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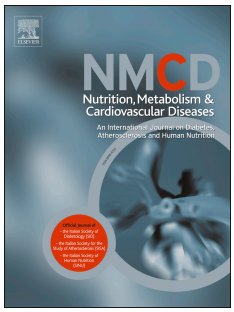

Metabolic syndrome associates with left atrial dysfunction

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Metabolic syndrome associates with left atrial dysfunction

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List of abbreviations

3ch = three-chamber

AF = atrial fibrillation

ATP = adenosine triphosphate

BMI = body mass index

BSA = body surface area

CMR = cardiovascular magnetic resonance

EDV = end diastolic volume

EF = ejection fraction

ESV = end systolic volume

^{1}H-MRS = ^{1}H-magnetic resonance spectroscopy

HF = heart failure

HDL = high-density lipoprotein cholesterol

HOMA-IR = homeostasis model assessment of insulin resistance

Hs-CRP = high-sensitivity C-reactive protein

LA = left atrium

LV = left ventricle

MetS = metabolic syndrome

MRI = magnetic resonance imaging

SA = short axis

SAT = subcutaneous adipose tissue

T2DM = type 2 diabetes mellitus

TG = triglyceride

VAT = visceral adipose tissue

Abstract

Background and aims

Obesity and metabolic syndrome (MetS) are risk factors of atrial fibrillation (AF), but limited data exist on their effect on left atrial (LA) function. The aim of the study was to evaluate the effects of cardiac, hepatic and intra-abdominal ectopic fat depots and cardiometabolic risk factors on LA function in non-diabetic male subjects.

Methods and results

Myocardial and hepatic triglyceride contents were measured with 1.5T ^{1}H-magnetic resonance spectroscopy and LA and left ventricular function, visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), epicardial and pericardial fat by magnetic resonance imaging (MRI) in 33 men with MetS and 40 men without MetS. LA volumes were assessed using a novel three-chamber orientation based MRI approach. LA ejection fraction (EF) was lower in MetS patients than in the control group (44 ± 7.7 % in MetS vs. 49 ± 8.6 % in controls, p=0.013) without LA enlargement, indicating LA dysfunction. LA EF correlated negatively with waist circumference, body mass index, SAT, VAT, fasting serum insulin, and homeostasis model assessment of insulin resistance index, and positively with fasting serum high-density lipoprotein cholesterol. VAT was the best predictor of reduced LA EF.

Conclusions

MetS associates with subclinical LA dysfunction. Multiple components of MetS are related to LA dysfunction, notably visceral obesity and insulin resistance. Further studies are needed to elucidate the role of mechanical atrial remodeling in the development of AF.

Keywords

Cardiovascular magnetic resonance, proton magnetic resonance spectroscopy, metabolic syndrome, obesity, left atrial, ejection fraction, atrial remodeling, visceral adipose tissue, cardiac steatosis.

Background

Overweight and obesity are major global health concerns affecting around 2 billion people worldwide [1]. Central obesity is particularly hazardous to health associating with metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM). In MetS, lipid overflow will ultimately lead to fat accumulation not only around the viscera but also to non-adipose tissue such as liver, pancreas, skeletal muscle, and heart [2]. MetS increases the risk for morbidity and mortality from cardiovascular diseases including heart failure (HF) [3, 4]. Left ventricular (LV) diastolic dysfunction with preserved systolic function is an early precursor of obesity cardiomyopathy leading eventually to HF. LV diastolic dysfunction has been associated with MetS and it has been shown to correlate with ectopic fat accumulation such as increased amount of pericardial or epicardial fat or hepatic fat content [5, 6].

Atrial fibrillation (AF) is the most common cardiac rhythm disorder and is associated with significant morbidity and mortality, especially that arising from stroke and HF, imposing a public health burden [7, 8]. The prevalence of AF increases with age from less than 0.16 % in people younger than 49 years to over 10 % in persons aged over 80 years [7]. AF is commonly associated with overweight and obesity while other major risk factors include male sex, hypertension, HF, coronary artery disease, diabetes, sleep apnea, and excessive alcohol use [8].

