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RESEARCH ARTICLE

Sympathetic withdrawal is associated with hypotension after hepatic reperfusion

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Abstract
Objective Post-reperfusion syndrome (PRS), severe hypotension after graft reperfusion during liver transplantation, is an adverse clinical event associated with poorer patient outcomes. The purpose of this study was to determine whether alterations in autonomic control in liver transplant recipients prior to graft reperfusion are associated with the subsequent development of PRS.
Methods Heart rate variability (HRV), systolic arterial blood pressure (SBP) variability, and baroreflex sensitivity of 218 liver transplant recipients were evaluated using 5 min of ECG and arterial blood pressure signals 10 min before graft reperfusion along with other clinical parameters. Logistic regression analyses were performed to assess predictors of PRS occurrence.
Results Seventy-seven patients (35 %) developed PRS while 141 did not. There were significant differences in SBP (110 ± 16 vs. 119 ± 16 mmHg, $P < 0.001$) and the ratio of low frequency power to high frequency power (LF/HF) of HRV (1.0 ± 1.4 vs. 2.1 ± 3.7, $P = 0.003$) between the PRS group and No-PRS group. In multivariate logistic regression analysis, predictors were LF/HF (odds ratio 0.817, $P = 0.028$) and SBP (odds ratio 0.966, $P < 0.001$).
Interpretation Low LF/HF and SBP measured before hepatic graft reperfusion were significantly correlated with subsequent PRS occurrence, suggesting that sympathovagal imbalance and depressed SBP may be key factors predisposing to reperfusion-related severe hypotension in liver transplant recipients.

Keywords Post-reperfusion syndrome · Liver transplantation · LF/HF · Heart rate variability

Introduction

Post-reperfusion syndrome (PRS) is defined as severe hypotension occurring within the first 5 min after graft reperfusion during liver transplantation surgery [1]. PRS is considered one of the most critical events that can occur during liver transplantation, because it may be associated with longer postoperative mechanical ventilation assistance and intensive care unit stay, as well as higher risk of postoperative acute renal failure and 1-year mortality [2–4]. However, the physiological mechanisms underlying PRS are not fully understood.

Hemodynamic regulation is influenced by cardiovascular autonomic mechanisms, which are mediated by afferent neural branches (i.e., the baroreceptor reflex) and efferent neural branches (i.e., parasympathetic and sympathetic pathways) [5]. Cardiovascular autonomic impairment has been reported to be linked with hypotension during general anesthesia [6–8]. In addition, chronic liver disease is associated with cardiovascular autonomic dysfunction, which is characterized by the impairment of sympathetic and parasympathetic reactivity [9–12]. These observations suggest that there is a relationship between cardiovascular autonomic control and hemodynamic stability during liver

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transplantation surgery. Furthermore, cardiovascular autonomic indices derived from power spectral analysis, such as the ratio of low frequency power to high frequency power (LF/HF) or the total power of heart rate variability (HRV), have attracted attention with regard to their potential use in predicting hypotensive episodes in patients undergoing anesthesia or hemodialysis [13–15]. However, the association between cardiovascular autonomic indices and reperfusion-related hemodynamic instability during liver transplantation remains to be established.

We hypothesize that cardiovascular autonomic function plays a significant role in maintaining arterial blood pressure (ABP) during liver transplantation surgery. The purpose of this study was to evaluate whether alterations in cardiovascular autonomic function such as a reduction in LF/HF in liver transplant patients can predict reperfusion-related hypotension.

Methods

Subjects

Two hundred eighty-one patients, who had undergone liver transplantation surgery at the Asan Medical Center between August 2009 and May 2010, were involved in this retrospective study. Sixty-three patients were excluded from the data analysis due to insufficient hemodynamic data for analysis ($n = 39$), cardiac arrhythmia during the data collection period ($n = 15$), or for being underage (<15 years) patients ($n = 9$). Of the remaining 218 patients, 88 had hepatitis virus-related liver cirrhosis, 78 combined hepatocellular carcinoma and liver cirrhosis, 21 alcoholic liver cirrhosis, 13 fulminant hepatic failure, 5 primary biliary cirrhosis, 4 retransplantation, 3 cryptogenic liver cirrhosis, 2 Wilson disease, 2 primary sclerosing cholangitis, 1 polycystic liver disease, and 1 autoimmune hepatitis. The study protocol was approved by the Institutional Review Board of the Asan Medical Center, Seoul, South Korea.

