

Significant Association Between Left Ventricular Diastolic Dysfunction, Left Atrial Performance and Liver Stiffness in Patients with Metabolic Syndrome and Non-Alcoholic Fatty Liver Disease

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Purpose: The constitutive elements of the metabolic syndrome (MetS) are linked with both non-alcoholic fatty liver disease (NAFLD) and cardiovascular disease. Controlled attenuation parameter (CAP), and vibration controlled transient elastography (VCTE), are able to detect and quantify NAFLD, while conventional and two-dimensional speckle tracking echocardiography (2D-STE) is capable to identify subclinical changes in cardiac function. We wanted to evaluate whether there is any correspondence between left ventricular (LV) diastolic dysfunction and different degrees of liver steatosis and fibrosis in MetS subjects with NAFLD.

Patients and Methods: A total of 150 adult subjects having MetS and a normal left ventricular (LV) systolic function were recorded in the study, while 150 age- and sex-matched adults without MetS were enrolled as controls. NAFLD was established by VCTE and CAP. The left heart systolic and diastolic function was evaluated by conventional and 2D-ST echocardiography. Left atrial (LA) stiffness was calculated as the ratio between the E/A ratio and the LA reservoir-strain.

Results: In univariate regression analysis, the variables associated with LV diastolic dysfunction in MetS patients were: liver steatosis grade ≥ 2 , liver fibrosis grade ≥ 2 , the longitudinal LA peak strain during the reservoir phase, the LA strain rate during ventricular contraction and the LA stiffness. In multivariate logistic regression, two variables were selected as independent predictors of LV diastolic dysfunction, namely the liver stiffness ($P=0.0003$) and the LA stiffness ($P<0.0001$). LA stiffness predicted subclinical LV diastolic dysfunction in MetS patients with a sensitivity of 45% and a specificity of 96% when using a cut-off value >0.38 , and was significantly correlated with liver steatosis stage ≥ 2 and liver fibrosis stage ≥ 2 .

Conclusion: The present study confirms the association between liver stiffness, LA stiffness and LV diastolic dysfunction in MetS patients. Our study suggests that liver elastography and 2D-STE should become habitual assessments in MetS patients.

Keywords: metabolic syndrome, strain and strain-rate imaging, left atrial stiffness, left ventricular diastolic dysfunction, liver elastography, liver steatosis and fibrosis

Introduction

Metabolic syndrome (MetS) is well-known for the concomitance of numerous cardiovascular risk factors (dyslipidemia, central obesity, hyperglycemia, insulin resistance, and hypertension). It typically marks sedentary, persons,¹ and is linked with an increased probability to develop stroke, diabetes, myocardial infarction, and

heart failure (HF).²⁻⁴ The occurrence of MetS boosted in the last years, endangering the general population's health.

Probably almost 25% of the adult persons have Met.¹ Some clinical researches suggest that MetS is associated with the existence of vascular atherosclerosis and heart failure.⁵ The HF syndrome is like an iceberg, with a visible segment that includes the symptomatic HF patients, and a much bigger invisible ("below the waterline") segment that includes the asymptomatic patients.^{6,7} Early identification of subtle left ventricular (LV) dysfunction in MetS, as well as the understanding of the contribution of all of the MetS elements in disturbing the myocardial structure and function, might improve the risk stratification of cardiovascular disease in MetS subjects. There is a particular connection between the left atrial (LA) performance and the LV function, with the goal to maintain the best possible cardiac work. The LA functions as a pool during the LV systole and isovolumic relaxation, as a drain during early LV diastole, and as a pump during late LV diastole. LA remodeling is associated with LV remodeling.⁸ Several studies suggest a prognostic role of the LA function for cardiac and all-cause deaths.⁹

Non-alcoholic fatty liver disease (NAFLD) became a common health problem due to the rising prevalence of the MetS, its occurrence fluctuating from 25% to 45% in Occidental Europe. This disorder is stated by a storing of lipids, mostly triglycerides, in over 5% of the liver cells, without an excessive alcohol intake or any other secondary cause. NAFLD involves both simple steatosis (a nonthreatening disorder, without hepatocellular injury, liver inflammation, or fibrosis), and nonalcoholic steatohepatitis (NASH). NASH is a more threatening disorder that associates the existence of hepatic steatosis, hepatocellular injury, and inflammation, with or without fibrosis.¹⁰ A recently published meta-analysis stated that 35% of the NASH patients evolve to cirrhosis in around 7 years. But, most NASH patients die because of a cardiac cause, and not because of the complications of liver disease.¹¹

Several studies suggested a relationship between NAFLD and LV dysfunction.^{4-6,12} However, the association between echocardiographically evaluated LA performance and NAFLD severity, demonstrated by liver vibration controlled transient elastography (VCTE) and controlled attenuation parameter (CAP), was not yet studied.