In obese patients without AF, left atrial (LA) enlargement has been related to hypertension and LV dysfunction [9]. However, magnetic resonance imaging (MRI) data regarding LA function in MetS is limited. Atrial remodeling is defined as a spectrum of pathophysiological changes in atrial structure and function that occur in response to stresses imposed by conditions such as hypertension, HF, T2DM, and obesity [10]. Atrial remodeling may be subdivided to structural remodeling, as measured by LA size, and mechanical remodeling, as measured by LA function. Milder, often subclinical forms of atrial dysfunction may show decreased LA ejection fraction (EF) without LA enlargement.

The aim of the study was to assess LA function in men with MetS without known heart diseases and to examine the association of different ectopic fat depots and cardiometabolic risk factors with LA dysfunction.

Methods

Study design

Study population consisted of 73 men from the same study cohort as previously described [5]. Subjects were allocated into two groups (MetS present and MetS absent), based on the following criteria: 1) waist circumference ≥94 cm, and 2) having ≥2 abnormal findings as per the harmonized definition of MetS [11]. Thirty-three participants fulfilled the criteria for MetS. In these participants, myocardial ischemia was excluded by means of adenosine stress perfusion MR. Exclusion criteria and medications are described in the supplemental material.

The study was approved by the Ethics Committee of the Department of Medicine, Hospital District of Helsinki and Uusimaa, and each subject provided written informed consent.

Demographics and biochemical measurements

Body mass index (BMI), waist circumference, blood pressure measurements and blood sample examination and analysis were performed as previously described [12].

CMR protocol and analysis

Cardiac MR images were acquired using 1.5T imager (Magnetom Avanto; Siemens, Erlangen, Germany) and analysis was performed by two radiologists with experience of CMR. Imaging parameters are provided in the supplement.

Three-chamber (3ch) oriented images were used for measuring LA area in a single plane (Figure 1 in supplemental material). All phases of the cine images were inspected and minimum and maximum LA area were planimetered using a diagnostic radiologic workstation (Impax 6 software, Agfa Healthcare, Mortsel, Belgium), and reported as LA 2D model. LA area measured in 3ch MR image is a reliable indicator of LA size [13] but volumetric CMR data based on 3ch images has not been reported. For 3D model of the LA we used prolate ellipsoid model, which is commonly used for estimating LA volume in echocardiographic studies. Volume of the ellipsoid was calculated according to formula: $V = \frac{4}{3}\pi abc$, where πab = 3chA, area measured in the 3ch image, and c =0.5*h, where h equals maximum craniocaudal diameter of the LA in a short axis (SA)-oriented image at the midline of the LA (Figure 2 in supplemental material). Both measurements were done in end-systolic and end-diastolic images to obtain minimum and maximum LA volumes, and to calculate EF. Volume parameters are reported also as indexed to the subject's body surface area (BSA).

Comparison of LA assessment of 3ch prolate ellipsoid model and traditional Simpson's method, considered as gold standard, was performed for a group (n=10) of study subjects with sufficient data available for both methods. In these subjects, LA volume was

planimetered from a stack of SA cine images with Simpson's method using dedicated software (QMass MR v.7.6, Medis Medical Imaging Systems, Leiden, Netherlands).

Quantification of cardiac, hepatic and abdominal fat depots by MRI and ^{1}H-MRS

For measuring myocardial and hepatic triglyceride (TG) content, ^{1}H-magnetic resonance spectroscopy (^{1}H-MRS) was performed in a 1.5T MR imager (Magnetom Avanto; Siemens). MRS protocol is presented in the supplement. Distributions of visceral and subcutaneous adipose tissue (VAT and SAT) and epicardial and pericardial fat were measured as previously described [5, 12].

Statistical analyses

All statistical analyses were performed with IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). Normality of continuous variables was analyzed by the Kolmogorov-Smirnov test. Logarithmic, square root or reciprocal transformation of variables was performed, if necessary. Data are presented as frequencies or percentages for categorical variables, as means ± SD for normally distributed continuous variables, and as medians (range) for skewed variables. Between-group differences were assessed by the Mann–Whitney U test, unpaired t-test, or the chi-square test, as appropriate. Depending on distribution of values, Pearson or Spearman correlation coefficients were used to assess the relationship between LA parameters and clinical parameters and results of ectopic fat quantification. Univariable linear regression model was used with and without age-adjustment to examine the possible factors of atrial dysfunction using LA EF as dependent variable. Multivariable stepwise regression analyses were performed to determine the independent predictors of LA EF. Three-chamber-based LA volume assessment and SA-based

Simpson's method were compared using Pearson correlation and Bland-Altman analysis. For all analyses, $p<0.05$ was considered statistically significant.

