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Differentiation of atrial fibrillation progression phenotypes using Troponin T

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ABSTRACT

Background: Electro-anatomical remodeling in atrial fibrillation (AF) is associated with disease initiation and progression. Troponin T (TropT) – a specific biomarker for *myocardial damage* – is associated with AF incidence. However, its association with AF progression is understudied. The aim of the current analysis was to investigate the association between TropT and AF progression phenotypes: persistent AF and left atrial low voltage areas (LVAs).

Methods: Patients undergoing first AF ablation were included into analyses. LVAs were determined using high-density maps and defined as <0.5 mV. Blood samples from femoral vein were collected before catheter ablation. The analysis of TropT serum concentrations was performed using a high-sensitive assay from Roche Diagnostics. Biomarkers, clinical, anthropometric and echocardiographic data were compared with healthy individuals from the epidemiological cohort.

Results: The study included 824 healthy individuals without overt cardiovascular disease (54 ± 10 years, 40% males) from epidemiological cohort and 241 AF patients (64 ± 11 years, 59% males, 59% persistent AF, 27% LVAs). Patients with AF had higher TropT levels and larger left atrium (LA), while healthy individuals had better renal function and ejection fraction (all $p < 0.001$). In clinical cohort, there were significant differences between TropT levels according to AF progression groups: paroxysmal AF without/with LVAs (n = 86/12), persistent AF without/with LVAs (n = 90/53): means 7.3, 12.9, 8.4, 11.3 pg/ml, $p < 0.001$, respectively. Similar findings were observed for LA and renal function (all $p < 0.001$). On ROC analysis, TropT significantly predicted LVAs (AUC 0.675, 95%CI 0.598–0.752, $p < 0.001$) in AF patients.

Conclusions: TropT may be useful to differentiate AF progression phenotypes.

1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia and 25% of Europeans will develop AF in their life [1]. AF progression, characterized by a switch from paroxysmal to persistent AF [2] and increased left atrial (LA) diameter [3], is associated with adverse outcomes after catheter ablation [4,5]. AF progression is accompanied by electro-anatomical remodeling which is evident as low voltage areas (LVAs) using periprocedural mapping during catheter ablation [6]. LVAs are detected in ~25% of AF patients and may require individually tailored ablation using additional lines. In addition, arrhythmia recurrences in AF patients with LVAs are significantly higher [6].

Up to date, LVAs detection is only possible invasively during AF catheter ablation. Therefore, a non-invasive prediction of LVAs using clinical, imaging or blood biomarkers would substantially improve the individual stratification of AF patients and differentiation of necessary therapeutic strategies. Recently, we could demonstrate that atrial natriuretic peptide (ANP) is associated with AF progression phenotypes defined by AF type and LVAs [7]. Furthermore, these findings have been confirmed by further analyses demonstrating that LA volume is associated with NT-proANP [8].

One of the most important prognostic cardiac markers used in clinical routine is Troponin T (TropT), which is highly predictive for

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myocardial damage and is the pathological hallmark of acute myocardial infarction or myocardial injury [9]. High-sensitivity TropT is also a strong and independent predictor of all-cause and cardiovascular mortality in patients with heart failure [10] and AF [11]. Furthermore, increased TropT is associated with AF incidence [12] and in patients with permanent AF its levels decrease after heart rate normalization [13].

However, the association of TropT with underlying LVAs in AF patients is unknown. Therefore, the aim of current study was to investigate the association between TropT and distinct AF progression phenotypes based on persistent AF and LVAs. We also analyzed differences in TropT levels between a clinical AF cohort and healthy individuals from an epidemiological adult cohort.

2. Methods

2.1. Study population

The study was approved by the local Ethical Committee (Medical Faculty, University of Leipzig), and patients provided written informed consent for participation. All methods were performed in accordance with the relevant guidelines and regulations.