In the present study, we meant to evaluate whether there is any correspondence between LV diastolic dysfunction and different degrees of liver steatosis and fibrosis in MetS subjects. We also wanted to see whether the LA performance could predict LV diastolic dysfunction and might be associated with the extent of NAFLD.

Patients and Methods

Subjects and Methodology

This case-control observational study was achieved from January 2019 to January 2020 in the Department of Cardiology, and in the Department of Gastroenterology and Hepatology of the Victor Babes University of Medicine and Pharmacy, Timisoara. We registered consecutive adult patients with MetS and a normal LVEF scheduled for a medical visit in the Cardiology Department that agreed to be evaluated by liver elastography. The control group consisted of adults with a normal LVEF and no MetS, selected to be sex- and age-matched with the enrolled MetS patients, and willing to participate in this study. The baseline characteristics were compared among the two groups. All subjects were assessed by VCTE, CAP as well as by two-dimensional (2D) conventional and speckle-tracking echocardiography (STE).

Inclusion criteria for the study group were the age ≥ 18 years and the presence of the MetS. Exclusion criteria were: chronic liver illness due to viral infections, excessive alcohol intake (> 20 g/day in women, >30 g/day in men), or use of drugs; systolic heart failure (LV ejection fraction $\leq 50\%$); heart failure with preserved LVEF, identified by NT-proBNP levels ≥ 220 pg/mL,¹³ known ischemic heart disease; a history of/or atrial fibrillation/atrial flutter on the initial electrocardiogram; moderate or severe valvular heart disease; cardiomyopathies; cardiac pacemakers; peripheral artery disease; a history of stroke; severe systemic illness or malignancy; chronic renal failure; pregnancy or lactation.

The diagnosis of MetS was stated on the 2006 IDF criteria: central obesity (waist circumference ≥ 94 in men and ≥ 80 cm in women), associated with any two of the following criteria: raised fasting plasma glucose (FPG) ≥ 100 mg/dL or treatment of previously diagnosed type two diabetes; increased triglyceride level ≥ 150 mg/dL or specific treatment for this lipid abnormality; reduced high-density lipoprotein cholesterol $<40/50$ mg/dL (men/women) or a treatment specific for this lipid abnormality; systolic BP (SBP) ≥ 130 or diastolic BP (DBP) ≥ 85 mmHg or treatment of previously diagnosed hypertension.¹⁴

Clinical Assessment

All patients were thoroughly examined and all the data were registered in the hospital records, which were used as a data source.

Smoking status was stated as current smoking or no smoking. Hypertension was established according to the

2018 ESC/ESH Guidelines for the management of arterial hypertension as a BP > 140/90 mmHg and/or current antihypertensive therapy.¹⁵ A 12-lead resting electrocardiogram (ECG) and laboratory tests were performed in all patients at the initiation of the study, before the liver and heart ultrasound examinations. Diabetes was identified in the presence of a FPG ≥ 126 g/mL or current treatment with insulin and/or an oral hypoglycemic agent.¹⁴

Vibration Controlled Transient Elastography (VCTE) and Controlled Attenuation Parameter (CAP) Measurements

VCTE was performed after an over 4 hours fasting period, by means of a FibroScan[®] device (EchoSens, Paris, France), by the same investigator. According to the European recommendations, the M/3.5 MHz or the XL/2.5 MHz transducer was used.¹⁶ The examiner performed ten liver stiffness measurements (LSM) in each patient, and their median value was computed. Trustworthy measurements were regarded as those having a median value with an interquartile range interval/median ratio lower than 30%.¹⁷ The LSM was stated in kilopascals (kPa). In order to differentiate the stages of fibrosis, we used the following VCTE cut-offs: F ≥ 2 : 8.2 kPa; F ≥ 3 : 9.7 kPa; and F4: 13.6 kPa.¹⁸ In order to separate the stages of steatosis, we used the following CAP cut-offs: S1 (mild) – 274 dB/m, S2 (moderate) – 290 dB/m, S3 (severe) – 302 dB/m.¹⁸

Conventional echocardiography was performed by the same investigator using a VIVID-5S, G.E. phased array ultrasonic scope with a 3.5 MHz transducer. The diameters of cardiac chambers were measured according to the American Society of Echocardiography guidelines.¹⁹ LV and LA volumes were calculated from the 4- and 2-chamber apical views and the ejection fractions were calculated using the biplane Simpson method. The LV diastolic function was evaluated using the pulsed Doppler examination in the 4- and 2-chamber apical view by placing the sample volume at the tip of the mitral leaflets. We measured the peak E (maximal protodiastolic velocity of the transmitral flow), the peak A (maximal telediastolic velocity), the E/A ratio, and the isovolumic relaxation time (IVRT). The cut-off values for LV diastolic dysfunction were E/A <0.8 and IVRT >100 msec; for LV systolic dysfunction: FEVS <50%. The LA maximum diameter was measured in the parasternal long-axis view. The maximal LA volume (LAVmax) was measured in the apical 4- and 2- chamber views, at the end of the T wave on