Results

Clinical and biochemical characteristics, body fat distribution and CMR data

Demographic differences between groups (Table 1) have been reported earlier in detail [5]. Briefly, subjects with MetS were older, had larger waist circumference, and higher BMI and blood pressure than subjects without MetS. All ectopic fat depots were larger in subjects with MetS than in controls. More unfavorable plasma lipid profile and markers of glucose metabolism were noted in participants with MetS as compared to controls.

LA CMR data is outlined in Table 1. BSA-indexed LA areas (2D model) or volumes (3D model) did not differ between groups. In 2D and 3D models, LA EF was higher in the group without MetS than in the MetS group. LV data (Table 1 in supplemental material) have been reported earlier [5].

Table 1. Clinical and biochemical characteristics, fat compartments and left atrial size and function.

	MetS present	Mets absent	p
N	33	40	
Age (years)	48.6 ± 6.8	40.4 ± 7.6	< 0.001
Body mass index (kg/m^2)	30.1 ± 4.7	24.1 ± 2.2	< 0.001
Waist circumference (cm)	107 (94 – 127)	88 (71 – 93.5)	< 0.001
Current smokers (N, %)	10 (32)	6 (15)	0.075
Heart rate (1/min)	69 ± 13	62 ± 8.8	0.006
Systolic blood pressure (mmHg)	132 ± 14	115 ± 9.9	< 0.001
Diastolic blood pressure (mmHg)	88 ± 9.9	74 ± 6.1	< 0.001
Total cholesterol (mmol/l)	5.1 ± 0.85	4.4 ± 0.80	0.001
High-density lipoprotein cholesterol (mmol/l)	1.1 ± 0.25	1.5 ± 0.39	< 0.001
Low-density lipoprotein cholesterol (mmol/l)	3.2 ± 0.79	2.5 ± 0.67	0.001
Triglycerides (mmol/l)	2.0 ± 1.0	0.83 ± 0.31	< 0.001
fP-ALT (U/l)	34 (16 – 260)	22 (7 – 59)	< 0.001
fP-glucose (mmol/l)	5.8 ± 0.58	5.1 ± 0.40	< 0.001
fS-insulin (mU/l)	9.2 (3.3 – 28)	3.0 (0.9 – 9.7)	< 0.001
HOMA-IR index	2.2 (0.75 – 6.8)	0.6 (0.2 – 2.2)	< 0.001
Hs-CRP (mg/l)	0.97 (0.03 – 12)	0.33 (0 – 5.8)	< 0.001
NT-proBNP (ng/l)	27 (5 – 151)	23 (5 – 74)	0.210
Myocardial triglyceride content (%)	0.970 (0.31 – 4.76)	0.450 (0.14 – 1.39)	< 0.001
Epicardial fat (mm^2)	895 (385 – 2020)	542 (251 – 1130)	< 0.001
Pericardial fat (mm^2)	1990 (750 – 6130)	611 (66 – 1580)	< 0.001
Hepatic triglyceride content (%)	6.04 (1.30 – 31.7)	0.880 (0.27 – 6.16)	< 0.001
SAT (cm^3)	4710 ± 1650	2050 ± 839	< 0.001
VAT (cm^3)	3380 (1260 – 5740)	883 (67 – 3170)	< 0.001
LA 3ch Area EF (%)	32.1 ± 6.3	36.8 ± 8.4	0.008
LA 3ch Area ED (mm^2)	2230 ± 470	1980 ± 320	0.012
LA 3ch Area ED/BSA (10^{-4})	10.2 ± 2.0	10.1 ± 1.6	0.786
LA 3ch Area ES (mm^2)	1520 ± 350	1250 ± 270	0.001
LA 3ch Area ES/BSA (10^{-4})	6.9 ± 1.5	6.3 ± 1.3	0.095
LA EF (%)	44 ± 7.7	49 ± 8.6	0.013
LA EDV (ml)	86 ± 23	79 ± 17	0.160
LA EDV/BSA (ml/m^2)	39 ± 9.7	40 ± 8.5	0.638
LA ESV (ml)	48 ± 15	40 ± 11	0.015
LA ESV/BSA (ml/m^2)	22 ± 6.5	20 ± 5.1	0.285

