International Journal of Cardiology 172 (2014) 196–201

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Infiltrated atrial fat characterizes underlying atrial fibrillation substrate in patients at risk as defined by the ARIC atrial fibrillation risk score ☆,☆☆

Larisa G. Tereshchenko [a,*], Patricia Rizzi [a], Nathan Mewton [a], Gustavo Jardim Volpe [a], Sindhoora Murthy [b], David G. Strauss [c], Chia Y. Liu [a], Francis E. Marchlinski [d], Peter Spooner [a], Ronald D. Berger [a], Peter Kellman [e], Joao A.C. Lima [a]

[a] The Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, United States
[b] Whiting School of Engineering, Johns Hopkins University, Baltimore, MD, United States
[c] Food and Drug Administration, Silver Spring, MD, United States
[d] Hospital of the University of Pennsylvania, Philadelphia, PA, United States
[e] National Institutes of Health, National Heart, Lung, and Blood Institute, Bethesda, MD, United States

ARTICLE INFO

Article history:
Received 11 June 2013
Accepted 6 January 2014
Available online 22 January 2014

Keywords:
Atrial fibrillation
Cardiac magnetic resonance
Intraatrial infiltrated fat
Risk score

ABSTRACT

Background: It is known that expanded epicardial fat is associated with atrial fibrillation (AF). However, infiltrated intraatrial fat has not been previously quantified in individuals at risk as determined by the ARIC AF risk score.
Methods: Patients in sinus rhythm (N = 90, age 57 ± 10 years; 55 men [63.2%]), in 3 groups at risk of AF as determined by the ARIC AF risk score [low (≤11 points; n = 15), moderate (12–18 points; n = 40), high (≥19 points; n = 23) risk of AF], and paroxysmal AF (n = 12) underwent cardiac magnetic resonance study. Intraatrial and epicardial fat was analyzed with a Dark-blood DIR-prepared Fat-Water-separated sequence in the horizontal longitudinal axis. OsiriX DICOM viewer (Geneva, Switzerland) was used to quantify the intraatrial fat area. Width of the cephalad portion of the interatrial septum was measured at the level of the fossa ovalis.
Results: Intraatrial fat monotonically increased with growing AF risk in study groups (low AF risk 16 ± 4 vs. moderate AF risk 32 ± 18 vs. high AF risk 81 ± 83 mm^2; ANOVA P = 0.012). Log-transformed intraatrial fat predicted ARIC AF risk score in multivariate ordered probit regression after adjustment for sex, race, left and right atrial area indices, and body mass index (β-coefficient 0.50 [95% CI 0.03–0.97]; P = 0.037), whereas epicardial fat did not. Interatrial septum width showed similar association (3.0 ± 1.4 vs. 5.0 ± 1.8 vs. 7.1 ± 2.7 mm; ANOVA P < 0.001; adjusted β-coefficient 2.80 [95% CI 1.19–4.41]; P = 0.001).
Conclusions: Infiltrated intraatrial fat characterizes evolving substrate in individuals at risk of AF.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia [1]. The estimated prevalence of AF increases with age, from 1% in general population to 8% in those older than 80 years [1]. AF is a major risk factor for serious cardiovascular events, such a stroke, heart failure (HF) and premature death [2]. Arterial remodeling with fibrosis and dilatation, hypertension and diastolic heart failure predispose to AF [3–5]. The aging population and the rising prevalence of chronic heart disease lead to a 66% increase in hospital admissions for AF. In spite of advances in radiofrequency ablation for the treatment of AF, the high recurrence of AF (up to 40%) during the first year after pulmonary vein isolation (PVI) procedure [6] supports the notion that primary prevention of AF, if successful, would be the most efficient strategy to decrease AF burden for patients and healthcare providers. NIH identified primary prevention of AF as especially important priority for future research [7]. However, mechanisms of AF are not completely understood, and data characterizing AF substrate early in the continuum of structural heart disease are lacking.

Epicardial adipose tissue (EAT) has recently emerged as a factor associated with paroxysmal [8] and persistent AF [9], and with AF recurrence after PVI [10]. In the Framingham Heart Study (FHS) higher EAT volumes were associated with higher odds of prevalent AF [11]. Mechanisms of EAT effect on the myocardium were studied in experiments, which confirmed paracrine properties of EAT and release of pro-inflammatory and pro-fibrotic substances (adipo-fibrokines) [12]. At the same time, autopsy studies have shown that EAT can infiltrate myocardium [13]. However, until recently there was no imaging modality available for in-vivo assessment of infiltrated intraatrial fat. In 2009, Kellman et al. [14] developed novel fat-water-separated MRI imaging approach, which enabled the assessment of infiltrated intraatrial fat.

