J Cardiovasc Electrophysiol. 2009 Jul;20(7):726-33. IF: 3.798

IV. Martinek M, Hassanein S, **Bencsik** G, Aichinger J, Schoefl R, Bachl A, Gerstl S, Nesser HJ, Purerfellner H. Acute development of gastroesophageal reflux after radiofrequency catheter ablation of atrial fibrillation. Heart Rhythm. 2009 Oct; 6(10):1457-62. IF: 4.559

V. Martinek M, Meyer C, Hassanein S, Aichinger J, **Bencsik** G, Schoefl R, Boehm G, Nesser HJ, Purerfellner H. Identification of a high-risk population for esophageal injury during radiofrequency catheter ablation of atrial fibrillation: Procedural and anatomical considerations. Heart Rhythm. 2010 Feb 24 (Epub ahead of print) PMID: 20188859. IF: 4.559

Publications not related to the thesis:

I. **Bencsik** G, Pap R, Sághy L. Intracardiac echocardiography for visualization of the Eustachian valve during radiofrequency ablation of typical atrial flutter. Europace. 2009;11(7):901.

II. Sághy L, Makai A, **Bencsik G**, Pap R. Coexistent right- and left-sided slow pathways participating in distinct AV nodal reentrant tachycardias. Pacing Clin Electrophysiol.2008 Oct;31(10):1348-50. IF: 1.578

III. Traykov VB, Pap R, **Bencsik G**, Makai A, Sághy L. Transition of narrow into wide complex tachycardia with left bundle branch block morphology and varying QRS duration: what is the mechanism? Pacing Clin Electrophysiol. 2007 Apr;30(4):547-50. IF: 1.578

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VI. Pap R, Traykov VB, Makai A, **Bencsik G**, Forster T, Sághy L. Ablation of posteroseptal and left posterior accessory pathways guided by left atrium-coronary sinus musculature activation sequence. J Cardiovasc Electrophysiol. 2008 Jul;19(7):653-8. IF: 3.798

List of abbreviations:

AEF – atrioesophageal fistula

AF – atrial fibrillation

AFCL – atrial fibrillation cycle length

CFAE – complex fractionated atrial electrogram

CL – cycle length

CS – coronary sinus

DF – dominant frequency

EU – esophageal ulceration

FFT – fast Fourier transform

GERD – gastroesophageal reflux disease

ICE – intracardiac echocardiography

ICL – interval confidence level

LA – left atrium

LAA – left atrial appendage

LET- luminal esophageal temperature

MSCT – multislice computed tomography

OIC – open irrigation catheter

PPI – proton-pump inhibitor

PVI – pulmonary vein isolation

PVs – pulmonary veins

RFA – radiofrequency ablation

RI – regulatory index

Summary

Catheter ablation using radiofrequency energy has gained acceptance as an effective treatment for atrial fibrillation (AF). Several technical approaches have been developed that correspond to pathophysiological concepts of AF initiation and maintenance. Isolation of pulmonary veins is identified as the cornerstone of any ablation approach.The additional ablation of fragmented or complex ostial or nonostial potentials or left atrial linear ablation has been recently introduced to modify the substrate besides isolating the trigger in order to improve the success rate of AF ablation, especially in patients with persistent AF. In our non-randomized, single-center, observational study we evaluated the acute effects of complex fractionated atrial electrogram (CFAE) ablation guided by automated detection on dominant frequency (DF) and regulatory index (RI) for the fibrillatory process. The termination rate by CFAE ablation was low (12.5% in paroxysmal and 10% in persistent AF). Changes in DF and RI after CFAE ablation were not significant (<0.25 Hz and max. 0.02 increase for RI) in comparison with other ablation steps. Based on our results CFAE ablation guided by a dedicated software algorithm and performed after standard pulmonary vein isolation (PVI) without CFAE remapping does not influence the fibrillatory process significantly. By virtue of the latter CFAE mapping and ablation should be performed always after PVI.

With introduction of additional extensive left atrial (LA) ablations the risk of complications have been increased. One of the most devastating complication of AF ablation is atrioesophageal fistula (AEF). Esophageal ulcerations (EU) have been proposed to be potential precursor lesions. In our large single-center study of more than 260 patients, we consistently screened patients for evidence of esophageal injury after AF ablation. In total, we found 2.2% of patients (6 of 267) presenting with EU. Parameters exposing a specific patient to risk of developing EU were persistent AF (5 of 95), additional lines performed (roofline: 6 of 114; LA isthmus: 4 of 49; coronary sinus: 5 of 66), and LA enlargement leading to sandwiching of the esophagus between the LA and thoracic spine. Multivariate analysis revealed LA-to-esophagus distance as the only significant risk factor. Not a single patient with PVI alone developed EU. With the use of a reasonable energy maximum of 25 W at the posterior LA wall using open irrigation catheters, we showed a low percentage of EU creation compared with other studies published. Identifying high-risk patients for esophageal injury

potentially has an impact on follow-up or treatment of these individuals by endoscopy or prophylactic treatment.

In our substudy (including 31 patients) we assessed the acute effect of radiofrequency ablation (RFA) on distal esophageal acidity using leadless pH-metry capsules. We found that a significant number of patients (19.2%) undergoing RFA of AF develop pathologic acid reflux after ablation. In addition, a subgroup of patients (16.1%) has a preexisting condition of asymptomatic reflux prior to ablation. This finding may explain a potential mechanism for progression of esophageal injury to atrio-esophageal fistulas. We recommend a regular screening for EU in high-risk patients with an extensive lesion set and treatment with proton-pump inhibitor (PPI) medication if EU is discovered. Moreover prophylactic PPI treatment of all patients undergoing RFA of AF have to be considered

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Introduction

Atrial fibrillation (AF) is the most frequent supraventricular arrhythmia with a prevalence of 1% in the general population. The prevalence of AF increases with age and reaches highest values (~20%) in a population older than 60 years (1). The number of patients suffering from AF is around 4.5 million in the European Union and AF is the leading diagnosis among arrhytmias responsible for hospitalization (2). AF is responsible for significant worsening of quality of life both in physical and mental terms and is considered as an independent factor which increases total cardiovascular mortality (3). The mortality rate of patients with AF is about double that of patients in normal sinus rhythm and linked to the severity of underlying heart disease (2). During 38 years of follow-up in the Framingham Study, 20.6% of men who developed AF had heart failure at inclusion versus 3.2% of those without AF; the corresponding incidences in women were 26.0% and 2.9% (4). Prevalence of AF in patients with heart failure as reflected in heart failure trials is 10-30%. The rate of ischemic stroke among patients with nonvalvular AF averages 5% per year, 2 to 7 times that of people without AF. One of every 6 strokes occurs in a patient with AF. Additionally, when transient ischemic attacks and clinically ‘silent’ strokes detected by brain imaging are considered, the rate of brain ischemia accompanying nonvalvular AF exceeds 7% per year. In patients with rheumatic heart disease and AF in the Framingham Heart Study, stroke risk was increased 17-fold compared with age-matched controls and attributable risk was 5 times greater than that in those with nonrheumatic AF (2). New epidemiological studies have shown that the prevalence of AF is increasing so the number of patients with AF in 2050 is expected to be around 16 million just in the United States (5). The same trends were found in countries of the European Union (6) so AF should be treated also as an important socioeconomic problem.

Drug treatment of AF is suboptimal despite the fact that huge efforts were made in basic research, development and drug industry. Even with most potent drugs the percent of patients free from arrhytmia recurrences in the paroxysmal form of the disease is below 60%. The side effects of these drugs are numerous and sometimes unacceptable serious. This therapeutic modality means a life-long treatment with significantly reduced quality of life (7). These facts motivated specialists to search for different treatment options. The treatment of AF came to a turning-point in 1998 by the revolutionary work of M. Haissaguerre and his group in which he proved that pulmonary veins (PVs) represents major sources and triggers for AF (8). PVs

(with their sleeve-like muscular extensions from left atrium) are the most important structures responsible for initiation of the fibrillatory process but they are also involved in perpetuation and maintenance of AF. The ablation treatment started as focal RFA in the PVs than moved towards the left atrium, first as segmental ostial ablation around the ostia of the veins which was than replaced by a continuous circular ablation approach. In latter years the circular ablation line is drawn in the antrum of the veins, far away from the ostia and it includes a part of the posterior wall of the left atrium. With this so-called „substrate modification" the success rates were increased. In the last decade the ablation treatment of AF evolved numerous nuances and different strategies. For that reason there are notable differences between these strategies among the centers performing AF ablation. The last international consensus document related to AF ablation was released in 2007 with aim to make AF ablation a more standardized therapeutic modality (9). In this document pulmonary vein isolation (PVI) is considered as a cornerstone of the ablation treatment, nonetheless other additional ablation targets were also described and underscored as techniques which are able to increase the success rate of the procedure. Such techniques are: ablation of complex fractionated atrial electrograms (CFAEs), continuous ablation lines between upper PVs, ablation line between left lower PV and mitral anulus (so-called „mitral isthmus"), anterior line and ablation of ganglionated plexi.

Ablation of complex fractionated atrial electrograms (CFAEs)

Highly fractionated local atrial electrograms were first recorded and classified by Konings et al. in 1994 during intraoperative right atrial mapping of human AF (10). They considered that areas showing high level of fractionation represent fields of slow conduction and/or pivotal points for reentrant wavelets in human atria which play an important role in the maintenance of AF. The description by Konings et al. was the indirect evidence for the multiple reentrant wavelet theory by Moe and Allesie which is one of the leading theories of AF in basic research (11,12). There are several proposed mechanisms in which CFAEs contribute to the maintenance of AF: focal re-entry or anisotropic conduction (10), pivotal points of re-entrant waves (13), wave fractionation at boundaries of high frequency rotors (14), and autonomic mechanisms related to ganglionated plexi (15). In 1996 Jais et al. identified complex atrial electrograms as markers of disorganisation and a possible source of AF. At the same time these areas were started to be ablated by the group from Bordeaux in patients with chronic AF. The first report of CFAE ablation as a succesfull strategy alone was published by Nademanee et al. in 2004 who reported (16) surprisingly high success rates (~91%) even in

patients with chronic AF by CFAE ablation alone (without isolation of pulmonary veins). CFAE ablation is interpreted mainly as a substrate modification and PVI as a technique which eliminates triggers for AF. PVI is a well-established ablation strategy – accepted as a gold standard technique for ablation treatment in AF - with remarkable long-term success rates in paroxysmal AF (2,17). Patients with persistent AF and a subset of patients with paroxysmal AF (~25%) require further ablation which modifies the substrate and increases the success rates (18-20). One of the methods for substrate modification is the above mentioned ablation of CFAEs which can be used alone or as an adjunctive strategy. A limitation of CFAE ablation is subjective visual assessment of local electrograms to determine CFAE points during AF leading to both high intra- and inter-observer variability in the interpretation of electrograms and low reproducibility of the results. To overcome this obstacle, new automated mapping algorithms have been introduced to supplement 3D mapping systems and provide a basis for the quantitative analysis of electrograms (21,22). In our study we were trying to determine the real effect of CFAE ablation on the global fibrillatory process. We decided to use an automated mapping algorithm (software) to detect areas with CFAEs, with the settings proposed by bioengineers who participated in the development of the software.