Data are expressed as means (±SD), medians (range) or as frequencies (%). Abbreviations: fP, fasting plasma; fS, fasting serum; hs-CRP, high-sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; NT-proBNP, N-terminal pro-brain natriuretic peptide; SAT,

subcutaneous adipose tissue; VAT, visceral adipose tissue; LA, left atrial; EF, ejection fraction; ED, end diastolic; ES, end systolic; BSA, body surface area.

Correlation analyses of clinical and biochemical parameters and body fat depots with LA size and function

In both 2D and 3D models of LA EF, age, waist circumference, BMI, fasting plasma glucose, fasting serum insulin, homeostasis model assessment of insulin resistance (HOMA-IR) index, high-sensitivity C-reactive protein (hs-CRP), hepatic TG content, VAT, and SAT correlated inversely with LA EF and high-density lipoprotein cholesterol (HDL) correlated positively with LA EF (Table 2). Scatter plots demonstrating the correlations of LA EF (3D model) with selected contributing factors of MetS are shown in Figure 1. Negative correlation of myocardial TG content, epicardial and pericardial fat with LA EF was noted in the 2D LA model, but these findings did not remain significant in the 3D LA model. Correlations between clinical and biochemical parameters and fat compartments and LA volumes are provided in the supplement (Table 2 in supplemental material).

Univariate linear regression analysis was performed for the 3D model of LA EF (Table 3). In age-adjusted linear regression model, regression coefficients with LA EF and waist circumference, BMI, SAT, VAT, fasting serum insulin, HOMA-IR index, and HDL were significant. Stepwise multivariable regression analysis was performed to further examine the relationship of ectopic fat depots and LA EF (Table 4). It revealed that VAT followed by SAT were the best predictors of reduced LA EF when age, BMI, and hepatic TG content were taken into account.

Table 2. Correlations between clinical and biochemical parameters and fat compartments and LA function.

Variable	LA EF (%) 2D model		LA EF (%) 3D model	
	β	*p*	β	*p*
Age	-0.249	0.034†	-0.260	0.026†
Body mass index	-0.372	0.001*	-0.270	0.021†
Waist circumference	-0.420	<0.001*	-0.349	0.002*
Systolic blood pressure	-0.103	0.386	-0.121	0.309
Diastolic blood pressure	-0.117	0.325	-0.146	0.216
SELECTED BIOCHEMICAL PARAMETERS				
High-density lipoprotein cholesterol	0.333	0.004*	0.316	0.006*
Low-density lipoprotein cholesterol	-0.022	0.856	-0.091	0.442
fP-glucose (mmol/l)	-0.314	0.007*	-0.269	0.021†
fS-insulin (mU/l)	-0.433	<0.001*	-0.371	0.001*
HOMA-IR index	-0.439	<0.001*	-0.373	0.001*
Hs-CRP (mg/l)	-0.361	0.002*	-0.281	0.018†
NT-proBNP (ng/l)	-0.158	0.181	-0.112	0.344
ECTOPIC FAT DEPOTS				
Myocardial triglyceride content (%)	-0.305	0.009*	-0.165	0.166
Epicardial fat (mm^2)	-0.260	0.026†	-0.124	0.294
Pericardial fat (mm^2)	-0.269	0.021†	-0.199	0.092
SAT (mm^2)	-0.415	0.001*	-0.356	0.003*
VAT (mm^2)	-0.450	<0.001*	-0.352	0.003*
Hepatic triglyceride content (%)	-0.370	<0.001*	-0.314	0.007*

Abbreviations: LA, left atrial; EF, ejection fraction; fP, fasting plasma; fS, fasting serum; Hs-CRP, high-sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; NT-proBNP, N-terminal pro-brain natriuretic peptide; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue. *p<0.01, †p<0.05

Table 3. Results of univariate regression analysis.

