

Assessment of Left Ventricular Diastolic Function in Young Adults with Nonalcoholic Fatty Liver Disease

CRISTIANA GIANINA MOISE¹, IONUȚ DONOIU²,
GEORGICĂ-COSTINEL TÂRTEA³, OANA MIREA², ION ROGOVEANU⁴

¹Doctoral school, University of Medicine and Pharmacy of Craiova, Romania

²Department of Cardiology, University of Medicine and Pharmacy of Craiova, Romania

³Department of Physiology, University of Medicine and Pharmacy of Craiova, Romania

⁴Department of Gastroenterology, University of Medicine and Pharmacy of Craiova, Romania

ABSTRACT: There is strong evidence that, in addition to increasing the risk of cirrhosis as well as hepatocellular carcinoma, nonalcoholic liver disease represents an independent risk factor for different diseases including cardiovascular and chronic kidney disease and also type 2 diabetes. Objective: to assess whether nonalcoholic fatty liver disease is associated with diastolic dysfunction of the left ventricle, independent of other classic risk factors. Methods: we included 79 patients aged 15-45, diagnosed with non-alcoholic liver disease, and a group of 80 healthy people in the same age group. We assessed left ventricular diastolic function using Doppler pulsed wave transmitral flow and Tissue Doppler Imaging methods. Results: there were lower velocities of E and e' wave, a decrease in E/A ratio and an increase in E/e' ratio in the group of patients with hepatic steatosis and in those with associated diabetes compared to the control group, but not the same was observed when comparing patients with steatosis alone vs. hepatic steatosis and associated diabetes mellitus. Conclusion: nonalcoholic steatosis is linked to echocardiographic features of early diastolic dysfunction that are present in patients suffering from diabetes.

KEYWORDS: Steatosis, echocardiography, left ventricle, tissue doppler imaging.

Introduction

Nonalcoholic fatty liver disease (NAFLD), which is the most common disease affecting the liver, is represented by several clinical and biological manifestations reflecting simple steatosis, characterized by an excess of hepatic triglycerides, or steatohepatitis [1].

Isolated liver steatosis has a benign character, but steatohepatitis could progress to liver cirrhosis and liver carcinoma.

Currently, hepatic steatosis is a medical problem of global interest due to the increased prevalence in the general population, the rising incidence in association with obesity and metabolic syndrome, and the possible serious evolution towards steatohepatitis, liver cirrhosis and liver failure.

Nonalcoholic steatosis is closely associated with components of the metabolic syndrome (obesity, diabetes mellitus and insulin resistance, hypertension and dyslipidemia), representing the metabolic syndrome's hepatic component.

Metabolic syndrome has a prevalence of about 22% in the general population and is associated with an increase in cardiovascular morbidity and mortality.

Studies have shown an increased prevalence of left ventricular remodeling and also diastolic dysfunction, features present in patients suffering from metabolic syndrome [2].

However, patients associating obesity and/or hypertension, that are considered independent risk factors for diastolic dysfunction, were generally included in these studies.

It is thus unclear whether changes in diastolic function and structural cardiac changes are the consequence of hypertension and/or obesity or the effects of insulin resistance on the myocardium.

In this study we aimed to investigate the diastolic function of the left ventricular in patients diagnosed with nonalcoholic steatosis and to assess its relation to other cardiovascular risk factors.

Material and Methods

Patients

The study included 79 young patients aged 15-45, diagnosed with nonalcoholic fatty liver disease, and a group of 80 healthy young people in the same age group. In the group of patients with NAFLD, 35 patients presented only liver damage, and 44 patients also presented diabetes (DM) in addition to liver damage. Patients with a history of cardiovascular disease, alcohol users, and those diagnosed with viral hepatitis were not included.

Abdominal ultrasound was the method used to screen patients who had increased levels of transaminases and suspicion of steatosis, being a

non-invasive and also available method, that is very useful for detecting hepatic steatosis with a sensitivity of 60-94%. Imaging changes characteristic of steatosis included hepatomegaly, diffuse accentuation of the echogenicity of the liver parenchyma, posterior attenuation and decreased visualization of the walls of the portal veins. It is known that the non-steatosis liver parenchyma has an echogenicity similar to that of the renal parenchyma but becomes hyperechoic in the case of fat infiltration. This hepatorenal contrast has been used as an imaging feature in the detection of hepatic steatosis.