Atrioesophageal fistula as a complication of ablation procedure

RFA of AF carries a higher complication risk than other conventional electrophysiology interventions. The major complication rate is around 4.5% (23) and includes the following conditions: pericardial tamponade, periprocedural thromboembolism, pulmonary vein stenosis, postprocedural arrhytmias, phrenic nerve injury, hemothorax, pneumothorax, esophageal injury/atrioesophageal fistula, coronary artery occlusion, vascular complications, air embolism, periesophageal vagal injury, radiation injury, mitral valve trauma. The incidence of atrioesophageal fistula (AEF) is low (0.04%), but the mortality rate is extremely high (~70%). AEF is responsible for 6.3% of all procedure-related deaths after AF ablation (24).The first clinical report of AEF as a complication of transvenous ablation was published by Pappone et al. in 2004 (25). Diagnosis of an AEF is difficult as it typically presents 2 to 4 weeks after the ablation procedure with the median of 12 days. Leading clinical symptoms are fever, chills (as a part of infective endocarditis), leukocytosis and progressive neurological events caused by septic and/or air embolism (leading to serious disabilities in survivors). Other less common symptoms are: pneumomediastinum, hemomediastinum, dysphagia, chest or abdominal pain, upper gastrointestinal bleeding. More dramatic presentations are septic shock and death. Endoscopy (and TEE) should be avoided as instrumentation of the

esophagus may cause rapid deterioration and even death, as noted in previous surgical cases (26, 27). Sensitivity of a barium swallow is low for detection of fistulas therefore the best diagnostic modalities are CT or MR (enhanced by contrast) imaging of the esophagus and mediastinum. Treatment options are very limited -including thoracic surgery or possible endoscopic stenting- therefore the emphasis should be on prevention. The esophagus is a thermosensitive structure and tissue damage results from conductive heating by the radiofrequency energy applied to the posterior wall of the left atrium (LA). Formation of AEF starts with the lesion/ulceration at the anterior wall (in the level of LA) of the esophagus deep in the inner layer of the organ. During the so-called „maturation process" the ulceration penetrates towards the outer layer and finally reaches the mediastinum and the LA. This process explains the delayed course of clinical symptoms. In the light of this hypothesis the esophageal ulceration can be interpreted as a potential precursor of fistulas. Marrouche et al. (28) and Nakagawa et al. (29) reported a surprisingly high incidence of asymptomatic esophageal ulcerations (35-46%) after RFA of AF which all healed during the next 4-8 weeks under PPI treatment.

New strategies were proposed to minimize the risk of AEF formation: reduction of ablation times and energies during ablation on the posterior wall (30), endoluminal temperature monitoring using a probe (31), preprocedural imaging of the esophageal course and/or visualisation of the anatomical relationship between the esophagus and LA by 3D electroanatomical mapping (32), real-time fluoroscopy visualisation of the esophagus by barium swallow (33), monitoring of esophageal course and micro-bubble formation by intracardiac echocardiography (34,35), introduction of open irrigated systems for ablation (28), esophageal cooling with water-irrigated intraesophageal balloon during the ablation (36), using pain as an indicator of temperature rise in the esophagus (37).

The purpose of our study was to investigate the incidence of esophageal ulceration (EU) as well as the identification of a high-risk population for esophageal injury.

Aims

1. To determine the acute effects of CFAE ablation guided by automated detection software on dominant frequency (DF) and regulatory index (RI) for the fibrillatory process. We compared this effect with the impact on DF and RI made by additional ablation steps during ongoing AF.

2. To prospectively investigate the incidence of esophageal ulceration (EU) in a large patient population undergoing RF ablation of AF. Additionally we aimed to link demographic data and lesion sets with anatomical information given by multislice computed tomography (MSCT) imaging and to correlate these data with the development of EU.

3. To assess the acute effect of RF ablation on distal esophageal acidity in a smaller group if patients.

Patients and methods

Patients included in these studies were all referred to the Elisabethinen University Teaching Hospital Linz for RFA of AF from September 2007 to June 2009.

Ablation procedure

Deep sedation was used in most of the patients; general anesthesia was performed only at patient preference or in those presenting with a serious sleep apnea condition. Using a transfemoral venous approach, a multipolar catheter was placed in the coronary sinus (CS).

Next a transseptal puncture with subsequent retrograde angiography of the PV was performed. For mapping and ablation, a 3.5-mm open-irrigated-tip quadripolar catheter (Navistar Thermocool 7-Fr, Biosense Webster, or Therapy Cool Path, Irvine Biomedical, Irvine, California) was used. To evaluate electrical disconnection between the LA and the PV, a

ring-shaped multipolar diagnostic catheter (Lasso, Biosense Webster, or Inquiry Optima, Irvine Biomedical) was introduced into the different PVs.

Our technique was to perform LA circumferential ablation (38) with the addition of further linear lesions (roof line between the left and right superior PV, mitral isthmus line between the left inferior PV and the mitral valve annulus, endocardial and epicardial ablations to disconnect the CS, and inferior line starting from the posterior septum next to the right inferior PV, dragging along the CS to a lateral position next to the left inferior LA) and focal RF applications at areas showing complex fragmented atrial electrograms (as depicted by an automated dedicated software of the Carto or NavX system). PV isolation lines were created approximately 1 cm away from the tubular ostium at the posterior aspect and anterior right PVs as well as at the ostium at the anterior aspect of the left superior PV. The 2 lesion sets encircling the left and right veins were at least 2 to 3 cm apart at the posterior LA wall. Lines and complex fragmented atrial electrogram ablations were performed only if AF could not be terminated by PV isolation alone or still was inducible after PV isolation. In these cases, the second step after PV isolation was roofline ablation; the order of additional ablation steps was the operators' decision (39). End points were PV disconnection (assessed by entrance block) in paroxysmal AF as well as termination of AF in persistent cases (either accomplished by RFA alone or conversion to atrial tachycardia and electrical cardioversion). Induction was performed by atrial burst pacing down to atrial refractoriness or isoproterenol infusion titrated up to a heart rate of 140 beats/min. The following settings were used: maximum temperature 43°C; 25 W energy delivered at the posterior wall, 20 W in the CS, and 30 W in all other locations; irrigation flow rate 17 to 30 ml/min; and no titration of energy. All patients were on uninterrupted coumadin at least 4 weeks prior to the procedure and 3 months thereafter. Target international normalized ratio for RFA was 2.0, and patients additionally received heparin intravenously, with an activated clotting time between 300 and 400 s during the ablation procedure. All RFA were performed using a 3D electroanatomic mapping system with MSCT integration (CartoMerge, Biosense Webster, Diamond Bar, California, in 47.8% of cases or NavX, St. Jude Medical, St. Paul, Minnesota, in 52.2% of cases). After the LA ablation if typical right atrial flutter was inducible the cavotricuspid isthmus was ablated with a conventional approach. In problematic cases we were using intracardiac echocardiography (ICE) to achieve block on the isthmus .

Study protocol to evaluate acute effects of CFAE ablation

41 consecutive patients were enrolled in this substudy. They were referred as symptomatic paroxysmal (n: 21) or persistent (n: 20) AF which was refractory to at least one antiarrhytmic drug. Paroxysmal and persistent AF were defined according to the classification proposed in the HRS/EHRA/ ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation (9). Patients referred for a second procedure were excluded. The baseline characteristics of the study population are presented in Table 1. The mean duration of AF in the group of patients with persistent AF was 6.7 months (in the range from 1 week up to 11.8 months). There was no patient with longstanding persistent AF included in the study. All patients provided written informed consent for the study protocol.

Table 1. Patient Characteristics

	Paroxysmal (n=21)	**Persistent (n=20)**	**P Value**
Age (years)	56 ± 8	55 ± 9	ns
Male	20 (95%)	18 (90%)	ns
Structural heart disease	5 (24%)	7 (35%)	ns
LA diameter (mm)*	40 ± 3	42 ± 6	ns
Hypertension	13 (61%)	10 (50%)	ns
Ejection fraction (%)	52 ± 3	50 ± 7	ns

Values are given as n (%) or as mean ± SD.

*Parasternal left atrial diameter

We designed the study to asses the effects of subsequent ablation steps on the fibrillatory process. The ablation endpoint for patients with paroxysmal AF was non-inducibility with pacing manoeuvres described below. We performed re-induction if PVI, CFAE, or roof line ablation resulted in conversion to sinus rhythm. For the patients with persistent AF, the endpoint for ablation was termination of AF which is defined as conversion to sinus rhythm or regularization to atrial tachycardia/flutter with cycle length variation <30 ms measured in the CS (40,41). In this group of patients, we did not perform re-induction.

After detailed 3D mapping (during ongoing AF), a standard wide area circumferential PVI was performed in every patient as described above. The endpoint for PVI was total elimination or dissociation of the PV potentials. For this first ablation step, information available on the CFAE map was not used. The second ablation step was targeting all the CFAE points outside the circular lines of previous PVI starting with the points presenting with the highest interval confidence level (ICL) towards the points with smaller ICLs. The endpoint for CFAE ablation was termination and/or non-inducibility of AF or elimination of all CFAE clusters with local electrogram diminution to<0.05 mV. The third and fourth ablation steps consisted of creating a roof and a mitral isthmus line (18,19). For both lines, we performed differential pacing manoeuvres in sinus rhythm to confirm block on the line. Patients without termination of AF after completing the mitral isthmus line were electrically cardioverted.

