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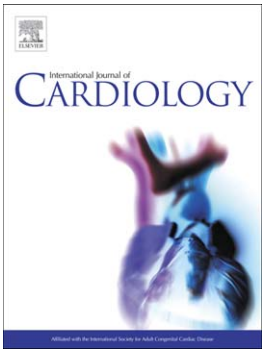

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Association between peripheral plasma markers and left atrial anatomy in patients with atrial fibrillation

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Left atrial (LA) size has been associated with cardiovascular outcomes and the success of different therapy strategies in patients with atrial fibrillation (AF) [1, 2]. The assessment of LA is therefore recommended in the clinical routine in all AF patients [3]. There are several imaging modalities to assess the LA, though echocardiography is widely available and thus the most frequently used. However, the echocardiographic LA diameter (LA-D) does not reliably reflect the true size of LA anatomy, as pathological LA is often enlarged asymmetricaly during AF progression [4-6].

Computer tomography (CT) is a modality that has been increasingly used to obtain three-dimensional (3D) images prior to AF catheter ablation. This provided new insights on the LA shape and volume, which have been proven to be better predictors of AF recurrences after LA ablation in comparison to the commonly used anterior-posterior LA diameter [4-6]. Recently we demonstrated that LA dilatation is more pronounced on the coronal plane, as represented by the transversal LA diameter (LA-TV) [7]. Furthermore, LA-TV was associated with AF recurrences and remained stronger predictor for rhythm outcomes compared with the echocardiographic LA diameter. We also demonstrated strong association between pro-inflammatory plasma markers and AF recurrences [8, 9]. However, whether LA size parameters are associated with peripheral plasma markers of inflammation is unknown.

Consequently, the present study (approved by the ethics committee) recruited 51 consecutive patients presenting for their first AF catheter ablation at Heart Center Leipzig. All patients gave informed consent according to institutional guidelines and the Declaration of Helsinki. Echocardiography and cardiac-CT with a multidetector 64-row helical system (Brilliance 64, Philips, Best, Netherlands) were performed (2±1 days) before the procedure. CT data were

reviewed using 3D reconstruction (EnSite Verismo, SJM, MN) and LA volume (LAV) was determined after exclusion of the atrial appendage (LAA) and the pulmonary veins (PV). LA was then centered on all three cutting planes and the superior–inferior (SI), transversal (TV) and anterior–posterior (AP) diameters were measured. Measurements were performed offline by an experienced observer and were repeated 4 weeks later by the same investigator and a second blinded reviewer. High sensitive interleukin 6 (hsIL-6) was analyzed from pre-procedural blood samples using a commercially available assay.

Catheter ablation was performed as previously described [10], with circumferential ablation of the ipsilateral pulmonary veins, verified with a multipolar circular catheter. In patients with persistent AF, additional linear lesions were added at the mitral isthmus and the posterior LA wall to create a "box" lesion. Follow-up was performed with repeated 7-day-Holter ECG recordings at 6, 12, 24 and 36 months. Recurrence was defined as any documented atrial tachycardia or fibrillation episodes of ≥30 s (after a 3 month blanking period).

Statistical analyses were performed with SPSS 17 (SPSS Inc., Chicago, USA). Parameters with a p-value <0.1 in the univariable analysis (UV), were introduced in multivariable analyses (MV) in order to identify with hsIL-6 levels independently associated parameters. A two-tailed p value <0.05 was considered significant.

The clinical characteristics of the study population are presented in **Table 1**. The intra- and inter-observer correlation coefficients were ≥0.88. We found a significant correlation between peripheral hsIL-6 and LA-TV (r^2=0.34, p=0.017) but not with LAV (p=N.S., **Figure 1)**. On univariable analysis, advanced age, higher BMI and lower eGFR as well as as well as with left atrial dimensions – e.g. LA-AP, LA-TV and LAD (but not LAV) – were significantly associated

with hsIL-6 levels. On multivariable analysis, the levels of hsIL-6 remained associated with age (r^2=0.28, p=0.029), BMI (r^2=0.33, p=0.011), renal dysfunction (eGFR<60 ml/min/1,73m², r^2=0.29, p=0.019), and LA-TV (r^2=0.38, p=0.012) but not with LAD or LA-AP.

Both electrical-anatomical remodeling and inflammation are known factors in AF pathogenesis. The present study demonstrates a significant association between different left atrial measurements and peripheral pro-inflammatory markers and adds to our understanding about the remodeling processes in patients with AF. The role of inflammation in AF pathogenesis is a well-known factor. Pro-inflammatory reactions may modulate the treatment success and, as previously demonstrated by our group, positively correlate with AF recurrences after radiofrequency catheter ablation [8, 9]. Recently, we also showed that anatomical LA changes cary a predictive value that is better represented with LA-TV or LAV than with the commonly used LAD [7]. The present data extend these studies and reveal the strong correlation between the plasma marker hsIL-6 and the anatomical atrial remodeling, as represented by the transversal (LA-TV) and not just the global (LAV) dilatation. These findings link pro-inflammatory changes with the left atrial remodeling and emphasize the close relationship between these important AF co-variables.

The small size of this study cohort and the limitations (loss) of follow-up prohibited further analysis of the impact of LA remodeling and hsIL-6 on ablation outcomes. The use of CT for the measurement of LA-TV prohibits its use in repeated routine follow-up studies, but since newer techniques, such as magnetic resonance imaging or 3D echocardiography, are becoming more widely available, soon this information could be assessed with no radiation.

These findings should be seen as hypothesis generating and point out the potential importance and scientific prominence of inflammation state in patients with AF. Certainly, larger clinical studies are needed to examine the practical implications of hsIL-6 or LA measurements for better patient selection and treatment strategy in early or advanced AF stages. Since a pro-inflammatory state is associated with anatomical LA remodeling, it remains to be examined whether AF patients might profit from anti-inflammatory treatment during or after invasive treatment.

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Table 1. Baseline characteristics of the study population

Variables	Study population n=51
Age, years	62 ± 10
Females	37 %
Persistent AF	59 %
BMI	30 ± 4.6
eGFR, ml/min/1.73 m^2	98 ± 30
Hypertension	88 %
Diabetes mellitus	18 %
CHA_2DS_2-VASs score	2 (2 – 3)
LA diameter, mm (Echo)	44 ± 6.5
EF, %	57 ± 11
LA-TV, mm (CT)	77 ± 11
LA-SI, mm (CT)	64 ± 8
LA-AP, mm (CT)	51 ± 12
LA-V, ml (CT)	141 ± 50
hsIL-6, ng/ml	1.6 (0.9 – 2.9)

Abbreviations: AF – atrial fibrillation, BMI - body mass index, eGFR - estimated glomerular filtration rate, TE - thromboembolic events, IQR - interquartile range, EF - ejection fraction, LA - left atrial, hsIL-6 - high sensitive interleukin 6 (hsIL-6)

Figure 1. Left atrial (LA) parameters and high sensitive interleukin 6 (hsIL-6) of 2 patients with the same LA volume. Anatomical changes on the coronal plane (bigger transversal diameter, LA-TV) are associated with higher hsIL-6 values (B, D).