Research Article

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Cirrhosis

Effect of ventriculo-arterial coupling on transplant outcomes in cirrhotics: Analysis of pressure-volume curve relations

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Background & Aims: Ventriculo-arterial coupling (VAC) reflects the interaction between ventricular performance and effective arterial load. Current criteria for cirrhotic cardiomyopathy focus only on cardiac function without addressing the effect of hyperdynamic, low-resistance circulation. We investigated alterations in VAC in cirrhotic patients and their associations with post-liver transplant all-cause mortality.

Methods: In this single institution cohort study, cirrhotic patients who underwent liver transplantation (LT) (n = 914) were retrospectively compared with healthy matched controls using noninvasively measured end-systolic ventricular elastance (Ees), arterial elastance (Ea), and VAC (Ea/Ees). All-cause mortality based on VAC values were investigated using a Cox hazard model with the inverse probability treatment weighting (IPTW) of propensity score.

Results: Cirrhotic patients had significantly lower Ees, Ea and VAC values than controls. Over a median of 30 months, 96 patients died after LT. In patients with a high model for end-stage liver disease score ($\geqslant$25), VAC of >0.61 (highest tertile) had poorer survival outcomes than patients with VAC of $\leqslant$0.50 (lowest tertile) (66.0% *vs.* 91.8%; Log-rank $p = 0.001$), and was independently associated with risk of mortality (hazard ratio, 2.44; 95% CI, 1.10–5.39; $p = 0.028$) compared with VAC of $\leqslant$0.61 after IPTW adjustment.

Conclusions: In cirrhotic patients, ventricular elastance and VAC values are lower than those in controls. However, in advanced cirrhotic patients, an increase in VAC value is associated with all-cause mortality after LT, suggesting that this non-invasive estimation of ventriculo-arterial uncoupling is an additional novel prognosticator in cirrhotic cardiovascular disorders.

Lay summary: In cirrhotic patients, cardiac dysfunction is latent and only manifests under stressful conditions because of arterial vasodilation. In this study, based on the pressure-volume curve of cardiac function, we investigated characteristics of the ventricular-arterial coupling in cirrhotic patients and further found that disparities in the ventriculo-arterial relationship are associated with graft failure and all-cause mortality after liver transplantation.

Introduction

Cardiovascular abnormalities in advanced liver cirrhosis (LC) are characterized by a hyperdynamic circulation featuring increased heart rate and high cardiac output, concomitant with decreased systemic vascular resistance [1]. As LC progresses, cardiac dysfunction, known as cirrhotic cardiomyopathy, is associated with prognosis after transjugular intrahepatic portosystemic shunt [2,3] or liver transplantation (LT) [4–6]. Specifically, diastolic dysfunction has been more emphasized for estimating clinical outcome in cirrhotic patients, whereas systolic dysfunction has limited prognostic implications in hepatorenal syndrome patients [7]. However, in most cirrhotic patients, cardiac dysfunction is latent and only manifests under stressful conditions because reduced ventricular contractility in these patients is masked by pronounced arterial vasodilation and increased arterial compliance. Therefore, a load-dependent index such as left ventricular ejection fraction (LVEF) is insensitive to detect systolic cardiac impairment in the resting state in cirrhotic patients [8,9]. Hence, a more appropriate index is required to evaluate the integration of the ventricular and arterial systems in cirrhotic cardiovascular disorders.

Interaction between the left ventricle and the arterial system has been explained on the basis of end-systolic pressure-volume relation [10,11]. Left ventricular end-systolic elastance (Ees), as quantified by the ratio of end-systolic pressure (ESP) to end-systolic volume (ESV), is an index of the load-independent ventricular contractile state [12]. Given this pressure-volume relationship, effective arterial elastance (Ea) can be calculated by the ratio of ESP to stroke volume (SV), indicating a net measure of arterial load [13]. The ratio of these values (Ea/Ees), designated ventriculo-arterial coupling (VAC), represents the integrated interaction of the ventricular and arterial systems [14–16].