Dependent variable: LA EF (3D model)	Beta	R^2	Adj. R^2	*p*
Age	-0.260	0.068	0.055	0.026
Body mass index ($^{-1}$)	0.318	0.101	0.089	0.006*
Waist circumference ($^{-1}$)	0.359	0.129	0.117	0.002*
Systolic blood pressure	-0.121	0.015	0.001	0.309
Diastolic blood pressure	-0.146	0.021	0.008	0.216
High-density lipoprotein cholesterol	0.316	0.100	0.087	0.006*
Low-density lipoprotein cholesterol	-0.091	0.008	-0.006	0.442
fP-glucose (ln)	-0.293	0.086	0.073	0.012
fS-insulin (ln)	-0.362	0.131	0.119	0.002*
HOMA-IR index (ln)	-0.371	0.138	0.125	0.001*
Hs-CRP ($^{-1/4}$)	-0.294	0.086	0.073	0.013
NT-proBNP (ln)	-0.165	0.027	0.014	0.163
Myocardial triglyceride content (ln)	-0.170	0.029	0.015	0.153
Epicardial fat (ln)	-0.137	0.019	0.005	0.247
Pericardial fat (ln)	-0.171	0.029	0.015	0.149
Hepatic triglyceride content (ln)	-0.267	0.071	0.058	0.024
SAT (ln)	-0.320	0.103	0.089	0.007*
VAT (ln)	-0.326	0.107	0.093	0.006*

Abbreviations: LA, left atrial; EF, ejection fraction; fP, fasting plasma; fS, fasting serum; Hs-CRP, high-sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; NT-proBNP, N-terminal pro-brain natriuretic peptide; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue. *$p<0.05$ after adjusting for age

Table 4. Results of stepwise multivariable regression analysis.

Dependent variable: LA EF (3D model)						
	Model 1		Model 2		Model 3	
	β	p	β	p	β	p
Age	-0.112	0.427	-0.164	0.189	-0.172	0.157
Body mass index ($^{-1}$)	0.170	0.324	0.169	0.421	0.318	0.007*
Hepatic triglyceride content (ln)	-0.007	0.973	-0.041	0.826	-0.067	0.698
SAT (ln)	-0.150	0.524	-0.320	0.007*	---	---
VAT (ln)	-0.326	0.006*	---	---	---	---
Adjusted R^2	0.093	0.006*	0.089	0.007*	0.088	0.007*

Abbreviations: LA, left atrial; EF, ejection fraction; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue. *p<0.01

Comparison of LA volume assessment by 3ch prolate ellipsoid method and SA volumetric method

LA measurements obtained with 3ch-based volume assessment correlated highly (r = 0.97 for end diastolic volume (EDV), r = 0.90 for end systolic volume (ESV), and r = 0.93 for EF, *p*<0.001 for all correlations) with volumetric SA-based Simpson's method. Bland-Altman analysis (Figure 3 in supplemental material) demonstrated mean difference of LA EDV -1.06 ±3.60 ml, LA ESV -1.54 ±3.12 ml and EF 0.83 ±3.16 %.

Discussion

To our knowledge, this is the first study utilizing MRI to assess LA function, and to combine the data with MRI and ^{1}H-MRS derived quantification of major ectopic fat depots including all three cardiac fat depots and liver, and a wide range of clinical parameters in subjects with MetS. We found that MetS is associated with subclinical LA dysfunction in male subjects free of cardiovascular disease. Cross-sectional correlation analysis revealed that LA dysfunction is

associated with several contributory factors of MetS including waist circumference, VAT, SAT, insulin resistance, and dyslipidemia.

LA function is important for optimum cardiac performance in three distinct phases. 1) LA serves as a reservoir of pulmonary venous return during LV systole. 2) During LV early diastole, it serves as a conduit and its function is modulated by LV diastolic performance. 3) At the late phase of LV diastole, LA acts as a pump boosting LV filling. In HF, with sustained increases in LV and LA pressure, LA dilatation occurs and LA contractile reserve becomes exhausted. In end-stage HF, this leads to a change of LA to a passive conduit dictated by ventricular distensibility [14]. In AF, the pump function of LA is lost due to dyssynchronous contraction of myocytes.

