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The Correlation of Hepatic and Systemic Hemodynamics During Liver Transplantation

Quantification of Hepatic Resistance as an Actual Value

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Abstract: The correlation between portal vein pressure (PVP) and flow (PVF) has not been established, and there is still lack of consensus about the optimal hemodynamics during liver transplantation (LT). We aimed to establish the correlation between systemic and hepatic hemodynamics during LT by applying the hepatokinetic power hypothesis, based on the law of energy conservation and hydrodynamics.

A total of 103 adult liver transplant recipients were enrolled in this study from September 2012 to December 2014. Systemic and hepatic hemodynamics were assessed intraoperatively to calculate the hepatokinetic power status. Severe surgical complications (Clavien–Dindo grade ≥III) were recorded as the main outcome measure, and potential covariates were evaluated including recipient, donor, donor–recipient match, surgery-related factors, conventional hemodynamics, and the intraoperative hepatokinetic power profile.

In multivariate analysis, hepatokinetic power gradient >4260 mL mmHg min^{-1} 100 g graft $weight^{-1}$ ($P = 0.001$), 2.2 < ratio of hepatokinetic power from the portal vein to the hepatic artery ≤8.7 ($P = 0.012$), and hepatic resistance of partial grafts ≤0.006 or >0.015 min mmHg mL^{-1} ($P = 0.012$) were associated with a higher risk. None of the conventional hemodynamic parameters, such as PVP, PVF, and hepatic venous pressure gradient, entered into this regression model (*c*-statistic = 0.916) when competing with hepatokinetic power indexes.

The hepatokinetic power hypothesis clarifies the correlation of systemic and hepatic hemodynamics in a simple, rational manner. The hepatic resistance, derived from the hepatokinetic power equation, can be quantified and has an effect on the incidence of severe surgical complications. This finding offers a new objective clinical approach to evaluate graft quality during transplantation.

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Abbreviations: BMI = body mass index, CVP = central venous pressure, HA = hepatic artery, HABR = hepatic arterial buffer response, HAF = hepatic artery flow, HKP_A = hepatokinetic power inflow from the HA, HKPG = hepatokinetic power gradient, HKP_P = hepatokinetic power inflow from the PV, HV = hepatic vein, HVPG = hepatic venous pressure gradient, ICU = intensive care unit, LT = liver transplantation, MAP = mean arterial pressure, MELD = model for end-stage liver disease, PV = portal vein, PVF = portal vein flow, PVP = portal vein pressure, SFSS = small-for-size syndrome, WIT = warm ischemic time.

INTRODUCTION

The optimal hemodynamics during liver transplantation (LT) has been a topic of discussion for many years, without a clear consensus. Early data suggested that graft size was the key to successful transplantation, and size mismatch was a critical limitation in LT due to the increased risk of small-for-size syndrome (SFSS).[1,2] Recent reports based on pathologic, clinical, and experimental data have shown that portal hyperperfusion is a crucial factor in the development of SFSS.[3–6] The evaluation of the hemodynamic status during LT thus becomes a major issue. The conventional parameters are portal vein pressure (PVP), portal vein flow (PVF), and hepatic venous pressure gradient (HVPG); the preferable parameter used depends on the center. Some groups have tried to explore the relationship between PVP and PVF and attempted to determine their superiority in clinical practice.[7–9] However, there is still no well-established formula that can properly explain this correlation. In this study, systemic and hepatic hemodynamics during LT were used to determine the equation of hepatokinetic power gradient and also to derive hepatic resistance. These newly proposed hepatokinetic power indexes during LT were correlated with severe in-hospital surgical complications and assessed for their relevance and feasibility.

MATERIALS AND METHODS

Formula Derivation

Energy is the capacity of a system to perform work, and kinetic energy is the energy of motion. The work is calculated as the constant force (F) exerted on a mass, multiplied by the displacement (d) moved in the direction of the force. According to the work–energy principle, the change in kinetic energy of an object is equal to the net work performed on it. Pressure (P_r) is the ratio of force to the area (A) over which that force is distributed. Therefore, kinetic energy can be expressed as (Fig. 1A):

