The role of cardiac computed tomography in the risk prediction of patients with atrial fibrillation

PhD Thesis

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1. INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia that increases the risk of stroke, heart failure and hospitalization. Around 0.4% to 1% of the general adult population has AF and this rate increases with age, especially over the age of 80 to >9%. The number of affected individuals is expected to double or even triple within the next twenty to thirty years. In the developed countries the prevalence is higher than in the developing nations. Moreover, the prevalence is lower in women than in men. The most common risk factors of AF are age, hypertension, valvular and ischemic heart disease, thyroid dysfunction, obesity, diabetes, chronic obstructive pulmonary disease, chronic kidney disease and smoking. Catheter ablation is an effective and safe procedure to treat AF. However in many cases recurrence occurs, approximately 20% to 45% of the patients experience recurrence of AF within 12 months after the catheter ablation.

AF can increase the risk of stroke about five times and since elder population is constantly growing AF will have an ascendant effect on stroke morbidity and mortality. Moreover, stroke due to AF likely to be more severe than non-AF related. In the setting of AF, the left atrial appendage (LAA) is the most common source of emboli. Additionally, according to Di Biase, LAA morphology is related to the risk of stroke. Moreover, the size of the LAA orifice area and the LAA flow velocity also correspond with the incidence of stroke. Therefore, it is important to better understand the anatomical and functional features of the LAA to understand AF related stroke pathogenesis.

2. OBJECTIVES

My thesis has three main aims. Firstly, we aimed to evaluate the relationship between LAA morphology and previous stroke or TIA in two large and distinct patient populations from the Semmelweis University, Budapest, Hungary and Leiden Medical Center, Leiden, the Netherlands.

Secondly, we aimed to evaluate whether posterior LA adipose tissue attenuation, as a marker of inflammation, is associated with PVI success rate.

Thirdly, we sought to determine the independent predictors of long-term recurrence of AF after catheter ablation procedure, depending on type of AF.

3. METHODS

3.1. Patient population

In our multimodality retrospective study, we enrolled 1) patients with drug-refractory AF who underwent CT before AF ablation by whom CT was clinically indicated for the evaluation of left atrial anatomy and 2) patients without documented AF who underwent clinically indicated coronary CTA for the assessment of CAD between January of 2014 and December of 2017. The presence and pattern of AF were defined according to the European Society of Cardiology Guidelines for the management of AF. Patient data were collected from two sites: Heart and Vascular Center, Semmelweis University (Budapest, Hungary) and Leiden University Medical Center (Leiden, The Netherlands). For the assessment of the predictors of AF recurrence, consecutive patients with symptomatic AF were included who underwent point-by-point radiofrequency catheter ablation in the Heart and Vascular Center of Semmelweis University, Budapest, Hungary between January of 2014 and December of 2017.

History of stroke/TIA was collected from patient's chart reviews. LAA flow velocity values were measured by TEE. LVEF was measured by transthoracic echocardiography (TTE). Exclusion criteria were age under 18 and non-diagnostic image quality of CTA. For the determination of AF recurrence predictors, we did not analyze cases of AF recurrences during the first 90 days after catheter ablation in order to exclude AF during this vulnerable „blanking period", which might be only a temporary phenomenon due to the inflammation, maturation and healing of the ablated lesions (1, 2).

3.2. Imaging procedure

Cardiac CTA examinations were performed with a 320-slice scanner (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan) or 256-slice scanner (Brilliance iCT 256, Philips Healthcare, Best, The Netherlands) with prospective ECG-triggered axial acquisition mode. For cardiac CTA 100-120 kV with 200-300 mAs tube current was used depending on patient anthropometrics. Image acquisition was performed with 128x0.625 mm detector collimation, and 270 msec gantry rotation time. For heart rate control, a maximum of 50-100 mg metoprolol was given orally and 5-20 mg intravenously, if necessary. Iomoprol contrast material (Iomeron 400, Bracco Ltd, Milan, Italy) was used with 85-95 ml contrast agent at a flow rate of 4.5-5.5 ml/sec from antecubital vein access via 18-gauge catheter using a four-phasic protocol. Bolus tracking in the left atrium was used to obtain proper scan timing. 0.8 mg sublingual nitroglycerin was given between the native and CTA examinations. CTA data sets were reconstructed with 0.8 mm slice thickness and 0.4 mm increment.