We found that in MetS, LA function is decreased as measured by LA EF without the enlargement of LA. Notably, our study subjects were asymptomatic and excluded for known heart diseases, including coronary artery disease, AF, and (clinical) heart failure. The decrease in LA EF indicates the presence of LA mechanical remodeling, an entity with increasing interest in the recent literature [10, 15]. When comparing LA measurements to patient outcomes, LA EF was found superior and incremental to LA volume with regard to the assessment of mortality risk in general population [16]. Lower LA EF has also been associated with a poorer prognosis in patients with HF [17] and non-ischemic cardiomyopathies [18]. LA remodeling can be reversible, especially at early stages, and may be treated with medications such as angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists [19]. Echocardiographic studies have also shown improved atrial function with weight loss [20].

Obesity and MetS are well-known risk factors of AF and decreased LA EF has been shown to increase the risk for AF independent of LA size [17, 21]. Among other causes, functional LA remodeling has been suggested as a factor preceding AF. However, the pathophysiological mechanisms of atrial remodeling and development of AF in obesity are complex and remain elusive. They include unfavorable genotype and lifestyle risk factors such as sleep apnea, hypertension, hyperlipidemia, T2DM, alcohol, and smoking, impaired diastolic function causing atrial stretch, focal adiposity, and inflammation resulting in scar tissue [8]. Consequently, structural, functional and electrical changes occur forming the substrate for AF. Evaluating LA function with a relatively simple 3ch CMR method may hence provide valuable clinical information to find particularly those obese persons at risk for developing AF or other cardiovascular events.

In our study, obesity and visceral obesity in particular were associated with LA dysfunction. Interestingly, with the exception of blood pressure, all other components (waist circumference, insulin resistance and dyslipidemia (low HDL)) of MetS were related to LA dysfunction. Waist and VAT were better predictors of LA dysfunction than BMI thus emphasizing the role of visceral obesity in LA remodeling respectively as earlier reported in LV remodeling [5]. In a recent population-based study, LA enlargement was associated with visceral obesity, but LA function was not evaluated [22]. In our study, liver fat was also associated with lower LA EF, but correlation did not remain significant after adjusting for age.

Insulin resistance is a key component of MetS associated with several pathogenetic abnormalities that lead to HF and increase cardiovascular mortality [4]. In our non-diabetic study population, insulin resistance was associated with LA dysfunction as shown by inverse

correlation of blood glucose and insulin levels, and HOMA-IR index with LA EF. Our finding is in line with an earlier MRI study reporting an association of T2DM and lowered LA EF [23]. Mechanisms to explain the role of obesity, insulin resistance or T2DM in cardiac dysfunction are diverse. Those include abnormalities in contractile proteins, impaired relaxation or contraction, impairment of glucose transport, influx of free fatty acids leading to increase of β-oxidation, oxidative stress, and lipotoxicity; impairment of microvascular circulation, and neurohormonal and sympathetic nervous system activation [4]. Neurohormonal abnormalities include imbalance of adipokine production, and overactivity of renin-angiotensin-aldosterone and endocannabinoid system. Adipokines are bioactive substances produced by adipose tissue and they largely function as modulators of inflammation [24]. Visceral obesity in particular leads to the upregulation of proinflammatory adipokines and the downregulation of anti-inflammatory adipokines which contribute to the pathogenesis of cardiovascular diseases. Additionally, renin–angiotensin system is contributor to and target of many components of MetS [4]. At the cardiac level increased angiotensin 2 activity promotes oxidative stress, and at the vascular level angiotensin 2 overproduction from hypertrophic adipocytes in obesity contribute to hypertension.

In our study population, cardiac steatosis was not a key factor of LA dysfunction although association of myocardial TG content with reduced LA EF in 2D model was noted. To our knowledge, there are no earlier ^{1}H-MRS studies where myocardial TG content has been examined in atrial dysfunction or AF. In contrast to other main ectopic fat depots, intramyocytic TG is not a stable deposit of adipose tissue, but a relatively rapidly changing pool of lipids where up to three or four-fold increase has been reported following 48–72 h fasting in lean subjects [25]. In the ventricles, normal heart utilizes fatty acids and glucose as main energy sources with a ratio of 3:1 [26]. In the setting of obesity, the balance is shifted

more towards consumption of fatty acids due to increased β-oxidation [27]. Under aerobic conditions, fatty acid oxidation yields more adenosine triphosphate (ATP) per gram of substrate but takes 10-15% more O_2 per amount of ATP than glucose [28]. During chronic hypoxia and heart failure, ventricular metabolism shifts from fatty acid to glucose utilization. For the atria, substrate preference has not been investigated but it may not differ from that in the ventricles [28]. Analogously, whether the measurement of the myocardial TG content from the ventricular septal wall corresponds to the TG content of the LA myocardium is unclear. Theroretically, myocardial TG content may act ambiguously in obesity-related subclinical atrial dysfunction, as it may increase due to accelerated free fatty acid uptake and β-oxidation, and decrease in response to the higher energy demand, oxidative stress, and increased glycolysis. In conclusion, the dynamical role of intramyocytic lipids will merit further studies.