$$\text{Network} = F \times d = Pr \times A \times d$$

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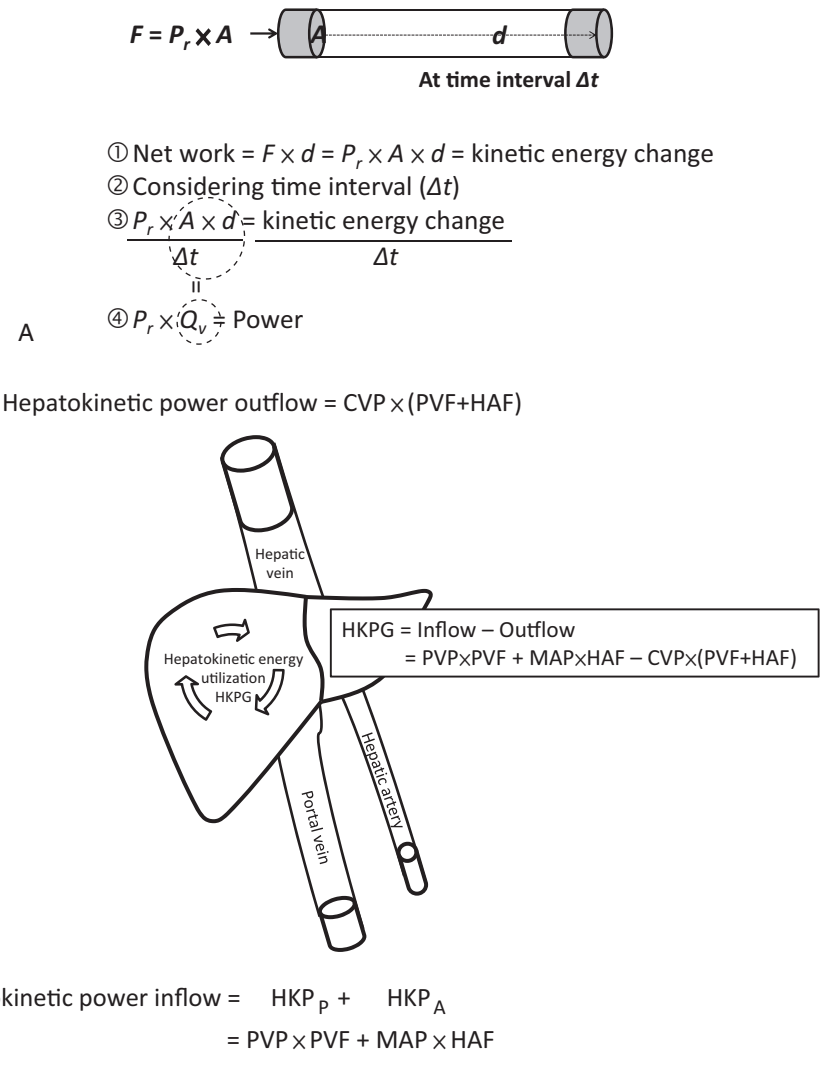

FIGURE 1. A, A stepwise substitution is performed to obtain the clinical applicable equation of hydrodynamic power. The dash circle infers the interchangeable items. The network performed on an object is equivalent to the constant force (*F*) multiplied by the displacement (*d*) it moved. The force can be calculated by the multiplication of the pressure (P_r) and the area (*A*) over which it is distributed. The movement of a volume during a certain time interval represents volume flow (Q_v). B, Application of hydrodynamic power to the hepatic circuit. The hepatokinetic power gradient represents the power difference between inflow and outflow. CVP = central venous pressure, HAF = hepatic artery flow, HKPG = hepatokinetic power gradient, HKP_A = hepatokinetic power form hepatic artery, HKP_P = hepatokinetic power form portal vein, MAP = mean arterial pressure, PVF = portal vein flow, PVP = portal vein pressure.

To obtain the rate of performing work or utilizing energy, termed as power (P_o), the equation is divided by the time interval (Δt):

$$P_o = \frac{F \times d}{\Delta} = \frac{Pr \times A \times d}{\Delta t}$$

In hydrodynamics, the rate of fluid flow (Q_v) is the volume of fluid that passes through a given surface per unit time. Therefore, the equation can be simplified to

$$P_o = \mathrm{Pr} \times Q_v$$

The kinetic energy derived from hepatic circulation is referred to as "hepatokinetic energy" in the context of this study. In the liver, inflow is mediated by the portal vein (PV) and hepatic artery (HA), whereas outflow is mediated by the hepatic vein (HV). The hepatokinetic power difference between inflow and outflow may be representative of the rate of the kinetic energy conversion or utilization by the liver parenchyma. After a serial substitution, the hepatokinetic power gradient (HKPG) can be presented as (Figure 1B):

HKPG = hepatokinetic power inflow from the PV (HKP_P) and HA (HKP_A) substrate outflow from the HV = PVP × PVF + MAP × HAF−CVP × (PVF + HAF)

where MAP is the mean arterial pressure, HAF the hepatic artery flow, CVP the central venous pressure.

The fluid resistance (*R*) is defined as the ratio of the pressure difference (ΔP_r) to the volume flow rate. The calculable pressure difference is inaccessible because the PV is in a low-pressure state and the HA is in a high-pressure state; however, flow is constant according to the principle of mass

conservation. After substitution, resistance can be presented as the power difference, divided by the square flow:

$$P_o = Pr \times Q_v$$

$$R = \Delta P_r / Q_v = \Delta P_o / Q_v^2$$

(Because the Q_v is conserved, the difference in pressure results in a difference in power.)

