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# Echocardiographic assessment of the left ventricular diastolic function in patients with non-alcoholic liver cirrhosis

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SOUHRN

**Cíl:** Vyšetřit funkci levé komory v diastole u pacientů s nealkoholickou steatózou jater a porovnat stupeň diastolické dysfunkce se závažností poškození jater.
**Metody:** Do studie bylo zařazeno 35 pacientů s nealkoholickou steatózou jater a 16 zdravých kontrolních osob odpovídajícího věku a pohlaví. Závažnost poškození jater byla hodnocena pomocí Childovy-Pughovy klasifikace. U všech pacientů bylo provedeno vyšetření jak klasickou, tak tkáňovou dopplerovskou echokardiografií. Plnicí tlaky levé komory byly odvozeny od hodnot rychlosti průtoku krve přes mitrální chlopeň a její anulus.
**Výsledky:** U pacientů s nealkoholickou steatózou jater (průměrný věk 53 ± 6 let) byla zjištěna významně vyšší srdeční frekvence než u kontrolních osob (86 ± 6,5 tepů/min vs. 72 ± 4; $p$ = 0,04). U 26 % pacientů byl na základě hodnot transmitrálních diastolických parametrů zjištěn mírný stupeň diastolické dysfunkce levé komory. Ve srovnání s kontrolními osobami byl vypočítaný plnicí tlak levé komory u pacientů s nealkoholickou steatózou jater významně vyšší (10 ± 3 vs 9 ± 1; $p$ = 0,002). Zvýšený plnicí tlak levé komory byl zaznamenán pouze u čtyř pacientů. U nich byla zjištěna pokročilejší forma poškození jater a na základě hodnot vtoku krve přes mitrální chlopeň byli vyhodnoceni jako osoby s normální funkcí levé komory v diastole.
**Závěry:** U čtvrtiny pacientů s nealkoholickou steatózou jater byla vyšetřením klasickou echokardiografií zjištěna mírná forma diastolické dysfunkce levé komory. Zvýšený plnicí tlak levé komory v klidu byl naměřen u 11 % pacientů. Použití více parametrů k hodnocení funkce levé komory v diastole u pacientů s cirhózou jater by mohlo pomoci odhalit případy s pseudonormální funkcí.


ABSTRACT

**Aim:** To assess the left ventricular diastolic function in patients with non-alcoholic liver cirrhosis and correlate the degree of diastolic dysfunction to the severity of liver impairment.
**Methods:** Thirty-five patients with non-alcoholic liver cirrhosis in addition to 16 age- and sex-matched healthy controls were studied. Severity of liver impairment was assessed using the Child-Pugh score. All participants were subjected to echocardiographic assessment using both the conventional and tissue Doppler echocardiography. The left ventricular filling pressure was derived from the transmitral and mitral annular velocities.

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**Results:** Patients with non-alcoholic liver cirrhosis (mean age; 53 ± 6) had significantly higher heart rate compared with the controls (86 ± 6.5 bpm vs 72 ± 4, $p = 0.04$). Mild degree of left ventricular diastolic dysfunction was detected in 26% of patients using the transmitral diastolic parameters. Compared with controls, the calculated left ventricular filling pressure was statistically significantly higher in patients with non-alcoholic liver cirrhosis (10 ± 3 vs 9 ± 1, $p = 0.002$). Elevated left ventricular filling pressure was detected in only 4 patients. These patients had more advanced form of liver impairment, and were categorized as having normal left ventricular diastolic function based on the mitral inflow indexes.
**Conclusions:** One fourth of patients with non-alcoholic liver cirrhosis had mild degree of left ventricular diastolic dysfunction using the conventional echocardiographic parameters. Elevated resting left ventricular filling pressure was detected in 11% of patients. The use of multiple parameters to assess the left ventricular diastolic function in patients with liver cirrhosis could unmask cases with pseudonormal pattern.

## Introduction

Liver cirrhosis is a major health problem that is associated with a wide range of cardiovascular abnormalities [1]. In the past 20 years, a number of evidences suggested that cirrhosis regardless of its etiology is associated with the development of hemodynamic changes and major cardiovascular anomalies known as cirrhotic cardiomyopathy [2–5]. This clinical entity has been repeatedly shown to have a negative prognostic impact, especially on the outcome of invasive procedures such as surgery, transjugular intrahepatic portosystemic shunt insertion (TIPS), and liver transplantation [6–9].