2.1.1. Clinical AF cohort

Patients undergoing first AF radiofrequency catheter ablation at the Heart Center Leipzig were recruited from October 2015 until April 2017. Exclusion criteria were pregnancy, age < 18 or >75 years, valvular AF, cancer, and acute or systemic inflammatory diseases. Paroxysmal and persistent AF were defined according to current guidelines [14]. Paroxysmal AF was defined as self-terminating within 7 days after onset. Persistent AF lasted longer than 7 days or required drugs or direct current cardioversion for termination. In all patients, transthoracic and transesophageal echocardiography was performed prior to ablation. All class I or III antiarrhythmic medications with exception of amiodarone were discontinued for at least 5 half-lives before the AF ablation procedure.

2.1.2. Healthy group

Individuals from the epidemiological LIFE-Adult Study [15] with available echocardiographic data and biomarker profiles were included as a healthy control group. Individuals younger than 40 years, with previous myocardial infarction, stroke, history of AF, pacemaker stimulation or missing laboratory data, as well as individuals with antiarrhythmic medication (e.g. beta-blockers, calcium-antagonists, other specific antiarrhythmic drugs) were excluded. Written informed consent was obtained from all individuals interested in participating in the LIFE-Adult Study.

2.2. Electro-anatomical mapping

The electro-anatomical mapping was performed for AF patients undergoing catheter ablation as previously described [7]. Briefly, electroanatomical voltage maps of the LA excluding the pulmonary veins were created using multielectrode spiral catheters with an interelectrode distance of 2–5–2 mm and an ablation catheter with a 3.5 mm electrode tip and contact measurement properties (SmartTouch Thermocool, Biosence Webster, Diamond Bar, CA, USA and TactiCath, St. Jude Medical, Saint Paul, MN, USA) as mapping catheter. Electroanatomical mapping was performed using 3D electro-anatomical mapping systems (Carto, Biosence Webster, Diamond Bar, CA, USA or EnSite Precision, St. Jude Medical) and defined as low voltage if <0.5 mV or dense scar if <0.2 mV; voltage >0.5 mV was defined as normal.

2.3. Laboratory measurements

Blood was drawn from all study participants after >8 h of fasting and analyzed on the same day. In AF patients, blood was drawn immediately after femoral vein puncture – before catheter ablation. All samples were processed in a highly standardized manner – details are described elsewhere [15]. Laboratory measurements of creatinine and TropT serum concentrations were taken on the same day at the Institute of Laboratory Medicine at the University Hospital Leipzig (accredited by ISO 15189 and 17025) according to the Quality Standards for Medical Laboratories of the German Chamber of Physicians (RiLiBÄK) using assays from Roche Diagnostics on Cobas 6000 or 8000 (Roche Diagnostics) clinical chemistry analyzers. The estimated glomerular filtration rate (eGFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation $\mathbf{eGFR} = \mathbf{141} \times \min(\mathbf{Scr}/\kappa, \mathbf{1})^{\alpha} \times \max(\mathbf{Scr}/\kappa, \mathbf{1})^{-1.209} \times \mathbf{0.993Age} \times \mathbf{1.018\ [if\ female]\ X\ 1.159}$ [**if black**], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

2.4. Statistical analysis

Data are presented as mean and standard deviation (SD) for normally distributed or median with interquartile range for skewed continuous variables and as proportions for categorical variables. The differences between continuous values were assessed using an unpaired *t*-test or the Mann–Whitney test, and a chi-square test for categorical variables. Correlations were performed using Spearman's rank correlation method.

Both univariable and multivariable analyses included clinically relevant factors associated with AF, which were available in both clinical AF and the epidemiological LIFE-Adult Study cohorts. In addition, all multivariable models were adjusted for age and gender. Multivariable analysis, which included variables with a p-value < 0.05 found in univariable analysis, was performed to identify independent predictors for the presence of LVAs.

Receiver operating characteristic (ROC) curves were generated for graphical illustration of TropT performance in predicting low voltage areas in AF patients, with the area under the curve (AUC) being equivalent to the c-index for determining the predictive value.