Signal processing and frequency domain analysis: in a study conducted by Haissaguerre et al. (41) serial measurements of CL in the CS have been used as a quantitative tool for monitoring substrate changes during ablation of ongoing AF. In addition, previous studies (42) emphasized that the CS provides the longest cycle length with least fragmentation, which permits univocal measurement of atrial activity. Because of the well-known strong inverse correlation between AFCL and DF, we presented these AFCL changes as changes in the DF after each different step of ablation (40). We defined changes in the DF as significant when the level of change was ≥ 0.25 Hz (which corresponds to ~10 ms cycle length change in the time domain for a DF of 5.0 Hz) and change in RI > 0.025 was considered statistically significant (40,41,44). Before ablation, we determined the mean DF and RI of the PVs and a mean DF and RI in the CS. The latter reflects the DF and level of organization of the fibrillatory process in LA. If the patient was not already in AF at the start of 3D mapping, AF was induced by rapid atrial pacing using a maximum current output (20 mA) at the shortest 1:1 atrial capture rate for up to 10 s. We performed induction from the mid-coronary sinus (CS) and the left atrial appendage (LAA) for three times at each site. Atrial fibrillation was

considered inducible if it persisted for ≥1 min. For offline measurements of DF and RI, we used a dedicated software implemented in the electrophysiological recording system (Dual Lab, Bard Electrophysiology). Analysis was performed on bipolar electrograms recorded from the proximal CS bipoles which showed minimal ventricular far-field potentials (<10% of atrial signal amplitude). We also performed measurements on distal CS and found statistically non-significant differences between results derived from proximal and distal CS with only one exception: in the group with persistent AF after mitral isthmus ablation, the RI was significantly higher and DF significantly lower than that measured on proximal bipoles of the CS. Nevertheless, this finding had no influence on basic trends and the main conclusion. The recording time was 32 s for each step of measurement. After signal preprocessing, a fast Fourier transform (FFT) was performed with a spectral resolution of 4096 (0.24 Hz) over a sliding 4 s window. All recordings and FFTs were visualized to prevent defining harmonics as DF in the cases of fractionated, splitted, or double potentials (43). The largest peak in the resulting magnitude spectrum was defined as DF. The RI is defined as the ratio between the computed area below the DF (and its harmonics) and the total power, and it was calculated as a mean value. Only mean values >0.20 were used (44). For measuring the DF of PVs, we used electrograms recorded from each Lasso bipole, defining the highest DF as the DF of the given pulmonary vein. To prevent potential miscalculations, we controlled every result manually (time domain analysis) determining the atrial fibrillation cycle length on CS (or Lasso) bipoles with online calipers at a paper speed of 100 mm/s by averaging 30 consecutive cycles. Because of the possible transitional cycle length (CL) variations, we measured the AFCL 10 cycles before termination and 1 min after the onset of AF. If the interelectrogram distance was <100 ms between two consecutive electrograms, they were counted as one signal.

Complex fractionated atrial electrogram mapping: reconstruction of the LA geometry was performed during ongoing AF with a recording time of 2.5 s for each mapping point. The recorded electrograms were analysed by a programmable software (CFAE Software Module, Biosense Webster) which provided online automated identification and electroanatomical display of CFAEs. The density of mapping was identical in every patient, as we acquired 80 points in the LA equally distributed in the following sequence: 15 points on the posterior wall (including posterior parts of PVs, region 1), 15 points on the anterior wall (including the mitral annulus, region 2), 15 points in paraseptal left atrium (including anterior parts of right PVs, region 3), 15 points on the anterior parts of the left PVs (including LAA, region 4), 10 points on the LA roof (region 5), and 10 points in the inferior LA (including the endocardial

aspect of the CS, region 6). Our division of the LA into six areas is comparable with partitions used in previous studies (22,45). For the reconstruction of CFAE maps, we applied the following settings: voltage threshold within 0.05–0.15 mV (before displaying the CFAE map, the level of noise was reconfirmed to stay below the level of 0.05 mV) and electrograms with cycle lengths between 50 and 120 ms were counted as CFAE. Our settings were similar to the settings used by other investigators (22,45,46). We applied the ICL to define the level of repetitiveness of the CFAE signals. We classified points according to their ICL into points with very high (>15), medium (10–15), and low ICL (5–10).

Endoscopy and endosonography of the esophagus

Endoscopy was performed in every patient (n:261) the day after the RFA procedure. Table 2. lists the demographic data of all study patients. Special emphasis was laid on the esophageal wall, and abnormalities were documented. EU were described as erythema or necrotic ulceration based on their macroscopic appearance. To exclude mucosal lesions caused by reflux or intestinal metaplasia as well as superficial mucosal erosions, endosonography was performed in each lesion as reported previously-Figure 1. If endoscopy revealed wall changes or injuries, a PPI in combination with sucralfate was started (pantoprazol or esomeprazol 40 mg twice per day and sucralfat 1g three times per day) because progression of EU to atrioesophageal fistula might be associated with reflux esophagitis and reflux creation during RFA has been reported. Repeat endoscopy was performed 2 weeks later; drugs were continued for 4 weeks. Assessment of the esophageal wall changes was performed by independent gastroenterologists who were blinded to the RFA procedure.

Table 2 Patient characteristics

	Esophageal ulceration		
	No	Yes	*P* value
Number of patients	261	6	
Demographic information			
Male, %	80.1	66.6	.350
Age, mean ± SD	57.6 ± 9.2	61.7 ± 4.5	.286
Weight, mean ± SD	86.2 ± 13.5	80.2 ± 12.2	.323
Disease characteristics			
Structural heart disease, %	21.8	33.3	.616
Arterial hypertension, %	42.9	33.3	.639
Diabetes mellitus, %	6.5	16.7	.345
Persistent atrial fibrillation, %	34.5	83.3	.023
Antiarrhythmic drugs failed	2.6 ± 1.6	2.5 ± 1.4	.874
Procedural characteristics			
First ablation procedure, %	73.2	50.0	.147
General anesthesia, %	14.2	16.7	.863
Duration of fluoroscopy	43.4 ± 19.1	50.3 ± 10.1	.532
Duration of procedure in minutes	225 ± 60	219 ± 18	.871

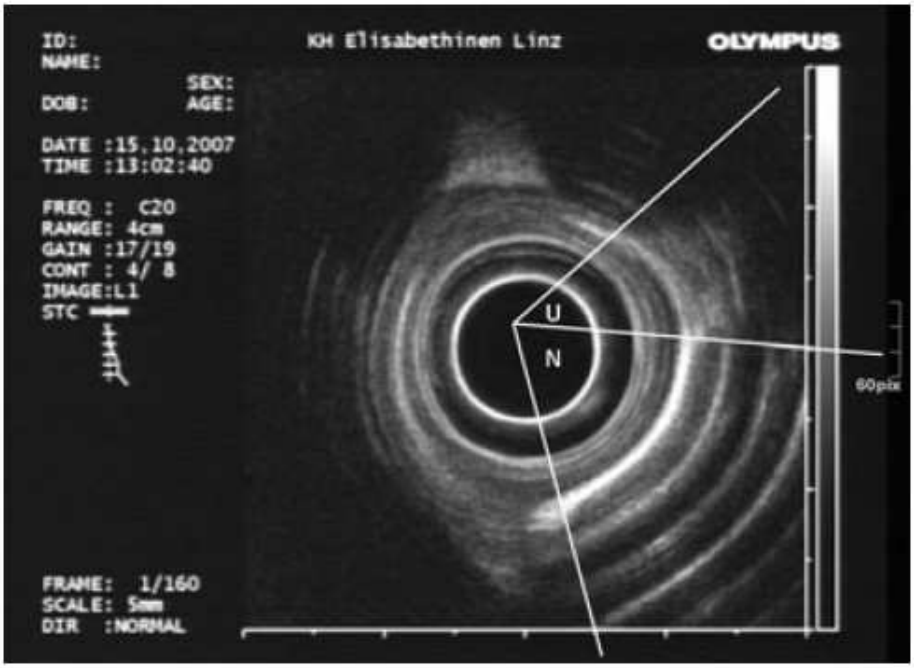

Figure 1. Endosonography of an esophageal necrotic ulcer. Segment N = normal tissue layering (mucosa, submucosa, muscularis externa, adventitia). Segment U = ulceration with homogenization of tissue and loss of layering. Other segments have no wall contact.

MSCT imaging and evaluation: each patient underwent MSCT 1 day before RFA using a 16-detector row system (Aquilion, Toshiba Medical Systems, Otawara, Japan). These data were imported into the Carto or Ensite NavX system to be processed for the fusion with the electroanatomic mapping as described previously. Craniocaudal scanning was performed during a single expiratory breath hold. A nonionic contrast agent (Ultravist 300, Bayer Schering Pharma, Zurich, CH) was administered via a cubital vein with an infusion rate of 3.2 ml/s, resulting in a total of 80 ml of contrast. The acquisition time was approximately 20 s; the in-plane resolution was 0.5 x 0.5 x 0.6 mm. Sagittal, axial, and coronal slices were reviewed by 2 independent physicians who evaluated the esophageal course, LA diameters, and PVs. Measurements included the following: the maximal (1) anteroposterior and (2) transverse diameter of the LA (the transverse diameter of the LA was defined as the distance between the midpoint of the right and left sides of the PV in oblique axial or axial images, and the anteroposterior diameter was measured at the midpoint of the transverse diameter); (3) the width of the anterior aspect of the esophagus that was in direct contact with the LA posterior wall; (4) the distance of the most anterior luminal aspect of the esophagus to the LA endocardium; (5) the shortest distance from LA endocardium to the thoracic spine with the esophagus lying in between; (6) the distance of the most posterior luminal aspect of the esophagus to the thoracic spine as described earlier; and (7) the craniocaudal distance showing an LA-to-esophagus distance of <5 mm (Figure 2). Interobserver variability of the MSCT measurements was determined by having 2 physicians performing all measurements in a blinded fashion. Ablationists were blinded to the MSCT results to ensure that the procedure was not altered by MSCT findings. To assess stability of the MSCT parameters, we assessed patients having repeat procedures and separate computed tomography scans performed for each RFA.

