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Research Article

Diastolic dysfunction assessment by pulsed-wave and tissue Doppler imaging in diabetic patients with nonalcoholic fatty liver disease

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Abstract. Objective: The purpose of the study was to assess if nonalcoholic fatty liver disease (NAFLD) in diabetic patients increases the risk and/or severity of diastolic dysfunction. Material and methods: 73 diabetic patients with NAFLD and a control group of 70 diabetic patients without NAFLD were studied. All patients had normal left ventricular systolic function and blood pressure values under medication. Left ventricular diastolic dysfunction was assessed by pulsed wave Doppler and tissue Doppler imaging, studying mitral inflow patterns and E wave, E' wave velocities, E/A and E/E' ratios. Results and conclusions: The frequency of diastolic dysfunction was significantly higher in diabetic patients with NAFLD versus controls, with a higher severity.

Key Words: nonalcoholic fatty liver disease, type 2 diabetes mellitus, tissue Doppler imaging, diastolic dysfunction

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is recognized as the hepatic expression of the metabolic syndrome, a cluster of cardiovascular risk factors, including type 2 diabetes mellitus (Ludwig *et al* 1980; Marchesini *et al* 2001). Observational studies have connected NAFLD with insulin resistance, suggesting that the presence of fatty liver and especially that of nonalcoholic steatohepatitis, promotes the development of glycoregulation disorders (Angulo 2002). The addition of NAFLD to glycoregulation disorders may increase the cardiovascular risk of these patients, independently of the presence of other components of the metabolic syndrome (Hamaguchi *et al* 2007; Targher *et al* 2007).

Diastolic dysfunction in diabetic patients is the main characteristic of diabetic cardiomyopathy and represents a prognostic factor for the development of diastolic heart failure with preserved ejection fraction (Kitzman *et al* 2001; Bella *et al* 2002; Wang *et al* 2003;8). The prevalence of diastolic dysfunction is higher in patients with metabolic syndrome compared with the general population, reaching 60% in diabetic patients (Celentano *et al* 1995; Raev 1994). Diastolic dysfunction impairs life quality, reducing exercise capacity and accounting for up to 50% of acute heart failure hospitalizations in patients with preserved ejection fraction (Kitzman *et al* 2001). Recently it was proven that diastolic dysfunction is a frequently met in patients with NAFLD and type 2 diabetes or arterial hypertension (Fallo *et al* 2009; Bonapace *et al* 2012).

Echocardiography is an accurate and noninvasive method of assessing diastolic dysfunction. Pulsed-wave Doppler evaluation of mitral inflow may prove difficult in differentiating normal from pseudo normalized patterns of moderate diastolic dysfunction. Tissue Doppler imaging is a sensitive, easy reproducible technique in evaluating myocardia function, based on the low frequency high amplitude signals reflected by the myocardium (Nagueh *et al* 1997; Zacharopoulou *et al* 2010). Regional myocardial function is quantified by myocardial velocities measured in cm/s in systole (S'), early diastole (E') and late diastole (A') respectively. Tissue Doppler parameters which have the best correlation with ventricular relaxation and compliance are E' and E/E' (Kasner *et al* 2007).

The aim of this study was to assess if the presence of NAFLD increases the risk of diastolic dysfunction development in diabetic patients, thus increasing the cardiovascular risk of these patients.

To this purpose, we studied diastolic dysfunction evaluated by tissue Doppler through the velocity of E' wave and the ratio E/E' in diabetic patients with NAFLD versus diabetic controls without NAFLD.

Material and methods

We studied 73 patients with type 2 diabetes, which had NAFLD and a control group of 70 diabetic subjects without proof of fatty liver. The patients were matched for age ± 2 years.

NAFLD was diagnosed by abdominal ultrasonography, using an Aloka SSD 4000 unit, based on the following criteria: increased

hepatic echogenity, hepatomegaly and posterior attenuation of the liver. All examinations were made by the same a well trained and experienced operator. Significant alcohol consumption was excluded through detailed history taking. Viral hepatitis B and C was excluded by determining HBs antigen and anti-hepatitis C antibodies respectively.

Patients in both groups had controlled blood pressure values by antihypertensive medication, and preserved left ventricular ejection fraction.