Left ventricular (LV) diastolic dysfunction is believed by some authors to be present in every patient with liver cirrhosis [10–13]. The transmitral E/A ratio has been widely used as the only definition criteria for the diagnosis of diastolic dysfunction in most of the previous studies evaluating cardiac function in patients with liver cirrhosis. The present study aimed at assessment of the left ventricular diastolic function in patients with non-alcoholic liver cirrhosis. We hypothesized that due to the U-shaped relation between the mitral inflow indexes and LV diastolic dysfunction [14], it is difficult to differentiate accurately patients with truly normal from those with pseudonormal pattern using these parameters unless the Valsalva maneuver is performed. Since proper performance of Valsalva maneuver might be difficult to achieve in patients with liver cirrhosis due to various neurological and mechanical barriers, we calculated non-invasively the LV filling pressure using the echocardiographic parameters for better assessment of LV diastolic function in these patients.

## Methods

### *Study population*

Thirty-five patients with established diagnosis of liver cirrhosis were included in this prospective study. Diagnosis of liver cirrhosis was based on clinical examination, abdominal ultrasonography, and laboratory findings. Severity of liver impairment was assessed using the Child-Pugh score (Table 1). None of these patients had alcoholic cirrhosis. Sixteen age- and sex-matched healthy subjects were also studied as controls. An informed consent was obtained from all participants. Patients with atrial fibrillation, significant valvular heart disease (more than mild regurgitation or stenosis), coronary artery disease, impaired LV systolic function (ejection fraction <50%), systemic arterial hypertension, diabetes mellitus, mitral annular calcification, and any amount of echocardiographically detected pericardial effusion were excluded from the study. Patients were subjected to full history taking, detailed clinical examination, laboratory investigations and, 12-lead surface electrocardiography. Both patients and controls were subjected to full echocardiographic assessment.

### *Echocardiography*

Examinations were performed with a commercially available Philips IE-33 echocardiographic machine (Philips Medical Systems, Andover, MA) equipped with a tissue imaging and Doppler transducer. Electrocardiographic monitoring was included in all studies. All measurements were averaged over 5 consecutive cycles. The LV cavity size, wall thickness, and ejection fraction (EF) were measured in accordance with American Society of Echocardiography recommendations. The left atrial volume (LAV) was measured using the prolate ellipse method [15].

### *Assessment of left ventricular diastolic function and filling pressure*

**Transmitral flow pattern:** Peak velocities of early (E) and late (A) diastolic filling, E/A ratio, and deceleration time were derived from Doppler recordings of the mitral inflow at the mitral leaflet tips and repeated with Valsalva maneuver. LV diastolic function was classified accordingly into four groups: normal, impaired relaxation, pseudonormal, and restrictive [16].

**Mitral annular velocity:** From the apical four chamber view using tissue Doppler imaging (TDI) while placing a 2.5 mm sample volume over the lateral mitral annulus, the early diastolic annular e' wave velocity was recorded and subsequently E/e' ratio was calculated. The pulmonary capillary wedge pressure (PCWP) was calculated using the E/e' ratio. PCWP = 1.24 (E/e') + 1.9 [17]. Filling pressure was considered elevated with a calculated PCWP of >12 mmHg [18].

### *Assessment of the stroke volume and cardiac output*

Using the zoom mode, the diameter of the left ventricular outflow tract (LVOT) was measured in the parasternal long axis view. The machine then calculated the cross sectional area (CSA) of the LVOT. The velocity time integral (VTI) across the LVOT was then obtained from the apical 5-chamber view using the pulsed wave Doppler. The stroke volume (SV) was then calculated by multiplying the LVOT velocity time integral by the LVOT cross sectional

area. The cardiac output (COP) was obtained by multiplying the SV by the heart rate.

Right ventricular (RV) dimensions and systolic function were measured in accordance to the guidelines [19].

### *Statistical analysis*

Data management and analysis were performed using the SPSS statistics for Windows; version 16.0 (Armonk; IBM Corporation, New York). Continuous variables, analyzed using Mann-Whitney U test or t-tests, were expressed as mean ± standard deviation (SD). Categorical variables, analyzed using the Chi-square or Fisher's exact test, were expressed as numbers and percentages. Correlation between variables was determined by the Spearman rho test. All statistical tests were two-sided. A value of $p < 0.05$ was considered statistically significant.