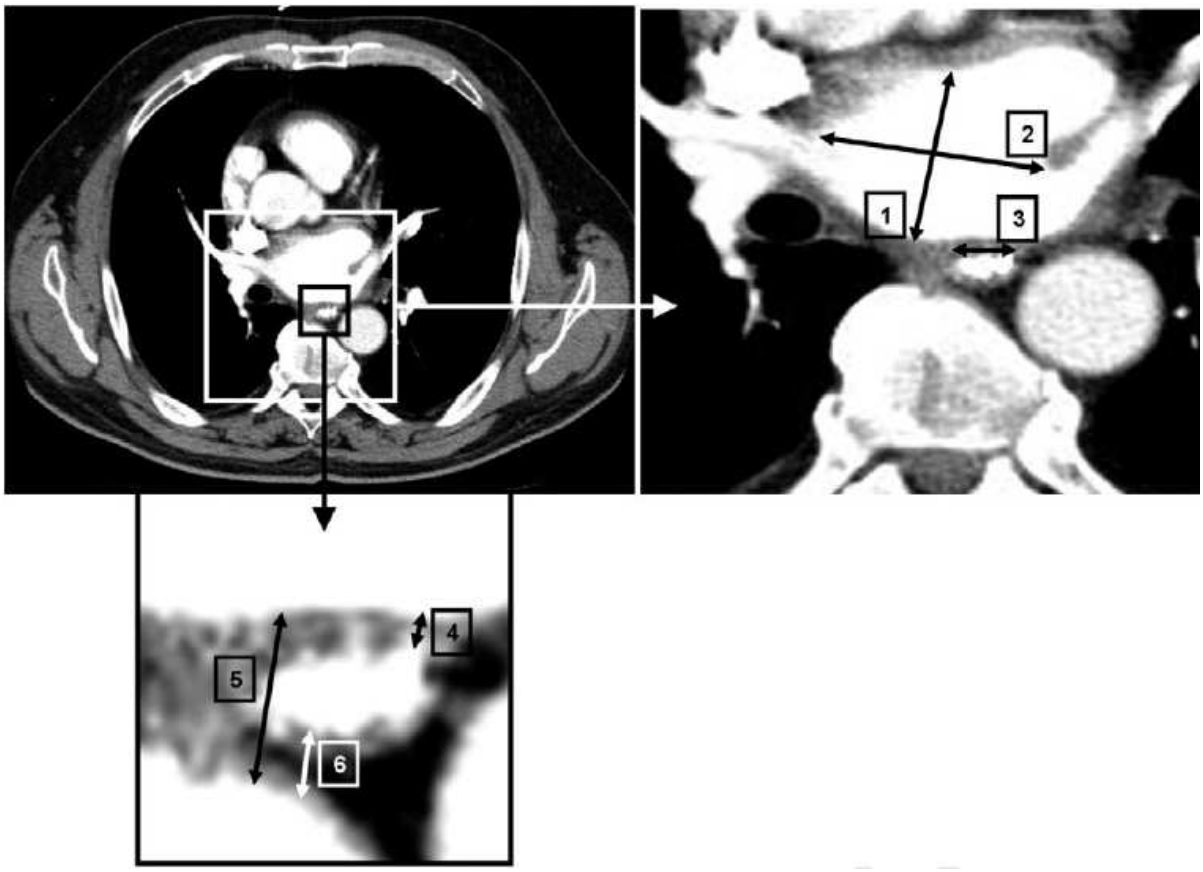

Figure 2. Multislice computed tomography measurements. **1:** Anteroposterior left atrial (LA) diameter. **2:** Transverse LA diameter. **3:** Width of the anterior esophageal wall directly in contact with the LA posterior wall. **4:** Distance of the most anterior luminal aspect of the esophagus to the LA endocardium. **5:** Shortest distance from LA endocardium to the thoracic spine with the esophagus situated in between. **6:** Distance of the most posterior luminal aspect of the esophagus to the thoracic spine.

Study protocol to assess the acute effect of RFA on distal esophageal acidity

The study population consisted of 32 consecutive patients referred for RFA of AF. All patients provided informed consent for inclusion into the study, which was approved by the local ethics committee. Patients included in the study had no history of dyspepsia or gastroesophageal reflux and were not taking drugs for gastroesophageal reflux disease (GERD). All probands underwent RFA and esophagoscopy 24 hours before and after ablation to exclude esophageal ulcerations. During the first endoscopy, a leadless pH-metry capsule (Bravo pH-metry capsule, Given Imaging GmbH, Hamburg, Germany) was fixed to the lower

esophageal wall to assess pH changes as well as the number and duration of refluxes. The DeMeester score, a standardized composite score of acidity and reflux, was calculated based on the measurements obtained (48). Table 3. lists the demographics of all study patients.

Table 3 Patient demographics

No. of patients	32
Male	28
Structural heart disease	9
Arterial hypertension	13
Diabetes mellitus	0
Paroxysmal atrial fibrillation	26
First ablation procedure	20
Age (yr)	56 ± 10
Weight (kg)	87 ± 12
Normal ejection fraction (%)	27
Left atrial parasternal diameter (mm)	40 ± 5

Esophageal endoscopy was performed in all patients the day before and after the RFCA procedure. Special emphasis was given to the esophageal wall. Abnormalities were documented by taking images and measuring the extent of the lesion and the aboral distance as well as the distance from the gastroesophageal junction. To differentiate mucosal lesions caused by preexisting reflux or intestinal metaplasia as well as superficial mucosal erosions or intramural hematomas (e.g., from transesophageal echocardiography), additional endosonography was performed on each macroscopic lesion. During the endoscopy prior to ablation, the aboral distance of the gastroesophageal junction was measured to locate the target for the pH-metry capsule (approximately 5 cm above the junction). A leadless pH-metry capsule then was inserted via an introducer and fixed to the lower esophagus by a vacuum system to assess acidity approximately 24 hours before and after RFCA (Figure 3). The Bravo pHmetry capsule (Given Imaging GmbH) is capable of transmitting pH measurements to an external data receiver every 30 seconds. The patient's position (supine, upright) also is recorded. The capsule is spontaneously released after a few meals with the swallowing of solid food. Patients were in a fasting state for approximately the same time span in the pre- and post-RFCA periods. Capsule position was assessed the day after RFCA by routine fluoroscopy and during the second endoscopy to exclude false measurements due to dislocation into the stomach or bowel. Based on the measurements transmitted from the

capsules, the DeMeester score was automatically calculated by the software. The DeMeester score is a standardized, well evaluated composite score for the assessment of pathologic reflux (normal score <14.7) that provides adequate sensitivity and specificity (48). The DeMeester score is based on six parameters: supine reflux, upright reflux, total reflux, number of reflux episodes, number of episodes longer than 5 minutes, and longest reflux episode. pH-metry itself remains the gold standard for the diagnosis of reflux disease and is sufficiently reproducible. If endoscopy revealed esophageal ulcerations, PPI in combination with sucralfate (pantoprazole or esomeprazole 2 x 40 mg and sucralfate 3 x1 g, respectively) was started. Repeat endoscopy was scheduled 2 weeks later in patients who presented with esophageal ulcerations.

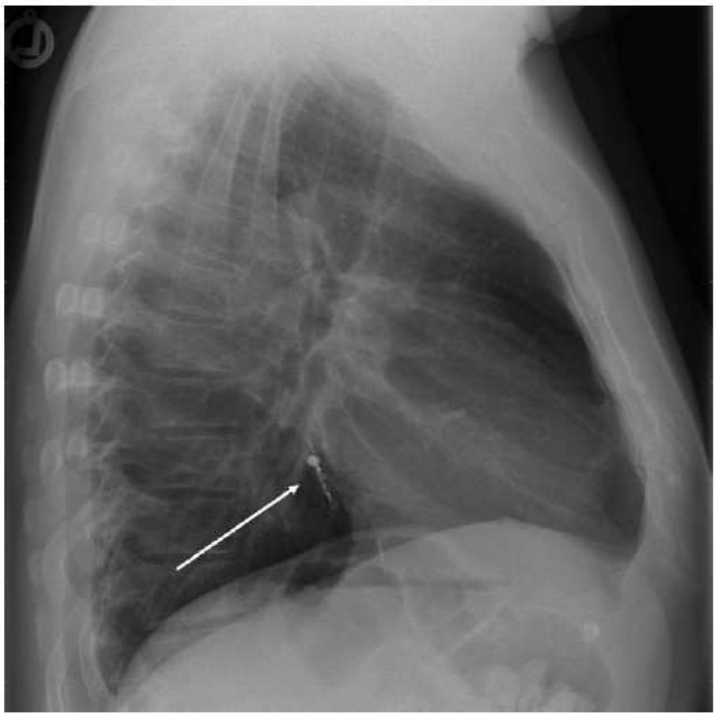

Figure 3. Chest X-ray film in the lateral view showing the Bravo capsule *(arrow)* placed in the distal esophagus.

Statistical analysis

All variables are presented as mean ± standard deviation, counts, or percentages. Continous variables were compared by independent-samples t-test. Comparing groups, we used cross-tabulations for nominal variables performing a chisquare, Cramer V, the Wilcoxon rank-sum, sign-exact test or Fisher exact test for small sample sizes, when applicable. A Student *t*-test for independent samples with a confidence interval of 95% was used for metric variables. Comparisons between preprocedural and postprocedural data were made by nonparametric Kolmogorov- Smirnov test for independent samples and small sample sizes. Correlation analysis was done using Spearman Rho (rs); 2-sided significance levels were given on the levels of 0.05 and 0 .01, respectively. Spearman Rho was used because MSCT data were not normally distributed. Multivariate regression analysis included all parameters showing significant *P* values in univariate analysis. Due to the high intercorrelation of anatomical parameters, we only included the most significant anatomical parameter into the multivariate model. Statistical significance was established at $P < 0.05$. All statistical analyses were performed using SPSS 12.0 statistical software (Chicago, IL, USA).