Anesthetic technique

General anesthesia for liver transplantation surgery was performed according to the Asan Medical Center institutional standard protocol. In brief, anesthesia was induced with intravenous thiopental sodium, fentanyl and vecuronium. After endotracheal intubation, anesthesia was maintained with 1 % isoflurane, a 50 % O_2/air mixture, and continuous infusion with fentanyl and vecuronium. ECG, end tidal CO_2 measurement, and pulse oximetry were monitored during general anesthesia. A twenty-gauge radial arterial catheter was used for monitoring ABP. A pulmonary artery catheter (Swan-Ganz CCOmbo V CCO/SvO_2/CEDV, Edwards Lifesciences Corp., CA, USA) was inserted and connected to a Vigilance system (Vigilance II, Edwards Lifesciences Corp., CA, USA) for monitoring hemodynamic variables such as central venous pressure (CVP), cardiac output (CO), and systemic vascular resistance (SVR). Mechanical ventilation was performed with tidal volume of 8–10 mL/kg and respiratory rate of 10 breaths/min to maintain normocapnia.

During inferior vena cava clamping before graft reperfusion, the piggyback technique was used to maintain hemodynamic stability. However, veno-venous bypass was used to minimize hemodynamic instability in cases where CO was reduced by more than 50 % during inferior vena cava clamping. With this bypass system, blood flowed from the femoral and portal veins to the heart via the internal jugular or subclavian vein.

Definition of PRS

Post-reperfusion syndrome was defined as a decrease in mean ABP greater than 30 % of the baseline value, for more than 1 min during the first 5 min after reperfusion of the liver graft during liver transplantation [1]. Recipients were categorized into two groups: PRS group (occurrence of PRS) and No-PRS group (no occurrence of PRS).

Data collection

Hemodynamic variables were routinely recorded during liver transplantation surgery with a computerized data acquisition system (DI-720U, DATAQ Instruments, Inc., Akron, OH) in all recipients at our institution. Beat-to-beat ECG and ABP data were digitized at a sampling rate of 500 Hz. Ten minutes before reperfusion of the transplanted liver graft, 5 min of stable ECG and radial ABP data were collected using this database system for the retrospective study. In addition, other hemodynamic variables (CVP, CO, and SVR) and laboratory variables (serum hemoglobin, serum platelet, serum sodium, and serum potassium) were collected for off-line analysis.

Data management

Offline data analyses were performed using signal processing software (CODAS, DATAQ; DADiSP/Adv DSP, DSP Development, Cambridge, MA, USA) and custom-written MATLAB (The MathWorks, Inc., Natick, MA, USA) program.

Beat-to-beat ECG R wave and systolic ABP (SBP) were manually inspected to confirm data quality. HRV was assessed using time and frequency domain indices in addition to nonlinear analyses. RR interval standard deviation (SDNN) and the root mean square of successive differences

in RR intervals (RMSSD) were calculated as representative time domain measures. SDNN and RMSSD are thought to correlate with total power and HF, respectively, of the frequency domain of HRV analysis [16].

Nonlinear HRV was analyzed using the Poincare plot analysis and sample entropy analysis. The Poincare plot analysis is a nonlinear method of analyzing HRV which involves analysis of a scatter plot of current versus preceding RR intervals [17]. SD1 and SD2 represent the standard deviations of points about the two axes of an ellipse fitted to the Poincare plot. SD1 is a measure of the shorter term RR interval variability and SD2 is a measure of the longer term variability. SD1 has been shown to correlate with HF of HRV and SD2 with both LF and HF of HRV [17, 18]. Sample entropy represents another nonlinear means of analyzing HRV, and is utilized to evaluate the degree of irregularity or unpredictability in the RR interval signal [19]. A higher value of sample entropy means greater unpredictability and irregularity, whereas a lower value means greater predictability and regularity.