The systolic and diastolic function of the left ventricle were assessed by echocardiography using a Vivid S5 unit. Systolic function was evaluated measuring the left ventricular ejection fraction and the systolic myocardial velocity (S') by tissue Doppler imaging.

Diastolic function was assessed by establishing the mitral inflow pulsed-wave Doppler pattern and by measuring the early diastolic myocardial velocity by tissue Doppler (E'), as well as the E/E' ratio.

The mitral inflow was interrogated in apical four chamber view, with the Doppler probe positioned at the tip of the mitral valve in diastole. The normal values were 0.72 m/s for the maximal early velocity of diastolic filling (E wave), 0.40 m/s for the maximal velocity of late diastolic filling (A wave), a E/A ratio of 1.9, 179 ms – the E wave deceleration time (139-219 ms), 127±13 ms the duration of ventricular filling by atrial contraction (ADur), 76 ms (54-98 ms) isovolumetric relaxation time (IVRT). IVRT was measured in apical five chambers view, with pulsed-wave Doppler probe positioned between the left ventricular outflow tract and the mitral valve, from the aortic valve closing signal to the beginning of the mitral inflow. The main limitation in using mitral inflow for the assessment of diastolic dysfunction is the difficulty to differentiate between the normal aspect of left ventricular relaxation and the pseudonormalized pattern in moderate diastolic dysfunction, in which left ventricular relaxation is altered and filling pressures are elevated.

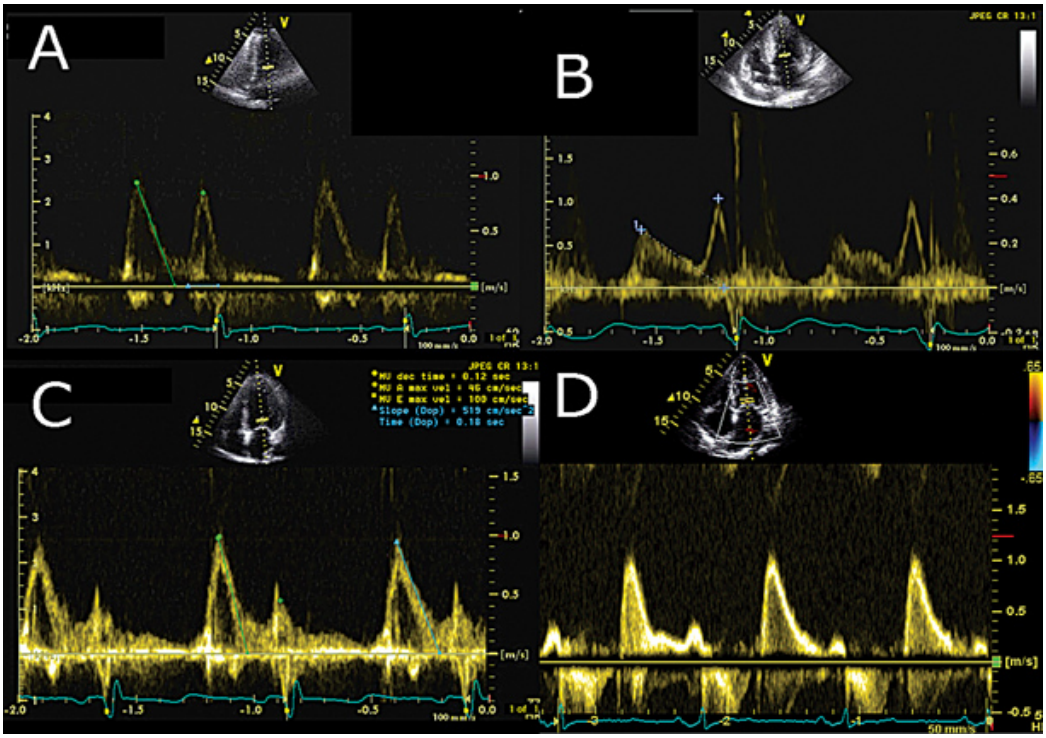

Figure 1. A. Normal mitral inflow pattern. B. Impaired relaxation. C. Pseudonormalised pattern. D. Restrictive pattern of diastolic dysfunction