Results

Acute effects of CFAE ablation on DF and RI for the fibrillatory process: Out of 21 patients with paroxysmal AF termination was reached by PVI in 19 (90%) and non inducibility in 13 (62%). In the remaining eight patients, CFAE ablation was performed as described previously. With this step of ablation, termination was reached in one patient (13%) who was also rendered non-inducible after completion of CFAE ablation. In the remaining seven patients, we performed roof line ablation and reached termination and subsequent non-inducibility in all seven patients (100%). Because of latter, there was no need for mitral isthmus ablation in paroxysmal group of patients. Using differential pacing manoeuvres in sinus rhythm, we confirmed bidirectional block along the roof line in every patient. Non-inducibility was tested after each step of ablation, i.e. after PVI, after CFAE ablation, and after completion of the roof line. The overall rate of non-inducibility in the paroxysmal group was 100% using the ablation steps described above. Pulmonary vein isolation in combination with CFAE ablation resulted in 67% of non-inducibility in this group of patients. In 20 patients with persistent AF, not a single termination was reached with PVI, in 2 patients

(10%) termination occurred during CFAE ablation. In the remaining 18 patients, we reached termination of AF with completion of the roof line in 7 patients (39%), and in the remaining 11 patients, mitral isthmus ablation was performed. We reached conduction block along roof line in every patient. In 7 out of the 11 (64%) patients undergoing mitral isthmus ablation, we completed the line using epicardial ablation from the distal CS but reached complete conduction block only in 5 out of the 11 patients (45%). Termination occurred during mitral isthmus ablation in four patients (36%). In the remaining seven patients, electrical cardioversion was performed. Therefore, the overall termination rate in a group of patients with persistent AF was 65% with the set of ablations described above.

In the paroxysmal AF group, the mean DF in the PVs was 6.41± 1.0 Hz and the mean RI in the PVs was found to be 0.30 ± 0.04. In patients with persistent AF, the mean DF of the PVs was 6.49 ± 0.8 Hz and the RI 0.28 ± 0.06. Values of DF and RI measured in the CS after different steps of ablation (in both groups) are presented in Table 4. The frequency gradient between PVs and CS was 0.94 ± 0.97 Hz in the paroxysmal and only 0.12 ± 0.58 Hz in the persistent group of patients. After PVI, the DF in the CS decreased and RI increased significantly in the paroxysmal AF group. After CFAE ablation in this group of patients, we found a non-significant decrease in DF and a small increase in RI. After (or during) completion of the roof line in paroxysmal AF patients, we recorded a further significant decrease in DF and a notable rise in the level of RI before termination of AF.

The changes in DF and RI in patients with paroxysmal AF after different steps of ablation are presented in Figures 4. and 5. and summarized in Table 4. In the persistent AF group, PVI led to a non-significant decrease in DF of the CS and to a remarkable increase in RI. After CFAE ablation, there was no significant change in DF and RI but after completion of the roof line DF decreased and RI increased significantly in the persistent AF group. With the accomplishment of mitral line, there was further significant decrease in DF and increase in RI. The changes in DF and RI in patients with persistent AF after different steps of ablation are shown in Figures 6. and 7. and summarized in Table 4.

	Paroxysmal AF		**Persistent AF**	
	DF (Hz)	RI	DF (Hz)	RI
Before ablation	5.46 ± 0.70 (m:5.65)	0.24 ± 0.03 (m:0.22)	6.37 ± 0.70 (m:6.38)	0.22 ± 0.02 (m:0.22)
After PVI	4.96 ± 0.31 (m:4.63)	0.32 ± 0.05 (m:0.34)	6.19 ± 0.73 (m:6.15)	0.31 ± 0.04 (m:0.31)
After PVI + CFAE abl	4.83 ± 0.29 (m:4.79)	0.33 ± 0.05 (m:0.32)	5.95 ± 0.86 (m:5.95)	0.33 ± 0.03 (m:0.32)
After PVI + CFAE + RL abl	3.93 ± 0.45 (m:4.01)	0.44 ± 0.05 (m:0.44)	4.51 ± 0.90 (m:4.53)	0.39 ± 0.04 (m:0.39)
After PVI + CFAE + RL + MI abl			3.60 ± 0.92 (m:3.68)	0.53 ± 0.07 (m:0.52)

Table 4. Overview of changes in DF and RI measured in CS after different steps of ablation.

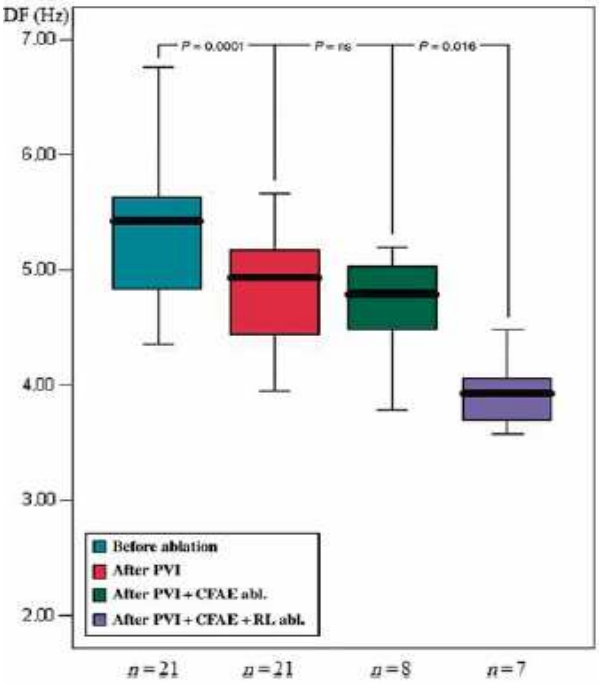

Figure 4. Boxplot presenting changes in DF measured on CS bipoles after different steps of ablation in a group of patients with paroxysmal AF. n: number of patients; after PVI (after pulmonary vein isolation), after PVI + CFAE abl. (after PVI and CFAE ablation), after PVI + CFAE + RL abl. (after PVI, CFAE and roof line ablation).

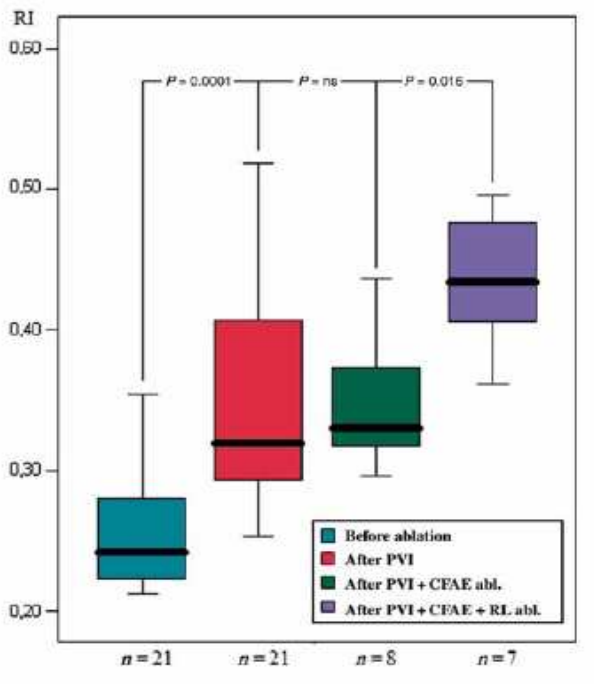

Figure 5. Boxplot presenting changes in regulatory index measured on CS bipoles after different steps of ablation in a group of patients with paroxysmal atrial fibrillation. Abbreviations as in Figure 4.

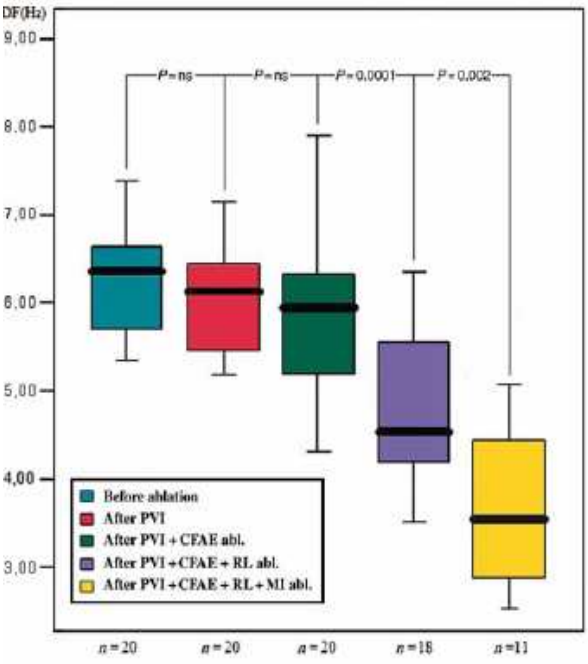

Figure 6. Boxplot presenting changes in DF measured on CS bipoles after different steps of ablation in a group of patients with persistent AF. After PVI + CFAE + RL + MI abl. (after PVI, CFAE, RL and mitral isthmus ablation). Other abbreviations as in Figure 4.

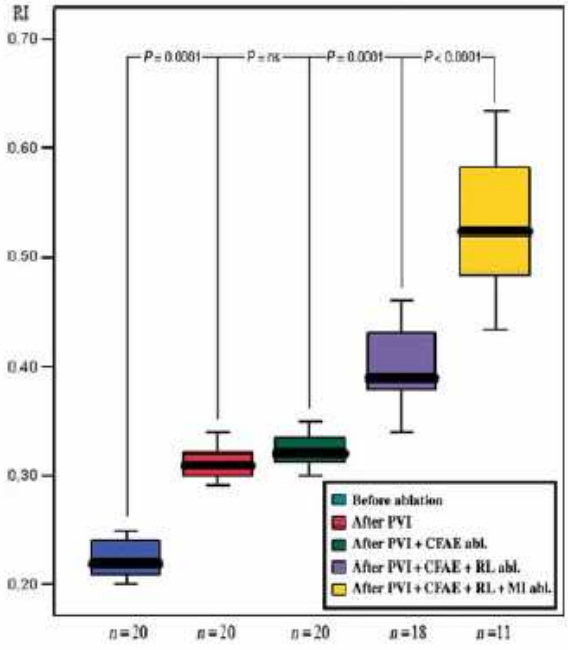

Figure 7. Boxplot presenting changes in RI measured on CS bipoles after different steps of ablation in a group of patients with persistent AF. For abbreviations see Figure 4.

