Cardiomyopathy&Heart Failure

High Flow-Mediated Vasodilatation Predicts Pulmonary Edema in Liver Transplant Patients

Shyh-Ming Chen,[1,2] Chao-Long Chen,[2,3] Han-Tan Chai,[1,2] Chee-Chien Yong,[2,3] Hsien-Wen Hsu,[2,4] Yu-Fan Cheng,[2,4] Morgan Fu,[1,2] Yu-Tung Anton Huang[5] and Chi-Ling Hang[1,2]

Background: Early pulmonary edema is common after orthotopic liver transplantation. Associated pathogenic mechanisms might involve increased activity of cardiac-inhibitory systems due to increased vasodilator production, mainly nitric oxide (NO). NO is primarily responsible for flow-mediated vasodilatation (FMD). We investigated the incidence of pulmonary edema in liver transplant patients and its correlation with FMD.

Methods: We prospectively evaluated traditional risk factors, Doppler echocardiographic findings, derived hemodynamic data, and brachial artery nitroglycerin-induced vasodilatation (NTD) and FMD within 1 week prior to liver transplantation in 54 consecutive liver transplant patients with cirrhosis. Post-transplantation chest roentgenography was performed daily. In-hospital outcomes, transfusion volume of blood components, and hemodynamic data during surgery and at the intensive care unit were analyzed.

Results: Twenty-nine patients (53.7%) developed radiological pulmonary edema within 1 week of transplantation. Diffuse-type interstitial and alveolar pulmonary edema constituted 13 cases (24.1%). Patients with pulmonary edema had higher pretransplantation Child-Turcotte-Pugh scores ($p = 0.01$), cardiac output ($p = 0.03$), FMD ($p < 0.01$), NTD ($p = 0.01$), and FMD/NTD ratio ($p = 0.02$). Although the total volume of intravenous fluid transfused was higher in the pulmonary edema group, the net fluid retention during surgery was statistically insignificant. The lengths of intensive care unit stay and hospitalization, as well as mortality rates, were not different in these groups.

Conclusions: The high incidence of pulmonary edema after living donor liver transplantation was associated with a high FMD and FMD/NTD ratio at pretransplantation. FMD is the only significant predictor associated with pulmonary edema. However, we observed no alteration in mortality rates.

Key Words: Cirrhotic cardiomyopathy • Flow-mediated vasodilatation • Liver transplantation • Pulmonary edema

INTRODUCTION

Liver transplantation is the treatment of choice for patients with advanced liver disease.[1] Despite careful cardiac evaluation before liver transplantation and the exclusion of patients with overt heart failure, 12%-56% of patients develop radiographic or clinical evidence of pulmonary edema.[2-4] Although most cases of pulmonary edema are mild and resolve with medical therapy, some patients develop severe heart failure.[5]

Myocardial dysfunction in patients with liver cirrhosis is known as cirrhotic cardiomyopathy (CCM). CCM is usually clinically silent; however, overt heart fail-

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[1]Section of Cardiology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital; [2]Chang Gung University College of Medicine; [3]Liver Transplant Program and Department of Surgery; [4]Department of Radiology, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung; [5]Department of Gerontological Care and Management, Chang Gung Institute of Technology, Taoyuan, Taiwan.

Address correspondence and reprint requests to: Dr. Chi-Ling Hang, Kaohsiung Chang Gung Memorial Hospital, No. 123, Tai Pei Road, Niao Sung District, Kaohsiung City, Taiwan. Tel: 886-7-731-3123 ext. 2363; Fax: 886-7-731-7123 ext. 2355; E-mail: samuelhang@hotmail.com