the ECG, just before the opening of the mitral valves (OMV). The minimal LA volume (LAVmin) was measured in the early phase of the ventricular diastole, at the end of the QRS complex, just after the closure of the mitral valves (CMV). The LA pre-atrial contraction volume (LAV-preA) was measured in the late phase of the ventricular diastole, at the onset of the P wave on the ECG. The values obtained from the two views were averaged; the difference between LAVmax and LAVmin represents the total LA stroke volume (tLASV). The difference between LAVmax and LAVpreA represents the passive LA stroke volume (pLASV), while the difference between LAV-preA and LAVmin represents the active LA stroke volume (aLASV). LA total ejection fraction (tLAEF, %) was calculated according to the formula $100 \times [\text{LAVmax} - \text{LAVmin}] / \text{LAVmax}$ and reflects the LA pool function; LA active ejection fraction (aLAEF, %) was calculated by the formula $100 \times [\text{LAVpreA} - \text{LAVmin}] / \text{LAVpreA}$ and reflects the LA pump function. LA passive ejection fraction (pLAEF, %) was calculated with the formula $100 \times [\text{LAVmax} - \text{LAVpreA}] / \text{LAVmax}$ and reflects the LA conduit (drain) function.^{19,20}

LA 2D- speckle tracking imaging (STI) was assessed by using the available Vivid EchoPAC software (GE Medical System) using a frequency set between 60 and 90 frames/s. Three consecutive cardiac cycles during breath-hold were recorded in LA focused 4- and 2- chamber apical views. The analysis of the images was performed offline. The LA endocardium and epicardium were automatically tracked and manually corrected. The LA was automatically divided into 6 segments. We evaluated the following parameters: the LA peak strain during the reservoir phase: just before the OMV (LAS-pool) and the LA peak strain during the pump phase (LAS-pump): at the onset of the P wave, as shown in Figure 1. The LA conduit strain was assessed as the difference between the calculated LA pool and pump strains. LA stiffness was calculated as the ratio of the E/A value to the LAS- pool. We also evaluated the LA peak strain rate (SR) during ventricular systole (LASR-v), the LA peak SR during early ventricular diastole (LASR-e), and the LA peak SR during late ventricular diastole/pre-atrial contraction (LASR-a). The data obtained from the two apical views were averaged.^{20–22} The patients with inadequate echocardiographic image quality were omitted from the study.

Ethics

Written informed consent was attained from all study participants. The study was done accordingly to the