Identification of a high-risk population for esophageal injury during RFA of AF: within the total study population (Table 2), 6 wall lesions were classified as EU (2 erythemas, 4 necrotic ulcers) created by RFA by means of localization and endosonographic appearance, thus giving a total risk of 2.2% (6 of 267). These wall abnormalities were located at 31 ± 7 cm aboral (range: 20 to 38 cm) or 7 ± 4 cm above the gastrointestinal junction (range: 4 to 14 cm) and showed transmurality with lack of wall layering in endosonography. A detailed description of all parameters possibly influencing EU creation is given in Table 4. Demographic or RFA procedural parameters with a significant influence in univariate analysis were type of AF (persistent) and additional LA lines, namely performance of a roofline, mitral isthmus line, and CS ablation. In no patient with PV isolation alone (without additional lines)

did EU develop. A variety of anatomical parameters showed significant *P* values in univariate analysis; the best predictive MSCT parameter was LA-to-esophagus distance.

Table 4 Procedural parameters and anatomical relationships

	Esophageal ulceration		
	No	Yes	*P* value
Type of atrial fibrillation			
Paroxysmal	171	1	.023
Persistent	90	5	
Sedation/anesthesia			
Deep sedation	224	5	.863
General anesthesia	37	1	
Additional ablation sites			
Roof line	108 of 261	6 of 6	.006
Left atrial isthmus line	45 of 261	4 of 6	.011
Coronary sinus	61 of 261	5 of 6	.004
Inferior line	26 of 261	2 of 6	.115
CFAE ablation	40 of 261	1 of 6	.636
Radiofrequency energy (Ws) delivered			
On posterior wall	24,739 ± 9,374	22,180 ± 17,360	.648
Total	71,440 ± 22,928	61,583 ± 41,960	.467
1 LA anteroposterior diameter	35.0 ± 6.0	43.2 ± 9.1	.001
2 LA transverse diameter	49.8 ± 6.4	58.3 ± 5.9	.001
3 LA to esophagus contact width	17.2 ± 5.2	22.5 ± 3.1	.013
4 LA to esophagus distance	2.5 ± 0.7	2.0 ± 0.3	.0001
5 LA to spine distance	13.5 ± 5.1	9.2 ± 1.6	.038
6 Esophagus spine distance	6.9 ± 4.1	5.0 ± 1.0	.255
7 Craniocaudal LA - esophagus contact (<5 mm LA* to spine)	60 ± 13	64 ± 24	.724

All measurements are given as counts or mean ± SD.
CFAE = complex fractionated atrial electrogram; LA = left atrium; Ws = Wattseconds (Joule).

In a multivariate model including LA-to-esophagus distance, type of AF, and additional LA linear lesions, the parameter LA to esophageal distance was the only independent predictor (Table 5). Of note, LA isthmus line and CS ablation showed a trend to significance (*P*=0 .08 and 0.07) all considering the limitation of an adjusted R^2 value of 0.11. Persistent AF highly correlated with LA enlargement presented by LA anteroposterior and transversal diameters, as expected (r_s = 0.563, *P*=0 .0001). Furthermore, these diameters were well or highly correlated with other anatomical measurements such as spine to LA distance and esophagus-to-LA contact width (r_s = - 0.152 to 0.398, *P*= 0.031 to 0.0001) showing a sandwiching and even compression of the esophageal course between the LA posterior wall and the spinal cord or adjacent aorta in these patients. Additionally, these sandwiched esophagi showed a decreased minimal distance from LA endocardium to esophageal lumen, thus mainly being influenced by a thinner LA posterior wall in enlarged atria. Additional linear lesions (subsuming all

linear lesions performed) as well correlated with the development of EU (r_s = 0.150, *P* = 0.014). In respect to robustness of MSCT measurements, data of 25 patients having repeat procedures with separate MSCT scans performed were analyzed. Within a mean time span of 9.2 months (range:3 to 16) between procedures, no statistical difference between all MSCT parameters was revealed on a case-to-case basis. Measurements differed between a minimum of 0.2 ± 0.1 mm (LA-to-esophagus distance, range: 0 to 1.2 mm) and a maximum of 2.2 ± 1.3 mm (LA transverse diameter, range: 0 to 5 mm) in mean (*P* > 0.1 for all parameters). Interobserver variability was 0.5 ± 0.8 mm.

Table 5 Multivariate analysis

	Esophageal ulceration	
	Standard coefficient	*P* value
Persistent atrial fibrillation	0.145	.8033
Roof line	0.195	.2663
Left atrial isthmus line	0.258	.0789
Coronary sinus	0.253	.0729
Left atrium to esophagus distance	−0.159	.0176
Significance (analysis of variance)		.001

Symptoms such as dysphagia or epigastric discomfort after RFA were quite infrequent in the overall population (7 of 267) and did not correlate with the finding of EU because none of these patients (0 of 6) experienced symptoms. In 17 patients presenting with coronary heart disease, only 3 were on clopidogrel at the time of RFA due to prior coronary stenting; EU developed in none of these. In all other patients, acetylsalicylic acid (n=10) or clopidogrel (n=4) were discontinued 10 days before the procedure. Only 7 patients of the overall population were taking PPIs at the time of RFA due to reflux disease; EU developed in none of these. No drug therapy showed significant impact on EU creation (*P* > 0.5). All esophageal lesions diminished after 2 weeks of PPI treatment as depicted by repeat endoscopy. AEF developed in no patients in the long-term follow-up. Other complications experienced were groin hematomas (n=16), arteriovenous fistulae (n =4), pericardial effusions without the need of drainage (n=5), congestive pneumonia (n=1), as well as transient ischemic attack (n=1).

Acute effect of RFA on distal esophageal acidity: one patient was excluded from analysis because the pH-metry capsule dislodged from the esophageal wall shortly after the procedure. pH-metry duration was 19.2 ± 3.8 hours prior to ablation and 18.7 ± 6.0 hours after ablation, excluding the time for the RFA procedure from analysis. Asymptomatic reflux as demonstrated by pathologic DeMeester score prior to RFCA was observed in 5 (16.1%) of 31 patients. One of these patients showed reflux esophagitis grade 2 by endoscopy but had no preexisting symptoms. Patients with a pathologic DeMeester score prior to ablation did not show significant progress in DeMeester score after RFA and were excluded from further analysis. pH-metry detected development of pathologic reflux in 5 (19.2%) of the remaining 26 patients with normal DeMeester scores at baseline (Figures 8 and 9). A detailed description of all variables possibly influencing reflux is given in Table 6. No distinct study parameter could be identified as causal for reflux development; only arterial hypertension showed a weak trend to significance. Within the total study population of 31 patients, 1 (3.2%) patient developed esophageal ulcerations created by RFA. Wall abnormality was located 39 cm aboral or 4 cm above the gastrointestinal junction and was evaluated further by endosonography. This patient belonged to the subgroup of patients who already had a pathologic DeMeester score prior to ablation. The patient had persistent AF, with PV isolation and roof line, LA isthmus line, and inferior lines performed. The esophageal ulcerations required 2 weeks to heal with use of PPI and sucralfate, and follow-up endoscopy revealed total restitution. No correlation was found between development of pathologic reflux and esophageal ulcerations.

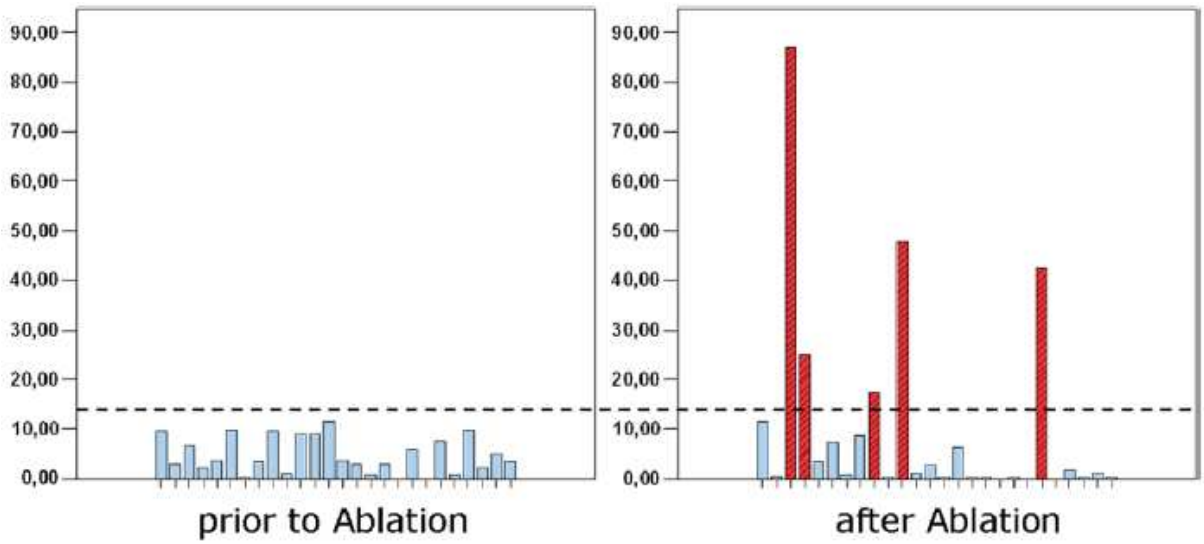

Figure 8. Bar chart of DeMeester scores before and after radiofrequency catheter ablation in the 26 patients with normal scores prior to ablation.