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ure can be precipitated by stresses such as transjugular intrahepatic portosystemic shunt insertion or liver transplantation.[6-8] The pathogenic mechanisms are thought to be due to the decreased activity of stimulatory pathways and increased cardiac-inhibitory activity.[9-12] The increased activity of cardiac-inhibitory systems is due to the increased production of vasodilator molecules, mainly nitric oxide (NO). Advanced liver disease is associated with changes in both hepatic sinusoidal resistance and systemic vascular resistance.[13] Sinusoidal NO production is impaired in cirrhotic subjects due to increased caveolin expression.[13,14] In contrast, NO production drive is increased in the peripheral arterial circulation, that causes vasodilatation and high cardiac output. Cirrhotic cardiomyopathy is defined as a syndrome in patients with cirrhosis characterized by blunted cardiac contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities, in the absence of known cardiac disease.[13]

Flow-mediated vasodilatation (FMD) is an endothelium-dependent process that reflects the relaxation of a conduit artery exposed to increased blood flow and therefore increased shear stress.[15] As shear stress increases, a number of vasodilators are released by the endothelium, including NO, prostaglandins, and endothelium-derived hyperpolarizing factors.[16,17] NO is thought to be the major factor responsible for the FMD response.[18] Therefore, we conducted this study to assess the incidence of pulmonary edema in liver transplant patients and its correlation with FMD.

MATERIALS AND METHODS

From May 2008 to April 2009, 67 patients received living donor liver transplants in our hospital. Fifty-four consecutive liver cirrhosis patients who were over 18 years of age and able to received FMD exams were prospectively enrolled in our study. All patients underwent pretransplantation evaluation including assessment of demographic parameters, severity of liver disease as measured by Child-Turcotte-Pugh (CTP) and model for end-stage liver disease (MELD) scores, renal function, hemodynamic parameters, and cardiac function (assessed by echocardiography). Endothelium-dependent vasodilatations were assessed by brachial artery FMD within 1 week before liver transplantation. Electrocardiogram (ECG) analysis and baseline serum biochemistry assays were performed before transplantation. Complete medical histories were obtained to evaluate major cardiovascular risk factors, including age, gender, hypertension, hypercholesterolemia, diabetes mellitus, family history of early coronary artery disease and cigarette smoking.

All patients received transplants from living donors through the piggyback procedure without venovenous bypass.[19,20] All patients were monitored for central venous pressure (CVP), pulse oximetry, end-tidal CO_2, ECG, arterial line for continuous blood pressure measurements, body temperature, and urine output. The patients were maintained on minimal intravenous fluids (1-1.5 mL kg^{-1} h^{-1}) during extrahepatic dissection and parenchymal transaction with a target CVP between 5 and 10 cm H_2O. If the CVP was higher than 10 cm H_2O, intravenous furosemide was given; a second dose of furosemide was given if the urine output was lower than 0.5 mL kg^{-1} h^{-1}. After completion of parenchymal transaction, blood loss, ascites, and intraoperative transudate loss were primarily replaced with 5% albumin and crystalloids to maintain a CVP of around 10 cm H_2O. Red blood cell transfusion was not given when the hemoglobin level was higher than 8.0 g/dL, and as long as the intravascular volume was sufficient to maintain normal hemodynamics. Laboratory data such as anesthesia time, hourly CVP, blood loss, blood transfusion, crystalloids administration, dose of furosemide given, and urine output were collected, compared, and analyzed. This study was approved by the Research Ethics Committee of our institution, and written informed consent was obtained from all patients.

Echocardiography

Echocardiography was performed with a 3.5-MHz phased array transducer probe (S3 transducer, Sonos 5500 and 7500; Philips Medical Systems, Bothell, WA, USA) through the left parasternal view and apical 4-chamber view according to the recommendations of the American Society of Echocardiography.[21] In the apical 4-chamber view, the inflow area of the left ventricle just below the level of the mitral annulus was the selected site for a Doppler recording of diastolic transmitral flow. Left ventricular end diastolic volume (LVEDV), left ven-

tricular end systolic volume (LVESV), left ventricular ejection fraction, stroke volume (SV), early maximal ventricular filling velocity (E), late ventricular or maximal filling velocity (A) during atrial systole, the E/A ratio, deceleration time (DT), and isovolumic relaxation time (IVRT) were calculated. The LVEDV and LVESV were calculated using the Simpson biplane method. SV was measured as the difference between LVEDV and LVESV obtained by the Simpson method. If there was valvular regurgitation, the regurgitant volume was subtracted to obtain the SV across the left ventricular outflow tract. Cardiac output (CO) and systemic vascular resistance (SVR) were calculated according to the following formulas:

