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Association of epicardial adipose tissue and left atrial size on non-contrast CT with atrial fibrillation: The Heinz Nixdorf Recall Study

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Aims Epicardial adipose tissue (EAT) is increased in subjects with atrial fibrillation (AF). Likewise, EAT is associated with left atrial (LA) size, as itself is a strong predictor of AF. We aimed to determine the association of EAT and LA size as computed tomography (CT)-derived measures with prevalent and incident AF and investigated whether both measures independently predict AF.

Methods and results Participants from the Heinz Nixdorf Recall study without known cardiovascular disease were included. At baseline, EAT, defined as fat volume inside the pericardial sac, and LA size, defined as an axial area at the level of the mitral valve, were quantified from non-contrast enhanced cardiac CT. AF was determined from electrocardiogram at baseline and also at 5-year follow-up examination. Overall, 3467 participants (age: 58.9 ± 7.6 years, 47% male) were included. Ninety-six subjects had AF (46 prevalent and 50 incident). A 1-standard deviation (SD) change of EAT was associated with nearly two-fold increased prevalence of AF in univariate analysis, which persisted after adjustment for AF risk factors [odds ratio (OR) (95% confidence interval, 95% CI): 1.38 (1.11–1.72), $P = 0.003$]. Ancillary adjusting for LA reduced the effect [1.26 (0.996–1.60), $P = 0.054$]. For incident AF, no relevant effect was observed for EAT when adjusting for risk factors [1.19 (0.88–1.61), $P = 0.26$]. In contrast, a 1-SD chance of LA was strongly associated with AF independently of EAT and risk factors [2.70 (2.22–2.20), $P < 0.0001$]. LA but not EAT as non-contrast CT-derived measures improved the prediction of AF over risk factors (receiver operating characteristics: 0.810–0.845, $P = 0.025$).

Conclusion LA size from non-contrast CT is strongly associated with prevalent and incident AF and ultimately diminishes the link of EAT with AF.

Keywords Epicardial adipose tissue • Left atrium • Atrial fibrillation • Cardiac computed tomography • Heinz Nixdorf Recall Study

Introduction

Epicardial adipose tissue (EAT) is associated with cardiovascular risk factors, coronary artery plaque burden, and coronary artery events.[1–4] Recently, an association of EAT with prevalent atrial fibrillation (AF) was described.[5,6] In addition, a strong link between EAT and left atrial (LA) size, as itself is a strong predictor of AF, was suggested.[7] Owing to its inflammatory activity, EAT was hypothesized to locally influence structural remodelling and therefore AF development.[8] However, data on the association of EAT with incident AF are rare and whether a potential effect is independent of LA size has not yet been evaluated.

Cardiac computed tomography (CT) is emergently performed for a variety of reasons including primary prevention purposes as it improves the prediction of first cardiovascular events.[9,10] Both EAT and LA size can be quantified from the same CT images without the need for extraradiation exposure or contrast media.[11,12]

The aim of the current analysis was to determine the association of EAT and LA size, as quantified by cardiac CT, with prevalent and

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incident AF in the general population without known cardiovascular disease. Moreover, we aimed to determine whether the influences of these CT-based measures on AF are independent of each other.

Methods

Study cohort

The Heinz Nixdorf Recall study is a population-based prospective cohort study, designed to assess the predictive value of novel markers for risk stratification in addition to traditional cardiovascular risk factors. The participants (aged 45–75 years) were randomly selected from mandatory lists of residence from the three adjacent cities of Bochum, Essen, and Mülheim and enrolled between 2000 and 2003. Details for recruitment and study design have been previously published.[9,13] An overall response rate was 56%. For this analysis, we excluded subjects with known coronary artery disease, history of myocardial infarction, history of open heart surgery (including bypass and valve surgery), prior stroke, pacemaker or defibrillator implantation, or known valvular heart disease at baseline. All participants provided written informed consent, and the study was approved by the institutional ethics committee.