Limitations

Study population was limited to men to exclude the effects of hormonal variability. As a potential source of bias, MetS subjects were older than controls. According to previous cross-sectional imaging studies in normal population, data concerning LA remodeling in aging is inconsistent. Earlier studies showed no significant influence of age on LA volume and function [29-31] but in recent study by Maceira et al. [32], a mild age influence on LA function was found. In our control population of 40 men, age did not correlate with LA size or function, but we still performed an age-adjustment for the linear regression analyses. Another source of bias is that the measurement of LA volume did not cover the whole volume of LA but was based on a single image plane of 3ch images with the third dimension taken into account by measuring the LA diameter in perpendicular SA plane. Absolute LA

volumes correlated well with those measured from SA images with Simpson's method considered as gold standard in our small study population, but a larger patient cohort incorporating a variety of atrial disease states will be needed to validate our novel method of deriving LA volumes from three-chamber oriented CMR images. Nevertheless, the absolute LA volume values we obtained were comparable to earlier CMR and multidetector computed tomography studies calculated with Simpson's method [31, 33, 34]. Phasic LA function analysis could have been informative to further evaluate the mechanism of atrial dysfunction and remodeling. Due to relatively small sample size high interrelationship of components of MetS limited the assessment of independent predictors of LA remodeling. Finally, due to cross-sectional study design, causal inferences are limited.

Conclusions

MetS associates with subclinical LA dysfunction as demonstrated by decreased LA EF without the enlargement of LA. According to previous knowledge, this represents LA mechanical remodeling that may result to incident of AF, HF or mortality from cardiovascular disease. We found that multiple co-factors of MetS are related to LA dysfunction, notably visceral obesity and insulin resistance. The role of cardiac steatosis in LA dysfunction was not essential and remains to be clarified. Due to the heterogeneous phenotype of MetS patients and multi-factorial mechanisms, risk stratification for obesity cardiomyopathy or HF for individual person remains unclear and merits further studies. In the clinical context, early recognition of obese patients with adverse atrial remodeling may help to focus intervention and improve patient outcome.

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Declarations

Competing interests

None.

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Availability of data

The data that support the findings of this study are available on request from the corresponding author [KN] on reasonable request. The data are not publicly available due to them containing information that could compromise research participant privacy/consent.