$$CO\ (L/min) = SV\ (L/beat) \times heart\ rate\ (beats/min)$$

$$SVR\ (dyn \cdot s \cdot cm^{-5}) = [80(MAP - mean\ RAP)]/CO$$

where MAP (mmHg) is the mean artery pressure and RAP (mmHg) is the right atrial pressure.

The E wave and its DT, the A wave, and the E/A ratio are popular indices of diastolic dysfunction. IVRT is the time interval between the closure of the aortic valve and the opening of the mitral valve. As myocardial relaxation falls, the rate of left ventricular pressure decline also falls. These changes result in prolongation of DT, reduction in E velocity, lengthening of the IVRT, and a compensatory increase in the A wave (E/A < 1.0).[22] In this study, mild diastolic dysfunction (impaired relaxation) was defined as DT > 220 ms or IVRT > 90 ms, and severe diastolic dysfunction (restrictive pattern) as DT < 150 ms or IVRT < 70 ms.[23] All echocardiograms were performed by the same operator.

FMD and nitroglycerin-induced vasodilation

Changes in brachial artery diameter during reactive hyperemia were measured by high-resolution ultrasound similar to and as described in other studies.[24,25] In short, ultrasound evaluation was performed with a 7.5-MHz linear array ultrasound probe (HP Sonos 2500, Andover, MA, USA) by a single dedicated cardiologist. Scans of the brachial artery were obtained 3-5 cm proximal to the right elbow in the longitudinal section. Arterial flow was determined with a pulsed-Doppler signal at the beginning, 60 s after cuff release, and at the end of the study. Increased blood flow was induced by a blood pressure cuff placed around the forearm, with 5-min inflation at 220-250 mmHg, followed by rapid deflation. Baseline images before cuff inflation and images following cuff deflation were recorded. Arterial diameter was measured at the end-diastolic phase (confirmed by the incident R wave on synchronized ECG monitoring) from digital recordings by using an automatic edge detecting system (LabVIEW 8.5; National Instruments, Austin, TX, USA) by a single observer blinded to the subjects' identities. FMD was the percentage of vessel response compared to the baseline image. Endothelial dysfunction is usually reflected by an impaired FMD response. A single dose (0.4 mg) of nitroglycerin spray was applied to determine the maximum obtainable vasodilator response, and to serve as a measure of endothelium-independent vasodilatation reflecting vascular smooth muscle function [nitroglycerin-induced vasodilatation (NTD)].

Pulmonary edema

Arterial oxygenation, chest roentgenograms (CXRs), and hemodynamic data (CVP, vital signs, and urine output) were collected to evaluate patients for pulmonary edema preoperatively and postoperatively in our liver intensive care unit (ICU). CXRs were performed daily on all patients at bedside, as a semi-erect film, in the immediate post-transplantation period, then, during hospitalization, as an erect film. CXRs were reviewed by 2 senior cardiologists who were blinded to the clinical parameters at that time. A radiologist's opinion was solicited if there was a disagreement in diagnosis between the 2 cardiologists.

A standardized method of interpreting the CXR was applied according to established methods.[26,27] The vascular pedicle width (VPW) was measured by dropping a perpendicular line from the point at which the left subclavian artery exits the aortic arch, and measuring across to the point at which the superior vena cava crosses the right mainstem bronchus. The cardiothoracic ratio (CTR) was calculated by dividing the widest transverse diameter of the cardiac silhouette by the widest transverse diameter of the thorax above the diaphragm.[27] Radiological pulmonary edema was diagnosed when CXR showed bilateral infiltrates consistent with edema and when the ratio of the partial pressure of oxygen in arterial blood to the inspired oxygen fraction ratio was less than 300.[28] Pulmonary edema was also graded as follows:

grade 0, no pulmonary edema; grade 1, basal interstitial markings; grade 2, interstitial and alveolar infiltrates; grade 3, diffuse alveolar flooding.[26,27,29]