Cardiovascular risk factor assessment

Traditional cardiovascular risk factors were measured at baseline with details being previously published.[14] Body mass index (BMI) was defined as weight divided by the square of height. Standardized enzymatic methods were used to determine serum total cholesterol level (T-C) and high-density lipoprotein cholesterol (HDL-C). Diabetes was defined as a history of diabetes, being on medical treatment or based on blood glucose levels as previously published.[15]

Cardiac computed tomography

As part of the study, subjects underwent cardiac CT for quantification of artery coronary artery calcification (CAC). Electron beam CT scans were performed utilizing a C-100 or C-150 scanner (GE Imatron, South San Francisco, CA, USA) without the use of contrast media. Imaging was prospectively triggered at 80% of the RR interval, and contiguous 3-mm thick slices from the right pulmonary artery to the apex of the heart were obtained at an image acquisition time of 100 ms. CAC was defined as a focus of at least four contiguous pixels with a CT density of >130 Hounsfield units (HU) and quantified using the Agatston method.[16]

Epicardial fat volume quantification

Epicardial fat volume was assessed using a dedicated workstation (Aquarius 3D Workstation, TeraRecon, San Matteo, CA, USA). The pericardium was manually traced from the right pulmonary artery to the diaphragm to determine a region of interest. Within the region of interest, fat was defined as pixels within a window of −195 to −45 HU and a window centre of −120 HU. Overall, only pixels with HU equivalent to fat within the pericardial sac were accounted as EAT (*Figure 1*). Reproducibility for the present cohort was previously tested in 100 subjects and was excellent [intraclass correlation coefficient (ICC) = 0.988, $P < 0.0001$ for inter-observer and ICC = 0.996, $P < 0.0001$ for intra-observer variability] as previously published and described together with further details of EAT quantification.[1]

LA size measurement

LA axial size was assessed from a single axial slice, with details being previously published.[11] Briefly, a reader with >2 years of experience reading cardiac CT (>2000 CT examinations prior to this analysis), who was blinded to the other presentation of the participants, manually traced the area of the LA at the level of the left ventricular outflow tract and the height of the mitral valve leaflets, excluding the pulmonary veins (*Figure 2*). Differentiation of LA from the aortic root and also from the RA was archived by comparing anatomy from slices above and below the selected slice, which allowed the reader to sufficiently estimate the LA borders. As previously reported, inter- and intra-observer variability was excellent.[17]

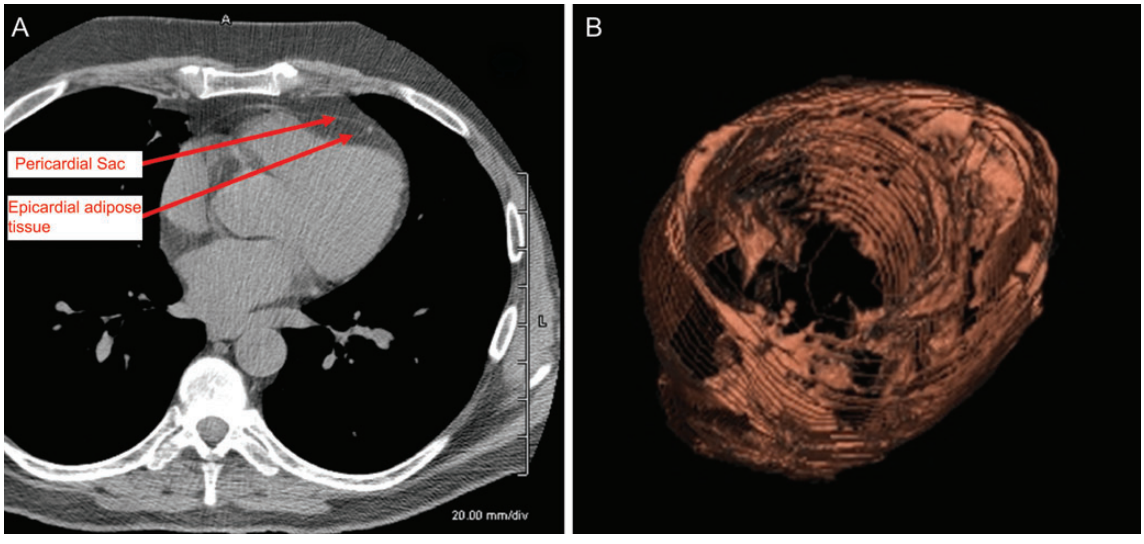

Figure 1 Measurement of EAT. The pericardium was manually traced from the right pulmonary artery to the diaphragm to determine a region of interest. Within the region of interest, fat was defined as pixels within a window of −195 to −45 HU and a window centre of −120 HU. Overall, only pixels with HU equivalent to fat within the pericardial sac were accounted as EAT.