Therefore, hepatic resistance (R_h) can be calculated as $R_h = \mathrm{HVPG}/(\mathrm{PVF} + \mathrm{HAF})^2$

Patient Population

From September 2012 to December 2014, a total of 111 patients underwent LT procedures in the Tri-Service General Hospital (Taipei, Taiwan). Our exclusion criteria were pediatric (age < 18 years) recipients and marginal graft recipients. We excluded 6 patients who had primary nonfunction, 2 of them received subsequent retransplantation. Three of the 5 patients having incomplete data were having primary nonfunction. Thus, a total of 8 patients were excluded and 103 patients were enrolled in this study. The medical records were assessed for their pre-, intra- and postoperative characteristics. The study was approved by the Institutional Review Board I of Tri-Service General Hospital, National Defense Medical Center (TSGHIRB No.: 1-102-05-081). All of the procedures were performed with the approval of the Ethics Committee.

Surgical Procedure

All patients were anesthetized using a standard protocol and the hemodynamic status was monitored strictly by the anesthesiologist. After endotracheal intubation, the anesthesiologist performed the catheterization of the internal jugular vein and femoral artery for pulse contour cardiac output monitoring routinely without exceptions. In the case of a partial graft, a right or left lobe graft was selected according to computed tomography scan volumetric analysis. All grafts were preserved in a histidine-tryptophan-ketoglutarate solution after adequate flushing through the PV and were implanted with a board end-to-side cavocaval anastomosis and an end-to-end portoportal reconstruction. In the case of right lobe grafts, the drainage veins from the anterior segments, such as V5 or V8, were reconstructed with artificial grafts (GORE-TEX® Vascular Grafts, Newark, DE) or with recanalized umbilical vein, or both if needed, to ensure the patency of hepatic outflow. All the hepatic arterial anastomoses were performed after PV reperfusion without simultaneous reperfusion. After the reconstruction of major vessels, biliary reconstruction was accomplished with an end-to-end choledochocholedochostomy using an interrupted suturing method, without the placement of a biliary stent or T-tube. After transplantation, the recipient was monitored in the intensive care unit (ICU) and extubated under the surveillance of the specialists.

Intraoperative Hemodynamic Measurements

All the hemodynamic parameters, which included PVF, HAF, PVP, CVP, and MAP, were measured and recorded routinely during the operation in the standard sequence. The timing points of hemodynamic measurements were (1) isolation of the PV of the recipient, (2) at reperfusion, (3) completion of the HA anastomosis, and (4) 30 min after vascular reconstruction or graft inflow modulations if required (Figure 2). The PVF and HAF (mL min^{-1}) were measured by using an ultrasonic transit time flowmeter (Transonic, New York, NY) with different probe sizes. The mean flow volume rates were determined and recorded. The PVP (mmHg) was measured by a direct puncture method with a 25-gauge needle after eliminating air from the system and zeroing at the level of the PV. The CVP and MAP were determined simultaneously by the anesthesiologists each time the hepatic hemodynamic measurements were obtained via the catheterization of internal jugular vein and femoral artery.

Postoperative Data and Complications

Postoperative complications that occurred during the same hospitalization for transplantation (in-hospital complications) were categorized using the Clavien–Dindo classification. Severe surgical complications were defined as a Clavien–Dindo grade≥ III.[10]

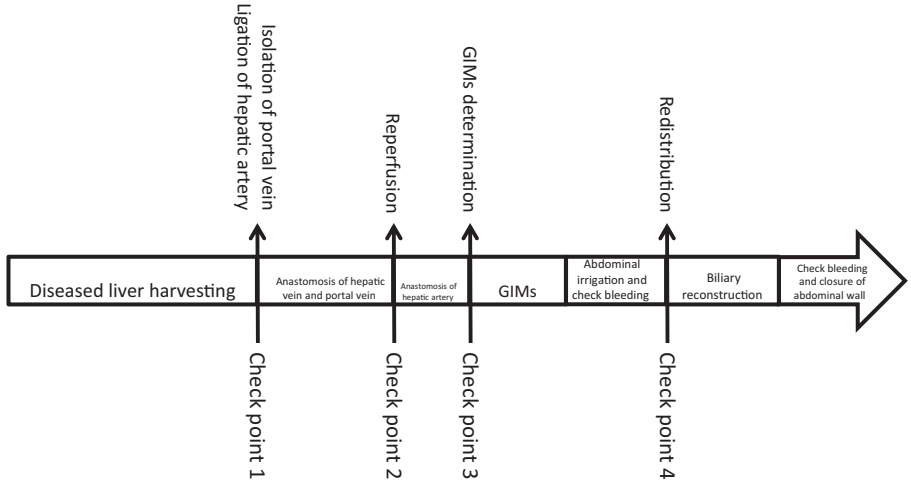

FIGURE 2. The checkpoints of systemic and hepatic hemodynamics that were used during transplantation. In this study, we focused on the equilibrium state—checkpoint 4. GIMs = graft inflow modulations.