Statistical analysis

The chi-square (χ^2) test was used for categorical data and analysis of variance (ANOVA) for continuous data to compare patient characteristics, diastolic heart function, and endothelial function before liver transplantation among the 3 pulmonary edema groups (grade 0, grade 1, and grades 2-3). We further calculated the Pearson correlation between grades of pulmonary edema and CTP score, and CTP score and corrected QT (QTc) interval. A step-wise multiple logistic regression (the Wald method) was performed to determine independent predictors associated with pulmonary edema in recipients after liver transplantation, incorporating factors such as CTP score, prothrombin time (international normalized ratio), leukocyte poor platelets (LPP) transfused during surgery, total fluid transfused during surgery, cardiac output, FMD, NTD, and FMD/NTD. A p-value of < 0.05 was considered to be significant, and all statistical analyses were conducted using SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Fifty-four consecutive advanced liver cirrhosis patients were enrolled in this study. One patient died postoperatively because of uncontrolled bleeding. The remaining 53 patients survived the hospitalization period. During hospitalization, 29 patients (53.7%) developed radiological pulmonary edema within 1 week of transplantation. Diffuse-type interstitial pulmonary edema and alveolar pulmonary edema (grade 2-3) constituted a total of 13 cases (24.1%). Baseline characteristics were similar in these groups except the CTP score and prothrombin time prolongation (p = 0.01 and 0.04, respectively) (Table 1). In this study, patients did not receive statin or beta-blockers before surgery. The severity of pulmonary edema (grading) was significantly correlated

Table 1. Patient characteristics before surgery and their association with the incidence and severity of posttransplant pulmonary edema

Variables	Pulmonary edema (mean ± SD)			p-value*
	Grade 0 (n = 25)	Grade 1 (n = 16)	Grades 2-3 (n = 13)	
Age	52.84 ± 8.36	55.81 ± 7.44	53.92 ± 7.14	0.50
Gender				0.69
Female	5 (20%)	3 (18.75%)	4 (30.77%)	
Male	20 (80%)	13 (81.25%)	9 (69.23%)	
MELD score	11.1 ± 3.0	10.1 ± 3.5	12.8 ± 4.6	0.15
CTP score	6.88 ± 1.90	7.38 ± 1.67	8.69 ± 1.38	0.01
HCC	12 (48%)	11 (68.75%)	6 (46.15%)	0.35
Cholesterol (mg/dL)	134 ± 24	124 ± 32	124 ± 48	0.53
Triglyceride (mg/dL)	71.6 ± 23.7	73.3 ± 45.9	72.3 ± 57.3	0.99
PT (INR)	1.20 ± 0.18	1.17 ± 0.12	1.34 ± 0.26	0.04
Hb (g/dL)	11.3 ± 2.2	11.4 ± 1.8	10.6 ± 2.7	0.53
DM	4 (16%)	2 (12.5%)	3 (23.08%)	0.74
HTN	3 (12%)	0 (0%)	1 (7.69%)	0.36
Current smoking	1 (4%)	2 (12.5%)	1 (7.69%)	0.60
Creatinine (mg/dL)	0.92 ± 0.25	0.90 ± 0.28	0.86 ± 0.26	0.79
Albumin (g/dL)	3.17 ± 0.66	3.10 ± 0.59	2.73 ± 0.40	0.09
BUN (mg/dL)	12.6 ± 4.9	16.6 ± 10.4	12.9 ± 5.6	0.20
Na (mEq/L)	139 ± 4	140 ± 5	137 ± 5	0.19
K (mEq/L)	3.59 ± 0.32	3.83 ± 0.58	3.76 ± 0.59	0.28

BUN, blood urea nitrogen; DM, diabetes mellitus; Hb, hemoglobin; HCC, hepatocellular carcinoma; HTN, hypertension; MELD, model end-stage liver disease; PT (INR), prothrombin time (international normalized ratio).