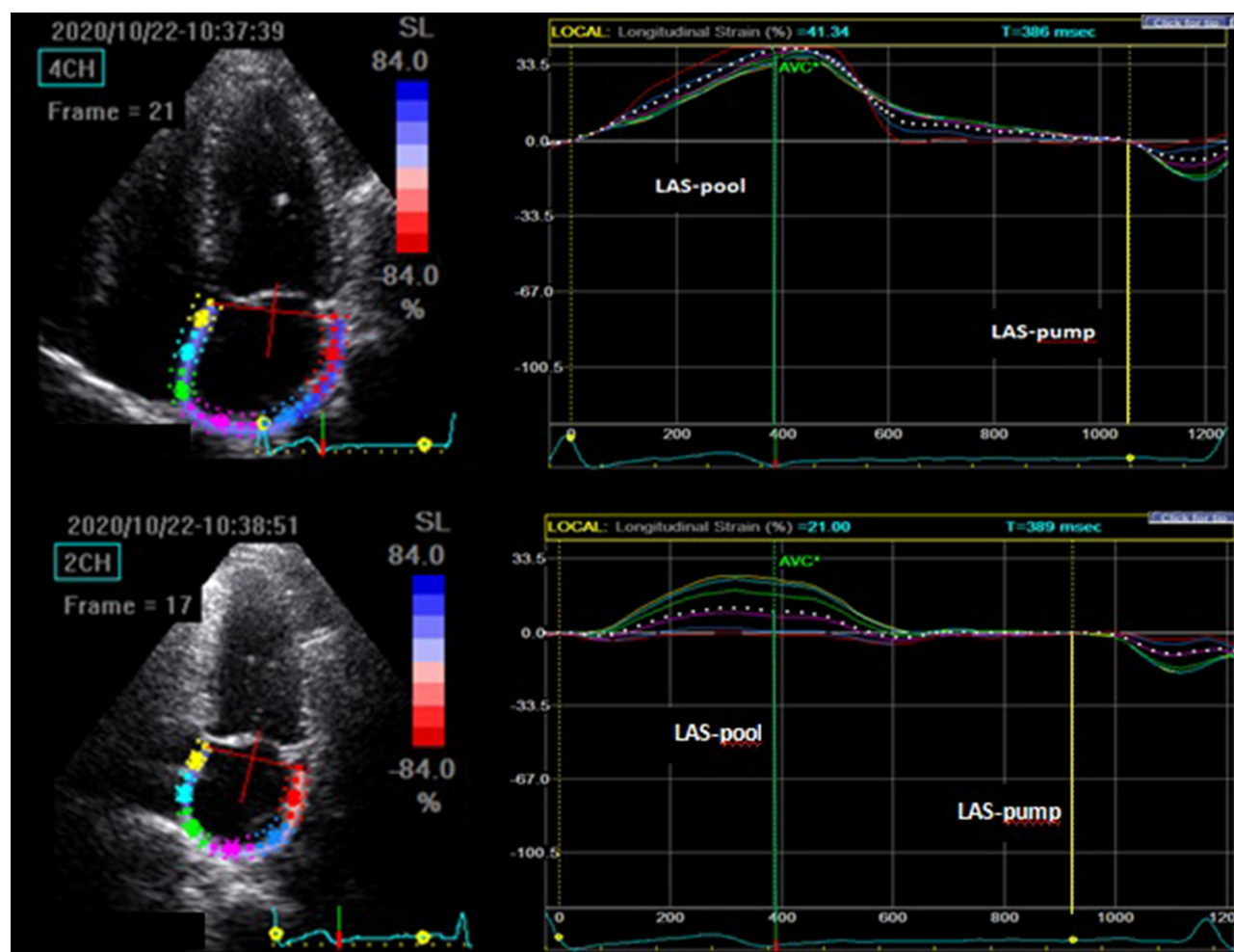


Figure 1 Two-dimensional speckle tracking echocardiography of the left atrium.
Abbreviation: LAS, left atrial longitudinal strain.

demands of the Human Rights Declaration of Helsinki and was approved by the Ethics Committee of the “Victor Babeș” University of Medicine and Pharmacy Timișoara.

Statistical Analysis

Statistical analysis was accomplished using the 19.6 version of the MedCalc statistical software (Belgium). Continuous data were given as mean \pm 1 standard deviation (SD). Categorical variables were given as numbers and percentages. The differences between the groups were compared using the paired *t*-test. The association between variables was measured using Pearson’s correlation coefficient. The factors significantly associated with LA dysfunction underwent univariate and multivariate logistic regression analysis. The identified independent predictors were compared using the receiver operating characteristic (ROC) curves. Values of $P < 0.05$ were considered statistically significant for all tests.

Reproducibility

The study was performed by one echocardiographer and one sonographer. For intra-observer reproducibility, the intra-class correlation coefficient (ICC) was calculated and showed a good intra-observer agreement. The ICC was 0.88 (95% CI 0.81–0.92) for echocardiography and 0.85 (95% CI 0.77–0.90) for liver ultrasonography.

Results

Of the 208 MetS subjects initially evaluated, 30 (16%) were excluded because of improper quality of the echocardiographic images, and 28 (15%) were removed because of validation failing at CAP and VCTE.

Finally, 150 MetS subjects were enrolled in the research group and 150 age- and sex- corresponding subjects without MetS were included in the control group. The baseline characteristics of the two groups are shown in

Table 1. The age of the subjects varied from 31 to 85 years (mean 62.4 ± 10 years). The frequency distribution of age is presented in [Figure 2](#). 164 subjects (54%) were males. We noted no significant differences among the two groups regarding the heart rate, the smoking status, the serum transaminase, and the low-density lipoprotein (LDL)-cholesterol levels. MetS patients were significantly more frequent hypertensive, diabetics obese. They presented higher values of triglycerides, glycosylated hemoglobin (HbA1c), FPG, and lower values of total cholesterol and of high-density lipoprotein (HDL) cholesterol.

The MetS patients had the following distribution of steatosis severity assessed by CAP: 21 (14%) –S0, 11 (7%) – S1, 11 (7%)–S2, and 107 (71%) – S3. Both liver steatosis and fibrosis were frequent and more severe in the MetS group ($P < 0.0001$, respectively $P = 0.04$), as shown in [Table 2](#).

Echocardiography data are shown in [Table 3](#). There were no significant differences between the two groups concerning the conventional parameters of LV structure and systolic function, but significantly more of the MetS patients presented LV diastolic dysfunction. We found no differences regarding the LA diameters, volumes and ejection fractions between the MetS patients and the controls.

By contrast, the 2D-STE identified subtle LA dysfunction in the MetS subjects, revealed by significant lower longitudinal strains and strain rates during the ventricular contraction, the ventricular early diastolic filling and the atrial contraction. LA stiffness was significantly higher in the MetS subjects ($P < 0.0001$).

In univariate regression analysis, the variables associated with LV diastolic dysfunction in MetS patients were: liver steatosis grade ≥ 2 , liver fibrosis grade ≥ 2 , the longitudinal LA peak strain during the reservoir phase, the LA strain rate during ventricular contraction and the LA stiffness. In multivariate logistic regression, two variables were selected as independent predictors of LV diastolic dysfunction, namely the liver stiffness ($P = 0.0003$) and the LA stiffness ($P < 0.0001$), as shown in [Table 4](#). The adjusted variable in multivariate analysis was the presence of the metabolic syndrome.