For frequency domain analysis of variability, 300 s time series data of beat-to-beat RR intervals and SBP were interpolated to 5 Hz to provide equidistant samples. Power spectral density was calculated by Welch's averaging periodograms method with 50 % data overlap, detrending, and application of a Hanning window. The areas under the power spectra in the low frequency (0.04–0.15 Hz) and high frequency (0.15–0.40 Hz) regions of HRV and SBP variability (SBPV) were integrated. Total power was defined as the area under the power spectrum in the frequencies $\leq$0.40 Hz. The HF of HRV was used as an index of cardiac parasympathetic activity, and the LF of SBPV was used as an index of sympathetic vasomotor control [20, 21]. The LF/HF of HRV was used as an index of sympathovagal balance [16].

Cardiac baroreflex sensitivity (BRS) was estimated by frequency domain transfer function analysis and time domain sequence analysis. Details of the transfer function analysis are provided in the previous study [22]. Briefly, the transfer function magnitude between SBP and RR interval was estimated using the cross-spectral method. We calculated the transfer function magnitude between HRV and SBPV separately as an index of BRS in the low frequency (BRS_{LF}) and high frequency (BRS_{HF}) regions when coherence was more than 0.5 [23]. Details of the sequence analysis are also provided in the previous study [24]. Briefly, the slope of the linear relationship between SBP and RR interval was determined whenever a baroreflex sequence (3 or more consecutive heartbeats increases in RR interval with a simultaneous increase in SBP or 3 or more consecutive heartbeats decreases in RR interval with a simultaneous decrease in SBP) was identified. The slope was calculated for sequences with correlation >0.85. The average of each slope was taken as a measure of baroreflex sensitivity (BRS_{SEQ}).

Statistics

The hemodynamic variables such as SBP, heart rate (HR), CVP, CO, and SVR were estimated as 5-min averaged values 10 min before the graft reperfusion during the liver transplantation surgery. All data are expressed as mean ± SD or number of recipients (percentage). The Chi-square test,

Table 1 Clinical characteristics and laboratory variables in liver transplant recipients

Variable	All ($N = 218$)	No-PRS group ($n = 141$)	PRS group ($n = 77$)	P value
Age, years	50.1 ± 8.9	49.4 ± 8.6	51.4 ± 9.2	0.106
Sex, M/F	162/56 (74 %)/(26 %)	107/34 (76 %)/(24 %)	55/22 (71 %)/(29 %)	0.471
BMI, kg/m^2	23.9 ± 3.2	24.0 ± 3.3	23.8 ± 3.0	0.731
DM	48 (22 %)	26 (18 %)	22 (29 %)	0.084
Hypertension	28 (13 %)	14 (10 %)	14 (18 %)	0.082
Child score	8.9 ± 2.6	8.7 ± 2.5	9.2 ± 2.8	0.269
MELD score	17.5 ± 9.9	17.4 ± 9.9	17.9 ± 9.9	0.708
Donor type, cadaver/living	20/198 (9 %)/(91 %)	11/130 (8 %)/(92 %)	9/68 (12 %)/(88 %)	0.342
Veno-venous bypass	38 (17 %)	28 (20 %)	10 (13 %)	0.201
Anesthesia duration, min	891 ± 139	892 ± 137	890 ± 144	0.928
Hemoglobin, g/dL	10.0 ± 1.4	10.1 ± 1.5	9.9 ± 1.2	0.438
Platelet, 10^9/L	37.2 ± 36.9	37.5 ± 38.7	36.6 ± 33.6	0.873
Sodium, mmol/L	138.2 ± 4.3	138.0 ± 4.3	138.6 ± 4.3	0.342
Potassium, mmol/L	3.8 ± 0.6	3.8 ± 0.6	3.8 ± 0.5	0.921

Data are expressed as mean ± SD or number of recipients (percentage) as appropriate. P values were measured by comparing values between recipients who developed the syndrome (PRS group) and who did not (No-PRS group)

PRS post-reperfusion syndrome, *BMI* body mass index, *DM* diabetes mellitus, *MELD* model for end-stage liver disease

Student's t test, or the Mann–Whitney rank sum test, as appropriate, was used for inter-group comparisons.