* Determined by ANOVA for continuous data and χ^2 test for categorical data.

with the CTP score (r = 0.31, p = 0.002).

LPP and total volume of intravenous fluid transfused during surgery was higher in the pulmonary edema groups (p = 0.04 and 0.04, respectively) (Table 2). But the net fluid retention were not statistically significant (p = 0.83) (Table 2).

Blood component transfusion volumes and CVP levels during intensive care, VPW, CTR, ICU stay, and hospital stay were similar in these groups (Table 3). Pulmonary edema did not prolong hospital stay or increase the risk of infection in our study, and resolved after administration of diuretics. The time-interval between administration of diuretics and resolution of pulmonary edema was about 2-3 days in every patient. Most of our patients (53 of 54, 98.1%) survived during the 1-year follow-up period without experiencing heart failure.

The myocardial function, including systolic and diastolic function parameters, before liver transplantation in these groups were similar, with the exception of CO (p = 0.03, Table 4). CO was significantly higher in the grades 2-3 pulmonary edema groups. No statistical difference in SVR was found between groups (Table 4).

In our laboratory, inter-observer variabilities of calculated FMD and NTD in 13 volunteers showed mean differences of 0.36% ± 2.06% (r = 0.87; p < 0.001) and 0.57% ± 4.48% (r = 0.90; p < 0.001), respectively. Intra-observer differences in FMD and NTD were 0.88% ± 1.75% (r = 0.86; p < 0.001) and 0.78% ± 5.58% (r = 0.86; p < 0.001), respectively.[24] FMD, NTD, and FMD/NTD were significantly higher in those with pulmonary edema (p < 0.01, p = 0.01, and p = 0.02 respectively; Table 4). The QTc interval was strongly correlated with the CTP score (r = 0.572, p < 0.0001) (Figure 1) and the incidence of diastolic dysfunction (mild and severe dys-

Table 2. Blood loss, blood transfusion, crystalloids administration, and urine output data during surgery

Variables	Pulmonary edema [median (range)]			p-value*
	Grade 0 (n = 25)	Grade 1 (n = 16)	Grades 2-3 (n = 13)	
Albumin (5%) (g)	2800 (800-8000)	2000 (1200-5600)	2800 (800-6800)	0.11
LPR + PRBC (g)	1887 (0-13066)	1518 (0-12502)	2685 (0-22414)	0.42
FFP (g)	568 (0-2629)	0 (0-2090)	913 (0-5173)	0.23
LPP (g)	0 (0-286)	0 (0-323)	110 (0-545)	0.04
Blood loss + urine (g)	1950 (200-1150)	1775 (0-13450)	2500 (400-35000)	0.61
Ascites (g)	0 (0-15000)	300 (0-8000)	100 (0-13600)	0.53
Total fluid transfused (g)	4653 (800-23981)	3567 (1200-20432)	6125 (1600-34497)	0.04
Net fluid retention (kg)	2412 (-670-12481)	1909 (-501-8432)	2235 (-503-8021)	0.83

FFP, fresh frozen plasma; LPP, leukocyte poor platelets; LPR, leukocyte poor pack red blood cells; PRBC, pack red blood cells.
* Using k samples median test (nonparametric method).

Table 3. Postoperative radiograph assessment and fluid data in the liver ICU

Variables	Pulmonary edema (mean ± SD)			p-value*
	Grade 0 (n = 25)	Grade 1 (n = 16)	Grades 2-3 (n = 13)	
VPW (cm)	7.35 ± 0.87	7.85 ± 0.97	7.69 ± 1.21	0.27
CTR	0.58 ± 0.06	0.60 ± 0.04	0.61 ± 0.05	0.18
CVP (cm H_2O)	7.40 ± 2.58	7.44 ± 1.90	7.38 ± 4.46	0.99
LPR in ICU (U)	3.76 ± 5.78	2.38 ± 3.81	1.69 ± 1.97	0.38
FFP in ICU (U)	1.88 ± 4.75	1.00 ± 2.19	0.15 ± 0.55	0.34
LPP in ICU (U)	4.32 ± 8.40	3.75 ± 9.52	0.92 ± 3.33	0.45
ICU stay (d)	17.3 ± 6.3	23.5 ± 31.2	17.9 ± 7.7	0.53
Hospital stay (d)	54.1 ± 17.1	59.38 ± 46.2	57.5 ± 32.6	0.87