Echocardiographic assessment of left ventricular diastolic function

Each patient was examined at the Cardiology Center of Craiova Clinical Emergency County Hospital with a single echocardiographic device (Vivid S6, GE Vingmed Ultrasound, Horten, Norway). According to the laboratory's internal protocol, all echocardiographic examinations were stored with the measurement of 3 cardiac cycles in DICOM format (Digital Imaging and Communications in Medicine) and post-processed offline using EchoPAC version 8.0 (GE Healthcare). Echocardiographic evaluation was performed after 5 minutes of rest. For the correct acquisition of the images, the patient was placed in left lateral decubitus. To synchronize the correct image acquisition with the stages of the cardiac cycle, the ECG was recorded simultaneously, by placing 3 electrodes on the

patient's anterior or posterior thorax in the recommended standard positions (red electrode at right clavicle, yellow electrode - left clavicle, green electrode-at the level of the left anterior axillary line).

The diastolic function of LV was assessed from the apical 4-chamber incidence by putting the Doppler pulsed-wave cursor at the level of the top of the mitral valve. The following echocardiographic parameters of the transmitral flow were evaluated: late diastolic inflow peak velocity (A wave), early diastolic inflow peak velocity (E wave), E/A ratio and E wave deceleration time (TDE). We also interrogated the early and late velocities of the mitral annulus, in the apical 4-chamber section, by placing Tissue Doppler Imaging (TDI) volume sample at the septal and lateral mitral annulus (Figure 1).

The resulting waves were represented by the negative e' wave (represents the early diastolic velocity) and a' wave (late diastolic velocity or atrial contraction). We also calculated the E/e' ratio in order to estimate the end-diastolic pressure of the left ventricle.

For patients in the control group, the same evaluations were performed within the same hospital.

The study was conducted taking into account the principles of the Declaration of Helsinki and it was also approved by the Hospital Ethics Committee. Each patient signed an informed consent prior to the study procedures.

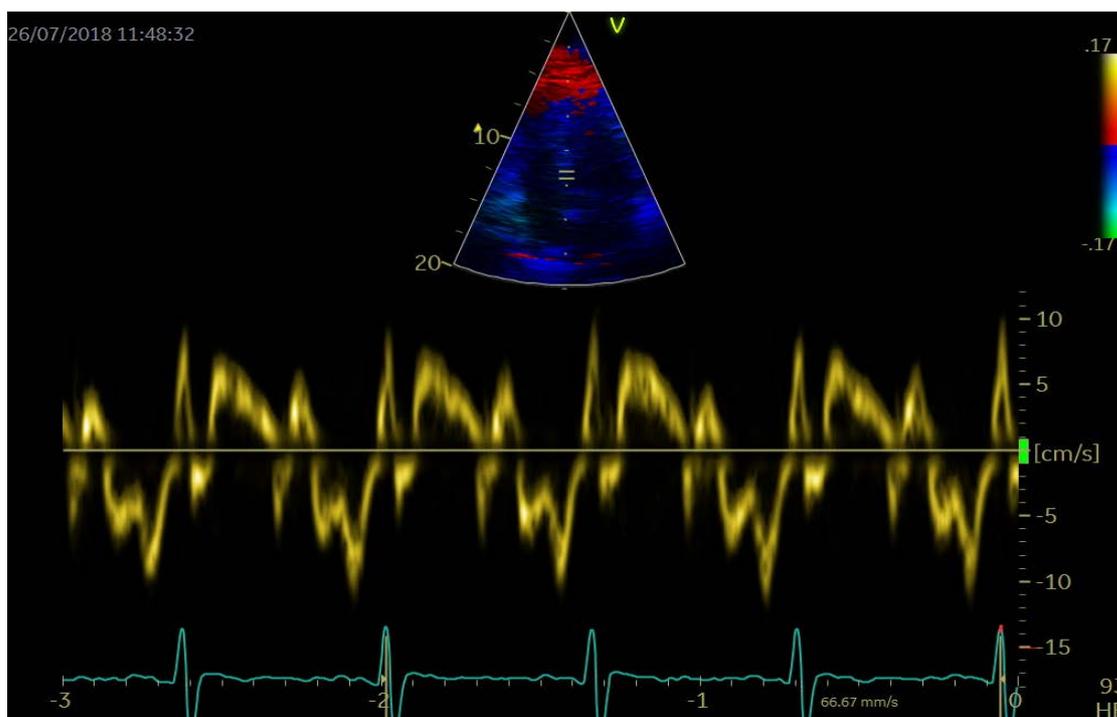


Figure 1. Tissue Doppler Imaging measurement of septal mitral annulus velocities.