Statistical Analysis

We used the free R 3.1.0 statistical software (R Foundation for Statistical Computing, Vienna, Austria) to perform statistical analysis. Two-sided P value ≤ 0.05 was considered as the criterion of statistical significance. We chose the Wilcoxon rank-sum test and Fisher's exact test to conduct univariate analysis for continuous and categorical variables respectively. Then, we fit logistic regression models to estimate the effects of predictors on the occurrence of severe in-hospital surgical complications in multivariate analysis. We applied basic model-fitting techniques for variable selection, goodness-of-fit assessment, and regression diagnostics and remedies in our logistic regression analysis. In stepwise variable selection procedure, all the univariate significant and nonsignificant relevant covariates listed in Tables 1 and 2 and some of the interactions (eg, donor–recipient gender match and graft types × hepatoki-hepatokinetic power indexes) were included in the variable list for selection to obtain the candidate final logistic regression model. We also fit generalized additive models to detect nonlinear effects of continuous covariates on the logit of the probability of having severe in-hospital surgical complications, and then we identified appropriate cut-off points for discretizing continuous covariates with nonlinear effects. Based on the substantive knowledge and our insights, we obtained the best candidate final logistic regression model manually by removing the covariates with P values > 0.05, one at a time, until all regression coefficients were significantly different from 0. We examined the estimated area under the receiver operating characteristic curve (ie, the c-statistic), adjusted generalized R^2, and the Hosmer–Lemeshow goodness-of-fit test to assess the goodness-of-fit of the fitted final logistic regression model. Finally, we used the statistical tools of regression diagnostics to detect the potential model and data problems.

RESULTS

Clinical Characteristics

Sixty-eight of the recipients were men (66%) and the mean age was 54.3 (9.4) years. The etiologies of the primary liver disease included hepatitis B (n = 52), hepatitis C (n = 29), alcoholic liver diseases (n = 30), hepatocellular carcinoma (n = 49), autoimmune hepatitis (n = 1), drug-induced hepatic failure (n = 1), and cryptogenic hepatic failure (n = 2). The mean postoperative intubation time was 26.6 (45.0) hours; mean ICU stay, 2.7 (2.1) days; and hospital stay, 23.4 (29.9) days. All the baseline characteristics of recipients, donors, donor–recipient match profile, and intraoperative findings are shown in Table 1.

Intraoperative Hemodynamics

For clarity, the intraoperative hemodynamics data are presented separately in Table 2. All the hemodynamics were measured at a baseline equilibrium state (check point 4, Figure 2) including systemic (CVP and MAP) and hepatic hemodynamics (PVF, HAF, and PVP). The hepatokinetic indexes derived from the equation of the HKPG are presented in Table 2 as well.

Risk Factors for the Development of Severe in-Hospital Surgical Complications

Twenty-five of the recipients had severe in-hospital surgical complications (24.3%) and the detailed descriptions are listed in supplemental Table 1 http://links.lww.com/MD/A480. The covariates in the univariate analysis are presented in categories in Table 1 and Table 2. Four variables were found to be associated with significant effects: preoperative massive ascites, donor gender, warm ischemic time (WIT) (Table 1), and MAP at equilibrium (Table 2). All the covariates and some of their interactions were entered into multivariate analysis, regardless of their significance in the univariate analysis, in order to assess any potential interactions. The results of stepwise multivariate analysis revealed that the body mass index (BMI) $\leq$24 or $\geq$34 (adjusted odds ratio [OR] 6.537, 95% confidence interval [CI] 1.67–32.42), model for end-stage liver disease (MELD) (OR 1.105, 95% CI 1.02–1.21), hepatitis C (OR 4.386, 95% CI 1.01–21.75), female-to-female gender match (OR 17.730, 95% CI 2.94–167.95), WIT > 50 min (OR 4.847, 95% CI 1.22–23.44), HKPG > 4260 mL mm Hg min^{-1} 100 g graft $weight^{-1}$ (OR 29.422, 95% CI 4.26–293.78), $2.2 < HKP_P/HKP_A \leq 8.7$ (OR 8.199, 95% CI 1.83–54.16), and hepatic resistance of partial grafts $\leq$0.006 or $>$0.015 min mm Hg mL^{-1} (OR 6.465, 95% CI 1.64–32.23) had significant effects on the occurrence of severe in-hospital surgical complications (Table 3). The c-statistic was 0.916, with a 95% CI of 0.859 to 0.972 (Figure 3).