☆ Financial support & relationships with industry: Study was partially supported by Cardiac Translational Research Implementation Program (C-TRIP) grant from NIH/National Heart, Lung and Blood Institute #P20HL101397 and the Leducq Foundation.
☆☆ Clinical Trial Registration Information at www.clinicaltrials.gov: NCT01353131.
* Corresponding author at: Carnegie 568, 600 N. Wolfe St., Baltimore, MD 21287, United States. Tel.: +1 410 502 2796; fax: +1 410 614 8039.
E-mail address: lteresh1@jhmi.edu (L.G. Tereshchenko).

0167-5273/$ – see front matter © 2014 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ijcard.2014.01.012

While EAT was shown associated with prevalent AF, the myocardial substrate that predisposes to AF in patients at AF risk but without diagnosed AF remains largely unknown. We hypothesized that infiltrated intraatrial fat is associated with AF risk as determined by the AF risk score.

2. Methods

2.1. Study population

We analyzed the data of an ongoing prospective observational cohort study Personalized Risk Identification and Management for Arrhythmias and Heart Failure by ECG and MRI (PRIMERI). Study was approved by the Johns Hopkins Institutional Review Board, and all study participants signed an informed consent upon entering the study. Study included the patients of the Johns Hopkins Hospital, who have had signs of structural heart disease on 12-lead ECG (wide spatial QRS-T angle ≥105° and/or the Selvester QRS score [15] ≥5). Exclusion criteria were age above 70 years, left ventricular ejection fraction (LV EF) ≤35%, or high risk of non-cardiac death due to concomitant non-cardiac diseases. The Johns Hopkins Hospital database was screened and study candidates were invited to participate.

At enrollment detailed medical history was collected, 12-lead ECG was recorded at rest by the Marquette MAC 5000 ECG system with 12SL TM algorithm (GE Medical Systems, Milwaukee, WI), and cardiac magnetic resonance (CMR) study was performed. In addition, Holter ECG (GE Medical Systems, Milwaukee, WI) was recorded during 30–45 min at rest and during 6-min walk.

2.2. Risk of AF assessment: the ARIC AF risk score calculation

AF risk was assessed by the Atherosclerosis Risk In Communities (ARIC) AF risk score, which was calculated as described by Chamberlain et al. [16]. ARIC AF risk score was selected since the PRIMERI study population was bi-racial, and included participants of similar to ARIC study age range. Nonetheless, due to minor age differences between PRIMERI and ARIC study populations, we applied slightly modified ARIC AF risk score. ARIC AF risk score was developed for individuals of 45–65 years of age, and was assigned a maximum of 8 points for individuals 60–64 years. We assigned 10 points for study participants ≥65 years of age.

Study participants were categorized into 4 groups. Patients with a documented history of paroxysmal AF comprised the AF group. Study participants without AF history were separated into 3 groups, based on ARIC AF risk score. Low AF risk group included subjects scoring ≤11 points, who had a 10-year predicted probability of developing AF [16] of <5%. As shown previously, patients scoring ≥19 points had >24% predicted probability of developing AF within 10 years [16], they comprised high AF risk group. Individuals scoring in between these two groups, (12–18 points) comprised moderate AF risk group.

2.3. Atrial CMR analysis

Patients underwent CMR with a 1.5-T scanner (Avanto, Siemens Healthcare, Erlangen, Germany) on the same day as the ECG recordings. All CMR functional analyses were performed on dedicated workstations with ARGUS (Siemens Healthcare, PA) by 3 experienced observers who were blinded to the results of the ECG analysis (NM, PR, CL). LVEF, left ventricular end diastolic volume (LVEDV), left ventricular end systolic volume (LVESV) and LV mass were calculated using Simpson's rule and its values normalized by body surface area (BSA) calculated with the Mosteller equation. The left atrium (LA) and the right atrium (RA) areas were measured at their maximum size in the end-systolic phase of the ventricles using the 4-chamber view, and normalized by BSA [17].

The presence of interatrial fat was assessed with a Dark-blood DIR-prepared Fat-Water-separated sequence [14,18] in the horizontal longitudinal axis (4 chamber view). The typical sequence parameters were: band width = 977 Hz/pixel; TE = 1.53, 3.76, 5.99, and 8.22 ms; TR ≈ 11 ms; flip angle = 12°; image matrix = 256 × 180; ECG triggered every RR interval with views per segment = 15; and breath-hold duration = 13 heartbeats, including one initial heartbeat discarded for transition to steady state. The multiecho GRE sequence incorporated a double inversion recovery dark blood preparation. The multiecho GRE sequence incorporated a dark blood preparation. OsiriX DICOM viewer (Geneva, Switzerland) was used to quantify the area of the structure of interest (Fig. 1). The width of the cephalad portion of the interatrial septum was measured in this study at the level of the fossa ovalis, as described by Shirani and Roberts [19]. Epicardial fat area was measured in the same horizontal longitudinal axis.

