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● *Original Contribution*

NEW DEFINITION CRITERIA OF MYOCARDIAL DYSFUNCTION IN PATIENTS WITH LIVER CIRRHOSIS: A SPECKLE TRACKING AND TISSUE DOPPLER IMAGING STUDY

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Abstract—There are no clear recommendations regarding cirrhotic cardiomyopathy (CC) evaluation in patients with pre-transplant liver cirrhosis. The roles of new methods, tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE) in the diagnosis and prognosis of cirrhotic cardiomyopathy remain controversial. We investigated the utility of TDI/STE parameters in cirrhotic cardiomyopathy diagnosis and also in predicting mortality in patients with liver cirrhosis. Left/right ventricular function was studied using conventional TDI (velocities) and STE (strain/strain rate). We assessed left ventricular diastolic dysfunction, graded into four new classes (I/Ia/II/III). Serum NTproBNP (N-terminal prohormone of brain natriuretic peptide), troponin I, β-crosslaps, QTc interval, arterial compliance and endothelial function were measured. Liver-specific scores (Child–Pugh, MELD, MELDNa) were computed. There was a 1-y follow-up visit to determine mortality. We observed resting biventricular diastolic myocardial dysfunction, not presently included in the definition of cirrhotic cardiomyopathy. We provided an improved characterization of cardiac dysfunction in patients with liver cirrhosis. This might change the current definition. However, the utility of STE/TDI parameters in predicting long-term mortality in patients with liver cirrhosis remains controversial. (E-mail: roxanasisu@gmail.com)

Key Words: **Cirrhotic cardiomyopathy, Speckle tracking echocardiography, New definition criteria, Mortality.**

INTRODUCTION

Liver cirrhosis (LC) is an important cause of mortality in adults worldwide (Hoyert and Xu 2012). Access to liver transplant (LT) has improved the prognosis of advanced LC (Martin et al. 2014). Because cardiac dysfunction has emerged as a leading cause of mortality after LT (Madhwal et al. 2012), an accurate and comprehensive pre-transplant cardiac evaluation is highly required, as already stated in LT guidelines (McCaughan 2012). However, the most updated pre-LT evaluation guideline provides only an algorithm for the evaluation of major cardiovascular diseases, without giving any clear recommendations with respect to "cirrhotic cardiomyopathy" (CC) (Martin et al. 2014).

CC includes a variety of structural myocardial changes, systolic and diastolic dysfunction and electrophysiological changes, in the context of augmented vascular function (Kazankov et al. 2011; Ripoll et al. 2011; Zardi et al. 2010). It seems to be present in 40%–50% of patients with LC (Espinosa et al. 2012; Møller and Henriksen 2010). Its diagnosis is based mostly on conventional echocardiography (Dowsley et al. 2012; Mahmood et al. 2012; Møller and Henriksen 2010; Zaky and Bendjelid 2015; Zardi et al. 2010), which identifies only the late stages of cardiac dysfunction. So far, there are only a few studies that are designed to characterize the intrinsic myocardial properties of LC, using new imaging methods: tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE) (Kazankov et al. 2011; Nazar et al. 2013; Sampaio et al. 2014). These might be essential to early detection and better definition of cardiac dysfunction in presumed high pre-load conditions. Moreover, serum levels of the N-terminal prohormone of brain natriuretic peptide (NTproBNP) and troponin I

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(TpI) are reported to be elevated in patients with LC. However, the exact role of these new echocardiography methods and biomarkers in CC diagnosis and prognosis is not well established (Alexopoulou et al. 2012; Merli et al. 2013; Møller et al. 2013; Nazar et al. 2013; Pimenta et al. 2010; Sampaio et al. 2013, 2014; Zaky and Bendjelid 2015).

Our aims were to detect early cardiac dysfunction in a cohort of patients with LC using newer and potentially more accurate methods (TDI and STE) and to correlate these findings with different cardiac biomarkers, severity of hepatic disease and parameters of vascular compliance and endothelial function. We also intended to improve the diagnosis of diastolic dysfunction in patients with LC and to test whether this detailed cardiovascular evaluation is useful in predicting mortality.

