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Impairment of the left ventricular systolic and diastolic function in patients with non-alcoholic fatty liver disease

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Abstract

Background: *Non-alcoholic fatty liver disease (NAFLD) is considered the liver component of the metabolic syndrome. We investigated the diastolic and systolic functional parameters of patients with NAFLD and the impact of metabolic syndrome on these parameters.*

Methods: *Thirty-five non-diabetic, normotensive NAFLD patients, and 30 controls, were included in this study. Each patient underwent transthoracic conventional and tissue Doppler echocardiography (TDI) for the assessment of left ventricular (LV) diastolic and systolic function. Study patients were also evaluated with 24-hour ambulatory blood pressure monitoring.*

Results: *NAFLD patients had higher blood pressures, increased body mass indices, and more insulin resistance than controls. TDI early diastolic velocity (E' on TDI) values were lower in NAFLD patients than the controls (11.1 ± 2.1* vs *15.3 ± 2.7; $p < 0.001$). TDI systolic velocity (S' on TDI) values were lower in NAFLD patients than the controls (9.34 ± 1.79* vs *10.6 ± 1.52; $p = 0.004$). E' on TDI and S' on TDI values were moderately correlated with night-systolic blood pressure, night-diastolic blood pressure, and night-mean blood pressure in NAFLD patients.*

Conclusions: *Patients with NAFLD have impaired LV systolic and diastolic function even in the absence of morbid obesity, hypertension, or diabetes.* (Cardiol J 2010; 17, 5: 457–463)

Key words: left ventricular function, non-alcoholic fatty liver disease, echocardiography

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the commonest cause of chronic liver disease [1, 2] and is associated with significant liver-related morbidity and mortality in population-based studies [3]. NAFLD is usually associated with obesity [4, 5], diabetes [6–8], dyslipidemia [6, 9–11], and insulin resistance [11–15]. NAFLD is the hepatic manifestation of the metabolic syndrome.

Metabolic syndrome is prevalent in the general population (approximately 22%) and is associated with increased cardiovascular morbidity and mortality [16, 17]. Recent studies have demonstra-

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ted a high prevalence of left ventricular (LV) remodeling and diastolic dysfunction in patients with metabolic syndrome [18–21]. However, these studies included patients with obesity and/or hypertension which are independent risk factors for diastolic dysfunction. Therefore, it is unclear whether impaired diastolic function and the changes in the cardiac structure are the consequence of hypertension and/or obesity or the effect of insulin resistance on the myocardium [22–24]. Currently, there are scarce data on alterations in LV structure and function in non-diabetic, normotensive patients with metabolic syndrome. In this study, we investigated LV systolic and diastolic function with echocardiography in normotensive, non-diabetic patients with NAFLD.

Methods

Thirty-five patients who were diagnosed with NAFLD by abdominal ultrasonography, and 30 healthy controls, were included in this study. The control group had completely normal ultrasonographic findings of the liver. Patients were consecutively enrolled from hospital admissions between December 2007 and April 2008. Patients with high blood pressure during the enrollment (mean value of three consecutive measurements done at five minute intervals ≥ 140/90 mm Hg) or those on any antihypertensive medication or with a high fasting blood glucose level (≥ 110 mg/dL) were excluded from the study. The following subjects were also excluded from this study: patients with diabetes mellitus, hypertension, severe morbid obesity [body mass index (BMI) > 35], stage > three chronic kidney disease, moderate or severe heart valve insufficiency, congenital heart disease, atrial fibrillation, established coronary artery disease (CAD), (patients who had history of myocardial infarction, unstable angina pectoris, angiographically proven significant coronary stenosis or had undergone revascularization), left ventricular ejection fraction < 40%, symptomatic heart failure, hemachromatosis, alpha1-antitrypsin deficiency, Wilson's disease, or autoimmune liver disease. In addition, patients with a history of chronic alcoholism or alcohol consumption greater than 200 g/week, with hepatitis B or C, or on medications that might affect liver function tests were excluded from the study. Subjects who refused to participate in the study were also excluded. All subjects gave informed consent and the study was approved by the local ethics committee.