2.4. Statistical analysis

STATA 12 (StataCorp LP, College Station, TX) was used for statistical analysis. Normally distributed variables were compared across study groups using a one-way ANOVA. Categorical variables were compared by Pearson's chi-square test. Pairwise correlations were studied between normally-distributed variables. Intraatrial fat area was log-transformed to normalize distribution. Ordered probit regression analysis was performed to study association between ARIC AF risk score (outcome, range 1–27) and log-transformed intraatrial fat, or interatrial septum width (predictors), adjusted by LA area index, RA area index, epicardial fat, body mass index, sex and race. Multiple linear regression analysis was employed to determine if intraatrial fat predicts interatrial septum width after adjustment for age, sex, race, and BMI.

3. Results

3.1. Study population

We analyzed data of 90 patients (mean age 57 ± 10 years). About half of the study population was comprised of men [n = 55 (61%)], and whites [n = 53 (59%)]. Screening QRS score indicated the presence of myocardial scar [20] (5.4 ± 2.1), and wide spatial QRS-T angle (114 ± 38) point to high likelihood of the presence of an underlying structural heart disease [21,22].

3.2. Clinical characteristics of patients at low, moderate, and high risk of AF

History of paroxysmal AF was known in 12 patients (Table 1). Successful PVI procedure was performed in 5 patients (41%), in whom amount of interatrial fat seemed to be smaller, as compared to AF patients without ablation procedures history (35 ± 18 mm^2 after PVI vs. 45 ± 57 mm^2 without PVI), although our study was not powered or designed to compare interatrial fat before and after PVI.

Relatively low predicted 10-years AF risk (<5%) as determined by the presence of ≤11 points, was found in the lowest quartile of the

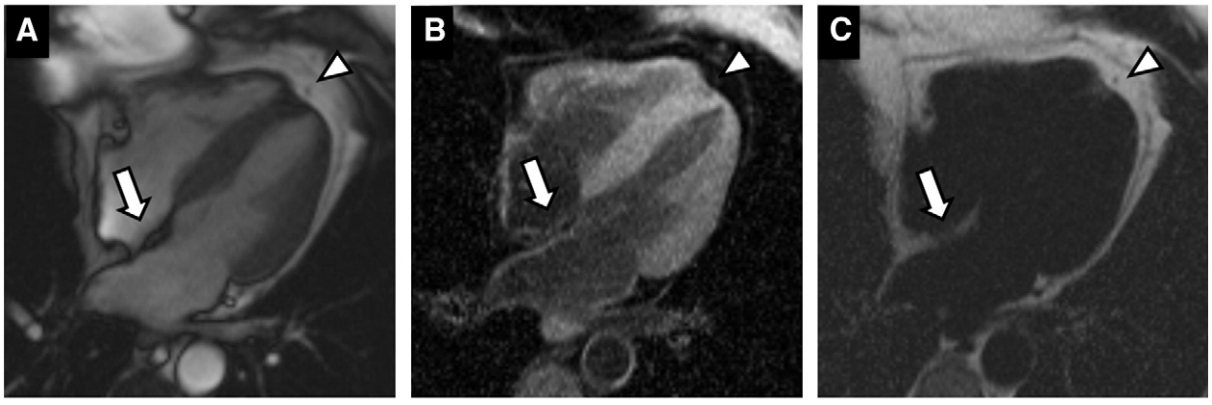

Fig. 1. Cardiac magnetic resonance (CMR) fat image by Fat-Water DB IR GRE sequence. Representative example of fat infiltration in the inter-atrial septum using a dedicated CMR sequence that allows fat and water imaging in separate. (A) Regular functional steady-state free precession (SSFP) sequence; (B) "Water phase" — fat signal is suppressed; (C) "Fat phase" — water signal is suppressed. A fat deposit can be observed in the inter-atrial septum (arrows), with an increased signal in the "fat phase" and decreased in the "water phase". The robust fat-water separation obtained with this sequence can be observed in the pericardial fat (arrow heads) imaging.

Table 1
Clinical characteristics of study participants.