Electrocardiogram recording and AF definition

Subjects' electrocardiogram (ECG) was recorded at baseline and after 5 years as previously described.[18] A standardized digital 12-lead resting surface ECG was sampled at 250 Hz and recorded on a MAC 5000® ECG recorder (GE Healthcare, Freiburg, Germany). ECGs were interpreted automatically using the integrated 12SL-Code®, which has been validated and used also by others.[19–21] ECG findings were coded and transferred to our database. Prevalent AF was defined as AF in the ECG at baseline examination, whereas incident AF was defined as AF in the ECG at 5-year follow-up examination in subjects who had sinus rhythm at baseline. Intermittent AF that was not present during the ECG was not assessed.

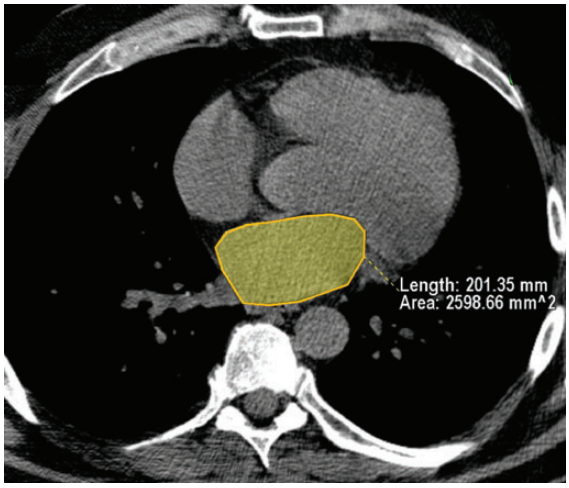

Figure 2 LA size measurement from an axial image from non-contrast-enhanced cardiac CT. The LA area was manually traced at the level of the left ventricular outflow tract and the height of the mitral valve leaflets, excluding the pulmonary veins.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD), whereas binary variables were shown as numbers and per cent (*n* and %). Differences between groups of AF vs. sinus rhythm were assessed using the *t*-test for continuous variables and χ^2 for binary variables. Correlation between EAT and LA size was determined using the Pearson correlation coefficient. Logistic regression analysis was performed to determine the association of EAT and LA size with overall as well as incident and prevalent AF. Adjustment for co-variables was performed using the following models: (1) unadjusted, (2) age and gender adjusted, (3) risk factor adjusted (including age, gender, BMI, systolic blood pressure, and antihypertensive treatment),[6] and (4) Model 3 + EAT/LA size. Odds ratios (ORs) and 95% confidence interval (95% CI) are depicted per each SD of LA/EAT.

Finally, *C*-statistics and receiver operating characteristics was performed to assess the value of both CT-based parameters (LA size alone and in combination with EAT) for the prediction of a combined endpoint of incident and prevalent AF in addition to AF risk factors. All analyses were performed using the SAS software (version 9.2, SAS Institute, Inc.). A *P*-value of <0.05 indicated statistical significance.

Results

Overall, 3905 subjects (mean age: 58.9 ± 7.6 years, 47% male) were included into our analysis, with details of baseline characteristics depicted in *Table 1*. Of the cohort, 46 subjects had prevalent AF at baseline. After 5 years (follow-up response 90.2%), 50 subjects showed a new onset of AF in the follow-up examination. Subjects with AF were older, more frequently male, and had higher BMI and higher values for most other cardiovascular risk factors (*Table 1*). EAT volume was ~1.5-fold higher in subjects with AF. Likewise, LA area was significantly higher in this subgroup (*Table 1*). EAT and LA size showed a distinct correlation ($r = 0.34$, $P < 0.0001$).

Association of CT-based measures with AF

Both EAT and LA size were significantly associated with AF in univariate analysis, while overall LA size demonstrated higher ORs (*Table 2*).