The relevant factors associated with PRS occurrence were included in the univariate logistic regression analysis. Variables with P values <0.1 in the univariate analysis were included in a multivariate logistic regression analysis to evaluate independent factors predicting the occurrence of PRS. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed using statistical software (SPSS Inc., Chicago, IL, USA).

Results

In a total of 218 liver transplant recipients, 77 recipients (35 %) developed PRS. Characteristics and laboratory test results of the liver transplant recipients are provided in Table 1. There were no significant differences in patient characteristics and laboratory test results between the PRS group and the No-PRS group.

Table 2 shows hemodynamic variables and cardiovascular autonomic indices 10 min before reperfusion of new liver graft during the liver transplantation. There were significant differences in SBP and LF/HF of HRV measured before graft reperfusion, but not in any other components of HRV, BRS, and SBPV between the two groups (Fig. 1).

In univariate logistic regression analyses, SBP and LF/HF of HRV were the only significant determinants of PRS occurrence during the liver transplantation surgery (Table 3). In multivariate logistic regression analysis, including SVR and histories of diabetes mellitus and hypertension ($P < 0.1$), the independent predictors of the occurrence of PRS were

Table 2 Hemodynamic variables and cardiovascular autonomic indices before reperfusion

Variable	All ($N = 218$)	No-PRS group ($n = 141$)	PRS group ($n = 77$)	P value
SBP, mmHg	116 ± 17	119 ± 16	110 ± 16	<0.001
HR, beats/min	84 ± 16	83 ± 15	85 ± 17	0.482
CVP, mmHg	5.7 ± 2.5	5.5 ± 2.5	5.9 ± 2.5	0.268
CO, L/min	6.6 ± 1.8	6.6 ± 1.6	6.7 ± 2.0	0.662
SVR, dyne s/cm^5	965 ± 311	987 ± 312	925 ± 309	0.160
Heart rate variability				
Time domain analysis				
SDNN, ms	7.7 ± 5.3	7.7 ± 5.3	7.6 ± 5.3	0.914
RMSSD, ms	4.3 ± 3.2	4.1 ± 2.2	4.6 ± 4.4	0.244
Frequency domain analysis				
TP, ms^2	48.0 ± 101.5	51.3 ± 109.2	41.8 ± 86.1	0.510
LF, ms^2	8.2 ± 28.3	9.9 ± 33.8	5.0 ± 12.9	0.219
HF, ms^2	6.0 ± 13.1	5.9 ± 12.8	6.3 ± 13.8	0.807
LF/HF	1.7 ± 3.1	2.1 ± 3.7	1.0 ± 1.4	0.003
Nonlinear analysis				
SD1, ms	3.0 ± 2.2	2.9 ± 1.6	3.3 ± 3.1	0.245
SD2, ms	10.2 ± 7.4	10.4 ± 7.5	10.0 ± 7.2	0.696
Sample entropy	1.4 ± 0.4	1.4 ± 0.4	1.3 ± 0.5	0.272
Systolic arterial blood pressure variability				
TP, mmHg^2	10.2 ± 11.1	10.6 ± 12.1	9.6 ± 8.9	0.511
LF, mmHg^2	0.9 ± 1.5	1.0 ± 1.4	0.8 ± 1.5	0.400
HF, mmHg^2	5.5 ± 7.1	5.5 ± 7.8	5.3 ± 5.4	0.804
Baroreflex sensitivity				
BRS_{LF}, ms/mmHg	2.2 ± 2.7	2.2 ± 2.3	2.2 ± 3.3	0.918
BRS_{HF}, ms/mmHg	2.1 ± 2.6	2.0 ± 1.9	2.3 ± 3.5	0.430
BRS_{SEQ}, ms/mmHg	1.6 ± 1.7	1.7 ± 1.7	1.6 ± 1.8	0.705

Data are expressed as mean ± SD or number of recipients (percentage) as appropriate. P values were measured by comparing values between recipients who developed the syndrome (PRS group) and who did not (No-PRS group)