	ARIC AF risk score ≤11 (n = 15)	ARIC AF risk score 12–18 (n = 40)	ARIC AF risk score ≥19 (n = 23)	ANOVA P value	Paroxysmal AF (n = 12)
Age (SD), year	54.0 (8.4)	59.2 (8.4)	62.8 (9.0)	0.013	57.6 (12.4)
Females, n (%)	12 (80.0)	17 (42.5)	1 (4.3)	<0.0001	2 (16.7)
Blacks, n (%)	11 (73.3)	17 (42.5)	3 (13.0)	0.001	4 (33.3)
Hypertension, n (%)	9 (60.0)	26 (65.0)	21 (91.3)	0.023	7 (58.3)
Hypertension history (SD), year	1.5 (3.2)	3.2 (5.5)	5.8 (7.3)	0.068	5.6 (8.3)
Diabetes mellitus, n (%)	4 (26.7)	11 (27.5)	4 (18.2)	0.416	2 (16.8)
Diabetes mellitus history (SD), year	1.8 (5.0)	2.8 (5.6)	0.9 (2.0)	0.292	0.7 (1.6)
Body mass index (SD), kg/m^2	28.9 (7.5)	31.7 (7.6)	32.3 (6.8)	0.343	30.6 (8.0)
History of MI, n (%)	1 (6.7)	5 (12.5)	8 (34.8)	0.035	4 (33.3)
History of PCI/CABG, n (%)	1 (6.7)	9 (22.5)	13 (56.5)	0.021	4 (33.3)
NYHA class ≥ II, n (%)	3 (20.0)	9 (22.5)	9 (39.1)	0.293	5 (41.7)
Systolic blood pressure (SD), mm Hg	137.2 (18.9)	147.3 (19.7)	159.6 (27.0)	0.017	136.4 (14.5)
Diastolic blood pressure (SD), mm Hg	88.3 (16.4)	86.6 (9.3)	91.6 (12.5)	0.357	78.1 (12.8)
eGFR, mL/min	64.7 (1.3)	64.3 (3.3)	65 (0)	0.535	65 (0)
Glucose (SD), mg/dL	109.0 (50.7)	119.1 (39.2)	141.3 (70.0)	0.170	124.5 (79.8)
Beta-blockers, n (%)	3 (20.0)	10 (25.0)	16 (69.6)	0.001	6 (50.0)
ACE-I or ARBs, n (%)	8 (53.3)	14 (35.0)	11 (47.8)	0.385	4 (33.3)
TZD, n (%)	1 (6.7)	11 (27.5)	5 (21.7)	0.249	1 (8.3)
Statins, n (%)	5 (33.3)	21 (52.5)	18 (78.3)	0.019	8 (66.7)
Current or former smoker, n (%)	7 (46.7)	21 (52.5)	11 (57.8)	0.817	7 (58.3)

MI = myocardial infarction; PCI = Percutaneous Coronary Intervention; CABG = Coronary artery bypass grafting; NYHA = New York Heart Association heart failure class; eGFR = estimated glomerular filtration rate; ACE-I = angiotensin-converting-enzyme inhibitor; ARBs = Angiotensin II receptor blockers; TZD = Thiazide diuretics.

risk score distribution in our study population (n = 15). The highest quartile of the risk score distribution (≥19 points) in our study characterized 23 participants with predicted probability of AF > 24%. Two middle quartiles of ARIC AF risk score (12–18 points, 40 participants) predicted wide range of AF risk probability, 5–24%.

As expected, the clinical characteristics of patients in the AF group were remarkably similar to clinical characteristics of participants in the high AF risk group (Table 1). Anticipated monotonically increasing prevalence of AF risk factors (age, male sex, white race, history of myocardial infarction and revascularization procedures, use of antihypertensive medication) was observed in individuals at growing AF risk. P wave duration on 12-lead ECG was significantly longer in patients at high AF risk (Table 2). There were no statistically significant differences in LV volumes, LVEF, LV mass, LA and RA indices, and epicardial fat across study groups (Table 2).

3.3. Infiltrated intraatrial fat and interatrial septum width in patients at low, moderate, and high risk of AF

Amount of intraatrial fat monotonically increased from low AF risk patients, to moderate AF risk patients, and then increased further to high AF risk patients (Fig. 2). Adjusted ordered probit regression analysis showed that increase in infiltrated intraatrial fat resulted in increase in the odds of having a higher ARIC AF risk score (Table 3).

Similarly, strong association between AF risk and width of interatrial septum was found (Table 2). Widening of interatrial septum was associated with increase in the odds of having a higher ARIC AF risk score (Table 3). Moreover, strong correlation between intraatrial fat and interatrial septum width was observed (Fig. 3), which was confirmed in multiple linear regression analysis after adjustment for age, race, sex, and BMI [β-coefficient 0.15 (95% CI 0.06–0.24); P = 0.002].

Table 2
ECG and structural parameters of the heart atria and ventricles.