Table 1 Baseline characteristics for total cohort and stratified by presence and development of AF

	Overall	No AF	AF at baseline	AF during follow-up	*P*-value*
N	3905	3809	46	50	
Age (years)	58.9 ± 7.6	58.8 ± 7.5	64.5 ± 7.4	65.3 ± 6.8	<0.0001
Gender (% male)	1642 (47.4)	1580 (46.9)	32 (69.6)	30 (60)	0.0006
BMI (kg/m^2)	27.7 ± 4.5	27.6 ± 4.4	31.1 ± 7.3	31.2 ± 5.5	<0.0001
Systolic blood pressure (mmHg)	132.0 ± 20.3	131.8 ± 20.3	134.8 ± 18.9	140.8 ± 19.6	0.004
Diastolic blood pressure (mmHg)	81.4 ± 10.6	81.3 ± 10.6	81.3 ± 11.6	82.3 ± 10.8	0.65
Hypertensive medication, *n* (%)	1042 (30.1)	1150 (30.2)	31 (67.4)	31 (62)	<0.0001
Total cholesterol (mg/dL)	231.2 ± 38.5	231.5 ± 38.5	217.1 ± 33.3	221.6 ± 38.4	0.002
HDLC (mg/dL)	59.3 ± 17.3	59.4 ± 17.3	48.8 ± 14.8	57.1 ± 19.1	0.0004
Lipid-lowering medication, *n* (%)	299 (9.1)	288 (9.1)	5 (11.4)	6 (12.4)	0.36
Diabetes, *n* (%)	386 (11.1)	366 (10.9)	16 (34.8)	4 (8)	0.002
LA area (mm^2)	1769 ± 443	1746 ± 402	2860 ± 940	2322 ± 687	<0.0001
EAT volume (cm^3)	94.0 ± 47.3	92.7 ± 46.1	147.1 ± 64.4	131.0 ± 64.9	<0.0001

*P-value for subjects without vs. with AF (at baseline or during follow-up).

Effects remained stable when adjusting for age and gender and ancillary for AF risk factors (age, gender, BMI, systolic blood pressure, and antihypertensive treatment). When both EAT volume and LA size were included in the same model, including risk factors, there was a trend towards higher EAT volume, however not reaching statistical significance. In contrast, LA size remained strongly and independently associated.

In gender-specific analysis, AF was more frequent in men compared with women [men: $n = 62$ (3.8%), women: $n = 34$ (1.9%)]. However, association of EAT tended to be stronger in women compared with men in univariate analysis [men: OR (95% CI): 1.80 (1.48–2.19); women: 2.46 (1.81–3.35), $P < 0.0001$ for both]. When adjusting for AF risk factors, similar results for both genders were found [men: 1.45 (1.11–1.88), $P = 0.006$; women: 1.34 (0.90–2.07), $P = 0.14$]. For LA size, higher ORs were found for women in unadjusted analysis [men: 2.72 (2.21–3.34); women: 4.46 (3.22–6.17), $P < 0.0001$ for both] and when adjusting for risk factors [men: 2.39 (1.91–2.99); 3.88 (2.56–5.87), $P < 0.0001$ for both].

There is a positive correlation of EAT with increasing age ($r = 0.21$; $P < 0.0001$). When stratifying by age group (45–54, 55–64, and ≥65), we found a significant association with AF for each age group, with a strongest link for subjects aged 55–64 [45–54: OR (95% CI): 1.72 (1.04–2.86), $P = 0.04$; 55–64: 2.52 (1.92–3.32), $P < 0.0001$; ≥65: 1.52 (1.22–1.90), $P = 0.0002$].

When stratifying AF by prevalent AF, change of EAT volume by 1 SD was associated with a more than two-fold higher prevalence of AF in univariate analysis, which was slightly attenuated but remained statistically significant after adjustment for age and gender, as well as additional adjustment for AF risk factors (*Table 3*). Stronger results were observed for CT-derived LA area, being associated with prevalent AF independent of risk factors. When both EAT volume and LA size were included in the same model in addition to traditional risk factors, there was also a trend towards higher EAT volume, however not reaching statistical significance, while LA size remained strongly and independently associated.

