**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.

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## INTRODUCTION AND AIMS

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. 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. 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. 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. 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. The same trends were found in countries of the European Union 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.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. 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. Catheter ablation using radiofrequency energy has gained acceptance as an effective treatment for atrial fibrillation. 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 complex fractionated atrial electrograms (CFAE) 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. 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. 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). The incidence of 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.The first clinical report of AEF as a complication of transvenous ablation was published by Pappone et al. in 2004. 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. 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. 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 (EU) can be interpreted as a potential precursor of fistulas. Marrouche et al. and Nakagawa et al.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.

Aims of our studies were:

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. Our technique was to perform LA circumferential ablation 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. 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. 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). 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).

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 Ablationof Atrial Fibrillation.Patients referred for a second procedure were excluded. After PVI 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. 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).

Endoscopy and endosonography of the esophagus

Endoscopy was performed in every patient (n:261) the day after the RFA procedure. 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. 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.

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. Craniocaudal scanning was performed during a single expiratory breath hold. 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. 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.

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. 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. Esophageal endoscopy was performed in all patients the day before and after the RFCA procedure. Special emphasis was given to the esophageal wall. To differentiate mucosal lesions

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. 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.

## 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%). 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. 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. 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. 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.

**Identification of a high-risk population for esophageal injury during RFA of AF:** within the total study population, 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). 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. 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. 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. 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. 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.

**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. 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.

## DISCUSSION

**Acute effects of CFAE ablation:** in previous animal and human studies, a high level of spatial and temporal stability of CFAEs was verified. 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. 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 which sites were already excluded from the fibrillatory process by PVI. On the basis of our results, the reasons for this low rate of termination in our study are the following.

1. In other studies 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. 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. 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.
4. We did not perform mapping in the right atrium and in the CS epicardially which may also contribute to a low termination rate.

**Identification of a high-risk population for esophageal injury during radiofrequency catheter ablation of atrial fibrillation:** 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. Based on our data LA-to-esophagus distance is the only significant predictor for EU creation in multivariate analysis. 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. There are 3 major issues possibly explaining differences among reports, namely catheters used, maximum energy settings, and energy titration methods.

**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. 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. 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. It is possible that cofactors such as acid reflux during the process of lesion healing are needed for progression from esophageal ulceration to fistula. 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%.

## CONCLUSION

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. 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.

**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.

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