The associations between the independent variables linked with LV diastolic dysfunction in MetS patients are presented in [Figure 3](#).

LA stiffness predicted subclinical LV diastolic dysfunction in MetS patients with a sensitivity of 45% and a specificity of 96% when using a cut-off value > 0.38 .

When comparing the receiver operating characteristics (ROC) curves of the two independent predictors of LV

Table 1 Clinical and Biochemical Characteristics of MetS and Control Groups

	With MetS (n=150)	Controls (n=150)	P value
Age (years)	62.4 ± 10	62.4 ± 10	1
Male sex n (%)	78 (52%)	78 (52%)	1
Systemic hypertension (n, %)	120 (80%)	68 (45%)	<0.0001
Diabetes mellitus (n, %)	134 (89%)	36 (24%)	<0.0001
Smoking (current, %)	15 (10%)	18 (12%)	0.58
Systolic BP (mmHg)	141.6 ± 18	131.27 ± 12	<0.0001
Diastolic BP (mmHg)	84.6 ± 11	73.23 ± 6.97	<0.0001
Heart rate (beats/min)	75.6 ± 11.4	73.11 ± 10.8	0.05
BMI (kg/m ²)	32.7 ± 5.2	26.7 ± 2.1	<0.0001
Weight (kg)	91 ± 7	77 ± 9	<0.0001
Waist circumference (cm)	112 ± 13	97.00 ± 4	<0.0001
Total cholesterol	174 ± 39	197 ± 44	<0.0001
HDL (mg/dL)	45.2 ± 12.7	48.3 ± 13	0.03
LDL (mg/dL)	109.4 ± 33	110.5 ± 32	0.76
Triglyceride (mg/dL)	159.1 ± 89.5	134.4 ± 80.4	0.01
FPG (mg/dL)	130 ± 42	109 ± 12	<0.0001
HbA1c	7.1 ± 0.9	5.2 ± 0.8	<0.0001
ASAT	24 ± 9	23 ± 5	0.23
ALAT	37 ± 7	36 ± 5	0.15
NT-proBNP	97 ± 19	96 ± 15	0.61

Notes: Data are expressed as mean \pm SD or number (percentage). Statistically significant values are highlighted in bold ($P < 0.05$).

Abbreviations: MetS, metabolic syndrome; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; ASAT, aspartate amino transferase; ALAT, alanine amino transferase.

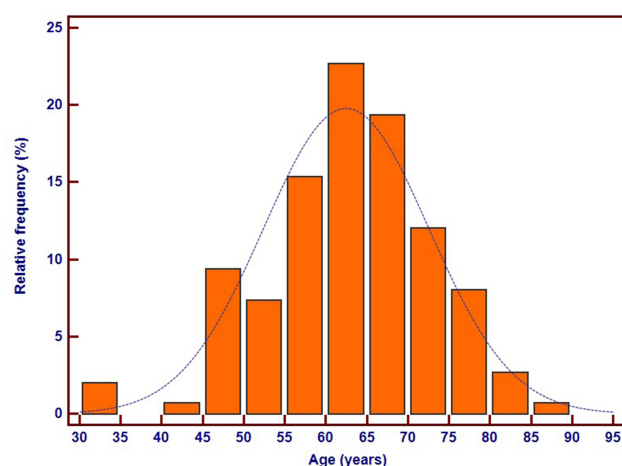


Figure 2 Frequency distribution of age in metabolic syndrome patients.

diastolic dysfunction, we found that the area under the curve (AUC) was slightly greater for the LA stiffness than for the liver stiffness measurement ≥ 2 , but the difference was not significant (Figure 4).

LA stiffness >0.38 was present in 36 (24%) of the MetS patients and in 12 (8%) of the control group subjects ($P<0.0001$). The relative risk of the MetS patients to have a $LA_{sf} > 0.38$ was 3.0 when compared to the control group (AUC=0.666, 95% CI 1.62 to 5.53, $P<0.001$). The $LA_{sf} > 0.38$ was positively associated with a liver fibrosis stage $F \geq 2$ ($r=0.59$, 95% CI 0.51 to 0.66, $P<0.0001$) and a liver steatosis stage $S \geq 2$ ($r=0.42$, 95% CI 0.32 to 0.51, $P<0.0001$).