PRS post-reperfusion syndrome, *SBP* systolic arterial blood pressure, *HR* heart rate, *CVP* central venous pressure, *CO* cardiac output, *SVR* systemic vascular resistance, *SDNN* standard deviation of all RR intervals, *RMSSD* root mean square of the successive difference in RR intervals, *TP* total power, *LF* low frequency power, *HF* high frequency power, *LF/HF* ratio of low frequency power to high frequency power, *SD1 and SD2* standard deviations obtained from Poincare analysis of RR interval variability (see text); BRS_{LF} baroreflex sensitivity in the low frequency region, BRS_{HF} baroreflex sensitivity in the high frequency region, BRS_{SEQ} baroreflex sensitivity measured by sequence method

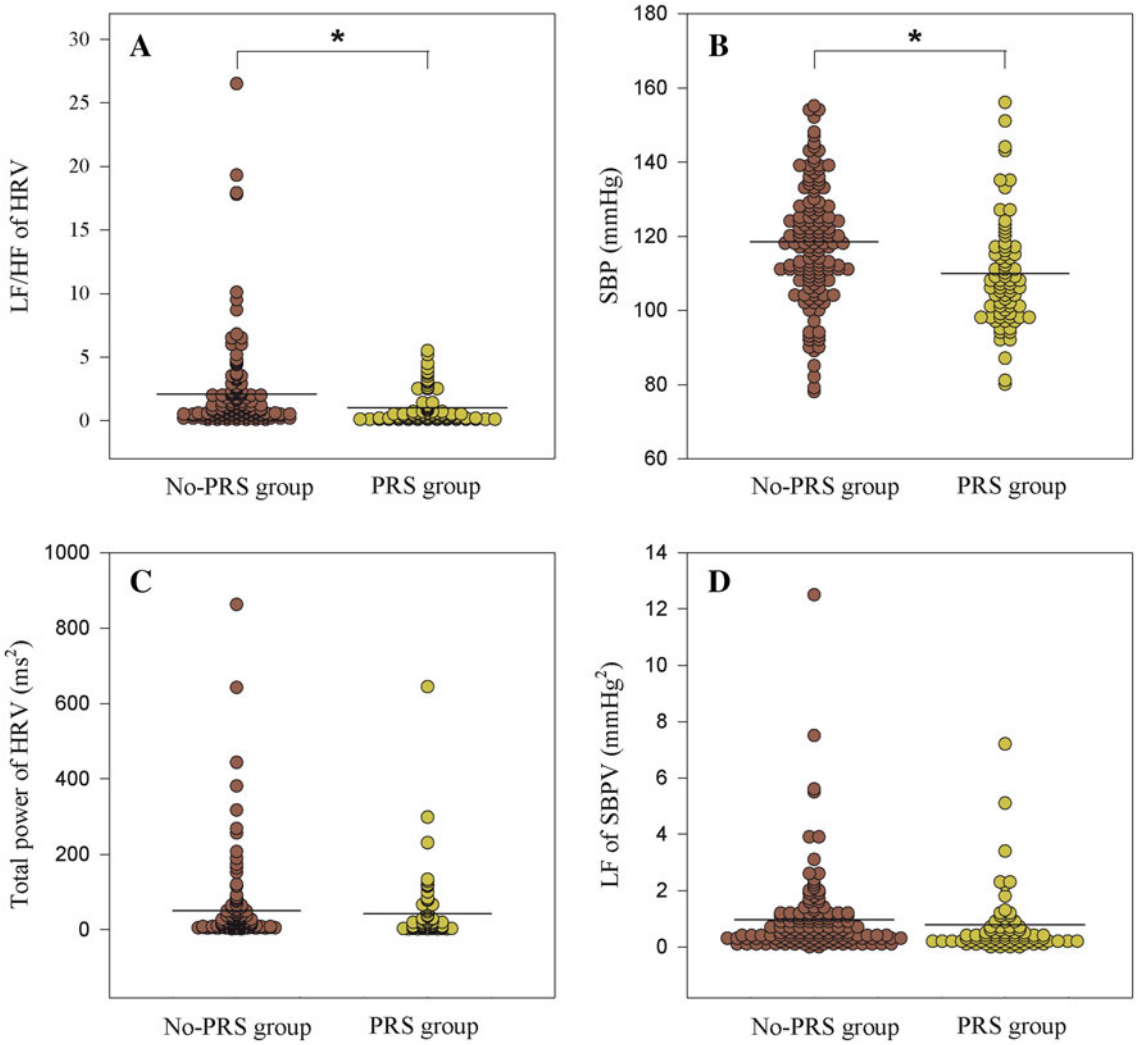

Fig. 1 Comparisons of **a** the ratio of low frequency power to high frequency power (LF/HF) of heart rate variability (HRV), **b** systolic arterial blood pressure (SBP), **c** total power of HRV, and **d** low frequency power (LF) of SBP variability (SBPV) between patients who subsequently developed the post-reperfusion syndrome (PRS group) and those who did not (No-PRS group) during liver transplantation. Note that there are significant decreases in LF/HF of HRV and SBP in the PRS group compared with the No-PRS group. *Straight lines* indicate mean value. *$P < 0.05$

also LF/HF of HRV (odds ratio, 95 % confidence interval 0.817, 0.682–0.979; $P = 0.028$) and SBP (odds ratio, 95 % confidence interval 0.966, 0.947–0.984; $P < 0.001$) (Table 3).

Discussion

The autonomic nervous system plays an important role in maintaining the ABP within a normal range. A defect in autonomic nervous system regulation may contribute to ineffective blood pressure control. A significant finding of this study is that in patients undergoing liver transplantation, patients who subsequently developed PRS, compared to those who did not, had a significantly depressed LF/HF of HRV measured prior to graft perfusion. The LF/HF is a measure of sympathovagal balance. The LF peak in the HR power spectrum is jointly mediated by the sympathetic and parasympathetic nervous systems