Currently, abdominal ultrasound is the preferred method for qualitative assessment of fatty infiltration of the liver. All study subjects underwent abdominal ultrasonography using a GE Logiq 500 device with a 7 MHz linear transducer (GE Medical Systems, Milwaukee, Wisconsin, USA). We used Hamaguchi et al's [25] scoring system based on hepatorenal echo contrast, liver brightness and deep attenuation, and vascular blurring criteria was used for the evaluation of NAFLD. Patients with a score ≥ 2 were labeled as NAFLD, and those with a score of zero were included in the control group.

All study patients underwent a thorough clinical, anthropometric, and laboratory investigation. Laboratory tests included hepatitis serology, liver function tests, fasting lipid profile, plasma glucose, insulin, and C-peptide. Insulin resistance (IR) was estimated using the homeostasis model assessment (HOMA-IR) according to the formula: HOMA-Index = fasting blood glucose [mg/dL] × immunoreactive insulin [μU/mL]/405 [26].

The height and weight of all subjects were measured and the BMI was calculated as weight [kg] divided by height^2 [m]. Waist circumference (WC; at the nearest half centimeter) was measured at the mid-point between the lower border of the rib cage and the iliac crest.

The echocardiographic examinations and the ambulatory blood pressure (BP) monitoring were performed on the same day for each patient. Twenty-four-hour ambulatory blood pressure monitoring (ABPM) was performed with a non-invasive recorder Tracker NIBP2 (Del Mar Reynolds Medical Ltd., Hertford, UK). Blood pressure readings were obtained automatically at 15 minute intervals from 6 am to 11 pm and at 30 minute intervals from 11 pm to 6 am. Average diastolic (DBP) and systolic (SBP) blood pressure over 24 hours, and average daytime and nighttime BP were calculated.

Echocardiographic measurements

All echocardiographic and Doppler assessements were performed by one operator, who was blinded for the clinical and laboratory results of the study group. Vivid 7 Dimension echocardiography equipment (GE, Vingmed, Horten, Norway) with a 2.5 MHz phased-array transducer was used for each study subject. Left ventricular dimension and wall thickness was measured from two-dimensional guided M-mode echocardiographic tracings at mid-chordal level on the parasternal long axis view. The M-mode traces were recorded at a speed of 50 mm/s. Ejection fraction was calculated using the Teicholz formula. The left ventricular mass (LVM) was estimated by using the anatomically validated formula of Devereux et al. [27]. It was indexed for body surface area to estimate the LVM index (LVMI).

Table 1. Clinical and biochemical characteristics of the study population.

Variables	NAFLD-patients (n = 35)	Controls (n = 30)	P
Age (years)	41.40 ± 6.25	39.20 ± 6.04	0.156
Sex (female)	14 (40%)	13 (43.3%)	0.545
Body mass index [kg/m^2]	30.44 ± 3.45	25.20 ± 1.63	< 0.001
Waist circumference [cm]	106.97 ± 8.99	92.67 ± 6.95	< 0.001
Fasting glucose [mg/dL]	97.94 ± 11.46	90.73 ± 5.91	0.003
Total cholesterol [mg/dL]	210.06 ± 41.16	199.93 ± 30.15	0.269
LDL-cholesterol [mg/dL]	128.49 ± 32.59	129.13 ± 27.38	0.932
HDL-cholesterol [mg/dL]	43.11 ± 7.89	46.87 ± 6.30	0.040
Triglycerides [mg/dL]	194.54 ± 94.38	111.07 ± 43.85	< 0.001
VLDL [mg/dL]	38.86 ± 18.80	22.40 ± 8.81	< 0.001
AST [U/L]	33.23 ± 13.33	23.07 ± 5.82	< 0.001
ALT [U/L]	66.57 ± 36.79	28.47 ± 12.89	< 0.001
ALP [U/L]	188.51 ± 48.65	195.40 ± 35.29	0.522
Fasting insulin [μU/mL]	14.75 ± 5.72	5.73 ± 1.23	< 0.001
C-peptide [ng/mL]	3.34 ± 1.28	1.74 ± 0.44	< 0.001
HOMA-IR	3.59 ± 1.51	1.28 ± 0.29	< 0.001