## Results

Mean age of patients with liver cirrhosis was 53 ± 6 with 62% of them were males. Ten patients were smokers. Only 6 patients (17%) were Child-Pugh class A, 14 (40%) were Child-Pugh class B and 15 (43%) were Child-Pugh class C. The majority of patients (97%) had ascites, 71% had jaundice, 60% of them had hematemesis and 85% were cachectic. Patients with non-alcoholic liver cirrhosis had significantly higher heart rate and more prolonged corrected QT interval compared with the controls (86 ± 6.5 bpm vs 72 ± 4, $p = 0.04$ and 446 ± 34 ms vs 350 ± 27, $p < 0.05$ respectively). Baseline characteristics of patients are summarized in Table 2. The LV internal dimensions, wall thickness and resting systolic function were normal in patients with liver cirrhosis. Compared with controls, however, the echocardiographically calculated stroke volume and COP values were much higher in patients with liver cirrhosis. There was statistically significant correlation between the severity of liver impairment as assessed by Child-Pugh classification and both the COP ($p < 0.001$, r = +0.5) and SV ($p \leq 0.02$, r = 0.4) with higher COP and SV detected in patients with worse Child-Pugh class. The LAV was also significantly increased in patients with liver cirrhosis. Only one patient with liver cirrhosis had dilated RV dimensions with impaired overall RV systolic function. Echocardiographic parameters in patients with liver cirrhosis and controls are illustrated in Table 3.

**Table 1 – Child-Pugh classification of severity of liver disease.**

| Parameter | | Points assigned | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Ascites | Absent | Slight | Moderate |
| Bilirubin, mg/dl | ≤ 2 | 2–3 | > 3 |
| Albumin, g/dl | >3.5 | 2.8–3.5 | < 2.8 |
| Prothrombin time:<br>Seconds over control<br>INR | <br>1–3<br><1.8 | <br>4–6<br>1.8–2.3 | <br>> 6<br>> 2.3 |
| Encephalopathy | None | Grade 1–2 | Grade 3–4 |

INR – international normalized ratio. Total score of 5–6 is considered grade A (well compensated disease); 7–9 is grade B (significant functional compromise); and 10–15 is grade C (decompensated disease).

**Table 2 – Clinical and laboratory characteristics of patients with liver cirrhosis.**

| | Patients with liver cirrhosis (n = 35) |
|---|---|
| Age, y | 53±6 |
| Male, % | 62% |
| Smoking, % | 28.5% |
| Post viral liver cirrhosis, % | 100% |
| Child-Pugh classification: A/B/C | 6/14/15 |
| Wasting, % | 85% |
| Jaundice, % | 74% |
| Ascites, % | 97% |
| Hematemesis, % | 60% |
| Melena,% | 60% |
| Resting heart rate, bpm | 86±6.5 |
| Hemoglobin, g/dl | 11.4±1.1 |
| Total bilirubin, mg/dl | 3.2±3.7 |
| Direct bilirubin, mg/dl | 2.3±2.9 |
| ALT, U/L | 46±29 |
| AST, U/L | 71±60 |
| Albumin, g/dl | 2.7±0.7 |
| Prothrombin time, s | 55±13 |
| Serum creatinine, mg/dl | 0.9±0.3 |

Data are expressed as mean ± SD or percentage as appropriate.
ALT – alanine aminotransferase;
AST – aspartate aminotransferase.

### *Diastolic functions and LV filling pressure*

Using the mitral inflow indexes, 9 patients (26%) had evidence of mild degree of LV diastolic dysfunction (impaired relaxation pattern). Patients with cirrhosis had significantly higher mitral A wave velocity and, lower mitral E/A ratio. Of the various mitral inflow indexes, only the mitral E/A ratio correlated with the severity of the liver impairment ($p = 0.04$, r = –0.335). Compared with the controls, the LV filling pressure was statistically significantly higher in patients with liver cirrhosis (10 ± 3 vs 9 ± 1, $p = 0.002$). Elevated LV filling pressure was detected in only 4 patients (11%) with

**Table 3 – Echocardiographic findings in the study population.**

| | Patients (n = 35) | Control subjects (n = 16) | *p* value |
|---|---|---|---|
| LVDD, cm | 5.5±0.5 | 5.1± 0.5 | 0.9 |
| LVDS, cm | 3.1±0.5 | 3.2±0.4 | 0.6 |
| LVEF, % | 68±4 | 66±6 | 0.6 |
| COP, L/m | 8.2±2.3 | 4.8±5.1 | <0.001 |
| SWTd, cm | 0.9±0.1 | 0.8±0.1 | 0.5 |
| PWTd, cm | 0.8±0.1 | 0.76±0.1 | 0.8 |
| LAV, ml | 41±12 | 31±5 | 0.001 |
| RV FAC, % | 54±6 | 48±4 | 0.01 |
| TAPSE, mm | 25±4 | 22±4 | 0.06 |
| Mitral E wave velocity, cm/s | 72±21 | 80±14 | 0.1 |
| Mitral A wave velocity, cm/s | 75±17 | 60±12 | 0.01 |
| Mitral E/A ratio | 0.9±0.2 | 1.4±0.3 | 0.001 |
| Mitral E wave deceleration time, ms | 182±44 | 179±19 | 0.6 |
| Lateral mitral e' velocity, cm/s | 9.2±2.5 | 12±4 | 0.01 |
| E/e' | 6.5±3 | 6±1 | 0.4 |
| PCWP, mmHg | 10±3 | 9±1 | 0.002 |