whereas the HF peak is solely mediated by the parasympathetic nervous system [5]. Thus, a depressed LF/HF is indicative of a relative decrease in sympathetic tone relative to parasympathetic tone. This observation implies that those liver transplant patients who have a relative depression in sympathetic tone relative to parasympathetic tone are at greater risk of developing PRS.

Liver transplantation surgery is considered the final option for patients with end-stage liver disease. However, liver transplantation involves substantial risk. Specifically, the extended clamping and unclamping of the inferior vena cava and the portal vein during the surgery pose a risk to the

Table 3 Logistic regression analysis of factors predicting post-reperfusion syndrome

Variable	Univariate analysis		Multivariate analysis	
	Coefficient (SE)	*P* value	Odds ratio (95 % CI)	*P* value
Age	0.027 (0.017)	0.107		
Sex (female vs. male)	−0.230 (0.320)	0.472		
DM (yes vs. no)	0.571 (0.333)	0.087	1.557 (0.761–3.184)	0.226
Hypertension (yes vs. no)	0.701 (0.408)	0.086	1.551 (0.640–3.762)	0.331
Child score	0.060 (0.054)	0.268		
MELD score	0.005 (0.014)	0.707		
Donor type (cadaver vs. living)	0.447 (0.474)	0.345		
Veno-venous bypass (yes vs. no)	−0.507 (0.399)	0.204		
Anesthesia duration	0.001 (0.001)	0.927		
Hemoglobin	−0.086 (0.110)	0.437		
Sodium	0.034 (0.036)	0.341		
Potassium	0.025 (0.253)	0.920		
SBP	−0.036 (0.010)	<0.001	0.966 (0.947–0.984)	<0.001
HR	0.007 (0.009)	0.458		
CVP	0.044 (0.057)	0.448		
CO	−0.164 (0.143)	0.249		
SVR	−0.001 (0.001)	0.099	1.000 (0.999–1.001)	0.579
Heart rate variability				
SDNN	−0.003 (0.027)	0.913		
RMSSD	0.050 (0.044)	0.259		
TP	−0.001 (0.002)	0.512		
LF	−0.010 (0.009)	0.264		
HF	0.003 (0.011)	0.806		
LF/HF	−0.209 (0.093)	0.024	0.817 (0.682–0.979)	0.028
SD1	0.071 (0.063)	0.259		
SD2	−0.008 (0.020)	0.694		
Sample entropy	−0.351 (0.319)	0.271		
Systolic arterial blood pressure availability				
TP	−0.009 (0.014)	0.510		
LF	−0.093 (0.112)	0.405		
HF	−0.005 (0.021)	0.803		
Baroreflex sensitivity				
BRS_{LF}	−0.006 (0.054)	0.917		
BRS_{HF}	0.042 (0.055)	0.443		
BRS_{SEQ}	−0.032 (0.085)	0.704		