Statistical analysis of data

All numerical data was represented as mean and standard deviation. Data was analyzed using Graph Pad software (version 8, La Jolla, CA, USA).

In order to perform statistical analysis we used the Student's t-test to compare the means of two data groups and the ANOVA test when we had to compare at least three data groups.

In all cases the value of P was calculated, and we considered that there is a statistically significant difference between the means of the compared groups when it was less than 0.05.

Results

In this study there were three groups of patients, namely the group of patients with hepatic steatosis (n=79) of which 35 patients had only steatosis (S) and 44 patients who had, in addition to steatosis, diabetes mellitus (S+DM) and the control group (N) represented by healthy young people (n=80) of similar age.

Clinical and demographic characteristics

Patients with hepatic steatosis and those who had associated diabetes had much higher blood pressure (126 ± 8 mmHg in group S and 126 ± 14 mmHg in group S+DM, $p=0.99$) compared to the control group (117 ± 7 mmHg, N vs. S $p<0.000$ and N vs. S+DM $p<0.000$).

In contrast, there were no statistically significant differences in heart rate. Also, the age of patients with liver steatosis (38 ± 5 years) was higher compared to the other two groups, namely the group that also associated diabetes (31 ± 8 years) and the control group (29 ± 5 years).

In the three groups, the patients with steatosis but also those with associated diabetes had a much higher weight (S= 98 ± 14 kg, S+DM= 78 ± 19 kg and N= 69 ± 14 kg) and body mass index compared to the control group (S= 98 ± 14 kg, S+DM= 78 ± 19 kg and N= 69 ± 14 kg).

All clinicopathological features assessed are presented as mean and standard deviation in Table 1 and the results of the ANOVA test for the three groups analyzed are presented in Table 2.

Table 1. Subjects clinical characteristics.

Variables	Steatosis (n=35)	Steatosis and Diabetes (n=44)	Control (n=80)
Gender (Male/Female)	20/15	26/18	51/29
Age	38 ± 5	31 ± 8	29 ± 5
Body weight (kg)	96 ± 14	78 ± 19	69 ± 14
Height (cm)	176 ± 8	170 ± 9	173 ± 9
Body mass index (kg/m^2)	30 ± 3	27 ± 6	23 ± 3.9
Body surface area (m^2)	2.1 ± 0.1	1.8 ± 0.2	1.8 ± 0.2
Heart rate (bpm)	77 ± 8	80 ± 10	80 ± 14
Systolic blood pressure (mmHg)	126 ± 8	126 ± 14	117 ± 7
Diastolic blood pressure (mmHg)	75 ± 9	80 ± 7	68 ± 5

Table 2. Statistical significance (P values) for the clinical variables.

Patients	Age	Height	Weight	BMI	BSA	HR	SBP	DBP
Normal vs. steatosis	<0.000	0.080	<0.000	<0.000	<0.000	0.650	<0.000	<0.000
Normal vs. steatosis+DM	0.180	0.400	0.01	<0.000	0.280	0.99	<0.000	<0.000
Steatosis vs. steatosis+DM	<0.000	0.020	<0.000	<0.015	<0.000	0.70	> 0.990	0.220

Echocardiographic characteristics

All examined patients had a normal left ventricular ejection fraction.

Standard echocardiographic parameters are shown in table 3 and the results of the ANOVA test in Table 4.

Conventional echocardiographic parameters showed lower velocities of E and e' wave (Figures 2, A and B) in patients with steatosis (E wave= 68 ± 11 cm/sec and e' wave= 9.8 ± 2.3 cm/sec) compared to patients with steatosis and diabetes mellitus (E wave= 74 ± 16

cm/sec and e' wave= 11 ± 3 cm/sec, $p=0.0008$) and with patients included in the control group (E wave= 85 ± 18 cm/sec and e' wave= 16 ± 2 cm/sec, $p=0.0001$).