A p-value < 0.05 was considered statistically significant, and all analyses were performed with SPSS statistical software version 23 (SPSS Inc., Chicago, USA).

3. Results

3.1. Clinical parameters

The study population included 241 patients from the clinical AF cohort and 824 individuals without overt cardiovascular diseases from the epidemiological LIFE-Adult Study. Clinical characteristics of both cohorts are presented in Table 1. Healthy individuals were significantly younger, had lower body mass index (BMI), heart rate, anteroposterior LA diameter, systolic/diastolic blood pressure and TropT levels than the AF cohort (all p < 0.001).

There were significant correlations between TropT and age (r^2 = 0.239, p < 0.001), left ventricular ejection fraction (EF) (r^2 = −0.212, p = 0.007) and eGFR (r^2 = −0.271, p < 0.001) in the AF cohort as well as between age (r^2 = 0.310, p < 0.001), male sex (r^2 = 0.204, p < 0.001) and eGFR (r^2 = −0.113, p = 0.001) in healthy controls. Furthermore, we observed a weak correlation between LA and TropT in the LIFE-Adult Study (r^2 = 0.096, p = 0.006), but not in AF cohort (r^2 = −0.011, p = 0.861).

Table 1
Baseline characteristics of the study population.

	Epidemiological cohort	Clinical AF cohort	PAF w/o LVAs	PAF with LVAs	CAF w/o LVAs	CAF with LVAs	p-Value*	p-Value**
	n = 824	n = 241	n = 86	n = 12	n = 90	n = 53		
Age, years	52 (46–62)	65 (57–72)	65 (56–71)	72 (63–74)	61 (54–71)	69 (64–75)	<0.001	<0.001
Gender, m/f (%)	60/40	41/54	44/56	58/42	27/73	55/45	<0.001	0.003
Persistent AF, %	–	59	0	0	100	100	–	–
LVAs, %	–	27	0	100	0	100	–	–
BMI, kg/m^2	26 (23–28)	29 (26–33)	28 (24–31)	30 (26–33)	30 (27–34)	30 (26–35)	<0.001	0.200
Systolic BP, mmHg	127 (117–138)	150 (134–166)	150 (131–165)	157 (141–165)	146 (135–166)	155 (144–170)	<0.001	0.071
Diastolic BP, mmHg	77 (71–83)	90 (80–100)	85 (80–98)	90 (77–100)	90 (84–100)	97 (86–110)	<0.001	0.002
Hypertension, %	21	81	70	100	81	96	<0.001	<0.001
Diabetes mellitus, %	3.5	22	13	0	22	43	<0.001	<0.001
eGFR, ml/min/1.73m^2	83 (71–98)	76 (64–89)	82 (68–94)	69 (59–91)	79 (68–91)	67 (55–81)	<0.001	0.001
LA diameter, mm	36 (33–39)	44 (40–48)	42 (38–45)	43 (37–48)	45 (41–50)	46 (43–50)	<0.001	<0.001
LV-EF, %	63 (59–67)	59 (50–65)	62 (56–65)	61 (44–64)	55 (49–60)	60 (50–65)	<0.001	0.029
Troponin T, pg/ml	3.8 (3.0–5.6)	8.4 (5.3–13)	7.3 (4.9–11.3)	12.9 (5.4–20.0)	8.5 (4.9–12.7)	11.3 (8.0–16.1)	<0.001	0.001

Abbreviations: **AF** – atrial fibrillation; **PAF** – paroxysmal AF; **CAF** – persistent AF; **LVAs** – low voltage areas; **w/o** - without; **m** – males; **f** – females; **BMI** – body mass index; **BP** – blood pressure; **eGFR** – estimated glomerular filtration rate; **LA** – left atrial antero-posterior diameter; **LV-EF** – left ventricular ejection fraction.
p-value* - comparison between epidemiological and AF cohorts; p-value** - comparison between AF progression phenotypes within AF cohort.