NAFLD — non-alkoholic fatty liver disease; LDL — low density lipoprotein; HDL — high density lipoprotein; VLDL — very low density lipoprotein; AST — aspartic acid transaminase; ALT — alanine transaminase; ALP — alkaline phosphatase

From the apical four-chamber view, pulse-wave Doppler recordings of the mitral inflow were obtained with the sample volume placed at the tips of the mitral valve leaflets. The following parameters were measured by pulse-wave Doppler: peak velocities of early (E) and late diastolic filling (A), deceleration time (DT), isovolumic relaxation time (IVRT). The ratio of early diastolic to late diastolic mitral inflow velocities was calculated (E/A).

The tissue Doppler echocardiography (TDI) program was set to pulse-wave Doppler mode. Filters were set to exclude high frequency signals. Gains were minimized to allow a clear tissue signal with minimal background noise. The TDI of the diastolic velocities was obtained from the apical four-chamber view. A 1.5-mm sample volume was placed at the lateral corner of the mitral annulus. Analysis was performed for early (E') and late diastolic velocity (A') and systolic velocity (S'). In addition, E/E' was calculated as another indicator of diastolic function. All Doppler signals were recorded with a chart recorder set at 100 mm/s. The averages of three cycles were used.

Statistical analysis

All statistical analyses were performed by SPSS for Windows, version 13.0 (SPSS Inc, Chicago, Illinois, USA). The two-tailed unpaired Student t-test or Mann-Whitney U test was used to compare the NAFLD group with the control group. The correlations between the parametric variables were investigated by Pearson correlation analysis. The categorical variables of the groups were compared by Pearson χ^2 test. A p value < 0.05 was accepted as statistically significant in all analyses.

Results

Thirty-five NAFLD patients (mean age 41.4 ± ± 6.2 years) and 30 controls (mean age 39.2 ± 6.0 years) were included in this study. The clinical and biochemical characteristics of the study population are reported in Table 1. The two groups were similar in age, gender, total cholesterol, low density lipoprotein (LDL)-cholesterol, and alkaline phosphatase (ALP) levels. The BMI values and WC of the NAFLD patients were significantly higher than the controls (30.4 ± 3.4 *vs* 25.2 ± 1.6 kg/m^2, $p < 0.01$, and 106.9 ± 8.9 *vs* 92.6 ± 6.9 cm, $p < 0.01$, respectively). Fasting glucose, triglyceride, very low density lipoprotein (VLDL), aspartic acid transaminase (AST), alanine transaminase (ALT), fasting insulin, C-peptide, and HOMA-IR levels in the NAFLD patients were significantly higher than in the control group. High density lipoprotein (HDL)-cholesterol levels were lower in NAFLD patients than controls. Eleven (31.4%) patients with NAFLD had low HDL [< 40 mg/dL (male), < 50 mg/dL (female)]; four (13.3%) control subjects had a low HDL. The BMI values of NAFLD patients were: one (2.8%) patient

Table 2. Ambulatory blood pressure parameters of the study patients.