Table 2 Logistic regression for the association of EAT and LA with both prevalent and incident AF

Model	EAT volume		LA area	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Unadjusted	1.99 (1.71–2.32)	<0.0001	3.24 (2.73–3.84)	<0.0001
Model 1	1.76 (1.47–2.10)	<0.0001	2.92 (2.45–3.49)	<0.0001
Model 2	1.38 (1.11–1.72)	0.003	2.73 (2.24–3.31)	<0.0001
Model 3	1.26 (0.996–1.60)	0.054	2.70 (2.22–3.30)	<0.0001

Model 1: age and gender adjusted. Model 2: age, gender, BMI, systolic blood pressure, and antihypertensive treatment adjusted. Model 3: Model 2 + EAT/LA.
ORs are depicted per each SD of EAT volume and LA area.
EAT, epicardial adipose tissue; LA, left atrial.

Table 3 Logistic regression for the association of EAT and LA with AF, stratified by prevalent and incident AF

Model	EAT volume		LA area	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Unadjusted				
Prevalent	2.10 (1.71–2.58)	<0.0001	3.65 (2.92–4.58)	<0.0001
Incident	1.78 (1.44–2.18)	<0.0001	2.29 (1.88–2.79)	<0.0001
Model 1				
Prevalent	1.86 (1.47–2.35)	<0.0001	3.38 (2.68–4.26)	<0.0001
Incident	1.57 (1.23–1.99)	0.0003	2.03 (1.65–2.50)	<0.0001
Model 2				
Prevalent	1.55 (1.16–2.09)	0.003	3.37 (2.60–4.37)	<0.0001
Incident	1.19 (0.88–1.61)	0.26	1.78 (1.42–2.25)	<0.0001
Model 3				
Prevalent	1.33 (0.95–1.87)	0.10	3.32 (2.55–4.32)	<0.0001
Incident	1.10 (0.81–1.50)	0.52	1.77 (1.40–2.23)	<0.0001

Model 1: age and gender adjusted. Model 2: age, gender, BMI, systolic blood pressure, and antihypertensive treatment adjusted. Model 3: Model 2 + EAT/LA.
ORs are depicted per each SD of EAT volume and LA area.
EAT, epicardial adipose tissue; LA, left atrial.

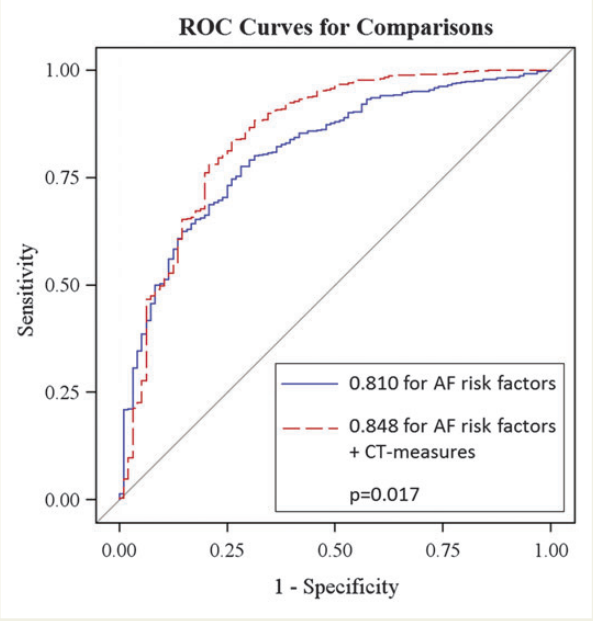

Figure 3 *C*-statistics for the improvement of the prediction of AF (prevalent and incident) by EAT and LA as non-contrast CT-derived measures over traditional AF risk factors, including age, gender, BMI, systolic blood pressure, and antihypertensive treatment.

When investigating the association of EAT volume with incident AF, we observed a 1.7-fold increase per SD of EAT volume in univariate analysis. This effect could no longer be observed when adjusting for AF risk factors. In contrast, LA size was also a strong predictor of AF after 5 years of follow-up, independent of age, gender, AF risk factors, and EAT volume.

Finally, we investigated whether CT-based measures, including both EAT and LA, improved the receiver operating characteristics. Both CT-derived measures together improved the area under the curve from 0.810 to 0.848 ($P = 0.017$, *Figure 3*). This effect was also predominantly driven by LA (receiver operating characteristics (ROC) from 0.810 to 0.845, $P = 0.025$), while EAT only marginally changed the area under the curve (ROC 0.845–0.848).