	ARIC AF risk score ≤11 (n = 15)	ARIC AF risk score 12–18 (n = 40)	ARIC AF risk score ≥19 (n = 23)	ANOVA P value	Paroxysmal AF (n = 12)
QRS score (SD)	4.0 (2.0)	4.8 (2.2)	5.7 (2.1)	0.062	4.0 (2.6)
Spatial QRS-T angle (SD), deg	119.6 (33.1)	106.9 (37.9)	110.5 (39.5)	0.561	124.0 (25.3)
P duration (SD), ms	106.7 (9.8)	110.0 (13.4)	118.5 (10.9)	0.007	115 (13.1)
PQ interval (SD), ms	168.0 (28.1)	172.6 (29.2)	184.7 (25.5)	0.150	187.0 (53.5)
Heart rate (SD), bpm	65.2 (11.4)	65.7 (10.5)	66.6 (10.6)	0.923	63.0 (9.8)
QRS duration (SD), ms	98.4 (22.4)	97.1 (18.0)	113.1 (25.8)	0.019	106.3 (20.6)
P-axis (SD), deg	48.3 (22.1)	45.7 (21.7)	50.3 (52.7)	0.876	49.1 (26.6)
QTc duration (SD), ms	437.3 (28.0)	424.0 (23.2)	432.5 (24.3)	0.156	424.2 (20.9)
LVEF (SD), %	57.3 (9.1)	63.4 (8.8)	57.7 (9.7)	0.036	56.6 (8.8)
LV mass index (SD), g/m^2	63.8 (13.9)	66.5 (23.0)	70.1 (11.4)	0.643	64.2 (10.9)
LVESVI (SD), mL/m^2	32.5 (11.9)	25.1 (10.4)	28.3 (11.9)	0.112	34.1 (15.4)
LVEDVI (SD), mL/m^2	74.1 (12.8)	64.1 (14.3)	66.1 (19.9)	0.137	76.9 (24.6)
Right atrium area index (SD), cm^2/m^2	9.4 (1.6)	8.7 (3.0)	9.0 (2.8)	0.780	9.9 (3.3)
Left atrium area index (SD), cm^2/m^2	11.9 (2.6)	10.1 (2.2)	10.1 (2.3)	0.064	11.2 (2.9)
Epicardial fat (SD), cm^2	13.3 (4.4)	14.0 (6.7)	17.5 (5.5)	0.114	13.3 (3.0)
Interatrial fat (SD), mm^2	16 (4)	32 (18)	81 (83)	0.012	40.7 (41.9)
Log-transformed interatrial fat (SD)	−1.87 (0.27)	−1.34 (0.67)	−0.69 (1.10)	0.021	−1.25 (0.87)
Atrial septum width (SD), mm	3.0 (1.4)	5.0 (1.8)	7.1 (2.7)	<0.0001	5.4 (2.8)

LVEF = left ventricular ejection fraction; LVEDVI = left ventricular end diastolic volume index; LVESVI = left ventricular end systolic index.

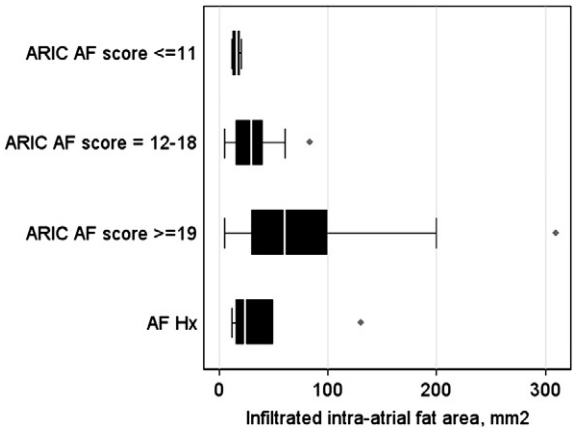

Fig. 2. Box-plot of infiltrated intraatrial fat area in groups of patients at AF risk and patients with paroxysmal AF. Median (*white vertical line crossing the box*) and interquartile range [IQR] (*box*). Whiskers specify the adjacent values, defined as the most extreme values within 1.5 IQR of the nearer quartile.

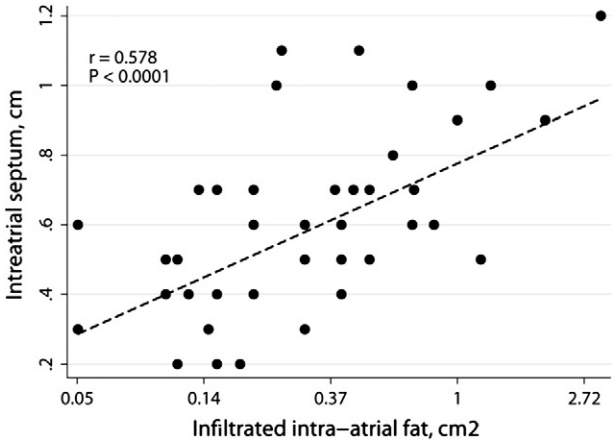

Fig. 3. Scatterplot of the interatrial septum width in cm (Y) against intraatrial fat area in cm^2 (X) with linear fitted line.