3.3. Measurement of left atrial and left atrial appendage volume

After defining LA and LAA borders with caution to the orifices of the PVs and the level of the mitral valve, we measured LA and LAAVs and determined LAA morphologies based on three-dimensional volume-rendered images using a semiautomated software (EP Planning, Philips IntelliSpace Portal, Philips Healthcare, Best, The Netherlands).

3.4. Determination of left atrial appendage morphologies

Since assessment of LAA morphology can be highly subjective, LAA morphologies were determined by consensus reading of three expert readers using rigorous definitions in order to minimize inter-observer variability. LAA morphologies were classified into four different types as previously described:

1.) **Cauliflower**, if LAA has limited length and the distal width exceed the proximal width;

2.) **Windsock**, if the primary structure is one dominant lobe with sufficient length;

3.) **Chicken wing**, if the dominant lobe has an obvious bend in the proximal part; and

4.) **Swan**, if LAA has a second sharp curve folding the dominant lobe back.

Representative examples can be seen in ***Figure 1***. In order to minimize subjectivity, LAA morphologies were determined by consensus reading of three expert readers.

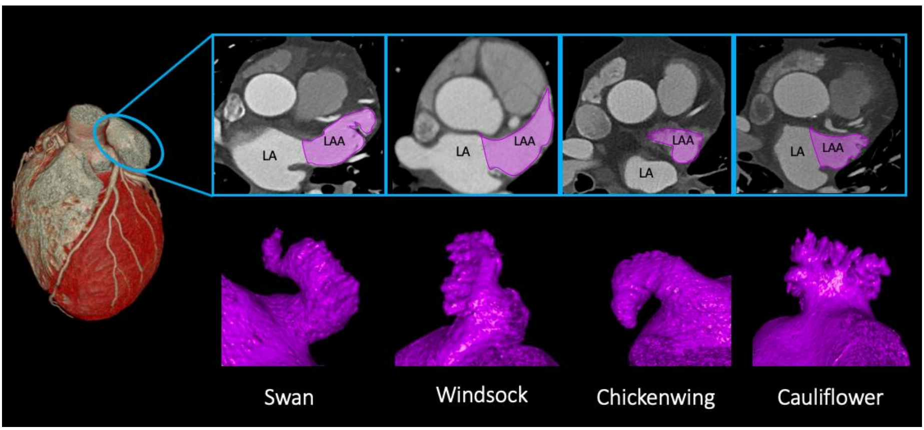

Figure 1. Representative examples of the various LAA morphology categories. *Abbreviations: LA = left atrium; LAA = left atrial appendage.*

3.5. Left atrial adipose tissue analysis

LA adipose tissue measurements were performed using MASS software (Leiden University Medical Centre, Leiden, the Netherlands). In short, a cross-sectional view of the LA was obtained from the mitral annulus to the LA roof from reconstructed 2-and 4-chamber views with a slice thickness of 2 mm. The LA adipose tissue located posterior of the LA was manually traced from the base of the LA until the mitral annulus. Adipose tissue was automatically recognized by the software as tissue with HU between −195 and −45, and the mean HU of the adipose tissue was calculated.

4. RESULTS

4.1. Anatomical characteristics of the LA and LAA in relation to the risk of stroke/TIA

4.1.1. Patient characteristics

In total, 1813 patients were included in this analysis (908 patients with AF and 905 patients without known AF). Mean age of the population was 59±11 years and 42% of the patients were female. Patients with AF were significantly older (61±10 vs 56±12, $p<0.001$), predominantly male (67% vs 49%, $p<0.001$) and had a higher prevalence of hypertension (57% vs 49%, $p<0.001$), obesity (22% vs 18%, $p=0.018$), and vascular disease (10% vs 7%, $p=0.011$), as compared with patients without known AF.