Discussion

In the current analysis, we investigated the association of EAT volume and LA size as two measures derived from non-contrast cardiac CT with prevalent and incident AF in a population-based cohort. We found that EAT was significantly associated with prevalent AF independent of age, gender, and AF risk factors; however, this effect was considerably reduced and no longer statistically significant, when correcting for LA size. This finding implies that the link of EAT with AF is ultimately explained by the link of EAT with LA size, which itself is a strong and independent predictor of AF. In gender-specific analysis, we found a stronger correlation of EAT with AF in women than in men. This finding, however, could be attributed to a stronger correlation of EAT with AF risk factor in women. When investigating the association of EAT volume with the development of AF during a 5-year follow-up period, the link between EAT and incident AF was predominantly explained by shared risk factor association. In contrast, LA size as measured from non-contrast cardiac CT was strongly associated with incident AF, independent of risk factors and EAT volume, significantly improving the prediction of prevalent and incident AF, enhancing the clinical value of this measure. Non-contrast CT-derived measure of LA showed a significant improvement in the prediction of AF, while the addition of EAT only marginally changed the area under the curve.

Recently, several studies described a link between EAT and prevalent AF. Al Chekakie *et al.*[5] described an association of EAT and AF in 273 patients undergoing cardiac CT, with even higher EAT volume in subjects with permanent compared with paroxysmal AF. These results were confirmed by Framingham investigators, acknowledging the need for further investigations.[6] Likewise, Shin *et al.*[8] found in a case–control study that not only overall EAT but also interaterial EAT thickness was higher in subjects with AF compared with healthy controls, suggesting that EAT may locally influence atrial remodelling and AF development. Similar results were found in our study for prevalent AF, with EAT volume being associated with AF independent of AF risk factors. However, when adjusting for LA size, associations of EAT with AF were attenuated. As a potential explanation, a link of EAT volume with LA size, as itself a strong predictor of AF, was found in our analysis described in the literature.[22,23] Therefore, we included LA size in our model, which ultimately diminished the association of EAT with prevalent AF.

While subjects with AF at follow-up examination had higher EAT volume at baseline compared with those remaining in sinus rhythm, a relevant effect was no longer present when adjusting for AF risk factors. Therefore, our results do not support the hypothesis of a long-term effect of EAT in the development of AF. Further studies with a longer follow-up period and more frequent ECG examinations are needed to confirm our results.

Besides the effect of adiposity, more and more evidence of an important role of inflammation in the development of AF was introduced in the literature. Recently, a link of high sensitive C-reactive protein with AF was described.[24] Likewise, EAT is endocrinally active, secreting several pro- and anti-inflammatory mediators.[25] Therefore, EAT is suggested to paracrinally influence the development of coronary atherosclerosis via an inflammatory pathway.[1,25] Besides the coronary arteries, the EAT also surrounds the LA and therefore may modulate inflammation, leading to LA remodelling. Moreover, a link of EAT with left ventricular mass and diastolic dysfunction was described in the literature, which may further influence LA remodelling, leading to the development of AF.[26]

The association of LA size with AF is well established in the echocardiography-based literature.[22] This finding is confirmed for our simple non-contrast cardiac CT-derived measure, showing a strong association with both prevalent and incident AF. With the advent of cardiac CT examinations with or without contrast media, information on the LA is readily available. Contrast-enhanced CT studies allow for three-dimensional (3D) quantification of LA size; however, they are relatively time consuming. In contrast, assessment of LA size from non-contrast cardiac CT based on a single area allows for only crude assessment of LA size, but can be performed within seconds even from picture archiving and communication system interfaces without the need of specified workstations or software

programmes. Also, the performed area measure was demonstrated to be superior to single LA dimension measurements, as routinely performed in echocardiography.[11] Moreover, it could be demonstrated that the area-based measure that was performed in this study shows good agreement with 3D volume and is highly reproducible,[11] allowing an easy and reliable estimation of LA size even from non-contrast-enhanced cardiac CT, but is also feasible as easy measure from contrast-enhanced CT. The fact that this crude assessment of LA size from even from non-contrast CT shows a highly robust association with AF is a key finding of our study.

Once cardiac CT is performed for primary prevention purposes, quantification of LA and, to a lower amount, also EAT may help to detect subjects at an increased risk for AF. Further studies are needed to define thresholds of CT-derived measures for clinical use.