Parameters	NAFLD-patients (n = 35)	Controls (n = 30)	P
Office SBP [mm Hg]	127.83 ± 9.14	121.93 ± 9.33	0.013
Office DBP [mm Hg]	79.40 ± 6.67	75.93 ± 7.39	0.051
24 h-SBP [mm Hg]	125.97 ± 9.25	120.93 ± 8.33	0.025
24 h-DBP [mm Hg]	78.03 ± 5.74	73.40 ± 6.36	0.003
24 h-MBP [mm Hg]	88.11 ± 6.10	83.53 ± 7.02	0.006
Day-SBP [mm Hg]	130.69 ± 10.84	125.00 ± 9.21	0.027
Day-DBP [mm Hg]	81.31 ± 7.22	76.67 ± 7.06	0.011
Day-MBP [mm Hg]	91.83 ± 7.59	86.67 ± 7.58	0.008
Night-SBP [mm Hg]	114.34 ± 9.04	110.80 ± 7.00	0.086
Night-DBP [mm Hg]	69.09 ± 6.81	65.07 ± 6.10	0.016
Night-MBP [mm Hg]	78.69 ± 6.91	74.93 ± 6.10	0.025

NAFLD — non-alkoholic fatty liver disease; SBP — systolic blood pressure; DBP — diastolic blood pressure; MBP — mean blood pressure

Table 3. Echocardiographic characteristics of the patients

Parameters	NAFLD-patients (n = 35)	Controls (n = 30)	P
IVS [cm]	0.98 ± 0.08	0.79 ± 0.07	< 0.001
PW [cm]	0.93 ± 0.09	0.75 ± 0.07	< 0.001
LVESD [cm]	3.19 ± 0.34	3.18 ± 0.23	0.913
LVEDD [cm]	4.87 ± 0.48	4.76 ± 0.25	0.243
EF (%)	63.40 ± 4.16	62.47 ± 4.31	0.379
LVM [g]	169.83 ± 39.81	114.77 ± 16.43	< 0.001
LVMI [g/m^3]	82.06 ± 16.88	59.17 ± 8.75	< 0.001
LA [cm]	3.68 ± 0.39	3.53 ± 0.34	0.113
S' [cm/s]	9.34 ± 1.8	10.6 ± 1.5	0.004

NAFLD — non-alkoholic fatty liver disease; IVS — interventricular septum diastolic thickness; PW — posterior wall diastolic thickness; LVESD — left ventricular end-systolic diameter; LVEDD — left ventricular end-diastolic diameter; EF — ejection fraction; LVM — left ventricular mass; LVMI — left ventricular mass index; LA — left atrial systolic diameter; S' — systolic velocity on tissue Doppler echocardiography

had BMI < 25 kg/m^2, 15 (42.9%) patients had BMI 25–29.9 kg/m^2, and 19 (54.3%) patients had BMI > 30 kg/m^2. Ten (33.3%) control subjects had BMI < 25 kg/m^2 and the remaining 20 (66.6%) control subjects had BMI 25–29.9 kg/m^2. Twenty-two (62.8%) NAFLD patients had a triglyceride level higher than 150 mg/dL, compared to six (20%) controls ($p < 0.01$).

Thirty-one (88.6%) patients with NAFLD had an increased WC [> 94 cm (male), > 80 cm (female)]; 14 (46.6%) control subjects had an increased WC. Although the patients in the NAFLD group were normotensive and non-diabetic, 11 patients (31.4%) had the metabolic syndrome, whereas no control subjects had the metabolic syndrome.

The office and ambulatory blood pressure parameters of the groups are reported in Table 2. All parameters, with the exception of the office DBP and the night SBP, were higher in NAFLD patients than in the controls.

The echocardiographic characteristics of the patients are reported in Table 3. Ventricular dimension, left atrium size and ejection fraction of the two groups were similar. However, interventricular septum wall thickness, posterior wall thickness, LVM, and LVMI values were higher in NAFLD patients than in the controls. S' on TDI values were lower in NAFLD patients than the controls (9.34 ± ± 1.8 *vs* 10.6 ± 1.5; $p = 0.004$).

Diastolic function parameters were significantly different in NAFLD patients (Table 4). Although the peak velocities of early (E) and late diastolic filling (A) were similar, E/A ratio was lower in NAFLD patients than the controls. NAFLD patients had increased DT and IVRT compared to the controls. E' on TDI values was lower in NAFLD patients than the controls (11.1 ± 2.1 *vs* 15.3 ± 2.7; $p < 0.001$). The indicator of LV filling pressure (E/E') was higher in NAFLD patients than the controls (6.64 ± 1.39 *vs* 4.91 ± 0.91; $p < 0.001$).