4.1.2. Anatomic characteristics of the LA and LAA according to AF status

Mean LA and LAA volumes were 94±31 and 7.7±4.3 mL, respectively in the overall population. In patients with AF, LA and LAA volumes were significantly larger compared with patients without known AF (LA volume: 109±32 vs 78±20 mL, and LAAV: 8.8±5.3 vs 6.6±2.5 mL, both $p<0.001$). Cauliflower was the most prevalent LAA morphology (53%) in the overall study population, followed by windsock (32%), chicken wing (11%), and swan LAA morphology (4%). No significant difference was found in LAA morphology between patients with vs without known AF, as it can be seen in ***Figure 2***.

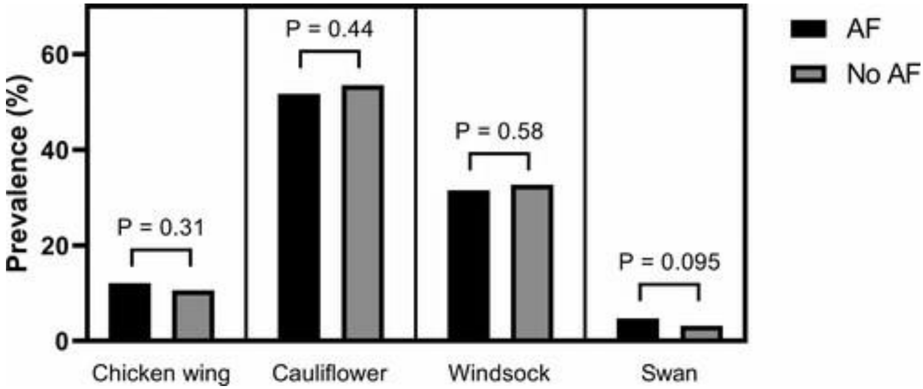

Figure 2. *Distribution of the four different types of LAA morphology in patients with and without known AF.*

4.1.3. Anatomic characteristics of the LA and LAA according to prior stroke/TIA

In total, 120 patients had a history of stroke or TIA (73 patients with AF and 47 patients without known AF). In patients with AF, LA and LAA volume were not significantly different between patients with and without prior stroke/TIA. In patients without known AF, LA volume was significantly higher in patients with prior stroke/TIA (86±23 vs 78±20 mL, *p*=0.011), while no significant difference was found for LAAV. Both in patients with and without known AF, the prevalence of chicken wing, cauliflower, and windsock LAA morphology was not significantly different between patients with and without prior stroke/TIA. In contrast, swan LAA morphology was significantly more prevalent in patients with prior stroke/TIA, both in patients with (11% vs 4%, *p*=0.009) and without known AF (11% vs 3%, *p*=0.003).

4.1.4. LAA morphology in relation to prior stroke/TIA

The stroke/TIA rate was the highest in patients with swan LAA morphology in the overall study population, as well as in patients with AF and without known AF, as it can be seen in ***Figure 3.***

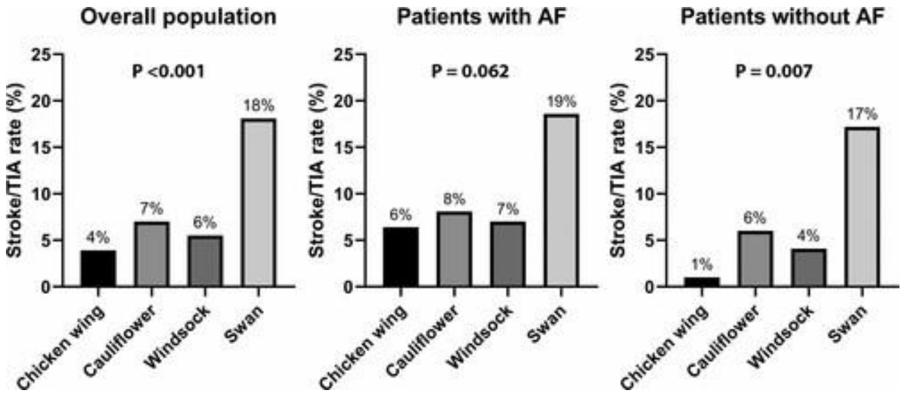

Figure 3. *The stroke/TIA rate in the overall patient population and in patients with and without known AF.*