Strength and Limitations

Strength of our study includes the population-based design without selection of the cohort to adiposity-related traits. Traditional cardiovascular risk factors were measured using highly standardized protocols, and EAT was quantified using a reproducible volume-based method. As a limitation, only AF prevalent at the time of the examination was included with potential to miss subjects with paroxysmal AF. Our results are based on a general population cohort with exclusion of prior cardiovascular disease, leading to event rates that may be considerably lower than in patient-based cohorts. Therefore, we might have biased our results towards the null. Finally, our study was conducted in a predominantly Caucasian population; hence generalization to other ethnic groups remains uncertain.

Conclusion

When comparing the association of EAT and LA size as CT-derived measures with AF, EAT shows an association with prevalent AF, but not with incident AF in the general population, while LA size predicts both incident and prevalent AF and ultimately diminishes the association of EAT with AF. Further studies with a longer follow-up and more frequent ECGs are needed to confirm our results.

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IMAGE FOCUS

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Fabry disease deposition mimicking a cardiac tumour and precipitating heart block

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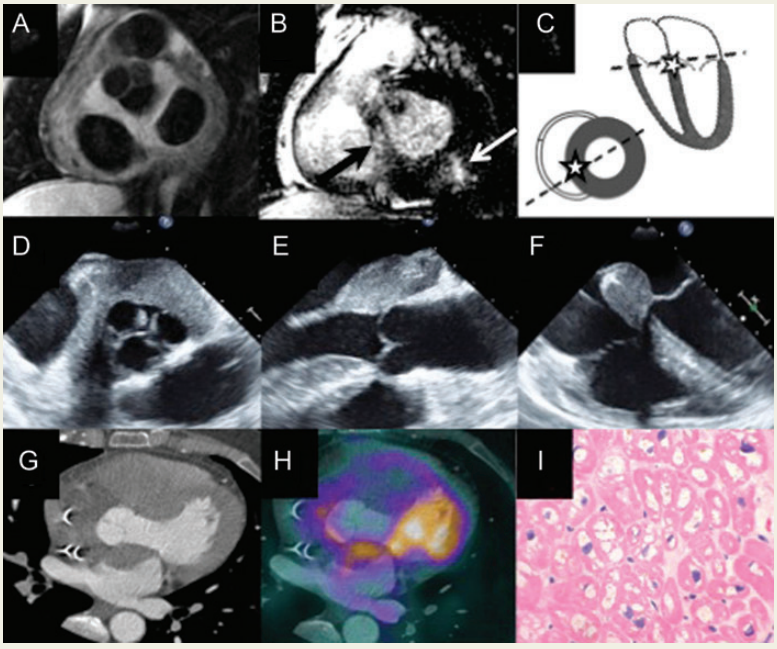

A 39-year-old female presented with syncope. She has Fabry disease (del.Ile239 mutation) on enzyme replacement therapy and also has a renal transplant secondary to Wegener's granulomatosus. An electrocardiogram demonstrated a complete heart block with a slow ventricular escape rhythm. Cardiovascular magnetic resonance imaging showed global left ventricular hypertrophy with more prominent thickening of the basal septum, left ventricular outflow tract (LVOT) and aortic root, and increased T_2 signal intensity in these areas (*Panel A*). Late gadolinium enhancement was observed in the basal inferolateral myocardium (*Panel B*, white arrow), the classic pattern of Fabry disease, and also in the basal septum in the vicinity of the Bundle of His (*Panel B*, black arrow and *Panel C*, Bundle of His indicated by star). A dual-chamber permanent pacemaker was inserted. Months later, an echocardiogram showed increased thickening of the LVOT myocardium and interatrial septum, which appeared like a mass on transoesophageal echocardiography (TOE) (*Panels D–F*). A computed tomography/positron emission tomography scan showed a soft tissue mass surrounding the aortic root (*Panel G*) with extension into the interatrial septum that demonstrated increased FDG uptake (*Panel H*), suggestive of a neoplasm or active inflammatory mass. However, TOE-guided endomyocardial biopsy excluded neoplasia and demonstrated typical histological features of cardiac Fabry disease including marked sarcoplasmic vacuolization (*Panel I*—H&E stain, original magnification 600×).

This case demonstrates the ongoing importance of multimodality assessment in complex cardiac pathology.