4. Discussion

Our study revealed important findings. We showed that in individuals without AF history, monotonically increasing amounts of infiltrated intraatrial fat were independently associated with the 10-year predicted probability of developing AF as determined by the ARIC AF risk score [16]. Thus, infiltrated intraatrial fat characterizes evolving substrate of per-clinical AF early in a continuum of structural heart disease. This observation opens a new avenue for mechanistic pathophysiological studies that are needed in order to explain mechanisms of fat infiltration of atria, and to develop therapies for prevention of fat infiltration.

In addition, we showed that the width of the interatrial septum strongly correlates with infiltrated intraatrial fat and therefore, may serve as its surrogate. While visualization and quantification of intraatrial fat requires special CMR procedure, measurement of interatrial septum width could be easily done on any 4-chamber CMR image. Future investigations of interatrial septum width in large epidemiological studies might improve our understanding of AF substrate development before AF onset.

4.1. ARIC AF risk score and early pre-clinical AF substrate

Several clinical AF risk scores exist. Framingham Heart Study (FHS) AF risk score was developed to predict 10-year AF risk in middle-aged to elderly whites [5], and was successfully validated [23]. Another risk score for AF incidence was developed in a prospective biracial community based cohort [16], Atherosclerosis Risk In Communities (ARIC). Recently, AF risk factors were identified in pooled analysis of 3 large cohorts (FHS, ARIC and the Cardiovascular Health Study [CHS]) and were externally validated in the Age, Gene and Environment—Reykjavik study (AGES) and the Rotterdam Study (RS) [24]. We choose ARIC AF risk score over FHS AF risk score because our study population is (1) bi-racial, and (2) relatively young (57 ± 10 years). In addition, the age at which significant cardiac murmur developed (FHS risk factor) was unknown in our study. ARIC AF risk score [16] was developed in a population study and is based on risk factors, commonly measured in clinical practice. Very few of our study participants were 65–70 years of age, whom we added two additional risk points for their age, as CHARGE-AF consortium demonstrated monotonically increasing AF risk for every 5 years of age [24]. Importantly, the use of ARIC AF risk score for the first time revealed an evolving pre-clinical AF substrate, as presented by the infiltrated intraatrial fat.

4.2. Infiltrated intraatrial fat: role in AF

Atrial fibrosis and fibrotic atrial cardiomyopathy [25] is associated with clinically manifest AF. Recent experimental study [12] provided evidence that secreted by EAT adipo-fibrokine Activin A can induce fibrosis of the myocardium. Importantly, experiments showed that fat tissue infiltrates myocardium and in situ elicit paractine effect of EAT secretome on the neighboring myocardium. Results of our study constitute the first evidence that in humans infiltrated intraatrial fat represents early pre-clinical AF substrate in individuals at AF risk. We speculate that the timely prevention of fat infiltration of atria might prevent AF development, and should be considered as a future therapy target.

More than a hundred years ago fatty heart was considered to be a common cause of cardiac death [26]. Pathologists described intramyocardial fat and fibrofatty infiltration many years ago [27], and the fact that adipocytes can infiltrate myocardium, is well known. However, this fact did not attract attention as until very recently there was no tool available for in-vivo fat infiltration assessment. Kellman et. al. first developed the methodology of in-vivo imaging of the infiltrated fat [14,18], which was used in this study. Our study underscores the importance of infiltrated fat imaging and quantification. At the same time we

Table 3
Multivariate ordered probit regression models predicting the ARIC atrial fibrillation risk score in individuals without AF history.

	Model 1		Model 2	
Predictor	β-Coefficient (95% CI)	P	β-Coefficient (95% CI)	P
Log-transformed intraatrial fat	0.50 (0.03-0.97)	0.037	–	
Interatrial septum, mm	–		1.80 (1.19–4.41)	<0.001
Left atrium area index, cm^2/m^2	0.20 (−0.19 to 0.23)	0.849	0.15 (0.001–0.30)	0.049
Right atrium area index, cm^2/m^2	0.11 (−0.08 to 0.30)	0.270	0.08 (−0.05 to 0.21)	0.227
Body mass index, kg/m^2	0.005 (−0.07 to 0.74)	0.897	0.04 (−0.01 to 0.095)	0.096
Epicardial fat area, cm^2	−0.018 (−0.08 to 0.44)	0.573	−0.01 (−0.06 to 0.04)	0.722

acknowledge that measurement of intraatrial fat requires special CMR techniques and is time consuming. Our finding of strong correlation between intraatrial fat and interatrial septum width on a standard 4-chamber CMR view suggests that the simple measure of interatrial septum width might serve as a marker of the degree of adipose tissue infiltration of the atria. Future studies are needed to test this hypothesis.