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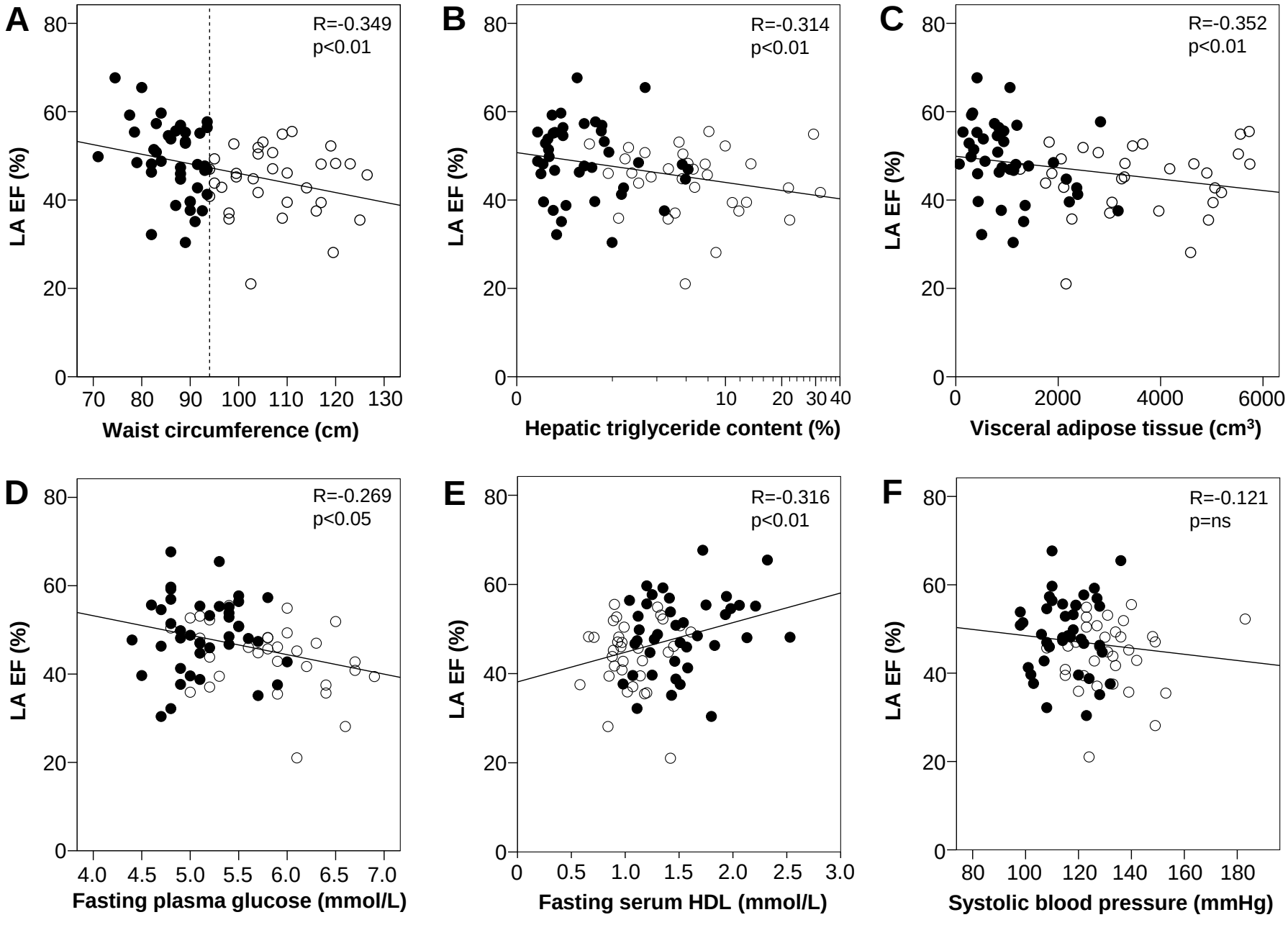
Figure legend

Figure 1. Correlations of left atrial (LA) ejection fraction (EF) with selected contributing factors of metabolic syndrome (MetS). LA EF correlates negatively with **(A)** waist circumference, **(B)** hepatic triglyceride content (logarithmic scale), **(C)** visceral adipose tissue, and **(D)** fasting plasma glucose levels, and positively with **(E)** fasting serum high-density lipoprotein cholesterol (HDL). Correlation of LA EF with **(F)** systolic blood pressure was non-significant. Open circles indicate subjects with MetS and closed circles subjects without MetS. Dashed line **(A)** displays cut-off value (94 cm) of waist circumference for MetS. Abbreviations: EF, ejection fraction; LA, left atrial; HDL, high-density lipoprotein cholesterol.


A
R=-0.349
p<0.01
LA EF (%)
Waist circumference (cm)
B
R=-0.314
p<0.01
LA EF (%)
Hepatic triglyceride content (%)
C
R=-0.352
p<0.01
LA EF (%)
Visceral adipose tissue (cm³)
D
R=-0.269
p<0.05
LA EF (%)
Fasting plasma glucose (mmol/L)
E
R=-0.316
p<0.01
LA EF (%)
Fasting serum HDL (mmol/L)
F
R=-0.121
p=ns
LA EF (%)
Systolic blood pressure (mmHg)

Highlights

- Metabolic syndrome associates with subclinical left atrial dysfunction.
- Multiple components of metabolic syndrome are related to left atrial dysfunction.
- Visceral fat was the best ectopic fat deposit to predict left atrial dysfunction.
- Role of cardiac steatosis in left atrial dysfunction was not essential.