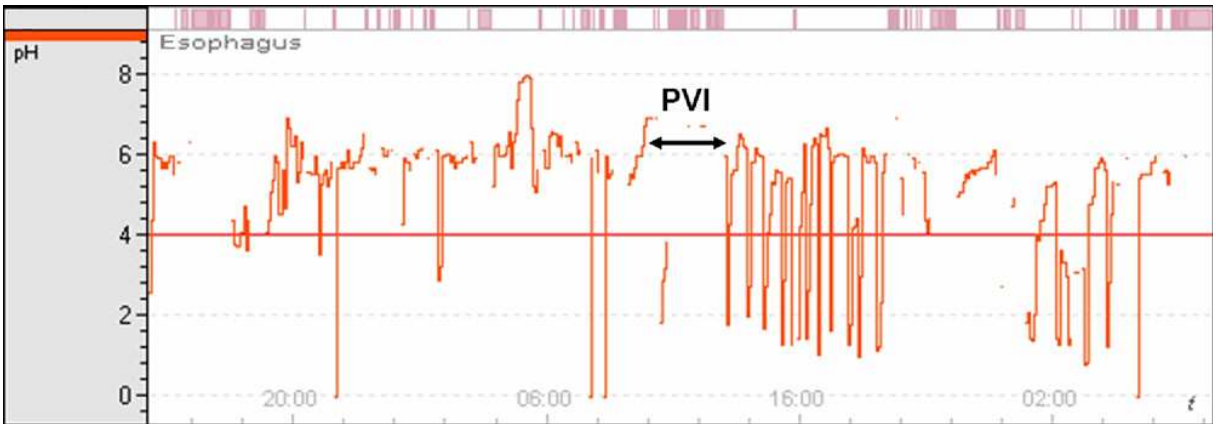

Figure 9. pH-metry plot of a patient who developed pathologic acid reflux after pulmonary vein isolation (PVI). x-axis = time; y-axis = pH values measured.

Table 6 Parameters

	Pathologic DeMeester score		
	No	Yes	*P* value
Gender			
Male	17	5	.999
Female	4	0	
Type of atrial fibrillation			
Paroxysmal	16	5	.976
Persistent	5	0	
Structural heart disease			
No	15	4	1
Yes	6	1	
Arterial hypertension			
No	14	0	.055
Yes	7	5	
Impaired ejection fraction			
No	15	4	1
Yes	1	0	
Procedure			
First	14	2	.936
Second/third	7	3	
Sedation/anesthesia			
Conscious sedation	12	3	1
General anesthesia	9	2	
Additional ablation sites			
Right atrial isthmus line	2	0	1
Left atrial isthmus line	4	1	1
Left atrial roof line	8	0	.601
Coronary sinus line	4	1	1
Complex fractionated atrial electrogram ablation	5	0	.976
Age (yr)	57 ± 10	56 ± 12	.815
Weight (kg)	86 ± 14	89 ± 5	.599
Smoking			
Nonsmokers	19	1	.367
Smokers	4	1	
Alcohol			
<1 unit per day	17	3	.252
>1 unit per day	3	2	
Beta blocker or calcium antagonist use			
No	19	2	.654
Yes	2	3	
Amount of radiofrequency energy delivered on posterior wall (Ws)	29,197 ± 8,623	22,774 ± 9,663	.237
Left atrial parasternal parameter (mm)	40 ± 6	41 ± 2	.824

Discussion

Acute effects of CFAE ablation

In previous animal and human studies, a high level of spatial and temporal stability of CFAEs was verified (45,49,50,51). We hypothesized that CFAE sites acquired during 3D mapping before ablation are stable without any shifting after PVI, and this would be applicable also for CFAE points outside the PVI antrum without need for a further and time-consuming CFAE remap. We targeted only the latter points in the LA considering CFAE points in the PV–LA junction regions already excluded from the fibrillatory process by previous PVI. The substantial reason for standard PVI was the fact that PVs are electrically not isolated after CFAE ablations. (22,52). This was convincingly shown in a study by Oral et al. (52). With our sequence of ablation in which targeting of CFAEs always followed PVI, we found a low rate of termination (10– 13%) and a negligible impact of CFAE ablation on the fibrillatory process reflected by insignificant changes in DF and RI compared with changes that were achieved by other ablation steps. This finding is not surprising knowing that there is a high clustering of CFAE points in the PV–LA junction regions (22,45,52,54) which sites were already excluded from the fibrillatory process by PVI. We found a small effect of CFAE ablation on the fibrillatory process despite the fact that energy used for CFAE ablation was higher than energy spent for creation of the roof line in both the paroxysmal and persistent group of patients (8300 vs. 6500 Ws and 14 560 vs. 5900 Ws). Also the mean energy used for CFAE ablation in the persistent group was higher than the mean value of energy spent for the creation of the mitral line (14 560 vs. 13 770 Ws). The mean time spent for CFAE ablation was 34 min (in a range from 15 to 58 min). Success rates of CFAE ablations reported in the literature are inconsistent. (15,46,52). In a recent study by Porter et al. (46) the acute termination rate with CFAE ablation guided by automated detection was 88% in paroxysmal and 20% in persistent AF. In a study by Verma et al. (53) termination occurred in 54% of cases during CFAE ablation. In both studies, the first step was ablation of CFAEs (including CFAE points adjacent to PVs) and the second was standard PVI. On the basis of our results, the reasons for this low rate of termination in our study are the following.

1. In studies described above (46,53) there was a high clustering of CFAE points in PV–LA junction regions (64–83%) and the acute termination of AF was achieved targeting CFAE points adjacent to PVs in ~50% of patients with paroxysmal AF. In a study by Schmitt et al. (54) the most common sites for termination of AF during CFAE

ablation were the regions of the PV ostia.

2. With PVI as a first step, we already covered these sites and reached termination in 90% and non-inducibility in 62% of patients with paroxysmal AF. Adding CFAE ablation to PVI, the termination rate increased just by 5% from 90 to 95% and non-inducibility from 62 to 67%.
3. In a study conducted by Porter et al. (46) mapping of the LA was performed with a mean density of 143 sites/patient which is doubling the mapping density in comparison with our mapping technique of 80 points/patient. As a result, they found a mean of 28 + 18 sites/patient with ICL >7, and we observed a mean of 14.5 + 6.5 sites per patient with ICL >5.
4. We did not perform mapping in the right atrium and in the CS epicardially which may also contribute to a low termination rate. By virtue of the latter observations, there is a possibility that the success rates of CFAE ablations simply correlates with the amount of tissue destroyed by ablation which is in sharp contrast to the aim of targeting selective CFAE sites to preserve left atrial myocardium as much as possible.

Study limitations

The major study limitation is the relatively low mapping density which subsequently resulted in a lower diagnostic accuracy of CFAE maps. Our recording time for each point during the mapping procedure was 2.5 s. However, in a recent study by Lin et al. (51) the highest consistency of CFAE mapping was achieved by ≥ 5 s recording time. We were using the 50–120 ms setting for electrogram cycle length (duration), which might be improved by a different setting as recently reported by Calo´ et al. (55) where a higher diagnostic accuracy could be obtained by a setting of 15–30 ms. In our paroxysmal AF patients, inducibility was assessed with pacing manoeuvres and not by isoproterenol infusion which has a higher specificity and sensitivity. We did not perform a CFAE remapping after PVI, so we cannot state that the CFAE points were absolutely the same (in same location with the same level of fractionation) before and after PVI. This issue was recently clarified by Roux et al. (56) at least for the patients with persistent AF. They demonstrated that the CFAE burden is significantly reduced after PVI, not just in the vicinity of the PVs but also in LA regions remote from the PVs. Our study only describes the acute effects of CFAE ablation, whereas Porter et al. (46) reported a notable long-term success rates with CFAE ablation followed by PVI.

Identification of a high-risk population for esophageal injury during radiofrequency catheter ablation of atrial fibrillation

We aimed to evaluate the individual impact of various additional linear lesions on the development of EU in a standardized ablation approach using a 25-W energy maximum at the posterior LA wall. Additionally, we wanted to link anatomical information gained by MSCT with the end point of EU, as no study has yet done. In this relatively large single-center study of more than 260 patients, we consistently screened patients for evidence of esophageal injury after LA ablation. The combination of this consecutive study with a former randomized trial gives us constant rates of EU of 2% to 3% in mean when using a 25-W maximum at the posterior LA wall in a total of more than 400 patients. The strengths of this study include its size (which is by far the largest study of consecutive endoscopic screening after RFA for AF); the implementation of demographic, procedural, and anatomical risk factors that are easily examined; and the clinically relevant study end point reported. As of today, no study has linked anatomical information gained by MSCT with the end point of EU development revealed by endoscopy after RFA of AF. Berjano et al. (57) hypothesized a low LA-to-esophagus distance to be predictive for the risk of EU in a theoretical model. Our data suggest this finding also to be true for the in vivo situation showing LA-to-esophagus distance to be the only significant predictor in multivariate analysis. As seen in other studies, LA-to-esophagus distance and LA-to-spine distance do inversely correlate with the finding of an enlarged LA diameter (58,59). This explains the higher risk of EU in patients with enlarged LA. Cury et al. (60) reported the anterior aspect of the esophagus to be in direct contact to the posterior LA wall in all cases, which also could be confirmed in all 267 patients. The sandwiching of the esophagus between the posterior LA wall anteriorly and the thoracic spinal column or aorta posteriorly, which is aggravated by LA enlargement, may predispose to EU and fistula formation. The hypothesis of overlapping lines at the posterior LA wall increasing the risk of EU may also be supported by our data, especially by the results of correlation analysis and by the fact that in no patient with PV isolation alone (without additional linear lesions) did EU develop when performing this specific ablation approach. The type of AF showed a high correlation to anatomical parameters as well as lesion set performed and should be considered as a confounding factor rather than a true risk factor. With a total EU appearance of 2.2% in the whole patient cohort, we report a much lower event rate than in most other studies published (4% to 48%) (28,58,61,62). Studies consistently screening for EU were small in sample size and reported a total of 11% and 26%

of esophageal injuries, respectively (58,61). There are 3 major issues possibly explaining differences among reports, namely catheters used, maximum energy settings, and energy titration methods. Data on catheter dependence of EU are confusing (28,62,63,64). It is likely that open irrigation catheters (OIC) facilitate the deeper lesion creations often required for PV isolation and that they increase the likelihood of contiguous transmural lesions possibly involving the esophagus. On the other hand, one possible explanation for the finding of OIC being superior to 8-mm-tip catheters in other studies is the duration of RF energy delivery to create the same lesion size and therefore a longer resistive heating of the esophageal tissue. A canine model revealed a significant difference in actual tissue temperatures, but no difference in luminal temperature between OIC and 8-mm-tip catheters (65). In our study, we again demonstrate a low incidence of EU using an OIC technique, confirming previous results of a randomized prospective trial. Temperature probes were used to monitor energy delivery and temperature increase in the esophagus in other studies (28,31,58,63,65). As stated in these studies, luminal esophageal temperature (LET) monitoring has major limitations, such as malalignment of the probe to the RFA catheter and posterior LA wall, the underestimation of intramural temperature by an intraluminal probe, and the too-slow LET increase to prevent EU. In addition, power does not correlate with esophagus temperature, and overheating even occurs when the ablation site is quite distant (31). The additional usage of intracardiac echocardiography (ICE) gives divergent study results (28,63,66). Cummings et al. (63) reported good correlation of microbubble formation and esophageal temperature increase. Another investigator group showed in an in vivo canine model that microbubble formation detected by ICE was occasionally absent during RF delivery around the PV ostia even with tissue temperatures over 80°C. Therefore, it is possible that microbubble formation is not a consistent marker of tissue overheating (68). Microbubble formation may even have the same problem as luminal temperature monitoring by a latency time too long to stop energy delivery and prevent EU, especially when showers of microbubbles occur (28,66). In contrast to another study published, we did not show any increased risk of general anesthesia versus deep sedation (2.7% vs. 2.2%) (61).