It was also observed a decrease in E/A ratio and an increase in E/e' ratio in the group of patients with hepatic steatosis (E/A ratio= 1.1 ± 0.2 and E/e' ratio= 7.4 ± 2.1) and in those with associated diabetes (E/A ratio= 1.3 ± 0.3 and E/e' ratio= 6.6 ± 1.9) compared to the control group (E/A ratio= 1.7 ± 0.5 and E/e' ratio= 5.4 ± 1.3).

Regarding the velocity of a' wave, it was observed an increase from 7.6±2cm/sec in the control group, to 8.7±2.4cm/sec in the group of

patients with steatosis and diabetes, respectively at 10.3±1.8cm/sec in patients presenting only steatosis without associating diabetes mellitus.

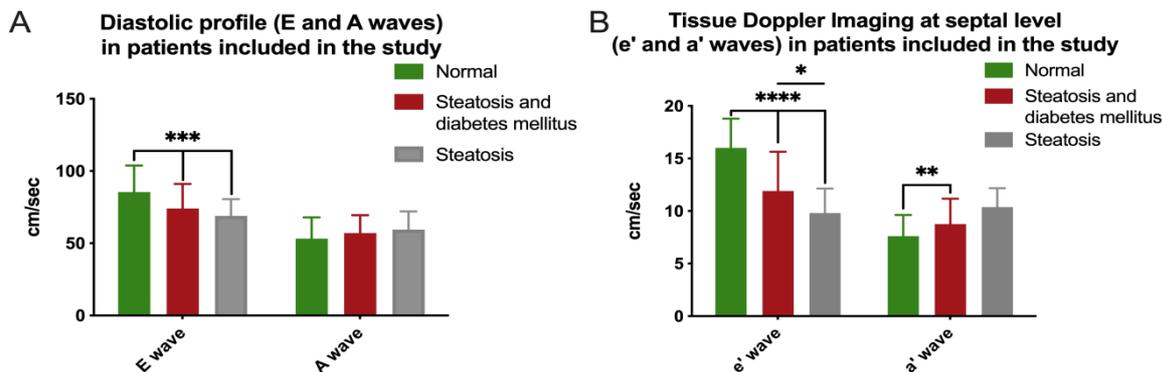


Figure 2. A-Left ventricular diastolic function in patients included in the study (E and A waves). B - e' and a' waves from tissue doppler imaging in patients included in the study.
 * p=0.01, ** p=0.001, *** p=0.0001, **** p < 0.0001.

Table 3. Left ventricular diastolic function parameters in the study groups.

Variables	Hepatic steatosis (n=35)	Hepatic steatosis and Diabetes mellitus (n=44)	Control group (n=80)
E wave (cm/s)	68±11	74±16	85±18
A wave (cm/s)	59±12	57±12	53±14
TDE (ms)	169±31	181±49	159±27
E/A ratio	1.1±0.2	1.3±0.3	1.7±0.5
e' wave (cm/s)	9.8±2.3	11±3	16±2
a' wave (cm/s)	10.3±1.8	8.7±2.4	7.6±2
E/e'	7.4±2.1	6.6±1.9	5.4±1.3

Table 4. Statistical significance (P values) for echocardiographic parameters.

Patients	E wave (cm/s)	A wave (cm/s)	TDE (ms)	E /A ratio	e' wave (cm/s)	a wave (cm/s)	E/e' ratio
Normal vs. steatosis	<0.000	0.470	0.450	<0.000	<0.000	<0.000	<0.000
Normal vs. steatosis+DM	<0.000	0.690	0.004	0.000	<0.000	0.080	<0.000
Steatosis vs. steatosis+DM	0.760	0.990	0.460	0.230	0.007	0.080	0.150

Discussions

Based on transmitral flow measurements, E-wave velocities as well as E/A ratio were lower in patients with hepatic steatosis (p<0.05) compared to the control group, results that were consistent with most studies conducted so far [3,4].

The study also showed a reduction in early diastolic wave velocities and an increase in the E/e' ratio in the hepatic steatosis group compared to the control group.

Most previous studies had similar results, showing the presence of left ventricular diastolic dysfunction in patients with NAFLD and in the absence of morbid obesity, hypertension or DM.

The presence of diastolic dysfunction of the left ventricle in these patients compared to the control group requires careful follow-up, with a rigorous control of cardiovascular risk factors to prevent heart failure.

