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Original article

Cardiac dysfunction in cirrhosis is not associated with the severity of liver disease ☆

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ABSTRACT

Background: Cirrhotic cardiomiopathy is described as the presence of cardiac dysfunction in cirrhotic patients. The aim of the study was to investigate factors associated with cardiac dysfunction in cirrhotic patients.

Patients and methods: Seventy-four cirrhotic patients and twenty-six controls performed a conventional echocardiography and Tissue Doppler Imaging (TDI) for systolic and diastolic function. Results were analyzed by using the Guidelines of American Society of Echocardiography.

Results: In patients with cirrhosis, left ventricular end-diastolic diameter was increased ($p<0.001$), peak systolic velocities were decreased (11.3 ± 2.7 vs 13.9 ± 1.4 cm/s; $p<0.001$) and left atrial volumes were increased (32.7 ± 8.3 vs 24 ± 8.5 ml, $p<0.001$) as well as cardiac mass (90.6 ± 23 vs 70.5 ± 22 g/m^2, $p<0.001$). Forty-seven cirrhotic patients (64%) showed diastolic dysfunction at rest: grade I in 37 and grade II in 10 patients. Systolic and/or diastolic dysfunction were not influenced by a more severe liver impairment. Diastolic dysfunction was more prevalent in patients with ascites vs those without (77% vs 56%; $p=0.04$).

Conclusion: A mild diastolic dysfunction at rest is frequent in cirrhotic patients but cardiac load conditions are confounding factors in this diagnosis. We did not identify an association between severity of liver disease and cardiac dysfunction.

1. Introduction

Historically, liver cirrhosis has not been associated with any cardiac abnormalities, despite the fact that a hyperdynamic state leading to increased cardiac output and decreased systemic vascular resistance has been described in patients with cirrhosis more than 50 years ago [1]. In the last 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. Overall these alterations are known as cirrhotic cardiomyopathy [2–4]. According to the 2005 World Congress of Gastroenterology, cirrhotic cardiomyopathy is defined as "a cardiac dysfunction in patients with cirrhosis characterised by impaired contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of other known cardiac disease" [5]. Systolic dysfunction, in cirrhotic patients, is characterized by a blunted increase in cardiac output and decreased contractility with exercise, pharmacological stress, and volume challenge [6]. Moreover cirrhotic patients have severe chronotropic incompetence, defined as significantly reduced cardiac response to exercise due to autonomic dysfunction with blunted sensitivity to sympathetic activation [7]. Diastolic dysfunction in cirrhotic patients has been associated with increased left ventricular wall thickness, subendocardial oedema, fibrosis and altered collagen structure, ultimately leading to altered relaxation [8]. Electrophysiological abnormalities have been related to plasma membrane and fluidity changes, adrenergic and post receptor signalling pathway defects and/or ion channel dysfunction [2]. The main electrophysiological changes in cirrhosis are prolongation at electrocardiography of the QTc interval and impaired electromechanical coupling likely as a result of potassium and calcium ion channel defects [9,10].

The criteria adopted for the diagnosis of diastolic dysfunction in cirrhotic patients need, however, to be interpreted with caution. Previous studies have based the diagnosis of diastolic dysfunction mainly on 2D-Doppler echocardiography parameters [11–13]. It is however well known that the E/A ratio is strongly influenced by loading

Abbreviations: decTime, deceleration time; EF, ejection fraction; IVRT, isovolumetric ventricular relaxation time; LAESV, left atrial end-systolic volume; LVEDD, left ventricular end diastolic diameter; LVEDV, left ventricular end diastolic volume; LVESD, left ventricular end systolic diameter; MAP, mean arterial pressure; PWDT, posterior wall diastolic thickness; SWDT, septal wall diastolic thickness; SWST, septal wall systolic thickness; TDI, tissue Doppler imaging.

☆ Disclosure: The authors have nothing to disclose No conflict of interest exist.

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conditions, and decompensated cirrhotic patients are frequently suffering a condition of fluid retention. Moreover it has not been completely defined how many parameters need to be altered for the diagnosis of diastolic dysfunction, therefore different criteria have been utilized in different studies. Furthermore, as diastolic dysfunction is physiological with advancing age, some authors have applied a correction for age [14], which was however not applied in other studies. The use of Tissue Doppler Imaging (TDI) can overcome some of this criticism, mainly because this echocardiography method is less influenced by the changes in cardiac load conditions [15]. The American Society of Echocardiography has included TDI parameters in the definition of diastolic dysfunction and these criteria have recently been updated [16]. Our study aimed at evaluating, in a selected group of cirrhotic patients, the relationship between cirrhotic cardiomiopathy evaluated by TDI and the severity of liver impairment.

2. Patients and methods

Cirrhotic patients, either admitted in hospital or followed as outpatients, were considered for the study. Diagnosis of cirrhosis was established through histology and/or a combination of clinical, biochemical and instrumental findings. Age <18 and >75 years, active alcohol abuse, surgical or radiological shunts, hepatocellular carcinoma (beyond Milan criteria) or recurrence of cirrhosis after liver transplantation were causes of exclusion. Patients with a history of past or present cardiac disease, severe arterial hypertension, chronic pulmonary disease or an abnormal 12 leads electrocardiogram were also excluded. Hospitalized patients with active complications were studied only after successful treatment. A total of 74 patients were then enrolled in this study and 26 sex and age-matched healthy subjects were studied with a similar protocol and constituted the control group.