Multivariable analysis showed an independent association between swan LAA morphology and prior stroke/TIA in the overall study population (odds ratio [OR]=3.40, $p<0.001$), and in patients with (OR=2.88, $p=0.012$) and without known AF (OR=3.96, $p=0.011$). Also, swan morphology remained significantly associated with prior stroke/TIA corrected for the CHA2DS2-VASc score (excluding prior stroke or TIA) in the overall study population (OR=3.50, $p<0.001$), as well as for patients with (OR=2.92, $p=0.010$) and without known AF (OR=4.29, $p=0.006$).

4.2. Posterior LA adipose tissue attenuation and AF recurrence

4.2.1. Patient characteristics

A total of 460 patients (66% male, age 61±10 years) were included in the analysis. There were 168 (37%) patients that developed AF recurrence after catheter ablation during a median follow-up period of 18 months (IQR: 6–32). Patients with AF recurrence after catheter ablation were older (62±10 vs 60±10 years; $p=0.038$), more often females (42% vs 30%, $p=0.012$), and had more often persistent AF (33% vs 18%, $p<0.001$).

4.2.2. The association between posterior LA adipose tissue attenuation and AF recurrence

Patients with higher posterior LA adipose tissue attenuation had more cumulative recurrence rates of AF than patients with lower posterior LA adipose tissue attenuation as it can be seen in ***Figure 4.***

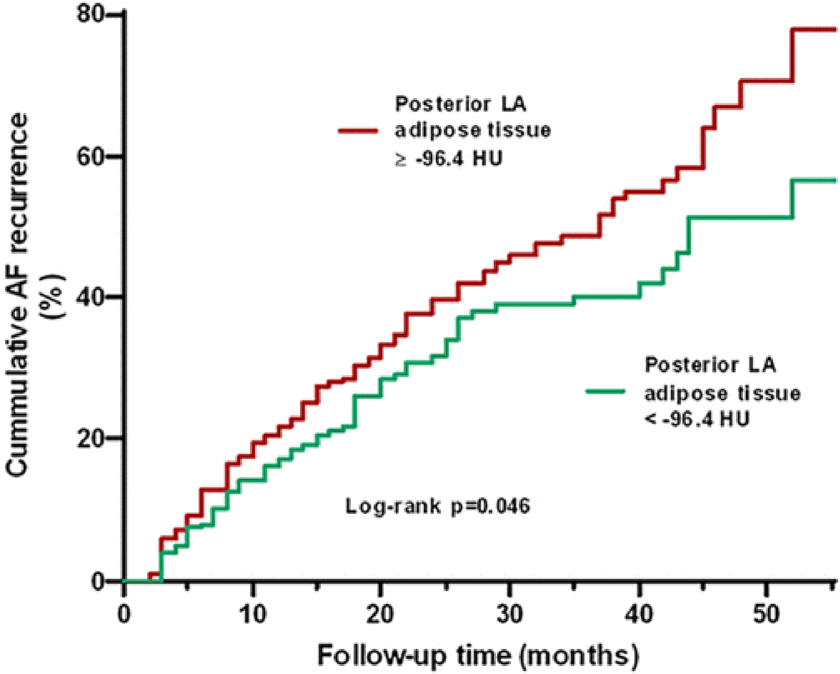

Figure 4. *Kaplan-Meier curve for AF recurrence after catheter ablation according to posterior LA adipose tissue attenuation.*

Table 1 summarizes the Cox regression analysis of the posterior LA adipose tissue mass and attenuation for AF recurrence. After correcting for known associates of AF, recurrence posterior LA adipose tissue attenuation (hazard ratio [HR]=1.26, p=0.181) remained a promising predictor of AF recurrence following catheter ablation.