Discussion

There is increasing evidence regarding the impact of the MetS on the left heart structure and function. Every constituent of the MetS is known to induce LV myocardial fibrosis. The same fibrotic changes were found in the myocardial walls of the LA and LV, consequent to the MetS components such as obesity, diabetes, and hypertension.^{23–25} While myocardial fibrosis progresses, diastolic compliance of the LV decreases and LV filling pressures increase, influencing the LA function. Galderisi²⁶ found an association between insulin resistance and LV diastolic parameters in hypertensive patients. Diabetes mellitus patients with a normal LV systolic function, with or without hypertension, were found to have had lower peak LA strains and strain rates than the controls.²⁴

The reported prevalence of LV diastolic dysfunction is 16% in the general population, 35% in individuals with metabolic syndrome, and 50% in individuals with prediabetes and overt type 2 diabetes.^{4,27} In our study, the prevalence of LV diastolic dysfunction was 52% in the MetS patients and 39% in the control group. The higher prevalence of the LV diastolic dysfunction could be explained by the fact that 89% of the MetS patients had diabetes and 80% were hypertensive.

The confirmation of cardiac dysfunction in persons with MetS was first done by clinical investigations applying conventional and tissue Doppler echocardiography.¹⁹ These methods proved to have several limits in assessing

Table 2 Evaluation of Liver Fibrosis and Steatosis

	MetS (n=150)	Controls (n=150)	P value
CAP, dB/m	335.2 \pm 51.2	255.56 \pm 60.8	<0.0001
Steatosis stage			
S0	21 (14%)	95 (63%)	<0.0001
S1	11 (7%)	15 (10%)	0.35
S2	11 (7%)	3 (2%)	0.03
S3	107 (71%)	37 (25%)	<0.0001
LSM, kPa	7.24 \pm 3.25	6.52 \pm 2.85	0.04
Fibrosis stage			
F0-I	87 (58%)	118 (79%)	0.0001
F2	28 (19%)	11 (7%)	0.002
F3	20 (13%)	14 (9%)	0.26
F4	15 (10%)	8 (5%)	0.10

Notes: Data are expressed as mean \pm SD or number (percentage). Statistically significant values are highlighted in bold ($P<0.05$).

Abbreviations: MetS, metabolic syndrome; CAP, controlled attenuation parameter; LSM, liver stiffness measurements; S, steatosis; F, fibrosis.

Table 3 Left Ventricular Echocardiographic Data in MetS and Control Groups

	MetS (n=150)	Controls (n=150)	P value
Conventional echocardiography			
LV End DD (mm)	49.00±3.20	48.69±2.94	0.38
LV End SD (mm)	30.34±2.50	29.85±2.68	0.10
LA diameter (mm)	3.34±0.36	3.27±0.38	0.10
LVEF (%)	51.7±0.6	51.8±0.2	0.05
LVFS (%)	37.93±2.91	38.00±3.50	0.85
E (m/s)	0.69±0.15	0.88±0.12	<0.0001
A (m/s)	0.89±0.17	0.61±0.10	<0.0001
E/A ratio	0.81±0.21	1.47±0.23	<0.0001
IVRT (msec)	110.1±18	105.3±21	0.02
LV diastolic dysfunction (n, %)	78 (52%)	59 (39%)	0.02
LA volumes (mL)			
Maxim	27.3±5.2	26.6±5.7	0.26
Pre-atrial contraction	17.7±5.1	18.0±4.5	0.58
Minim	11.50±4.2	12.16±3.5	0.14
LA ejection fraction (%)			
Total	58.2±4.0	57.8±3.4	0.35
Passive	37.9±4.7	38.8±3.9	0.07
Active	35.6±15.0	33.4±12.3	0.16
2D Speckle tracking echocardiography			
LAS-pool (%)	44.0±4.6	47.4±3.5	<0.0001
LAS-pump (%)	17.4±2.3	19.7±1.8	<0.0001
LASR-v (1/sec)	1.3±0.5	3.2±1.2	<0.0001
LASR-e (1/sec)	-1.0±0.3	-1.5±0.5	<0.0001
LASR-a (1/sec)	-1.5±0.7	-1.4±0.6	0.18
LA stiffness	0.34±0.12	0.20±0.04	< 0.0001

Notes: Data are expressed as mean ± SD or number (percentage). Statistically significant values are highlighted in bold ($P < 0.05$).

Abbreviations: MetS, metabolic syndrome; LV, left ventricle; End SD, end systolic diameter; End DD, end diastolic diameter; LA, left atrium; EF, ejection fraction; FS, fractional shortening; E, protodiastolic filling wave; A, end diastolic filling wave; IVRT, isovolumic relaxation time; LA, left atrium; 2D, two dimensional; LAS, left atrial longitudinal strain; LASR-v, left atrial longitudinal strain rate during ventricular contraction; LASR-e, left atrial longitudinal strain rate during ventricular passive filling in early diastole; LASR-a, left atrial longitudinal strain rate during pre-atrial contraction.

cardiac function, such as the poor sensitivity, the angle dependency, and the inability to reveal subtle declines in myocardial contractility. Two-dimensional speckle-tracking echocardiography (2D-STE) proved to be a more trustworthy manner for the recognition of emerging ventricular dysfunction, by using a quantitative assessment of myocardial deformation.²⁸ 2D-STE was lately used for the assessment of the atrial performance too, permitting a precise, angle free assessment of the atrial deformation.²⁹