4.3. Role of interatrial septum in atrial arrhythmogenesis

Conditions, affecting interatrial septum, are known to be associated with a higher rate of supraventricular arrhythmia. Massive adipose tissue infiltration of the interatrial septum [28] was shown to be associated with atrial arrhythmias, requiring antiarrhythmic medications [29]. High prevalence of atrial arrhythmia (25–50%) was noticed in patients with atrial septal aneurysm [30]. Many abnormalities of the interatrial septum are considered to be of unknown clinical significance. It remains unknown whether specific features of interatrial septum itself, or associated abnormalities are related to the pathogenesis of atrial arrhythmia. Development of the interatrial septum has been intensely studied [31]. However, the exact mechanism for the genesis of the adipose tissue in the interatrial septum is unknown. Further studies are needed to compare fibrofatty infiltration of interatrial septum and other areas of atrial myocardium, both in AF patients and in subjects at risk of AF.

In addition, other mechanisms other than fat infiltration pathological processes in interatrial septum are plausible. Hypertrophy of the interatrial septum, with subsequent fibrosis, might contribute to interatrial septum thickening, as well. Unlike LV, LA myocardium is thin and does not sustain hypertrophy long-term. Future studies are needed to explore possible interaction between intraatrial fat infiltration and atrial myocytes hypertrophy.

While our study was not designed to compare interatrial fat before and after PVI, we have found that AF patients with PVI history have smaller amounts of interatrial fat, as compared to AF patients without PVI history. We speculate that interatrial septum puncture facilitates local fibrosis, which plays a role of confounding factor in this study.

4.4. Limitations

Several limitations of this study should be acknowledged. First, we did not measure the EAT volumetrically, which might explain the absence of associations between ARIC AF risk score and epicardial fat in our study. Previously FHS study analysis showed that epicardial fat is associated with prevalent AF [11]. However, the goal of this study was quantification of intraatrial fat, but not epicardial fat. At the same time, intraatrial fat in this study was not measured volumetrically as well. Meaningful findings of our study suggest that measurement of intraatrial fat area might be sufficient. However, future study with volumetric measurement of intraatrial fat is needed to validate our approach. Secondly, this study population is small, and the statistical power of the study is limited. Moreover, patients with AF history, and patients at AF risk in our study differed largely in their clinical characteristics, and therefore, likely in the substrate of AF development, too. However, unique CMR technique was used in this study, which for the first time allowed the quantification of infiltrated intraatrial fat. Third, we used slightly modified ARIC AF risk score in order to determine AF risk in study participants. However, applied in this study AF risk score was similar to recently reported CHARGE AF consortium risk score [24], which was developed in the largest to date sample of general population and therefore provided optimized AF risk stratification. Importantly, our study was cross-sectional. Future prospective studies are needed to validate association between interatrial infiltrated fat, and AF development. Lastly, AF in our study was diagnosed based on carefully collected past medical history, review of medical record, recorded 12 lead ECG and 30–45 min Holter ECG. We recognize that silent paroxysmal AF might be missed, as study was not designed for 30-day ECG monitoring or implantation of a loop recorder. Future studies are needed to determine association between silent AF and interatrial fat.

References

[1] Fuster V, Ryden LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2011;123:e269–367.

[2] Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. Am J Med 2002;113:359–64.

[3] Anderson DC, Yolton RL, Reinke AR, Kohl P, Lundy-Ekman L. The dizzy patient: a review of etiology, differential diagnosis, and management. J Am Optom Assoc 1995;66:545–58.

[4] Rosen MR. Mechanisms of cardiac arrhythmias: focus on atrial fibrillation. J Gend Specif Med 2001;4:37–47.

[5] Schnabel RB, Sullivan LM, Levy D, et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. Lancet 2009;373:739–45.

[6] Calkins H, Brugada J, Packer DL, et al. HRS/EHRA/ECAS expert Consensus Statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. A report of the Heart Rhythm Society (HRS) Task Force on catheter and surgical ablation of atrial fibrillation. Heart Rhythm 2007;4:816–61.

[7] Benjamin EJ, Chen PS, Bild DE, et al. Prevention of atrial fibrillation: report from a national heart, lung, and blood institute workshop. Circulation 2009;119:606–18.

[8] Shin S, Yong H, Lim H, et al. Total and interatrial epicardial adipose tissues are independently associated with left atrial remodeling in patients with atrial fibrillation. J Cardiovasc Electrophysiol 2011;22:647–55.