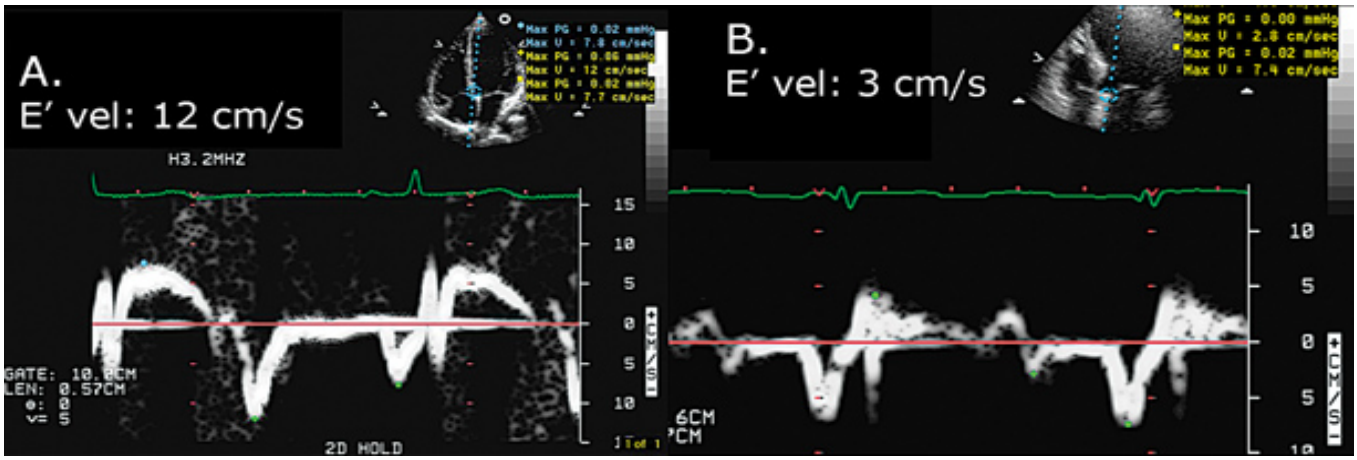

Figure 2. Tissue Doppler velocities at the level of the interventricular septum in apical four chamber view

In this situation, tissue Doppler imaging is the method of choice for differential diagnosis.

Figure 1 illustrates the three degrees of severity of diastolic dysfunction (1B, C, D), compared with the normal aspect of the mitral inflow (1A). Impaired relaxation pattern (1B) is characterized by reduced velocity of E wave, a E/A <1 ratio, increased EDT and IVRT. In the pseudo normalized pattern (figure 1C) the maximum velocities of E and A waves are normal, as are the E/A ratio, EDT, IVRT. The restrictive pattern is presented in figure 1D, with increased E wave velocity, reduced A wave velocity, IVRT, and E/A ratio>2.

Tissue Doppler imaging was obtained by placing the Doppler probe at the level of the lateral mitral ring or at the level of the interventricular septum, in four apical chamber view; the obtained velocities are similar, but inversed compared with the traditional mitral inflow by pulsed-wave Doppler, as illustrated in figure 2.

Diastolic flow is represented by two negative waves: E' corresponding to diastolic relaxation, simultaneous with the T wave on the ECG, a parameter relatively independent of the filling pressures, and A' wave – the maximal late annular velocity, corresponding to atrial contraction. E'/A' ratio is normally >1. The E' velocity decreases with age, from 9 cm s^{-1} to 6 cm s^{-1} in subjects over 60 years old at the level of the interventricular septum, and from 11 cm s^{-1} to 7 cm s^{-1} at the level of the lateral mitral ring.

The differentiation of the normal pattern from the pseudonormal one was based on the Valsalva maneuver, which, in patients with diastolic dysfunction decreases the E/A ratio<1 or at least by 50%. The E' wave velocities was <8 cm s^{-1} and the E/E' ratio >15 in the pseudonormal pattern, whereas in normal subjects the E' wave velocity was>10 cm s^{-1} and the E/E'<8 cm s^{-1}.