DISCUSSION

There has been much debate concerning the optimal hemodynamics during LT that will yield the best graft survival, and most clinicians rely on PVP or PVF. The recommended limit for PVP is < 15 to 20 mmHg, which is believed essential for a successful living donor LT.[11–13] The ideal range for PVF is 100 to 260 mL min^{-1} 100 g^{-1}; graft inflow modulations would be required if the PVF is >250 mL min^{-1} 100 g^{-1} to prevent SFSS.[8,14–17] Instead of considering each parameter individually, the correlation between hepatic and systemic hemodynamics has been investigated as well. In 1981, Lautt introduced hepatic arterial buffer response (HABR), which signifies that alterations in PVF can be counteracted by changing the HAF, with the goal of maintaining the total blood flow to the liver.[18] In addition, hepatic hemodynamics have been shown to be affected by systemic hemodynamic conditions, where HVPG (HVPG = PVP − CVP) of <10 to 15 mm Hg was considered to have some clinical value in predicting the outcome after LT.[9,19,20] In 1963, Bradley proposed the Wheatstone bridge model for obtaining approximate values for some variables and parameters of the splanchnic, collateral, and hepatic circuits in cirrhosis.[21] Subsequently, Moreno et al directly measured PVF and PVP in patients with cirrhosis, and demonstrated a marked reduction in flow associated with a nearly constant plateau of PVP.[7] They proposed that this lack of correlation between PVP and PVF is an indication of the complex relationships between the resistances and the implied pressure gradients of patients with cirrhosis. Recently, Sainz-Barriga et al also showed that there was no obvious correlation between PVF and PVP. They believe that Ohm's law could better characterize the relationship; however, they were unable to derive a concise formula, which could interpret these complicated correlations in a simpler manner.[9]

In light of previous studies, the major limitations in exploring the correlation of the hemodynamics within the hepatic circulation are the complexity of regulatory contributors and the fluctuating nature of the system. According to the law of energy conservation, energy can be neither created nor destroyed, but it can change forms; therefore, kinetic energy

TABLE 1. Risk Factors for Severe Surgical Complications in the Univariate Analysis

Variables	Total	No Complications n = 78	Complications n = 25	*P* value*
Recipient variables				
Age (years), mean ± SD	54.3 ± 9.4	53.3 ± 9.5	57.2 ± 8.7	0.062
Gender (male), n (%)	68 (66)	55 (80.9)	13 (19.1)	0.097
Body mass index ($kg\,m^{-2}$), mean ± SD	25.4 ± 4.3	25.5 ± 3.8	25.3 ± 5.5	0.511
Primary liver disease				
Hepatitis B, n (%)	52 (50.5)	43 (82.7)	9 (17.3)	0.112
Hepatitis C, n (%)	29 (28.2)	18 (62.1)	11 (37.9)	0.072
Alcoholic liver cirrhosis, n (%)	30 (29.1)	25 (83.3)	5 (16.7)	0.317
Liver cirrhosis, n (%)	99 (96.1)	74 (74.7)	25 (25.3)	0.570
Hepatocellular carcinoma, n (%)	49 (47.6)	39 (79.6)	10 (20.4)	0.491
Child-Turcotte-Pugh score, mean ± SD	9.5 ± 2.4	9.4 ± 2.5	10.0 ± 1.9	0.481
MELD score, mean ± SD	17.1 ± 9.1	16.4 ± 8.9	19.1 ± 9.6	0.160
Preoperative complications				
Hepatic encephalopathy, n (%)	42 (40.8)	31 (73.8)	11 (26.2)	0.816
Ascites, n (%)	51 (49.5)	32 (62.7)	19 (37.3)	0.003*
Variceal bleeding, n (%)	38 (36.9)	29 (76.3)	9 (23.7)	1.000
Preoperative comorbidities				
Diabetes mellitus, n (%)	38 (36.9)	30 (78.9)	8 (21.1)	0.639
Hypertension, n (%)	23 (22.3)	16 (69.6)	7 (30.4)	0.423
Renal function impairment, n (%)	25 (24.3)	20 (80.0)	5 (20.0)	0.789
Donor Variables				
Age (years), mean ± SD	31.4 ± 8.5	30.7 ± 7.7	33.6 ± 10.4	0.122
Gender (male), n (%)	56 (54.4)	47 (83.9)	9 (16.1)	0.040*
Graft type, n (%)	–	–	–	1.000
Full-size graft†	13 (12.6)	10 (76.9)	3 (23.1)	1.000
Right lobe graft	66 (64.1)	50 (75.8)	16 (24.2)	1.000
Left lobe graft	21 (20.4)	16 (76.2)	5 (23.8)	1.000
Segment VI-VII graft	3 (2.9)	2 (66.7)	1 (33.3)	0.570
Graft weight (g), mean ± SD	729.3 ± 275.4	746.7 ± 289.6	674.8 ± 221.6	0.244
LDLT, n (%)	90 (87.4)	68 (75.6)	22 (24.4)	1.000
Recipient-donor match profile				
GRWR (%), mean ± SD	1.09 ± 0.45	1.09 ± 0.44	1.08 ± 0.47	0.797
Degree of kinship, n (%)	–	–	–	0.935
Brain-dead donors	13 (12.6)	10 (76.9)	3 (23.1)	1.000
Paternity	75 (72.8)	55 (73.3)	20 (26.7)	0.444
Siblings	6 (5.8)	5 (83.3)	1 (16.7)	1.000
Cousins	1 (1.0)	1 (100.0)	0 (0.0)	1.000
Couple	8 (7.8)	7 (87.5)	1 (12.5)	0.676
ABOi, n (%)	8 (7.8)	6 (75)	2 (25)	1.000
Operative variables				
Operative time (min), mean ± SD	650.4 ± 94.9	647.5 ± 88.6	659.6 ± 113.7	0.872
Cold ischemia time (min), mean ± SD	95.5 ± 44.8	91.7 ± 39.6	107.6 ± 58.0	0.405
Warm ischemia time (min), mean ± SD	47.6 ± 31.8	46.0 ± 34.0	52.5 ± 23.4	0.036*
Intraoperative blood loss (mL), mean ± SD	1629.7 ± 1134.1	1636.9 ± 1108.7	1607.3 ± 1233.6	0.859
Fluid supplement (mL), mean ± SD	5284.8 ± 1847.8	5169.2 ± 1738.4	5645.4 ± 2153.4	0.258
Splenectomy, n (%)	36 (35.0)	26 (72.2)	10 (27.8)	0.631
Hepatic outflow reconstruction, n (%)				
Vein graft	12 (11.7)	10 (83.3)	2 (16.7)	0.726
Artificial vascular graft	6 (5.8)	5 (83.3)	1 (16.7)	1.000