3.2. AF progression phenotypes

To analyze the differences of biomarkers profiles as well as clinical and echocardiographic data, we defined four groups of AF progression phenotypes: group 1 – paroxysmal AF without LVAs (n = 86); group 2 – paroxysmal AF with LVAs (n = 12); group 3 – persistent AF without LVAs (n = 90); and group 4 – persistent AF with LVAs (n = 53) as previously described [7]. Compared to controls, the TropT levels were significantly higher in the AF cohort (Table 1, Fig. 1). However, the highest TropT levels were observed in patients with LVAs. In ROC analysis, TropT significantly predicted LVAs (AUC 0.675, 95% confidence intervals [CI] 0.598–0.752, p < 0.001).

Similar findings were observed for age and gender: AF patients with LVAs were significantly older, more frequently female, had larger antero-posterior LA diameter and lower eGFR levels (Table 1, Figs. 2–3).

3.3. Multivariable analysis

The multivariable analysis was performed to analyze significant variables between healthy controls and the AF cohort (Supplemental Fig. 1) as well as between AF patients with persistent AF and/or LVAs (Supplemental Figs. 2–3). There were significant differences in age (odds ratio [OR] 1.097, 95%CI 1.063–1.133, p < 0.001), BMI (OR 1.176, 95%CI 1.110–1.245, p < 0.001), LA diameter (OR 1.177, 95%CI 1.117–1.241, p < 0.001), EF (OR 0.895, 95%CI 0.859–0.933, p < 0.001) and TropT levels (OR 1.180, 95%CI 1.100–1.266, p < 0.001) between the healthy and AF cohort.

Analyzing risk factors for persistent AF in the AF cohort, multivariable analysis revealed that diabetes (OR 5.641, 95%CI 1.872–17.004, p < 0.001) and LVAs (OR 4.736, 95%CI 1.765–12.709, p < 0.001) were relevant for AF type, while LA diameter did not reach significance (OR 0.989, 95%CI 0.960–1.019, p = 0.481). However, LA diameter (OR 1.093, 95%CI 1.009–1.184, p = 0.029), persistent AF (OR 4.884, 95%CI 1.771–13.466, p < 0.001) and TropT (OR 1.044, 95%CI 1.008–1.081, p = 0.016) were significantly associated with the risk for LVAs presence in AF patients, while age did not reach significance (OR 1.053, 95%CI 0.992–1.117, p = 0.091).

4. Discussion

4.1. Main findings

To the best of our knowledge, the current study is the first analyzing the impact of TropT as a predictor for electro-anatomical remodeling in AF patients. First, we found that TropT levels were significantly associated with AF progression. Furthermore, TropT levels were significantly higher in an AF cohort compared to an epidemiological healthy cohort. Finally, beside persistent AF and LA size, TropT levels were significant predictors for the LVAs presence.

4.2. TropT as biomarker for cardiovascular outcomes

As a marker of cardiomyocyte damage, TropT plays an important role in ischemic heart disease. However, its impact is also relevant to other cardiac and cerebrovascular comorbidities, such as hypertension,

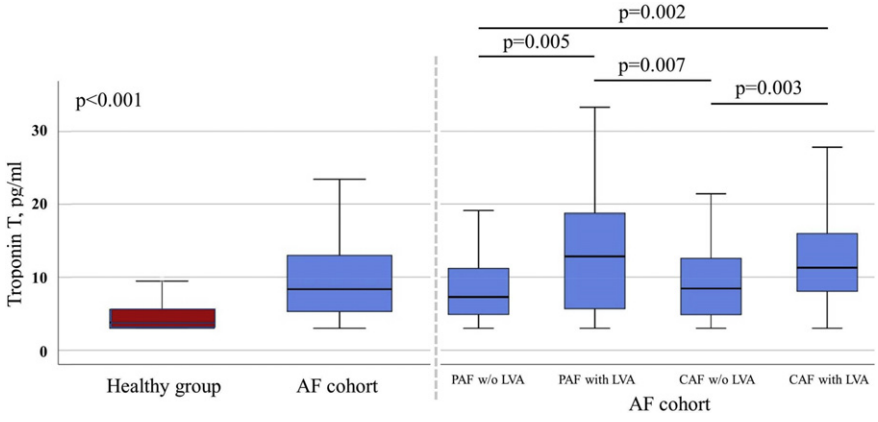

Fig. 1. TropT levels in controls and AF patients accordingly to progression phenotypes.