Data are expressed as mean ± SD
COP – cardiac output; LAV – left atrial volume; LVDD – left ventricular dimension at diastole; LVDS – left ventricular dimension at systole; PCWP – pulmonary capillary wedge pressure assessed by echocardiography; PWTd – posterior wall thickness in diastole; RV FAC – right ventricular fractional area change; SWTd – septal wall thickness in diastole.

**Table 4 – Clinical and echocardiographic findings in patients with elevated filling pressure and those with normal filling pressure.**

| | Patients with elevated filling pressure (n = 4) | Patients with normal filling pressure (n = 31) | *p* value |
|---|---|---|---|
| Age, y | 50±7 | 53±6 | 0.5 |
| QTc, ms | 464±15 | 442±34 | 0.1 |
| ALT, U/l | 34±25 | 47±30 | 0.4 |
| AST, U/l | 48±19 | 74±63 | 0.1 |
| Albumin, g/dl | 2.4±0.3 | 2.7±0.7 | 0.2 |
| LVDD, cm | 5.0±0.3 | 5.1±0.6 | 0.5 |
| LVDS, cm | 3.1±0.3 | 3.1±0.5 | 0.8 |
| LVEF, % | 69±1.5 | 67±0.4 | 0.2 |
| SWTd, cm | 0.87±0.1 | 0.9±0.1 | 0.8 |
| LAV, ml | 48±7.5 | 40±12 | 0.1 |
| Mitral E wave velocity, cm/s | 106±11 | 68±17.5 | 0.001 |
| Mitral A wave velocity, cm/s | 84±10 | 73±18 | 0.1 |
| Mitral E/A ratio | 1.3±0.04 | 0.9±0.3 | 0.05 |
| Lateral mitral e' velocity, cm/s | 9.2±2.5 | 12±3 | 0.1 |
| E/e' | 12±3.5 | 5.8±1.3 | 0.04 |
| PCWP, mm Hg | 17±4.5 | 9±1.6 | 0.04 |

Data are expressed as mean ± SD
ALT – alanine aminotransferase; AST – aspartate aminotransferase; COP – cardiac output; LAV – left atrial volume; LVDD – left ventricular dimension at diastole; LVDS – left ventricular dimension at systole; PCWP – pulmonary capillary wedge pressure assessed by echocardiography; PWTd – posterior wall thickness in diastole; QTc – corrected QT interval; RV FAC – right ventricular fractional area change; TAPSE – tricuspid annular plane systolic excursion, SWTd – septal wall thickness in diastole.

non-cirrhotic liver cirrhosis. All patients with elevated LV filling pressure (75% were females) had more advanced form of liver impairment. Heart rate, LV wall thickness, LV internal dimensions, and COP were not statistically different from patients with normal filling pressure. The mitral E wave velocity and E/A ratio were much higher in patients with elevated filling pressure reflecting worse, rather than better, diastolic function. The mean LAV in patients with elevated filling pressure was higher than that of patients with normal LV filling pressure; however, such difference was not statistically significant. The clinical characteristics of patients with elevated and normal LV filling pressure are shown in Table 4.

## Discussion

In this study, we found that about 25% of patients with non-alcoholic liver cirrhosis had evidence of LV diastolic dysfunction using the mitral inflow indexes. All these patients showed mild degree of LV diastolic dysfunction in the form of relaxation abnormality (reversed E/A ratio). Four more patients (11%) had elevated LV filling pressure as assessed by the equation previously described by Nagueh et al. [17]. Interestingly, all patients who were diagnosed as having elevated LV filling pressure in our study had apparently normal mitral inflow indexes suggesting that these parameters failed to identify accurately patients with advanced stage of diastolic dysfunction in patients with liver cirrhosis. We believe that the main reason for such discrepancy is the inability of patients with liver cirrhosis, especially those with tense ascites, to perform accurately the Valsalva maneuver. Many of our studied patients were uncooperative and anxious during the echocardiographic assessment, mostly secondary to the advanced stage of liver cell failure, and accordingly, performance of Valsalva maneuver by such patients was somehow difficult and unreliable. Additionally, many factors in this particular group of patients, other than the LV diastolic dysfunction per se, might be responsible for changes in the mitral inflow indexes such as the presence of tense ascites, tachycardia, anemia, the hyperdynamic status, and the abnormal preload.