Table 1. *Uni- and multivariable Cox regression analysis for AF recurrence after catheter ablation.*

	Univariable analysis		Multivariable analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Posterior LA adipose tissue mass (per one unit increase)	1.00 (0.97-1.03)	0.970	1.01 (0.97-1.04)	0.759
Posterior LA adipose tissue attenuation ≥-96.4 HU	1.37 (1.00-1.86)	0.047	1.26 (0.90-1.76)	0.181

4.3. Independent predictors of AF recurrence after radiofrequency catheter ablation in patients with paroxysmal and persistent AF

4.3.1. Patient characteristics

A total of 561 patients were included in the current analysis. Mean age was 62± 10 years and 34.9% of the patients were female. Recurrence of AF was reported in 40.8% of the patients (34.6% in patients with paroxysmal and 53.5% in those with persistent AF). Median recurrence-free time was 22.7 (IQR: 9.3–43.1) months (21.8 [9.4–43.2] months in paroxysmal and 23.6 [9.0–42.6] months in persistent AF). The proportion of individuals aged >65 years (40.7% vs 49.3%; p=0.046), female gender (30% vs 41.9%; p=0.005), persistent AF (25.9% vs 43.2%; p<0.001), and LVEF <50% (6.9% vs 21.0%; p<0.001) were significantly higher in patients with AF recurrence. Moreover, patients with AF recurrence had significantly higher iLAV (54.4±19.3 mL/m^2 vs 61.8±23.9 mL/m^2; p<0.001), LAAV (7.6±3.2 mL vs 8.8±5.2 mL; p=0.002) and LAA orifice area (387.6 ± 140.5 mm^2 vs 454.4±167.7 mm^2; p<0.001).

We also examined the differences of the clinical and imaging parameters between patients with paroxysmal and persistent AF. Those patients with persistent AF had significantly higher proportion of age > 65 years (41.0% vs 50.8%; p=0.030), hypertension (67% vs 85.9%; p<0.001) and LVEF<50% (6.6% vs 24.9%; p<0.001). Regarding the CT parameters, we measured significantly higher iLAV (51.0±15.9 mL/m^2 vs 70.4±25.6 mL/m^2; p<0.001), LAAV (7.4±3.0 mL vs 9.5±5.6 mL; p=0.002), LAA orifice area (385.2±132.8 mm^2 vs 475.2±179.7 mm^2; p<0.001) and lower LAA flow velocity (35.3±13.4 cm/s vs 31.7±12.0 cm/s; p<0.001). Detailed data on the clinical and imaging parameters by AF type can be seen in ***Figure 5.***