GRWR = graft-to-recipient weight ratio, ABOi = ABO incompatible liver transplantation, LDLT = living donor liver transplantation, MELD = model for end-stage liver disease, SD = standard deviation.

* Two-sided *P* value < 0.05 was considered statistically significant.

† All full-size grafts were from brain-dead donors.

is considered as the integrator of the hepatic circuit, which can be calculated from available clinical information. Microscopically, it is impossible to measure and evaluate energy conversion in different forms, such as chemical energy, thermal energy, gravitational energy, and electric energy, either intracellularly or intercellularly. Macroscopically, kinetic energy is the major source of energy in the hepatic circulation because the body temperature is constant and intraoperatively, the patient

TABLE 2. Risk Factors Related to Hemodynamics for Severe Surgical Complications in the Univariate Analysis

Variables	Total	No Complications n = 78	Complications n = 25	*P* Value*
Hemodynamics at equilibrium†				
Systemic hemodynamics				
CVP (mmHg)	10.2 ± 4.3	10.3 ± 4.3	9.8 ± 4.7	0.459
MAP (mmHg)	78.8 ± 11.6	80.1 ± 11.1	74.8 ± 12.3	0.041*
Hepatic hemodynamics				
HAF (mL min^{-1})	120.5 ± 80.9	127.0 ± 86.9	100.0 ± 55.1	0.310
HAF (mL min^{-1} 100 g of GW^{-1})	16.9 ± 10.9	17.1 ± 10.3	16.2 ± 12.8	0.397
PVF (mL min^{-1})	1315.3 ± 492.7	1300.4 ± 474.4	1361.7 ± 553.8	0.709
PVF (mL min^{-1} 100 g of GW^{-1})	194.4 ± 79.7	190.4 ± 81.1	206.9 ± 75.4	0.350
PVP (mmHg)	15.8 ± 4.5	15.8 ± 4.5	15.9 ± 4.7	0.746
HVPG (mmHg)‡	5.7 ± 3.2	5.5 ± 3.1	6.1 ± 3.5	0.484
Hepatokinetic power profiles				
HKP_P (mmHg mL min^{-1})	20595.6 ± 9677.5	20560.5 ± 9758.9	20705.0 ± 9615.7	0.764
HKP_A (mmHg mL min^{-1})	9688.9 ± 6943.4	10393.1 ± 7467.2	7491.7 ±4399.8	0.136
Power inflow (mmHg mL min^{-1})§	30284.5 ± 11170.0	30953.7 ± 11061.4	28196.7 ± 11476.8	0.226
HKPG (mmHg mL min^{-1})	15988.3 ± 7825.6	16301.4 ± 7667.6	15011.5 ± 8386.7	0.444
HKPG (mmHg mL min^{-1} 100 g of GW^{-1})	2334.3 ± 1217.2	2321.7 ± 1124.7	2373.8 ± 1495.3	0.631
HKPG/power inflow	0.53 ± 0.16	0.53 ± 0.16	0.52 ± 0.15	0.803
HKP_P/HKP_A	3.7 ± 4.5	3.7 ± 5.0	3.5 ± 2.2	0.185
Resistance (min mmHg mL^{-1})	0.0096 ± 0.0073	0.0101 ± 0.0076	0.0082 ± 0.0059	0.223
Resistance (min mmHg mL^{-1} 100 g of GW^{-1})	0.0015 ± 0.0014	0.0015 ± 0.0014	0.0014 ± 0.0013	0.556

CVP = central venous pressure, GW = graft weight, HAF = hepatic artery flow, HKP_A = hepatokinetic power of hepatic artery, HKPG = hepatokinetic power gradient, HKP_P = hepatokinetic power of portal vein, HVPG = hepatic venous pressure gradient, MAP = mean arterial pressure, PVF = portal vein flow, PVP = portal vein pressure.