We used the Data Analysis module of Microsoft Excel 2007 ® (for the descriptive statistics and the Student T test, as well as the Fischer test) and SPSS® (for the Chi square and Shapiro-Wilk tests).

Results

The clinical characteristics of the two patient groups are presented in table 1. Both groups followed a normal distribution pattern (confirmed using both graphical representation – histograms, and statistical – Shapiro- Wilk test), with equal variances (confirmed by the F test – using the ANOVA regression of the Data Analysis). When following the evaluated parameters (table 1), there were no significant differences between the groups (using the T- test: two sample assuming equal variances for quantitative parameters and Chi square test for qualitative parameters - with a CI of 95%, p-value>0.05), although a tendency towards a higher BMI and abdominal circumference, as well as higher blood glucose and cholesterol was observed in the NAFLD group (non-statistically significant). This insures that the various factors that could influence the final result, listed in table 1 (like age, sex or blood glucose) are equally distributed among the two groups, eliminating their effect upon the final result, and making the two groups comparable. Thus, the final results of this study can be applied to the general population.

The frequency of diastolic dysfunction was significantly higher in diabetic patients with NAFLD compared with controls (Chi square test, two tails, 73% vs. 56%, p<0.05).

Table 1. Clinical characteristics of patients and controls

	Control group 70 patients	NAFLD 73 patients	P
Age (years) (mean ± 1 SD)	57 ± 4	58 ± 3	NS
Sex M/F	48/22	53/20	NS
Blood pressure (SBP/DBP mm Hg) (mean)	158/92	160/98	NS
Blood glucose a jeun mg dl^{-1} (mean)	126	132	NS
HbA1c % (mean)	6,8	7,1	NS
Total cholesterol mg dl^{-1} (mean)	234	245	NS
LDL cholesterol mg dl^{-1} (mean)	128	135	NS
Triglycerides mg dl^{-1} (mean)	255	269	NS
BMI (mean)	26	28	NS
Abdominal circumference (cm) (mean)			
M	104	108	NS
F	88	90	NS

Patients with NAFLD had also more severe diastolic dysfunction compared to controls as illustrated in figure 3.

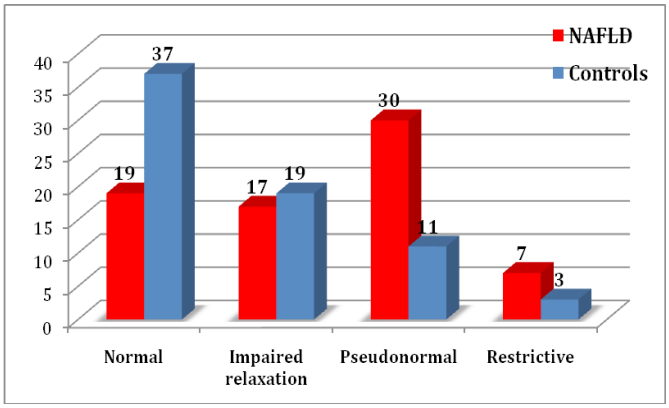

Figure 3. Diastolic dysfunction in diabetic patients with NAFLD versus controls

In table 2 are presented the pulsed-wave Doppler velocities for both patient groups.

Table 2. Pulsed-wave Doppler velocities for patients and controls

	NAFLD	Controls	P
E wave velocity (m s^{-1})	0.87 ± -0.19	0.66 ± -0.17	<0.05
A wave velocity (m s^{-1})	0.47	0.46	NS
E/A	1.85	1.4	<0.05
EDT	172	210	<0.05
ADur	0.35	0.42	NS
IVRT	48	98	<0.05

Patients with NAFLD had a significantly lower early diastolic E' wave velocity – assessed by tissue Doppler imaging – compared with controls (7.8±1.3 cm s^{-1} versus 9.5±1.6 cm s^{-1}, p<0.05 - T - test: two sample assuming equal variances). E/E' ratio was significantly higher in patients with NAFLD versus

control (11.5±1.3 versus 6.94 ± 1.2, p<0.05 - T - test: two sample assuming equal variances).
In table 3 are presented the mean values of tissue Doppler measured velocities: E', E'/A' and E/E' ratios, in diabetic patients with NAFLD with normal diastolic function and pseudo normalized pattern of diastolic dysfunction (T - test: two sample assuming equal variances – p<0.05).