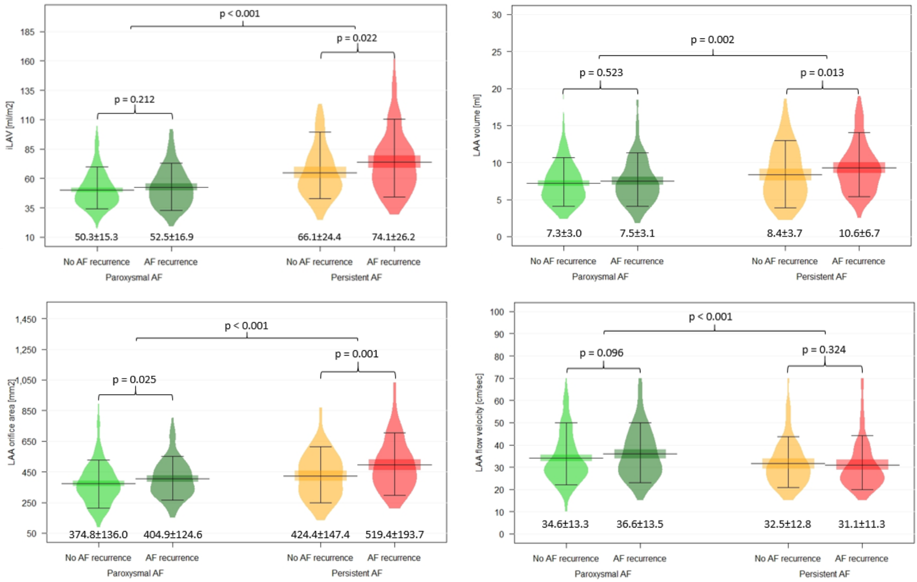

Figure 5. *Comparison of LA and LAA parameters between patients with and without AF recurrence, as stratified by AF type.*

4.3.2. Predictors of AF recurrence

Significantly higher iLAV and LAAV values were measured in patients with persistent AF recurrences, and larger LAA orifice area values were measured both in paroxysmal and persistent recurrences, as reported in ***Figure 12***. To explore the associations between the various examined parameters and AF recurrence, Cox proportional hazards regression analyses were performed, as stratified by AF type. After adjustment LVEF <50% (HR=2.17, *p*<0.001) and LAAV (HR=1.06, *p*=0.029) remained a significant predictor of AF recurrence in patients with persistent AF, while in paroxysmal AF no independent predictors could be identified in the multivariate analysis. Kaplan–Meier curves of AF recurrence-free survival in persistent AF stratified by LVEF and LAAV can be seen in ***Figure 6.***

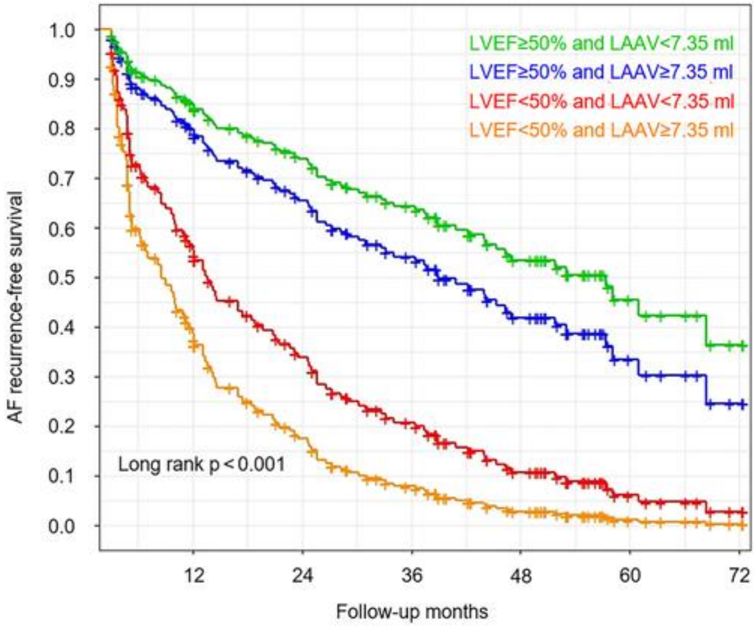

Figure 6. *Adjusted AF recurrence-free survival according to LVEF and LAAV in patients with persistent AF*

5. CONCLUSIONS

We showed in two large and distinct cohorts of patients with and without documented AF that LAA swan morphology is associated with higher prevalence of stroke and/or TIA.

We also aimed to determine the predictors of AF recurrence after catheter ablation procedure. Based on our results, posterior LA adipose tissue attenuation is a promising novel and tissue-specific biomarker of AF recurrence. Higher attenuation of the posterior LA adipose tissue might signal local inflammation and serve as an imaging biomarker of increased risk of AF recurrence. We have also demonstrates that beyond left ventricular systolic dysfunction, LAA enlargement is an independent predictor of AF recurrence after catheter ablation in persistent AF. Our results suggest that preprocedural assessment of LVEF and LAAV might contribute to optimal patient selection and aid to improve long-term results of ablation procedures in patients with persistent AF.

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