* Two-sided *P* value < 0.05 was considered statistically significant.

† The hemodynamics were measured at least 30 min after hepatic artery reconstruction or graft inflow modulations (check point 4 in Figure 2).

‡ HVPG = PVP − CVP.

§ Power inflow = HKPP + HKPA.

lies horizontally on the operating table. This implies that there may be only trivial thermal and/or gravitational potential energy differences. As such, kinetic energy inflow and outflow can be assessed clinically during LT by measuring the associated systemic and hepatic hemodynamic parameters. This measurable kinetic energy of the hepatic system may be termed as "hepatokinetic energy," and the gradient refers to the kinetic energy difference between the inflow and outflow. To obtain the available clinical data, a time interval was utilized and hepatokinetic energy was transformed into power by dividing the time interval. This suggested the rate of hepatokinetic energy change. Likewise, the HKPG represents the power difference

TABLE 3. Multivariate Analyses of the Factors Associated With Severe Early Complications

Covariate	Estimate	Standard Error	z Value	*P* Value	Odds Ratio	95% CI of Odds Ratio
Severe surgical complications (intercept)	−8.463	1.822	−4.643	<0.001	–	–
Recipient variables						
BMI ≤ 24 or ≥ 34	1.877	0.743	2.527	0.012	6.537	1.67–32.42
MELD	0.100	0.042	2.366	0.018	1.105	1.02–1.21
Hepatitis C	1.478	0.770	1.921	0.055	4.386	1.01–21.75
Donor variable						
Female–to–female gender match	2.875	1.003	2.866	0.004	17.730	2.94–167.95
Operative variables						
Warm ischemia time >50 min	1.578	0.739	2.135	0.033	4.847	1.22–23.44
Hepatokinetic profiles						
HKPG* > 4260	3.382	1.053	3.212	0.001	29.422	4.26–293.78
2.2 < HKP_P/HKP_A ≤ 8.7	2.104	0.840	2.506	0.012	8.199	1.83–54.16
Hepatic resistance of the partial graft† ≥ 0.006 or >0.015	1.866	0.747	2.500	0.012	6.465	1.64–32.23

BMI = body mass index, HKP_A = hepatokinetic power of hepatic artery, HKPG = hepatokinetic power gradient, HKP_P = hepatokinetic power of portal vein, MELD = model for end-stage liver disease. Goodness of fit: n = 103, adjusted generalized $R^2 = 0.578 > 0.3$, the estimated area under the ROC curve = 0.916, and Hosmer–Lemeshow F test $P = 0.992 > 0.05$ (df = 9.93).

* HVPG (mL mmHg min^{-1}100 g graft $weight^{-1}$).

† Hepatic resistance (min mmHg mL^{-1}).

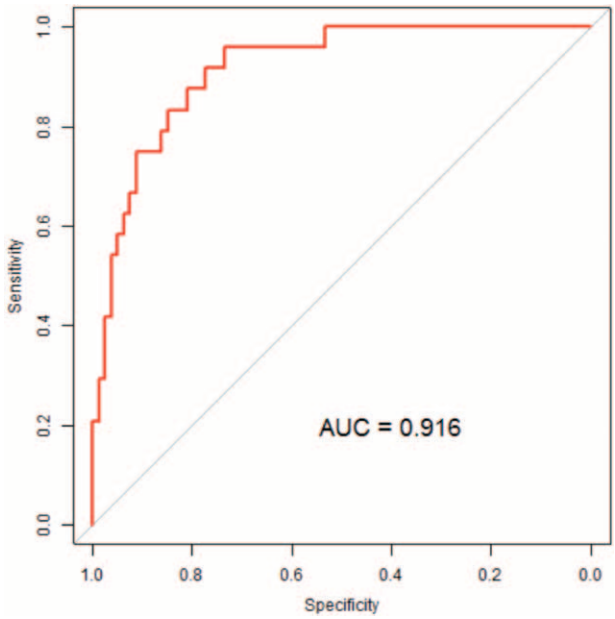

FIGURE 3. The receiver operating characteristic curve of our regression model for predicting severe in-hospital surgical complications with a *c*-statistic of 0.916.

between the inflow and outflow. Mechanically, HKPG is the rate of kinetic energy utilization by the liver parenchyma, which can be considered as a restrictor that converse energy in a fluid network.