[9] Al Chekakie MO, Welles CC, Metoyer R, et al. Pericardial fat is independently associated with human atrial fibrillation. J Am Coll Cardiol 2010;56:784–8.

[10] Tsao HM, Hu WC, Wu MH, et al. Quantitative analysis of quantity and distribution of epicardial adipose tissue surrounding the left atrium in patients with atrial fibrillation and effect of recurrence after ablation. Am J Cardiol 2011;107:1498–503.

[11] Thanassoulis G, Massaro JM, O'Donnell CJ, et al. Pericardial fat is associated with prevalent atrial fibrillation/clinical perspective. Circ Arrhythm Electrophysiol 2010;3:345–50.

[12] Venteclef N, Guglielmi V, Balse E, et al. Human epicardial adipose tissue induces fibrosis of the atrial myocardium through the secretion of adipo-fibrokines. Eur Heart J 2013 Mar 22. http://dx.doi.org/10.1093/eurheartj/eht099.

[13] Tansey DK, Aly Z, Sheppard MN. Fat in the right ventricle of the normal heart. Histopathology 2005;46:98–104.

[14] Kellman P, Hernando D, Shah S, et al. Multiecho dixon fat and water separation method for detecting fibrofatty infiltration in the myocardium. Magn Reson Med 2009;61:215–21.

[15] Selvester RH, Wagner GS, Hindman NB. The Selvester QRS scoring system for estimating myocardial infarct size. The development and application of the system. Arch Intern Med 1985;145:1877–81.

[16] Chamberlain AM, Agarwal SK, Folsom AR, et al. A clinical risk score for atrial fibrillation in a biracial prospective cohort (from the Atherosclerosis Risk in Communities [ARIC] study). Am J Cardiol 2011;107:85–91.

[17] Maceira AM, Cosin-Sales J, Roughton M, Prasad SK, Pennell DJ. Reference left atrial dimensions and volumes by steady state free precession cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2010;12:65.

[18] Kellman P, Hernando D, Arai AE. Myocardial fat imaging. Curr Cardiovasc Imaging Rep 2010;3:83–91.

[19] Shirani J, Roberts WC. Clinical, electrocardiographic and morphologic features of massive fatty deposits ("lipomatous hypertrophy") in the atrial septum. J Am Coll Cardiol 1993;22:226–38.

[20] Strauss DG, Selvester RH, Lima JA, et al. ECG quantification of myocardial scar in cardiomyopathy patients with or without conduction defects: correlation with cardiac magnetic resonance and arrhythmogenesis. Circ Arrhythm Electrophysiol 2008;1:327–36.

[21] Tereshchenko L, Han L, Cheng A, et al. Comparison of predictive value of the spatial Qrs-T angle and its variability for risk stratification of ventricular arrhythmia. J Am Coll Cardiol 2011;57:E147.

[22] Yamazaki T, Froelicher VF, Myers J, Chun S, Wang P. Spatial QRS-T angle predicts cardiac death in a clinical population. Heart Rhythm 2005;2:73–8.

[23] Schnabel RB, Aspelund T, Li G, et al. Validation of an atrial fibrillation risk algorithm in whites and African Americans. Arch Intern Med 2010;170:1909–17.

[24] Alonso A, Krijthe BP, Aspelund T, et al. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. J Am Heart Assoc 2013;2:e000102.

[25] Teh AW, Kistler PM, Lee G, et al. Long-term effects of catheter ablation for lone atrial fibrillation: progressive atrial electroanatomic substrate remodeling despite successful ablation. Heart Rhythm 2012;9:473–80.

[26] Osler W. The principles and practice of medicine designed for use of practitioners and students of medicine. New York: D. Appleton; 1892.

[27] Shirani J, Berezowski K, Roberts WC. Quantitative measurement of normal and excessive (cor adiposum) subepicardial adipose tissue, its clinical significance, and its effect on electrocardiographic QRS voltage. Am J Cardiol 1995;76:414–8.

[28] Heyer CM, Kagel T, Lemburg SP, Bauer TT, Nicolas V. Lipomatous hypertrophy of the interatrial septum: a prospective study of incidence, imaging findings, and clinical symptoms. Chest 2003;124:2068–73.
[29] Hutter Jr AM, Page DL. Atrial arrhythmias and lipomatous hypertrophy of the cardiac interatrial septum. Am Heart J 1971;82:16–21.
[30] Mügge A, Daniel WG, Angermann C, et al. Atrial septal aneurysm in adult patients: a multicenter study using transthoracic and transesophageal echocardiography. Circulation 1995;91:2785–92.
[31] Rojas CA, El-Sherief A, Medina HM, et al. Embryology and developmental defects of the interatrial septum. Am J Roentgenol 2010;195:1100–4.