Study limitations

Our study has several limitations. First, this was an observational, nonrandomized study; therefore, unaddressed confounding factors may be present and not accounted for. As no esophagoscopy was performed prior to RFA, we can only assume that the location in the

anterior esophagus, distant from the gastroesophageal junction, makes the EU likely to be RFA-related. With the use of endosonography, we were able to prove the transmurality of the injuries, which is not common for other esophageal lesions. Spatial volume averaging could influence MSCT measurements; however, we anticipate that these effects should be minimal using a 16-slice MSCT scanner with an in-plane resolution of 0.6 mm. Heading in the same direction, interobserver variability and differences between scans of the same patient in repeat procedures were quite low, perhaps mostly influencing the parameter of LA-to-esophagus distance because this has the lowest dimension. Even knowing that, also this parameter correlated well with other related parameters measured. Additionally, potential esophageal movements cannot be accounted for in a single MSCT measurement. At least the supine body position is comparable during MSCT and RFA. Anatomical data were highly intercorrelated, and not all presented high R values in correlation analysis, showing different impacts on EU. Multivariate analysis was performed, showing a high significance with the major limitation of a rather weak R^2 value. This mainly reflects the low number of EUs experienced and other potential factors influencing EU creation not considered in our multivariate model (e.g., contact force, lesion transmurality, maximum energy used at posterior LA wall, etc.). The end point of visible esophageal mucosal injury may underestimate the true incidence of intramural lesions (tip of the iceberg) because the mode of EU creation and especially AEF still remains unclear. Pathophysiologic concepts include ischemic, autonomic, or direct tissue damage, as well as acute reflux creation (28,57,58,63). We cannot exclude that endoscopy 24 h after RFA solely reveals direct tissue damage, whereas other possible mechanisms of injury may develop later on. However, we believe that a transmural lesion is an end point of interest concerning the potential development of AEF. Electrophysiologists were blinded to findings on MSCT scan in our study. In reality, operators typically have CT merge information including esophageal imaging available or ICE imaging for monitoring during RFA, the latter of which permits real-time visualization of the esophagus. Therefore, although this study demonstrates a low incidence of esophageal ulceration, the true incidence may be even lower. Although studies have not consistently demonstrated the superiority of additional monitoring procedures, this technology is available in real life.

Acute effect of RFA on distal esophageal acidity

Animal studies (until now presented only as abstracts) have shown stepwise development of reflux and erosive esophagitis, speculated be an effect of radiofrequency damage to the vagal plexus surrounding the distal esophagus sustained during LA ablation (29). In addition, these

studies showed the potential progression of esophageal ulcerations to fistulas in the absence of anti-gastroesophageal reflux disease (anti-GERD) medication in few cases (68). The mechanism of fistula creation in human remains unclear. Fistula has never been reported as an acute complication, thus making the hypothesis of a pure mechanical effect unlikely. One possible mechanism is the parallel development of esophageal injury and gastroesophageal acid reflux creating the late complication of atrioesophageal fistula. Therefore, treatment with PPIs after RFA of AF is common clinical practice in many institutions, especially in the setting of esophageal injury detected by endoscopy. Asymptomatic preexisting (5/31) or newly developed acid reflux (5/26) is common in patients undergoing RFA for AF. Damage to efferent vagal neurons of the lower esophagus by conductive heating is a possible mechanism to explain the acute effect on the lower esophageal sphincter resulting in the development of gastroesophageal reflux (69). Even a temporary influence on efferent neurons may explain the acute effect, as vagal stimulation has been shown to decrease sphincter tone (70). Due to the study design, we could assess only the acute effect on the lower esophageal sphincter; whether this situation remains chronic cannot be determined in our study setting. The true mechanism of reflux creation, which also might simply be caused by the prolonged supine position of the patient, cannot be proved by our study design. Only animal studies with autopsy may possibly explain the true pathogenesis. The method of sedation or anesthesia did not play any adjunctive role in our patient cohort. Because AEF has never been reported as an acute complication but always presented late (9 days to 4 weeks after RFA), it seems likely that the direct mechanical effect on the LA posterior wall is not the only factor leading to fistula creation. It is possible that cofactors such as acid reflux during the process of lesion healing are needed for progression from esophageal ulceration to fistula. In concordance with the results of a larger series using the same ablation approach, the prevalence of EU creation is low in patients undergoing RFA using a 25-W power limit at the posterior LA wall. In regard to our data, only patients with PV isolation and more than one additional LA line were at risk for developing EU. No patient undergoing PV isolation alone developed esophageal injury. Assuming that both factors of reflux (32.3% [10/31] of patients) and esophageal ulcerations (2%–3%) are needed for latent development of atrio-esophageal fistula, then approximately 0.0646% to 0.0969% of all patients are at risk for fistula formation. This explains the low prevalence of AEF and matches the findings of the second worldwide survey on RFA for AF, which reported 0.04%. The actual number of patients progressing to AEF might be highly dependent on the use of anti-GERD medications, ablation approach, and maximum energy used for RFA. Assuming higher rates of EU as reported by other studies,

the number of patients possibly developing both risk factors (EU and reflux) will increase substantially (28,63). Despite the low prevalence, AEF is a serious complication with a mortality as high as 50% to 80% therefore, this complication must be prevented by all means. Because no distinct risk factors for *reflux creation* could be identified and a considerable number of asymptomatic patients showed acid reflux prior to RFA, no suggestions for prevention of this phenomenon can be offered by this study. With regard to the second parameter of AEF creation, PPIs and sucralfate have been shown to be effective in *healing esophageal ulceration* after RFCA. All esophageal lesions resolve within 2 to 4 weeks, as seen in our single patient.

Study limitations

Our study represents a single-center, nonrandomized, observational study. Because the statistical power of this study is limited by the small patient numbers, statistical tests for small sample sizes were used. Larger studies on this topic are needed. This study reports data on the first 24 hours before and after RFA of AF; therefore, no conclusions can be made regarding the evolution of acid reflux outside of this time range. This study lacks a control group to eliminate confounders that could increase reflux after LA ablation. Therefore, we can only show the actual occurrence of reflux after and asymptomatic reflux before RFA and cannot draw conclusions about the pathogenesis of, or possible impact on, fistula formation. This study should develop new ideas for future investigation on a potentially life-threatening complication of RFA of AF. pH-metry studies have shown the day-to-day variability of reflux to be approximately 20% (71). However, patients in our study who developed pathologic reflux showed a minimum increase of 90% in DeMeester score, thus making a variability effect unlikely. We cannot prove the concept of AEF creation by the two factors of reflux and EU because all patients with one or both factors were treated with anti-GERD medication. A proof of concept in humans is impossible because of ethical reasons. Animal studies are needed to prove the concept of progression from esophageal injury to AEF by the cofactor of acid reflux. Our limited study population consisted of symptomatic as well as asymptomatic individuals. Because consistent data about the patients' symptoms after hospital discharge are lacking, we cannot correlate reflux or EU with patient complaints.

New observations

1. On the basis of our results, CFAE ablation guided by a dedicated software algorithm and performed after standard PVI without CFAE remapping does not influence the fibrillatory process significantly. Our results strongly suggest that CFAE mapping and ablation have to be performed always after PVI.
2. We identified high-risk patients for esophageal injury during RFA of AF. These are: patients with short LA-to-esophageal distance and patients with more than one additional LA line. With the use of energy maximum of 25 W at the posterior LA wall we showed a low percentage of EU creation compared with other studies.
3. We proved that significant number of patients undergoing RFA of AF develop pathologic acid reflux after ablation, therefore prophylactic PPI treatment had to be considered in every patient referred for AF ablation.

Conclusions

Complex fractionated electrogram ablation guided by a dedicated software algorithm and performed after PVI in the LA regions outside of the circular PVI lines without CFAE remapping after isolation of the veins had no significant impact on the fibrillatory process and plays a minor role in achieving higher rates of termination and non-inducibility in AF. This is observed for both paroxysmal and persistent AF. In contrast, both PVI and linear lesions are effective in changing the fibrillatory substrate. Implicitly we concluded that CFAE mapping and ablation should be performed always after pulmonary vein isolation.

In our study we identified potential demographic, anatomical, and procedural risk factors for esophageal injury in a large patient population undergoing a standardized RFA for AF. Multivariate analysis revealed the anatomical risk factor of a small LA-to-esophageal distance as the most important factor in EU development. With the use of a reasonable energy maximum of 25 W at the posterior LA wall using open irrigation catheters, we showed a low percentage of EU creation compared with other studies published. No visualization of the esophageal course, ICE, or LET monitoring was used. Our data give new insights into risk

factors for EU development, especially on the linkage of these parameters and the correlation to each other. Identifying high-risk patients for esophageal injury potentially has an impact on follow-up or treatment of these individuals by endoscopy or prophylactic PPI treatment.

Preferably, *prevention of esophageal ulceration* should be the first goal in RFA. Patients with more than one additional LA line are at risk for esophageal ulceration creation, provided the maximum energy delivered at the posterior wall is reduced to 25 W. Therefore, it would be reasonable to screen for esophageal ulcerations in high-risk patients with an extensive lesion set and treat them with anti-GERD medication if esophageal ulceration is discovered. Furthermore, prophylactic PPI treatment (limited to 2 to 4 weeks) of all patients undergoing RFA of AF must be discussed, especially if endoscopy is not performed.

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