A fundamental notion of speckle-tracking imaging is represented by the strain, measured as a percentage (%) and stated as the fractional shortening of a myocardial segment. The strain can be measured in every segment of the heart chamber (regional strain). The average of all these findings results in the peak strain (PS), signifying the peak ventricular performance.²⁸

LA dysfunction could have an important role in the pathophysiology of heart failure with preserved LV

Table 4 Correlations Between LV Diastolic Dysfunction and 2D-Speckle Tracing Parameters of the Left Atrium

Variable	Univariate Analysis			Multivariate Analysis		
	β	SE	P	β	SE	P
Liver steatosis \geq S2	0.84	0.25	<0.001	-0.56	0.37	0.12
Liver fibrosis \geq F2	2.04	0.29	<0.0001	1.38	0.38	0.0003
LAS-pool	-0.05	0.02	0.04	0.01	0.03	0.68
LAS-pump	-0.04	0.04	0.43			
LASR-v	-0.21	0.09	0.01	0.20	0.11	0.07
LASR-e	-0.36	0.25	0.15			
LA stiffness	9.23	1.30	<0.0001	8.29	1.81	<0.0001

Notes: Statistically significant values are highlighted in bold ($P < 0.05$). The adjusted variable in multivariate analysis was the presence of the metabolic syndrome.

Abbreviations: LA, left atrium; LAS, left atrial longitudinal strain; LASR-v, left atrial longitudinal strain rate during ventricular contraction; LASR-e, left atrial longitudinal strain rate during ventricular passive filling in early diastole.

ejection fraction (HFpEF).³⁰ LA strain values are related to invasively determined LV filling pressures. They decrease gradually with increasing LV diastolic dysfunction grades and could be used to detect and evaluate the severity of LV diastolic dysfunction.³¹

As the diastolic and systolic heart failure patients have similar mortality risk rates, it is of vital importance to detect early, preclinical changes in cardiac function and to implement optimal therapeutic strategies.³² It was demonstrated that functional remodeling is preceding the structural remodeling consisting of the dilatation of the cardiac chamber.^{20,30} Accordingly, although in our study the LA diameters, volumes, and ejection fractions between the MetS subjects and the controls did not differ significantly, the 2D-STE measured LA deformation, evaluated

by the peak LA strains and strain rates was significantly impaired in the presence of the MetS ($P < 0.0001$).

As already established, the LA reservoir strain is significantly associated with the degree of LA myocardial fibrosis evaluated by cardiac magnetic resonance imaging or by histopathology sampling,^{33,34} and it is significantly linked with the invasively quantified LV filling pressure. Its predictive capacity for cardiovascular events is superior to that of the LA maximal volume.⁹ But, its diagnostic and predictive abilities are exceeded by another parameter that evaluates the LA structure and function- the LA stiffness. This factor indicates the adjustment in LA pressure needed to expand the LA

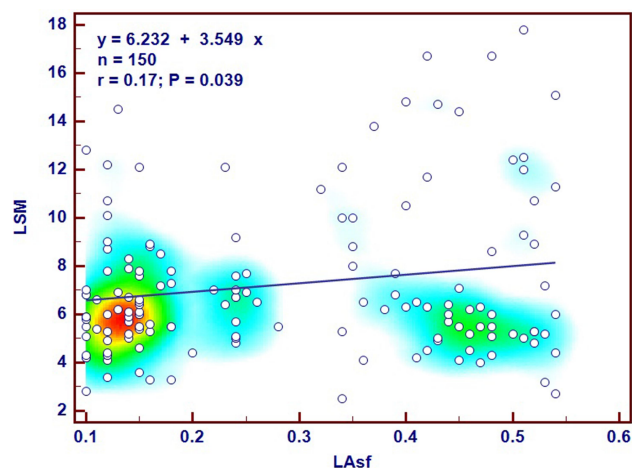


Figure 3 Correlations between the independent variables associated with subclinical LV diastolic dysfunction in metabolic syndrome patients.

Abbreviations: LSM, liver stiffness measurement; LASf, left atrial stiffness; AUC, area under the curve.

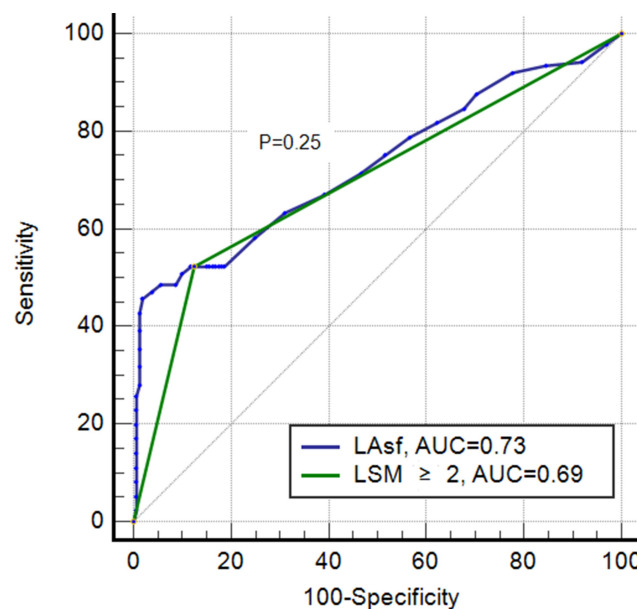


Figure 4 Comparison of the receiver operating characteristics (ROC) curves of the independent variables associated with subclinical LV diastolic dysfunction in metabolic syndrome patients.