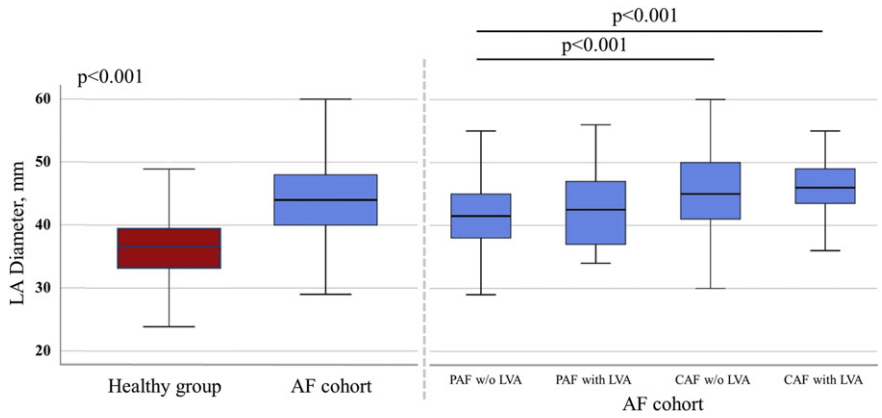

Fig. 2. LA diameters in controls and AF patients accordingly to progression phenotypes.

heart failure, stroke, or renal dysfunction. Recently, it has been shown that in chronic heart failure, increased TropT levels predict all-cause and cardiovascular mortality [10]. Therefore, it is assumed that TropT release is a consequence of myocardial ischemia of any cause or cardiomyocyte damage caused by inflammatory infiltration and myocardial apoptosis [10].

Although TropT has been never considered as a biomarker associated directly with AF pathogenesis, it has been recently demonstrated that increased TropT levels are associated with AF incidence [12]. Furthermore, the importance of TropT has been analyzed in large AF cohorts and implemented into the ABC scores for the prediction of thromboembolic and bleeding complications [16,17] as well as mortality [11] in AF patients.

4.3. TropT as a biomarker for electro-anatomical remodeling

The association of TropT and AF most likely results from cardiomyocyte damage that accompanies AF. Common features in AF-related cardiomyocyte-damaging pathomechanisms are apoptosis, as reflected by increased caspase 3 levels and activity [18], programmed cell death [19], and imbalance of enzymes involved in reactive oxidative species elimination [20].

TropT measurements are relevant for the prediction of AF incidence and permanent AF [12,13]. In the current study, analyzing 241 AF patients and 824 healthy controls, we confirmed the association of increased TropT levels in AF. Furthermore, we analyzed whether AF progression could be mirrored by TropT levels and focused on distinct AF progression stages as characterized by a switch from paroxysmal to persistent AF [2] and LVAs presence [6]. Interestingly, LVAs was associated with significantly higher TropT levels while AF type was not. While LVAs directly mirrors pro-fibrotic remodeling [21] with ongoing pathological pro-apoptotic decline of cardiomyocytes, AF type switch is a more multifactorial read-out, not necessarily involving cardiomyocyte decay.

Pro-fibrotic remodeling as represented by LVAs is a well-known reason for cardiomyocyte decay. Remodeling of extracellular matrix in fibrosis results in myocardial stiffening, replacement of contractile components and reduced oxygen diffusion. As a result, the workload of the remaining cardiomyocytes increases, while at the same time the physiological environment is getting out of balance. This leads to cardiomyocyte death and contributes further to the described processes resulting in a vicious circle [22].