All patients were informed about the opportunity of being included in a study aimed at a more complete cardiovascular assessment and those enrolled gave a written consent. The study was approved by the Local Ethical Committee.

2.1. Clinical evalutation

On the day of the study, heart rate and blood pressure were measured. Blood pressure was measured by sphygmomanometer and the mean arterial pressure (MAP) was calculated as (systolic pressure + diastolic pressure × 2)/3. Patients provided a detailed clinical history and had a clinical examination and blood tests (including haematology and biochemistry profile). Liver function was quantified by Child-Pugh and MELD scores [17,18]. Therapies assumed in the last weeks were recorded. Patients were followed up until death or liver transplantation for 12 months.

2.2. Electrocardiographic evaluation

A 12 leads electrocardiogram was done in each patient and QTc interval was estimated according to Bazett's formula: QTc = QTmax/square root of RR interval.

2.3. Echocardiography

Echocardiography was performed by an experienced operator in accordance with the recommendations of the American Society of Echocardiography [18], using an Aplio CV (Toshiba Industrial System 2004) system operating with a 3.5 MHz transducer. From a long axis parasternal view, the left ventricular (LV) systolic and diastolic septal wall thickness (SWST and SWDT), posterior wall thickness (PWTs and PWTd) and the LV diameter (LVESD and LVEDD) were measured in M-mode. The LV mass and LV geometry were calculated accordingly. LV volumes and LV Ejection Fraction (LVEF) were estimated using Simpson's modified biplane method. An LVEF above 50% was considered normal. Left atrial end-systolic volume was calculated with monoplane method in apical 4-chambers views using the following formula: volume = $8\ (A1)^2/3\pi\cdot(L)$.

Pulsed Doppler examination of the LV inflow was performed with the sample volume placed between the mitral leaflet tips. The following parameters were recorded and measured: peak early (E wave) and atrial (A wave) flow velocities, their ratio E/A, and the E-wave deceleration time. TDI was obtained from the four chamber apical view and tissue velocity were calculated. The myocardial peak systolic velocity (S′) was measured in lateral mitral annulus to define systolic function. Tissue velocities were also measured in the lateral mitral annulus during the diastole to obtain peak myocardial velocities during early (E′) and atrial filling (A′) phases. Isovolumetric Ventricular Relaxation Time (IVRT) was measured by TDI. To evaluate ventricular filling pressure also E/E' ratio was calculated. The intra observer variation for echocardiographic measurements was <10%. Systolic and diastolic functions were defined according to American Society of Echocardiography 2009 [16]. Diastolic dysfunction was divided in three grades of increasing severity. Mild diastolic dysfunction (grade I) was defined as mitral E/A ratio <0.8, decTime >200 ms, IVRT ≥100 ms, annular E' <8 cm/s and E/E′ lateral ratio <8; moderate diastolic dysfunction (grade II) as mitral E/A ratio between 0.8 and 1.5, E/E′ lateral 9 to 12 and E′ <8 cm/s and severe diastolic dysfunction (grade III) as E/A ≥2, decTime <160 ms, IVRT ≤60 ms, E/E′ lateral >12. The patient's assessment, taking into consideration the patient age and heart rate, was always performed by the senior cardiologist (C.T.).

2.4. Statistical analysis

All the values are reported as means ± SD and p values <.05 were considered as significant. Data were analyzed as continuous or categorical by using the Student T test for parametric data and the Mann–Whitney U test or Wilcoxon for non-parametric data; the Chi-square test was used for the comparison of dichotomist data. Correlations were explored by means of logistic and linear regression analyses. Survival rate was calculated according to the Kaplan–Meier method and survival curves were compared with the log rank test. The software used for the analysis was NCSS (Number Cruncher Statistical System) 2007.

3. Results

3.1. Patients characteristics

Seventy-four cirrhotic patients were included in the study (Table 1). The prevalent etiology of cirrhosis was post-viral, followed by post-alcoholic. Age, sex distribution and severity of liver disease were similar in patients with alcoholic and viral origin of liver disease.

As expected, liver dysfunction was more severe in hospitalized (49 patients) than ambulatory patients (25 patients). Twenty-three hospitalized and 2 non-hospitalized patients were studied in the presence of mild ascites. Patients were not assuming drugs potentially affecting the QT interval except 26 patients who were under beta-blockers at a dosage between 20 and 40 mg/daily. A prolonged QTc interval (>440 ms) was reported in 45% of patients with a similar prevalence in those assuming vs those not assuming beta-blockers.

3.1.1. Echocardiographic characteristics

Left ventricular end-systolic and end-diastolic diameters were significantly increased in cirrhotic patients compared with the healthy controls (30.4 ± 6 vs 27.6 ± 4 mm, p = 0.02 and 50.4 ± 5.8 vs 44 ± 4.4 mm, p = <0.0001, respectively), however left ventricular volumes were similar (Table 2). Left ventricular ejection fraction was always within normal limits in cirrhotic patients, while the peak systolic velocities recorded with TDI (S′) were significantly decreased. The decrease in S′ was particularly evident in post-alcoholic patients