### *Diastolic dysfunction in patients with liver cirrhosis*

LV diastolic dysfunction in patients with liver cirrhosis was previously reported in many studies, the majority of these studies used the mitral inflow indexes to assess the presence and severity of the LV diastolic dysfunction in these patients [10,12,13,20]. Papastergiou et al. found that up to 59% of patients with liver cirrhosis had diastolic dysfunction as assessed by the mitral inflow indexes. The majority of these patients had grade I diastolic dysfunction [21]. Comparable findings were also reported in a previous study that assessed the LV diastolic using the tissue Doppler imaging [22]. The abnormality of the LV relaxation is believed to occur in patients with cirrhosis secondary to LV hypertrophy seen in patients with hyperdynamic circulation [23]. Evidence of LV hypertrophy, however, was not detected in our study.

There are conflicting data about the correlation between the presence of ascites in patients with liver cirrhosis and the prevalence of LV diastolic dysfunction [12,20,23]. In an earlier study, LV diastolic dysfunction showed a significant improvement after total paracentesis in patients with tense ascites suggesting that LV diastolic dysfunction in these patients might be in part secondary to physical factors such as higher hemodynamic overload, increased intrathoracic pressure, and elevation of the diaphragm by abdominal fluid accumulation [24]. Similar improvement of the diastolic function was also showed in patients with liver cirrhosis following liver transplantation, both at rest and during exercise, at 6 and 12 months' follow-up examinations [25]. In our study, however, we could not make a correlation between the presence of ascites and the elevation of the LV filling pressure since all, except one, patients had ascites. This reflects the type of patients with more advanced stage of the disease usually referred to our tertiary care hospital.

### *Post-interventional cardiac complications, can we add something?*

Cardiac related causes account for 7–15% of all deaths after liver transplantation [8,26]. Up to 56% of patients with liver cirrhosis, most of them with no previous history of cardiac disease, develop clinical or radiographic evidence of pulmonary edema during their post-transplantation hospital course [27]. Moreover, other surgical stresses including TIPS have also been reported to be accompanied by an increase in the pulmonary capillary wedge pressure and to precipitate overt heart failure in these patients [28]. Unfortunately, predicting patients who are more prone to the development of post-transplantation/TIPS cardiac complications is still a big challenge [1,29]. Two-dimensional and dobutamine stress echocardiography were utilized to predict the development of adverse cardiac events following liver transplantation and both had a low predictive value [27]. Similarly, the occurrence of immediate post-transplantation left sided heart failure in a previous case-control study had no association with previous or concurrent events [30]. An earlier study, however, that assessed the utility of the mitral E/A ratio to predict ascites clearance and mortality after TIPS insertion found that an E/A ratio of $\leq 1$ was predictive of slow ascites clearance and death after TIPS [6]. These findings are in agreement with a previous study showing that the mitral E/A ratio measured at 4 weeks after TIPS insertion and not at baseline, was the only independent predictor of survival following this procedure [7]. According to our study, we suggest that assessment of the LV filling pressure, rather than simple assessment of the mitral inflow parameters could play a role in better identification of patients at higher risk for development of post-operative heart failure and pulmonary congestion. The mitral E/A ratio could not detect patients with elevated filling pressure as previously mentioned. Additionally, we also suggest that diagnosis of LV diastolic dysfunction in these patients using the mitral inflow parameters only can be misleading since changes in the mitral indexes could reflect many hemodynamic derangements in patients with cirrhosis rather than true LV diastolic dysfunction.

### *Limitations*

The small number of patients enrolled in the study was an important limitation. The LV filling pressure was not assessed invasively. Whether the pre-transplantation LV filling (both at rest and during exercise) can affect the

post-transplantation outcome need to be investigated in further studies.

## Conclusion

The resting LV filling pressure in patients with liver cirrhosis is elevated in about 11% of patients. Proper and meticulous assessment of the LV diastolic function is crucial in these patients, especially in those who are scheduled for liver transplantation, and should not be based only on the mitral inflow indexes. Many factors might be responsible for the inability of the mitral indexes to identify patients with high filling pressure and unmask the diastolic abnormality when a pseudonormal pattern is present.

### Conflict of interest
None declared.

### Ethical statement
The study protocol complies with the Declaration of Helsinki and its amendments and was approved by the local ethics committee.

### Informed consent
Informed consent was obtained from all participants.

### Funding body
None.

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