4.4. Future directions

Currently, an invasive catheter-based LVAs detection is not useful for general stratification of AF patients. A perfect alternative would be a peripheral biomarker, accessible by minimal invasive blood withdrawal, allowing the prediction of AF progression stage and individualized therapy. It is very unlikely that one single biomarker will fulfil these criteria as AF is multi-facetted disorder including polymorphic mechanisms during its development and perpetuation. Therefore, future studies should focus on analyzing well-defined AF progression stages characterized by LA imaging, clinical scores and a panel of biomarkers to identify the best prognostic combinations. The results of our study pave the way toward a more individualized AF management by screening for characteristics of AF progression resulting in refinement of therapy, follow-up strategies and disease prevention.

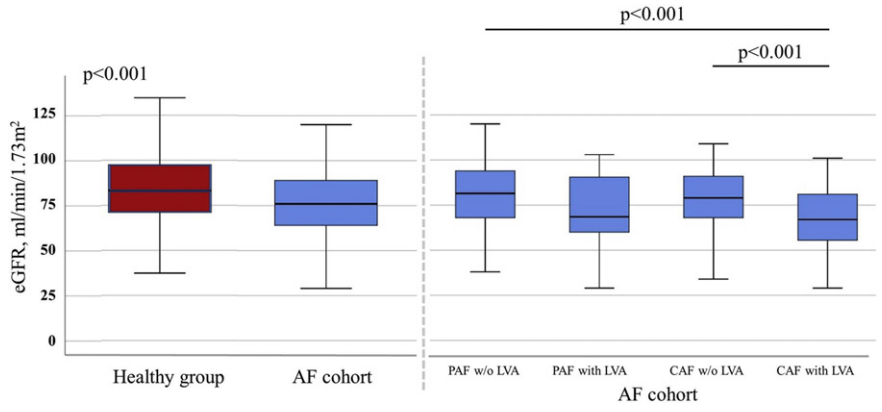

Fig. 3. eGFR in controls and AF patients accordingly to progression phenotypes.

4.5. Strengths and limitations

In current retrospective analysis we demonstrated that TropT levels are associated with AF in general and with AF progression. The phenotypes describing AF progression are well defined, reproducible and highly important for therapeutic strategy. Both cohorts used for the analysis are well characterized following established protocols. Nevertheless, we cannot rule out that some of the healthy controls suffered paroxysmal AF as long-term ECGs were not obtained. Importantly, the current study was not planned as a case-control study. We used a healthy group from an epidemiological cohort to demonstrate differences in clinical, echocardiographic parameters and biomarker profiles compared to a clinical AF cohort. Therefore, the results of current analysis should be considered as hypothesis-generating. Furthermore, neither the clinical nor the epidemiological cohort included patients with left ventricular EF < 35%, myocardial infarction within last 3 months or symptomatic aortic stenosis. Thus, the impact of the TropT levels predicting LVAs in such specific patient sub-groups is unknown. Finally, patients with paroxysmal AF and LVAs represent a rare patient group which is reflected by a small sample number ($n = 12$). Consequently, group wide comparisons with this patient group are of less power compared to other groups. Nevertheless, the differences in biomarker profiles were obvious and we assume that longitudinal biomarker measurements are superior to single determinations in terms of interpretability. This should be elucidated in further studies.

5. Conclusion

TropT levels are higher in AF patients than in healthy controls. Furthermore, TropT seems to be a specific marker of electro-anatomical remodeling in AF and has the potential to define AF progression stage.

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Authors' contribution

JK, SZ – concept/design; JK, PB, RBu, RBa, AT – data collection; JK, SZ, PB – analysis and interpretation; JK, SZ – statistics; YJB, AW, RBu, RBa, JT – laboratory analyses; JK, SZ, PB – drafting article; GH, ML, AH, HT, JT – critical revision of article; JK, GH – patient inclusion; JK, SZ, PB, AH, HT, JT – approval of article.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.09.006.

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