Abbreviations: MetS, metabolic syndrome; LASf, left atrial stiffness; LSM, liver stiffness measurement; AUC, area under the curve.

volume to a certain degree.^{30,31,35} Kurt showed that LA stiffness can be used to discriminate between HF with preserved LVEF and asymptomatic LV diastolic dysfunction.³⁶ LA stiffness also proved to have a superior correlation with the extent of LA fibrosis than the LA strain.³⁴ The fact that two variables that are obtained with different echocardiographic techniques, and point toward the LV filling pressure, are used to calculate LA stiffness, might justify the diagnostic accuracy of the LA stiffness. We found that LA stiffness was superior to LA volume and LA strain parameters in identifying subclinical LV diastolic dysfunction and that this parameter was significantly correlated with a liver stiffness measurement ≥ 2 . In our study, analyzing the ROC curve of the LA stiffness predictive capacity for LV diastolic dysfunction in MetS subjects, we found that the cut-off value of 0.38 had a high specificity (96%) and a sensitivity of 45%, completing the echocardiographic requirements to avoid false-positive statements.³⁷ 12% to 16% of the NAFLD patients die due to coronary artery disease (CAD), while the CAD-related mortality is only 1–3% in those without NAFLD.³⁸ This finding suggests a solid link between NAFLD and CVD mortality. This association could be clarified by several possible theories. A possible explanation could be the fact that NAFLD is associated with myocardial insulin resistance,³⁹ as well as with impaired cardiac structure and function.⁴⁰ Several studies pointed to the impact of the NAFLD on LV diastolic dysfunction.^{40–42} Fotbolcu reported abnormal LV diastolic function in non-hypertensive and non-diabetic NAFLD subjects.⁴³ Another study revealed impaired LV diastolic function, demonstrated by cardiac ultrasound imaging; in obese adolescents with NAFLD.⁴⁴ Cardiac magnetic resonance imaging exposed decreased myocardial strains and LV diastolic dysfunction in adult subjects with NAFLD and without a known cardiac disorder.⁴⁵ Despite the evidence that subjects with NAFLD are exposed to LV structural abnormalities and diastolic dysfunction, the link between myocardial and hepatic fibrosis was not yet confirmed because of the inadequate utilization of ultrasonography and computed tomography. Our study participants were thoroughly investigated by liver CAP and VCTE and to identify and grade liver steatosis and fibrosis, and by conventional and 2D-STE for cardiac structural and functional assessment. The present study confirmed the association between liver fibrosis ≥ 2 stiffness and left ventricular diastolic dysfunction in MetS patients. The MetS patients in our study had a 3 fold higher risk for having an increased LAsf when compared to the control group ($P < 0.001$). The increased LAsf is another parameter indicating LV diastolic dysfunction. A LAsf > 0.38 was positively

associated with a liver fibrosis stage $F \geq 2$ and a liver steatosis stage $S \geq 2$ ($P < 0.0001$).

Early recognition of both heart and liver disorders in MetS subjects is extremely important, as suitable life-style changes and medical therapy might prevent or at least delay the occurrence of heart failure and of liver cirrhosis. These measures might decrease morbidity and mortality, as well as the expenses to cover the health assurance.

Limitations

The evaluation of liver involvement was performed non-invasively, although liver biopsy is the gold standard assessment method. CAP, VCTE, and STE trustworthiness are dependent on image quality. LA stiffness is a valuable parameter in LV diastolic evaluation, but its cut-off values need to be validated in more numerous and larger patient cohorts.

Conclusion

In MetS patients, the LV diastolic dysfunction, assessed by conventional echocardiography, was significantly and independently associated with a hepatic fibrosis stage ≥ 2 . Another predictor of the LV diastolic dysfunction, the LA stiffness, assessed by b2D-STE, was independently associated with both liver steatosis stage ≥ 2 and liver fibrosis stage ≥ 2 . Our study suggests that that CAP, VCTE, and 2D-STE should become habitual assessment in MetS patients. The newer parameters resulting from STE have shown better sensitivity than the conventional ones, and a significant correlation with liver stiffness.

Disclosure

Prof. Dr. Ioan Sporea reports personal fees from General Electric, Philips, Siemens, Toshiba/Canon, outside the submitted work. The authors report no other conflicts of interest in this study.

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