CTR, cardiothoracic ratio; CVP, central venous pressure; d, days; FFP, fresh frozen plasma; ICU, intensive care unit; LPP, leukocyte poor platelets; LPR, leukocyte poor pack red blood cells; VPW, vascular pedal width.
* Determined by ANOVA for continuous data and χ^2 test for categorical data.

Table 4. Diastolic heart functions and endothelial function before liver transplantation and their association with posttransplant pulmonary edema

Echocardiography and ECG finding	Pulmonary edema (mean ± SD)			p-value*
	Grade 0 (n = 25)	Grade 1 (n = 16)	Grades 2-3 (n = 13)	
E/A ratio	1.06 ± 0.33	1.14 ± 0.38	0.99 ± 0.26	0.51
< 1	10 (40%)	7 (44%)	7 (54%)	0.54
1-2	15 (60%)	8 (50%)	6 (46%)	
> 2	0 (0%)	1 (6%)	0 (0%)	
Deceleration time	252 ± 59	224 ± 52	226 ± 30	0.16
> 220 ms	16 (64%)	9 (56%)	9 (69%)	0.92
150-220 ms	8 (32%)	6 (38%)	3 (23%)	
< 150 ms	1 (4%)	1 (6%)	1 (8%)	
LA size (mm)	33.8 ± 4.1	34.2 ± 5.6	35.7 ± 4.1	0.47
Isovolumic relaxation time (ms)	101 ± 20	101 ± 15	101 ± 18	0.99
EF (%)	71.1 ± 6.7	73.6 ± 7.2	74.2 ± 9.0	0.38
Stroke volume (mL)	82.4 ± 25.3	83.8 ± 23.8	85.2 ± 21.2	0.95
TRPG (pulmonary hypertension) (mmHg)	16.2 ± 13.0	12.8 ± 12.3	13.0 ± 11.6	0.61
LVEDV (mL)	113 ± 33	112 ± 33	113 ± 27	0.99
Cardiac output (L/min)	5.61 ± 1.39	5.90 ± 1.67	7.14 ± 2.15	0.03
SVR (dyn·s·cm^{-5})	1237.8 ± 465.5	1172.9 ± 297.6	1003.8 ± 327.8	0.22
LVESV (mL)	30.4 ± 11.5	29.2 ± 14.8	27.9 ± 14.0	0.86
QT interval (ms)	433 ± 27	450 ± 28	453 ± 27	0.06
FMD	1.96 ± 3.80	6.05 ± 6.20	6.91 ± 2.74	< 0.01
NTD	12.08 ± 7.09	20.51 ± 11.36	16.17 ± 7.71	0.01
FMD/NTD	0.19 ± 0.39	0.33 ± 0.30	0.55 ± 0.36	0.02

E/A ratio, the ratio between early (E) and late (atrial-A) ventricular filling velocity; EF, ejection fraction; FMD, flow-mediated vasodilatation; LA, left atrium; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; NTD, nitroglycerin-mediated vasodilatation; QT, the interval between the start of the Q wave and the end of the T wave in the heart's electrical cycle; SVR, systemic vascular resistance; TRPG, tricuspid regurgitation pressure gradient.
* Determined by ANOVA for continuous data and χ^2 test for categorical data.