Table 4. Diastolic functional parameters of the study patients.

Parameters	NAFLD-patients (n = 35)	Controls (n = 30)	P
E [cm/s]	71.1 ± 11.2	74.9 ± 13.5	0.363
A [cm/s]	58.2 ± 9.2	54.3 ± 9.1	0.279
DT [ms]	192.8 ± 33.4	166.7 ± 34.2	< 0.001
IVRT [ms]	107.3 ± 12.1	94.8 ± 12.6	< 0.001
E/A ratio	1.25 ± 0.28	1.42 ± 0.34	0.028
E′ [cm/s]	11.1 ± 2.1	15.3 ± 2.7	< 0.001
E/E′ ratio	6.64 ± 1.39	4.91 ± 0.91	< 0.001

NAFLD — non-alkoholic fatty liver disease; E — early diastolic filling velocity; A — late diastolic filling velocity; DT — deceleration time; IVRT — isovolumic relaxation time; E′ — early diastolic velocity on tissue Doppler echocardiography

The correlation analysis

In the NAFLD patients, E' on TDI value was moderately correlated with night-SBP (r = –0.37, p = 0.026), night-DBP (r = –0.49, p = 0.003), night-MBP (r = –0.49, p = 0.003) and S' on TDI was correlated with night-SBP (r = –0.37, p = = 0.028), night-DBP (r = –0.42, p = 0.012), night--MBP (r = –0.42, p = 0.011). However, in the control group, E' on TDI was correlated with office-SBP (r = –0.41, p = 0.024) and S' on TDI was weakly correlated with LVMI (r = –0.37, p = 0.04). There was no significant correlation between BMI, WC, HOMA-IR, E' on TDI, and S' on TDI.

Discussion

Our findings indicate that LV diastolic and systolic function is significantly impaired in normotensive, non-diabetic NAFLD patients compared to healthy, age-matched control subjects. In addition, the ambulatory blood pressure recordings revealed that the patients with NAFLD had higher BP values than the controls, although they were normotensive at the baseline office visit.

Most population studies assess cardiovascular risk in terms of the manifestations of obesity, including dyslipidemia, diabetes mellitus, and hypertension. These disorders usually occur together and are referred to as the metabolic syndrome [28, 29]. They are almost always initiated by excessive weight gain. The risk estimates from the Framingham Heart Study suggest that up to 78% of hypertension in men and 65% in women can be directly attributed to increased body weight [30]. In addition, epidemiological studies indicate that excessive weight gain is a consistent predictor for subsequent development of hypertension, metabolic syndrome, and NAFLD.

Multiple mechanisms contribute to LV dysfunction in obesity, including lipotoxicity associated with cardiac steatosis and lipoapoptosis, alterations in fatty acid metabolism, overproduction of cardioinhibitory cytokines, up-regulation of some neurohormones (especially angiotensin II), myocardial fibrosis and chronic overload with LV dilatation and hypertrophy, and increased oxygen consumption [31–33]. Insulin resistance may represent a link between obesity and LV dysfunction. Elevated insulin levels in patients with IR stimulate myocyte growth and interstitial fibrosis. Insulin also causes sodium retention and activates the sympathetic nervous system which can affect cardiac performance [32, 33]. Moreover, alterations in myocardial metabolism, including progressive increases in fatty acid turnover, may impair LV contractility [31]. Finally, chronic sodium retention increases BP levels which in turn will cause myocardial tissue damage, myocardial fibrosis, and impairment of the LV function in response to LV pressure overload [34].