SE standard error, *CI* confidence interval, *DM* diabetes mellitus, *MELD* model for end-stage liver disease, *SBP* systolic arterial blood pressure, *HR* heart rate, *CVP* central venous pressure, *CO* cardiac output, *SVR* systemic vascular resistance, *SDNN* standard deviation of all RR intervals, *RMSSD* root mean square of the successive difference in RR intervals, *TP* total power, *LF* low frequency power, *HF* high frequency power, *LF/HF* ratio of low frequency power to high frequency power, *SD1 and SD2* standard deviations obtained from Poincare analysis of RR interval variability (see text), BRS_{LF} baroreflex sensitivity in the low frequency region, BRS_{HF} baroreflex sensitivity in the high frequency region, BRS_{SEQ} baroreflex sensitivity measured by sequence method

patients. In particular, reperfusion of the transplanted liver graft through the portal vein may induce severe cardiovascular collapse, and this severe hemodynamic change may adversely affect perioperative morbidity and mortality [2–4].

Many attempts have been made to determine the causes of PRS during liver transplantation to be able to develop strategies to minimize the risk of developing PRS [25, 26]. However, the underlying mechanisms of PRS occurrence remain unclear. We hypothesized that the occurrence of PRS would be associated with altered cardiovascular autonomic regulation. To our knowledge, this is the first study to evaluate underlying mechanisms of reperfusion-related hypotension during liver transplantation with regard to alterations in cardiovascular autonomic control.

Hemodynamic homeostasis involves an interaction between the disturbances to cardiovascular function and the responses of the cardiovascular control systems to these disturbances. The autonomic nervous system is the most important efferent limb of the cardiovascular control system [27]. Thus, cardiovascular autonomic regulation is thought to play a role in maintaining hemodynamic stability during the severe stressful events of liver transplantation surgery.

Patients with end-stage liver disease are known to demonstrate abnormal cardiovascular autonomic function, especially decreased HRV and BRS, and inappropriate circulatory response to various stimuli [11, 12, 28, 29]. Moller et al. [11] suggested that head-up tilt can induce abnormalities in sympathetic control and vascular reactivity, which lead to hemodynamic instability in patients with liver cirrhosis. Also, Lunzer et al. [12] reported that cardiovascular regulation to reflex sympathetic activation is impaired in patients with liver disease, and that autonomic dysfunction is associated with the impairment of reflex vascular homeostatic responses to stimulation.

On the basis of the results in this study and other studies, we can suggest that autonomic dysfunction contributes to reperfusion-related hemodynamic instability in liver transplant recipients with PRS. The impairment in autonomic balance may impact the HR response to hypotension as well as sympathetic vasoconstriction reflex mechanisms.

The autonomic indices of patients in both the PRS and No-PRS groups in this study were depressed compared to normal awake subjects published in the previous studies [16, 24]. In addition, low LF/HF of HRV measured prior to graft reperfusion was significantly associated with the development of hypotension after hepatic reperfusion. The LF/HF of HRV is a well-established marker of altered sympathovagal balance under a wide variety of conditions [16]. Decreased LF/HF of HRV is indicative of a change in autonomic balance toward decreased sympathetic activity [30]. Our results suggest that a low value of LF/HF of HRV may indicate a decreased capacity for activating sympathetically mediated HR and vasoconstriction mechanisms in response to hypotension, thus predisposing to the development of PRS following reperfusion. These results are in agreement with the result of previous studies showing that hypotension episodes during hemodialysis are significantly associated with decreased LF/HF [13, 31]. Although altered cardiovascular autonomic control may not provide the entire explanation for the occurrence of graft reperfusion-related hypotension during liver transplantation surgery, the evaluation of HRV indices, including LF/HF appears to be particularly helpful in predicting PRS occurrence.