METHODS

Population

We prospectively evaluated consecutive patients with LC referred to our echocardiography laboratory with a diagnosis of cirrhosis based on clinical, laboratory, ultrasonographic, endoscopic and/or histologic criteria, confirmed by two experienced gastroenterologists (M.R. and C.S.P.). Inclusion criteria were age >18 y, sinus rhythm, and left ventricular (LV) ejection fraction (LVEF) > 50%. Exclusion criteria were history of any cardiac disease, diabetes mellitus, ongoing pulmonary or renal disease, any disease or neoplasia with an estimated survival <12 mo, hemochromatosis, encephalopathy greater than grade 2, uncontrolled ascites, recent gastrointestinal bleeding (<2 mo) or ongoing infection and abnormal electrocardiogram (ECG). Patients with more than mild valvular heart disease and patients who were technically unsuitable for STE/TDI analysis were also excluded.

Demographic and clinical data (age, sex, body mass index, heart rate, systolic and diastolic blood pressure, liver cirrhosis etiology, encephalopathy and a complete clinical examination), as well as treatment with all potentially cardiovascular active drugs, were recorded on enrollment. All eligible patients underwent clinical evaluation, 12-lead ECG, blood sample collection and a complex echocardiographic and vascular evaluation, all performed during the same day. Beta blockers were interrupted as per protocol 48 h before assessment. A group of healthy controls, matched on age and sex with LC patients, also prospectively enrolled, underwent the same evaluation. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in an *a priori* approval by the institution's human research committee. It was registered on ClinicalTrials.gov (NCT01713478) and was approved by the local institutional ethics committee. Informed consent was obtained from all patients before enrollment.

Electrocardiographic and echocardiographic evaluation

The QT interval was corrected (QTc) with Bazett's formula. A detailed echocardiographic evaluation (conventional, STE, TDI) was performed by two experienced echocardiographers (R.C.R. and S.M.B.), using a GE Vivid 7 ultrasound machine (GE Medical System, Horten, Norway). A standard transthoracic study was performed to define anatomy and valvular and ventricular function according to the American Society of Echocardiography (ASE) guidelines (Lang et al. 2015). Mitral and tricuspid inflow velocities were assessed using pulsed-wave (PW) Doppler in the apical four-chamber view and to record LV outflow tract velocity in the apical five-chamber view. End-expiratory PW tissue Doppler velocities were acquired in the apical four-chamber view, with the sample positioned at the septal, lateral mitral annulus and at the lateral tricuspid annulus.

For STE, apical four-, two- and three-chamber views, as well as short-axis views at the level of papillary muscles, were obtained using conventional 2-D gray-scale echocardiography, during breath hold, with a stable ECG recording. Particular attention was given to obtaining adequate gray-scale imaging, to allow reliable delineation of myocardial tissue and extra-cardiac structures. The frame rate was set between 60 and 80 frames/s. Data were analyzed offline, using EchoPac PC software, Version BT12 (GE Medical Systems), with selection of the most stable cardiac cycle for generation of the strain curves.

LV systolic function was assessed from indexed LV volumes and dimensions, LVEF, cardiac index (CI) and LV mass, according to the ASE guidelines (Lang et al. 2015). LV volumes and LVEF were calculated using the biplane method of disk summation (modified Simpson's rule). STE allowed measurement of the global longitudinal, radial and circumferential strain and LV global longitudinal systolic strain rate, by use of previously validated methods (Mor-Avi et al. 2011) (Fig. 1).

LV diastolic function was evaluated according to the most recent recommendations (Kuwaki et al. 2014; Nagueh et al. 2016), We assessed four parameters, proposed by the most recent DD guidelines: medial and lateral diastolic annular velocities (E'_m and E'_l), E/E' ratios (E' = average from E'_m and E'_l), left atrial (LA) indexed volume (LAVi) and peak velocity of tricuspid (TR) jet. We used the cutoff values established by the guidelines: $E/E' > 14$, $E'_m < 7$ cm/s or $E'_l < 10$ cm/s, LAVi ≥34 mL/m^2 and TR velocity >2.8 m/s. LV diastolic function is normal if more than half of the available variables do not meet the cutoff values for identifying abnormal function. LV diastolic dysfunction is present if more than half of the available parameters meet these cutoff values. The study is inconclusive if half of the parameters do not meet the cutoff values (Nagueh et al. 2016). We also evaluated the following parameters of diastolic function derived from the mitral inflow profile, to