Patients with NAFLD and associated DM also had, compared to the control group, reduced E wave velocities, reduction of E/A ratio, reduction of diastolic e' wave velocity and increase of E/e' ratio.

Our data showed that in patients with diabetes and nonalcoholic fatty liver disease, even if the morphology and systolic function of the left ventricle are preserved, characteristics of the diastolic dysfunction were observed.

In terms of frequency of the diastolic dysfunction, it was significantly higher in patients associating diabetes and NAFLD liver disease compared to the control group, results that were similar in other studies [9,10].

We also compared the group with hepatic steatosis vs. the group with DM and steatosis and found a statistically significant reduction of the e' wave.

The rest of the parameters used to assess the diastolic function of the left ventricle had no statistically significant changes.

Therefore, it is not clear whether the association of DM in patients with hepatic steatosis further alters ventricular diastolic function.

However, there is data in the literature that has shown that in patients associating diabetes and NAFLD, characteristics of early subclinical diastolic dysfunction were observed by using Tissue Doppler imaging technique, which is now the most widely used diagnostic approach for assessing subclinical left ventricular dysfunction.

In addition, because diastolic dysfunction was not detected by using conventional echocardiography, the results of our study provide further evidence that Tissue Doppler imaging method has higher accuracy and sensitivity compared to conventional echocardiography in terms of early detection of left ventricular diastolic function in patients with diabetes and hepatic steatosis [5-8].

Conclusions

Left ventricular diastolic function may be affected before systolic function in patients with nonalcoholic fatty liver disease.

Nonalcoholic steatosis is associated with echocardiographic features of early diastolic dysfunction in patients suffering from diabetes.

Further studies are needed to determine whether measures against nonalcoholic fatty

liver disease delay or eventually prevent the development of diastolic dysfunction in patients with diabetes.

Conflict of interests

None to declare.

References

1. Byrne CD, Targher G. NAFLD: A multisystem disease. *J Hepatol*, 2015, 62: S47-S64.
2. Moise GC, Donoiu I, Rogoveanu I. Ventricular structure and function in non-alcoholic fatty liver disease. *CorSalud*, 2021, 12(4):425-431.
3. Goland S, Shimoni S, Zornitzki T, Knobler H, Azoulai O, Lutaty G, et al. Cardiac abnormalities as a new manifestation of nonalcoholic fatty liver disease: echocardiographic and tissue Doppler imaging assessment. *J Clin Gastroenterol*, 2006, 40(10):949-955.
4. Pacifico L, Di Martino M, De Merulis A, Bezzi M, Osborn JF, Catalano C, et al. Left ventricular dysfunction in obese children and adolescents with nonalcoholic fatty liver disease. *Hepatology*, 2014, 59(2):461-470.
5. Fang ZY, Prins JB, Marwick TH. Diabetic cardiomyopathy: evidence, mechanisms, and therapeutic implications. *Endocr Rev*, 2004, 25(4):543-567.
6. Maya L, Villarreal FJ. Diagnostic approaches for diabetic cardiomyopathy and myocardial fibrosis. *J Mol Cell Cardiol*, 2010, 48(3):524-529.
7. Fang ZY, Yuda S, Anderson V, Short L, Case C, Marwick TH. Echocardiographic detection of early diabetic myocardial disease. *J Am Coll Cardiol*, 2003, 41(6):611-617.
8. Galderisi M. Diastolic dysfunction and diabetic cardiomyopathy: evaluation by Doppler echocardiography. *J Am Coll Cardiol*, 2006, 48(8):1548-1551.
9. Saluja M, Kumar K, Swami YK, Meena SR, Goyal S. Association between Non-alcoholic Fatty Liver Disease and Left Ventricular Diastolic Dysfunction in Patients of Type 2 Diabetes. *J Assoc Physicians India*, 2019, 67(8):20-24.
10. Bonapace S, Perseghin G, Molon G, Canali G, Bertolini L, Zoppini G, Barbieri E, Targher G. Nonalcoholic fatty liver disease is associated with left ventricular diastolic dysfunction in patients with type 2 diabetes. *Diabetes Care*, 2012, 35(2):389-395.

*Corresponding Author: Ionuț Donoiu, Department of Cardiology,
University of Medicine and Pharmacy of Craiova, 2 Petru Rareș Street, 200349 Craiova, Romania,
e-mail: ionut.donoiu@umfvcv.ro.*