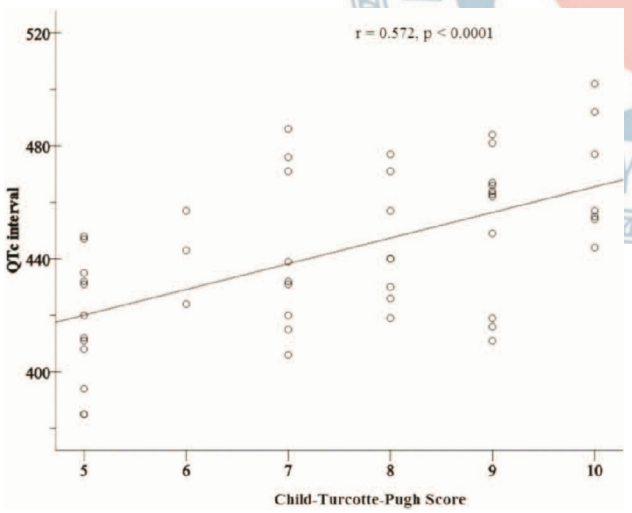

Figure 1. *Correlation between Child-Turcotte-Pugh (CTP) score and QTc interval.*

function) was high (37 of 54, 68.5%) in all of our patients, as measured by Doppler echocardiography (DT ≥ 220 ms or ≤ 150 ms) (Table 4). This incidence did not include those with pseudo-normalization of mitral flow by Doppler echocardiography. These results illustrate the variability in the severity of CCM in liver transplant candidates.[30] In the step-wise multiple logistic regression analysis, only FMD (odds ratio 1.32, 95% confidence interval: 1.10-1.59, p < 0.001) was found to be a significant predictor associated with pulmonary edema in our study subjects.

DISCUSSION

Pulmonary edema (whether cardiogenic or non-cardiogenic)[31] is a common occurrence following liver transplantation.[3,29] Its mechanism has important implications for treatment.[31] In this study, the total volume of fluid transfused was higher in pulmonary edema patients, but the net fluid retention did not differ significantly in these groups. Pulmonary edema may occur by the rapid fluid shift in high cardiac output patients

owing to imbalance of Starling forces.[32,33]

Although uncommon, transfusion-related acute lung injury (TRALI), a potentially fatal complication,[34] has been investigated.[3,29] Passively transfused antibodies have a role in most cases of TRALI.[35,36] Pulmonary edema mostly occurred within 6 h of blood product transfusion without signs of heart failure in TRALI cases.[37] In our study, these groups of patients developed pulmonary edema after more than 6 h of transfusion and had better prognoses, which were different from patients with TRALI.[38]

This study demonstrated a correlation between the severity of liver dysfunction and the degree of pulmonary edema. One of these explanations is the presence of CCM. CCM was first addressed by a consensus of international experts during the World Congress of Gastroenterology in 2005.[39] Liver cirrhosis induces a "hyperdynamic" state, characterized by a decrease in systemic vascular resistance and an increase in cardiac output, which were manifested in this and another study.[40] The hyperdynamic state of the heart before liver transplantation is possible attributable to the increased production of vasodilator molecules, mainly NO.[41,42] This phenomenon contributes to increased endothelium-dependent relaxation in the arteries of the systemic and splanchnic circulation, which was manifested by increased FMD and FMD/NTD results in our study, as shown in Table 4.[43,44] A rapid change of hemodynamic parameters (decreased CO, increased systemic vascular resistance) rendered these groups of patients prone to pulmonary edema.[40] Overt heart dysfunction has been reported when patients with cirrhosis experience physiological stress or major surgery such as liver transplantation.[45-47] CCM is also characterized by the presence of systolic and diastolic dysfunction, which are best observed in stress situations, and electrophysiological abnormalities.[48] A prolonged QT interval has been related to the severity of liver disease and the degree of portal hypertension.[49-51] Torregrosa et al. showed that cirrhosis leads to increased ventricular wall thickness and ejection fraction.[52] Although the basal diastolic function was similar, stress caused cirrhotic patients to exhibit diastolic dysfunction with lower ventricular peak filling rates, abnormal systolic responses, and reduced exercise capacity as measured by heart rate, stroke volume, cardiac output, ejection fraction, and cardiac index.[52] The severity of CCM is directly correlated with the severity of liver disease.[39] Cardiac dysfunction associated with liver cirrhosis can be subtle. Cardiomyopathy can produce significant morbidity and mortality during the perioperative period of liver transplantation.[2] With restoration of normal blood flow patterns, the increased afterload has been shown to lead to severe pulmonary edema in ~56% of patients.[4]