Keywords: Cirrhotic cardiomyopathy; Liver transplantation; Pressure-volume relationship; Ventricular elastance.

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Ventriculo-arterial uncoupling, occurring in various clinical conditions, can predict morbidity and mortality [17,18]. In cirrhotic patients, typically reduced arterial loads may contribute to a change in the slope between ESP and ventricular volume. Therefore, VAC in such patients may differ from that found in healthy subjects. However, to our knowledge, no study has systematically examined how the low-resistance, hyperdynamic circulation in LC influences pressure-volume relationships such as VAC.

In this study, we hypothesized that pressure-volume relationships, including Ea, Ees, and VAC, in cirrhotic cardiomyopathy patients who had undergone LT would differ from those measured in healthy matched controls. We further examined whether disparities in the ventriculo-arterial relationship are associated with graft failure and all-cause mortality after LT.

Patients and methods

Study population and healthy matched controls

In this observational cohort study, we retrospectively evaluated data that had been collected for 1111 consecutive adult patients who underwent LT at a single tertiary institution (Asan Medical Center, Seoul, Korea) between October 2009 and October 2012. A total of 197 patients were excluded for the following reasons: LT performed because of acute fulminant hepatic failure without chronic liver disease (n = 39), retransplantation after initial graft rejection (n = 32), valvular disease with more than moderate grade regurgitation or any stenosis degree (n = 4), significant obstructive coronary artery disease (n = 6), open cardiac surgery history (n = 3), atrial fibrillation (n = 4), chronic kidney disease (n = 14), or incomplete echocardiographic data (n = 95). This left 914 patients who had undergone both pulsed-wave transmitral flow measurement and tissue Doppler imaging. After approval from the local research ethics committee (protocol number 2015–0192), we analyzed patient data in accordance with the ethical standards of the 1964 Declaration of Helsinki and its amendments.

A cohort of healthy controls comprised individuals who underwent transthoracic echocardiography and laboratory examination between October 2009 and October 2012 in the Health Screening and Promotion Center of our institution. Using appropriate procedures to protect anonymity, we reviewed laboratory and echocardiographic findings, and questionnaires. Healthy candidates were selected if they had normal liver function test results; no liver or kidney disease, including hepatic tumors, hepatitis, or hepatitis virus carriers; and no significant cardiovascular disease history, including obstructive coronary artery disease, valvular disease, arrhythmia, or aortic disease. We excluded those with incomplete documentation, leaving a pool of 10,145 healthy individuals. From this, we selected subjects matched with the patients who had undergone LT for age (within 1 year), sex, and hypertension and diabetes mellitus history. Data from 912 matched pairs were available for analysis.

Pre-transplant evaluation and baseline characteristics

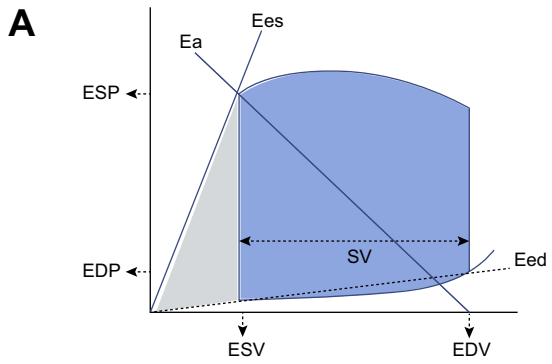
All transplant recipients had undergone routine preoperative evaluation. Medical history and physical examination included etiology of end-stage liver disease; variceal bleeding, hepatic encephalopathy, or intractable ascites history; comorbidity with hypertension or diabetes; and current medications at the time of LT, including beta-blockade, vasopressors, or inotropics. A baseline QT interval corrected for heart rate using Bazett's formula was measured on preoperative electrocardiography. Laboratory tests included measuring the prothrombin time, platelet count, and hemoglobin, total bilirubin, albumin, aspartate aminotransferase, alanine aminotransferase, serum creatinine, and B-type natriuretic peptide levels. We determined disease severity based on the model for end-stage liver disease (MELD) score and Child-Turcotte-Pugh classification. Donor- and operation-related variables included donor type, donor age, antibody (ABO) compatibility, macro- and microsteatosis, cold and warm ischemic times, graft-recipient weight ratio, and operating time.