Table 3. Tissue Doppler velocities in patients group

	NAFLD Normal diastolic pattern	NAFLD Pseudonormal diastolic pattern	P
E' (cm s^{-1})	12	7	p<0.05
E'/A'	2	0.9	p<0.05
E/E'	7	16	p<0.05

Conclusions and discussions

In the metabolic syndrome and type 2 diabetes mellitus diastolic dysfunction is the consequence of metabolic abnormalities and structural remodeling, which result in abnormal relaxation and increased myocardial rigidity (Boudina & Dale 2007). The multiple metabolic abnormalities are the result of insulin signaling, glyco, lipotoxicity and increase in interstitial fat deposits, affecting consequently the myocardial function at a tissular level (Fang 2004; Brownlee 2005; Ouwens *et al* 2007). Endothelial dysfunction is associated as well to these abnormalities, resulting in vascular remodeling and systemic and coronary atherosclerosis. This translates in an increase in arterial rigidity, high blood pressure and pulse pressure. There is an increase in afterload and myocardial oxygen demands, with a decrease in myocardial perfusion, thus diminishing cardiac efficacy. As a consequence, myocardial hypertrophy, autonomic dysfunction and diastolic dysfunction develop, as the first stage of diabetic cardiomyopathy. In late stages, diastolic dysfunction worsens as a result to structural myocardial abnormalities, as cardiac steatosis, interstitial fibrosis and the alterations in extracellular matrix (Nitenberg *et al* 1993; Diamant *et al* 2007).
NAFLD is defined as the fatty infiltration of the liver in patients without significant alcohol consumption, with a spectrum ranging from simple steatosis to steatohepatitis, histologically similar to alcoholic hepatitis, with a possible progression to end stage liver disease (Ludwig *et al* 1980). Considered at first an incidental finding, NAFLD is accepted today as a component of the metabolic syndrome, associated with significant cardiovascular risk factors like obesity, hypertension, dyslipidemia, diabetes mellitus and insulin resistance (Targher *et al* 2007). Moreover, NAFLD may be a independent cardiovascular risk factor as well as a detrimental factor for the severity of the other elements of the metabolic syndrome associated with it (Targher *et al* 2007; Hamaguchi *et al* 2005).
Our study showed that NAFLD in type 2 diabetes mellitus was associated with a higher frequency of diastolic dysfunction compared to diabetic patients without NAFLD. Moreover, the diabetic patients with NAFLD had a higher severity of diastolic dysfunction. Pulsed-waved Doppler was limited as a diagnostic method due to the difficulty to interpret the pseudonormalised pattern of mitral inflow. Tissue Doppler imaging was used for differentiating between the normal and pseudonormalised pattern of mitral inflow. Tissue Doppler parameters that have significantly differed for NAFLD patients were E' wave velocity and the E/E' ratio, parameters that are recognized as having the best correlation with left ventricle relaxation and myocardial compliance indexes (Wang *et al* 2003). These data suggest the fact that NAFLD, regardless of the presence of diabetes, further impairs the stiffness and relaxation of the left ventricle. This translates in earlier development of diastolic heart failure and a higher cardiovascular risk.
Data from studies performed on small groups of patients have shown that patients with NAFLD, in the absence of other cardiovascular risk factors included in the metabolic syndrome, present alterations in left ventricular geometry and early diastolic dysfunction (Bonapace *et al* 2012). Other studies have shown that NAFLD is associated with a significant decrease in E' wave velocity, this parameter being described as the only one to correlate with NAFLD (Goland *et al* 2006). In another study, diastolic dysfunction and insulin resistance were independently associated with NAFLD, in multivariate analysis (Brea *et al* 2005). Poanta et al showed that patients with type 2 diabetes and NAFLD did not present an abnormal intima-media thickness, a known risk factor for cardiovascular events, but their study was performed on a small number of subjects (Poanta *et al* 2011).
In conclusion, in patients diagnosed with NAFLD the assessment of diastolic dysfunction by tissue Doppler imaging detects early changes in myocardial stiffness and compliance, which precede the late stages of myocardial dysfunction.

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