It is well-established that the metabolic syndrome and insulin resistance affect LV geometry and function [35–42]. The presence of insulin resistance altered the cardiac structure and contractile function at the level of the myocyte in an animal study [23]. This finding has been also demonstrated in humans [35, 36]. Whether or not the insulin resistance is independently associated with cardiac remodeling is unknown. The influence of insulin resistance on LVM has been observed in normotensive diabetic patients. In addition, fasting plasma insulin was found to be the strongest independent predictor of LVM [38]. Iacobellis et al. [35] reported that insulin resistance in obesity in the absence of diabetes was associated with an increased LVM and changes in LV geometry. However, not all studies in the non-diabetic population

supported their results. When adjusted for BMI and BP, insulin resistance was not an independent determinant of LVM [41].

There is limited data on the influence of the metabolic syndrome on LV function, especially in patients without hypertension, diabetes, and obesity. A slight increase in plasma glucose levels was associated with abnormal diastolic function, independent from LV hypertrophy in non-diabetic patients with treated hypertension [41]. Another study that evaluated the association of insulin resistance and LV diastolic indices in uncomplicated hypertension, demonstrated an independent association between the prolongation of IVRT and plasma leptin levels [42]. The effect of the metabolic syndrome on the LV diastolic function has also been demonstrated in the Strong Heart Study [19]. Changes in LV geometry and function correlated well with BMI in the previous studies that included patients with marked obesity. Recently, two studies in obese populations revealed that decreased systolic and early diastolic velocities on TDI and BMI were the only predictors of LV systolic and diastolic dysfunction [43, 44].

In our study, we found mild abnormalities in the LV structure, including increased LVM, LVMI and LV wall thickness in patients with NAFLD compared to the controls. Our patients with NAFLD were heavier than the controls, but did not have morbid obesity. Although all of the NAFLD patients were normotensive and non-diabetic, they had higher BP recordings, higher BMIs, and higher levels of insulin resistance than the controls. The impairment on systolic and diastolic function could reflect the cumulative effect of increased weight, elevated BP, and insulin resistance. The correlation analysis revealed that night systolic, diastolic, and mean BP levels were associated with E' on TDI and S' on TDI values. However, the sample size of our study was relatively small which did not allow us to perform multivariate analysis for determining independent predictors of LV systolic and diastolic impairment. Although the previous studies revealed that the NAFLD patients had impaired diastolic function, we demonstrated the relationship between LV functions and BP values by using ambulatory BP monitoring [45, 46]. Therefore, we suggest that a larger study with ABPM should be designed to evaluate the relationship between the systolic and diastolic functions and the BMI, HOMA, and BP levels in patients with NAFLD.

Limitations of the study

The primary limitation of this study is the small size of the study population. However, our study included highly selected (normotensive and non-diabetic) patients with NAFLD. Secondly, we could not rule out the presence of silent CAD, since we did not evaluate the patients with stress tests or coronary angiography prior to their enrollment. However, the clinical, echocardiographic and electrocardiographic evidence was reliable enough to exclude patients with ischemic heart disease. Thirdly, the BP levels of patients with NAFLD were higher than the control group, although both groups were normotensive. While this population did not have overt JNC-7 Stage 1 hypertension, the vast majority of our patients would be diagnosed with pre-hypertension. Given this, it is not entirely surprising that the study group had a higher incidence of subtle echocardiographic findings consistent with LV systolic and diastolic dysfunction. Apparently, we cannot state which parameter out of BP, HOMA or BMI is associated with LV function. If our study population had included a patient subgroup with similar BP levels between controls and NAFLD cases, we could have determined specifically which one out of BP, HOMA or BMI affected LV function. We believe that our study, despite its limitations, increases awareness of the possibility of LV dysfunction in both NAFLD and metabolic syndrome patients without overt hypertension.

Conclusions

In conclusion, we found that there was significant impairment on systolic and diastolic function in the non-diabetic and normotensive NAFLD patients compared to the controls. We suggest that patients with NAFLD require aggressive cardiac risk factor modification and closer follow-up for the prevention of diastolic and systolic heart failure.

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