Echocardiographic measurements

Two-dimensional and Doppler transthoracic echocardiography examinations using a commercially available ultrasound system (Philips iE33; Philips Medical Systems, Andover, MA) were performed at the institution's echocardiography laboratory. According to the American Society of Echocardiography recommendations [19], an experienced sonographer examined cardiac structures and function and attending staff cardiologists with no knowledge of patient characteristics interpreted and confirmed them. Left ventricular dimension and wall thickness, ESV, end-diastolic volume (EDV), SV, and left ventricular mass index were recorded. LVEF was measured using a modified Simpson's biplane method or the Teichholz method. The size of the left atrium and ascending aorta were measured. Pulsed-wave Doppler parameters included transmitral peak rapid filling and atrial velocity (E and A), deceleration time, and E/A ratio. Using tissue Doppler imaging measurements, peak systolic (s', an index of global systolic function) and early and late diastolic velocities at the septal mitral annulus (e' and a', respectively) were recorded, and the E/e' ratio were calculated. Further, systolic and diastolic blood pressures and heart rate were also recorded.

Variables derived from left ventricular pressure-volume relations

To quantify ventricular contractility noninvasively, we calculated Ees as ESP divided by ESV [12]. For arterial load, Ea was the ratio of ESP to SV, and VAC was defined as the ratio of Ea to Ees (Fig. 1A) [15]. For these equations, ESV and SV were obtained from echocardiographic results. ESP was defined as 0.9 x systolic blood pressure determined by noninvasive blood pressure measurement at the same time as echocardiographic examination [13]. End-diastolic elastance



End-systolic pressure (ESP)	= systolic blood pressure x 0.9
Arterial elastance (Ea)	= ESP/stroke volume (SV)
End-systolic LV elastance (Ees)	= ESP/end-systolic volume (ESV)
End-diastolic LV elastance (Eed)	= EDP/end-diastolic volume (EDV)
Ventriculo-arterial coupling (VAC)	= Ea/Ees
Stroke work (SW)	= ESP x SV
Potential energy (PE)	= ESP x ESV/2
Pressure-volume area (PVA)	= PE + SW
LV work efficiency	= 100 x SW/PVA

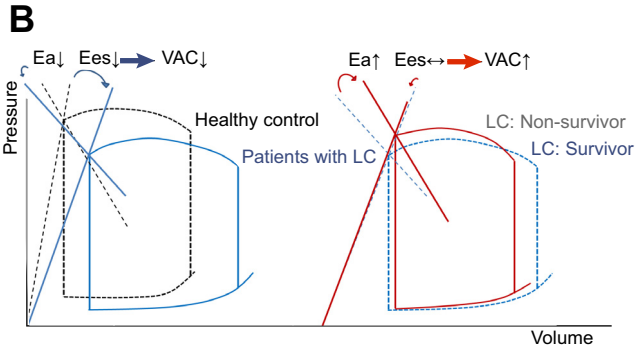


Fig. 1. Pressure-volume loops of the left ventricle. (A) Measurement of parameters derived from a pressure-volume loop of the left ventricle. (B) Example of pressure-volume loops. Compared with a healthy control (black dashed lines), the LC patient has decreased Ees, Ea, and VAC on a right-shifted pressure-volume loop (blue lines). Compared with a survivor, Ees is similar, whereas Ea is higher in a patient who died (red lines). Consequently, VAC increases and stroke volume decreases compared with values for the survivor (blue dashed lines). (This figure appears in colour on the web.)