In the present study, the total power of HRV was not significantly different between the two PRS and No-PRS groups. In previous studies, total HRV power has been found to be associated with the development of hypotension during general anesthesia [15, 32]. Hanss et al. [15] reported that preoperative total power of HRV is associated with the occurrence of hypotension and bradycardia during anesthesia, and that HRV may be a suitable tool to identify preoperatively patients at high risk of hemodynamic events. However, it should be noted that our study population involves only liver transplant recipients receiving general anesthesia compared to previous studies involving broader groups of patients undergoing anesthesia [15, 32]. In addition, it has been demonstrated that both chronic liver disease and anesthetic agents can depress cardiovascular autonomic function [9, 10, 33, 34]. Therefore, we could postulate that some of the HRV indices might not be useful when severely depressed due to concurrent conditions (e.g., liver disease and anesthesia).

Interestingly, we found that the LF of SBPV and SVR were not significantly different between PRS group and No-PRS group. However, it is not clear whether reperfusion-related severe hypotension may be associated with the sympathetic dysfunction of peripheral origin or the inhibition of the central regulatory mechanism of the sympathetic nervous system. Therefore, further study would be required for clarifying the relationships between central and peripheral sympathetic dysfunction as the underlying mechanism of reperfusion hypotension in liver transplant recipients.

We also found that SBP in the PRS group was decreased compared to that in the No-PRS group, and that low SBP before graft reperfusion is a significant determinant of PRS occurrence in liver transplant recipients. This observation suggests the hypothesis that maintaining a more elevated intra-operative SBP prior to reperfusion may reduce the risk of developing PRS.

The role of serum potassium as an underlying mechanism of PRS occurrence has been the subject of considerable debate [35, 36]. In the present study, serum potassium levels measured before graft reperfusion were not significantly different between the PRS group and the No-PRS group. The reason is not clear why in this study the serum potassium level was not significantly associated with PRS occurrence. One possible explanation is that serum potassium level was controlled strictly during the anhepatic phase by the administration of insulin, sodium bicarbonate, or diuretic according to our institutional standard anesthetic protocol (serum potassium level 3.8 ± 0.6 mmol/L).

In this study, veno-venous bypass application during inferior vena cava clamping was not significantly associated with graft reperfusion-related severe hypotension. This finding is consistent with a previous study in which the occurrence of the syndrome of cardiovascular collapse following graft reperfusion was similar whether veno-venous

bypass was used or not [37]. Therefore, although veno-venous bypass application is known to be useful for maintaining hemodynamic stability during inferior vena cava clamping, it does not appear to be preventive of PRS.

The present study has several limitations. Cardiovascular autonomic dysfunction (depression) due to the patient conditions (severe liver disease and anesthesia) likely affected the autonomic parameters measured. For example, it is likely that general anesthesia depresses the LF peak and the use of mechanical breathing increases the HF peak, thus depressing the LF/HF. However, since the same conditions and methods were applied to both patients with and without PRS, we could conclude that low LF/HF was significantly correlated with PRS occurrence. Nonetheless, the results of our study need to be interpreted with caution. Because overall cardiovascular autonomic indices were too small to provide sufficient information about baroreflex mechanisms [38], the role of cardiovascular autonomic control on PRS occurrence may be unremarkable in helping patient evaluation or diagnosis. Secondly, this study involved retrospective analysis of previously collected data. Lastly, the study focused mainly on whether analysis of cardiovascular parameters obtained clinically just prior to reperfusion was predictive of PRS. We did not evaluate hemodynamic variables and cardiovascular autonomic indices under resting conditions. Therefore, further study involving resting data will be needed to fully understand the relationship of cardiovascular autonomic measures to PRS.

Conclusions

We found that depressed sympathovagal balance and a lower resting SBP were associated with the occurrence of post-reperfusion severe hypotension during liver transplantation. This finding also suggests that altered sympathovagal balance with sympathetic withdrawal is associated with hemodynamic instability after acute stressful events such as reperfusion in liver transplant recipients. Our results further emphasize the importance of the beneficial role of the cardiovascular autonomic control system as a defense mechanism for maintaining blood pressure stability during liver transplantation. We also found that decreased SBP prior to graft reperfusion was associated with increased risk of the development of post-reperfusion hypotension. This finding suggests the hypothesis that maintaining a higher SBP prior to reperfusion may reduce the risk of PRS.

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Conflict of interest The authors have no conflicts of interest regarding this manuscript.

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