We demonstrated diastolic dysfunction of the left ventricle and electrophysiological abnormalities (i.e., QTc prolongation) in our patient population, which are 2 diagnostic criteria for CCM.[53] Three types of diastolic dysfunction have been identified: mild dysfunction (impaired relaxation), moderate dysfunction (pseudo-normalization), and severe dysfunction (restrictive pattern).[23] Mild and severe diastolic dysfunction was seen in 68.5% of our liver transplantation recipients. Moderate diastolic dysfunction (pseudo-normalization) of the left ventricle required tissue Doppler echocardiography, which was not done in this study. The QTc interval was strongly correlated with liver function test (CTP score; $p < 0.0001$) and was marginally higher in the pulmonary edema groups ($p = 0.06$). The study described herein is the first report to suggest a relation between post-transplantation pulmonary edema and CCM. In this patient cohort, the course of the post-liver transplantation pulmonary edema was benign and responded well to diuretics with the assistance of appropriate hemodynamic monitoring.

FMD is currently the standard for noninvasive assessment for vascular endothelial function.[54] On the one hand, in liver cirrhosis, endothelial dysfunction is characterized by impaired endothelium-dependent relaxation in the liver microcirculation. On the other hand, increased endothelium-dependent relaxation in the arteries of the systemic and splanchnic circulation has been demonstrated.[44] This "NO paradox," the pathophysiological basis of CCM,[55] may contribute to pulmonary edema after liver transplantation. Patients with CCM had higher FMD in our study.

One major problem in the management of CCM is the lack of human or animal studies in the literature on specific pharmacological treatments. Although afterload reduction is currently a mainstay in the treatment for non-cirrhotic chronic heart failure, the marked peripheral vasodilatation and decreased effective circulat-

ing volume could complicate or even preclude this approach. A single dose of the beta-blocker propranolol has been shown to improve the prolonged QT interval in cirrhosis patients.[56] According to the DECREASED III study, presurgical use of a beta-blocker and fluvastatin improves postsurgical cardiac outcome.[57] In a study by Safadi et al., the use of perioperative beta-blockers in liver transplantation patients has been shown to be significantly protective against nonfatal myocardial infarction and death.[58] Further studies on the efficacy of beta-blockers and other drugs in the treatment of CCM are needed.

This study has a number of limitations that should be addressed. First, the patient population was small. Second, diagnoses of pulmonary edema were made by CXR without invasive pulmonary artery catheterization. As suggested by the published guidelines, transthoracic echocardiography should be the first approach in assessing left ventricular and valvular function in these patients.[59] Routine use of pulmonary artery catheterization increases the rate of complications such as hematoma, bleeding, and sepsis. The reported rate of adverse advents related to catheterization ranges from 4.5% up to 9.5%.[60] Newer echocardiographic techniques such as tissue Doppler imaging of the mitral-valve annulus may increase the sensitivity of left ventricular systolic and diastolic dysfunction.[60] Left ventricular CO derived by Doppler echocardiography has been previously validated by thermodilution and cineangiography measurements.[61-64] Other noninvasive methods for CO measurement such as the carbon dioxide rebreathing technique or the bioimpedance technique were not used in this study.[65] In addition, the systemic vascular resistances before liver transplantation only showed a trend to be lower in pulmonary patients, a result probably due to the small patient population. We did not measure NO levels in our patients, and FMD after liver transplantation was also not done. Further prospective studies are needed to validate our finding.

CONCLUSION

In conclusion, the high incidence of pulmonary edema after living donor liver transplantation was associated with a high FMD and FMD/NTD ratio at pre-transplantation. FMD is the only significant predictor associated with pulmonary edema. However, we observed no alteration in mortality rates.

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