At present, liver resistance is considered to be important; however, it can only be subjectively evaluated according to a surgeon's experience based on the color and consistency of the implanted grafts at the time of reperfusion. In Bradley's Wheatstone bridge model, there are 5 measures of resistance, and 4 major pressure levels (Figure 4A). To our knowledge, the currently available clinical data are insufficient to obtain a numerical solution for this model; thus, its clinical applicability is hindered. Our model focused on the hemodynamics after the implantation of healthy grafts, which involves less intra- and extrahepatic shunting; in this case, the major resistance sources are hepatic arterial, portal venular, and postsinusoidal after vascular reconstruction (Figure 4B). Apparently, the hepatic arterial and portal venular resistances are calculable[8]; however, the postsinusoidal resistance is not because of the difficulty in obtaining the postsinusoidal pressure. Additionally, the correlation of the 3 major sources of hepatic resistance does not only involve mere addition or multiplication. In order to derive the clinically useful resistance in a simple manner, these 3 resistances were considered together as a single resistor, which is grossly representative as the graft resistance (Figure 4C). Hepatic resistance is a comprehensive representative for these objective characteristics and may serve as a subjective parameter of clinical value. Fundamentally, this model is similar to the electronic–hydraulic analogy, and compared to Bradley's Wheatstone bridge model, the hepatokinetic power model is highly simplified and provides a method to quantify hepatic resistance as an actual value.

In the multivariate analysis, we assessed the value of these hepatokinetic power-related parameters by comparing the significance of each with the other covariates, including the conventional parameters, such as PVP, PVF, and HVPG. Notably, we had performed subgroup analyses to explore the applicability of our "hepatokinetic power profile" concept and formula to liver transplantations with 2 kinds of liver grafts, partial and full-size grafts. We found that among the covariates that significantly affected the occurrence of severe in-hospital surgical complications, the hepatokinetic model-related covariates were hepatic resistance of partial grafts, HVPG, and the ratio of HKP_P to HKP_A. Conversely, the conventional parameters failed to show significance in the regression model. When the hepatic resistance of partial grafts is ≤ 0.006 or >0.015 min mmHg mL^{-1}, the risk of having severe in-hospital surgical complications increases. If the hepatic resistance is ≤ 0.006 min mmHg mL^{-1}, it may indicate dysfunction of the intrinsic or extrinsic vascular regulatory mechanisms and failure to maintain a dynamic equilibrium. On the contrary, if hepatic resistance is >0.015 min mm Hg mL^{-1}, it may imply potential vascular obstruction, such as venous or arterial thrombosis, or excessive HKPG. An HKPG of 4260 mmHg mL min^{-1} 100 g graft $weight^{-1}$ was the upper limit of the power gradient found in this study, which works in concert with excessive HKPG that may subsequently cause immoderate hepatic resistance. This result might explain the restricted capacity of kinetic energy utilization in an implanted graft, or it could indicate the ability of a graft to convert kinetic energy. Compared to full-sized grafts, partial grafts are more susceptible to hemodynamic fluctuation; this phenomenon may result from the limited reservoir capacity, relatively reduced hepatic artery flow, and inadequate outflow reconstruction with graft congestion. Excessive kinetic power inflow or reduced outflow or both will result in a hepatokinetic energy overload; therefore, the transplant surgeon should re-evaluate not only the vascular anastomoses but also the systemic hemodynamics and consider the appropriate medical or further surgical interventions. The last finding associated with the hepatokinetic model is that the ratio of HKP_P to HKP_A within the range of 2.2 to 8.7 represents an increased risk, although this is still difficult to explain based on our present understanding. Our hypothesis is that transplant grafts can be categorized into 2 groups, HKP_P or HKP_A predominant, which depends on the final result of the HABR. This phenomenon may indicate preservation of the HABR of the implanted graft and facilitate the achievement of hemodynamic equilibrium.[22]

The other risk factors for severe surgical complications identified in this regression model included BMI ≤ 24 or ≥ 34, MELD score, hepatitis C, female-to-female gender match, and WIT >50 min. Some of them have been reported and some have only been partially discussed by other study groups. Patients with higher MELD scores are expected to have longer ICU stays and higher retransplant rates.[23–26] In a recent study of 1522 patients at University of California, Los Angeles, with MELD scores ≥ 40 undergoing orthotopic LT, MELD score, pretransplant septic shock, cardiac risk, and comorbidities were independent predictors of a futile outcome.[27] Additionally, recipient age, post-operative complication grade 4, hepatitis C, and metabolic syndrome were identified as predictors of survival in the same study. In our predictive model, we also identified that hepatitis C was a risk factor for poorer surgical outcomes. It has been suggested that the patients with hepatitis C have worse outcomes after LT in various studies.[28–30] Besides, we found a WIT >50 min was an independent risk factor for severe in-hospital surgical complications. Prolonged WIT has been documented to significantly influence initial graft function.[31,32] In a large retrospective study, a WIT ≥ 75 min was a significant risk factor for 1-day mortality due to graft failure.[33]

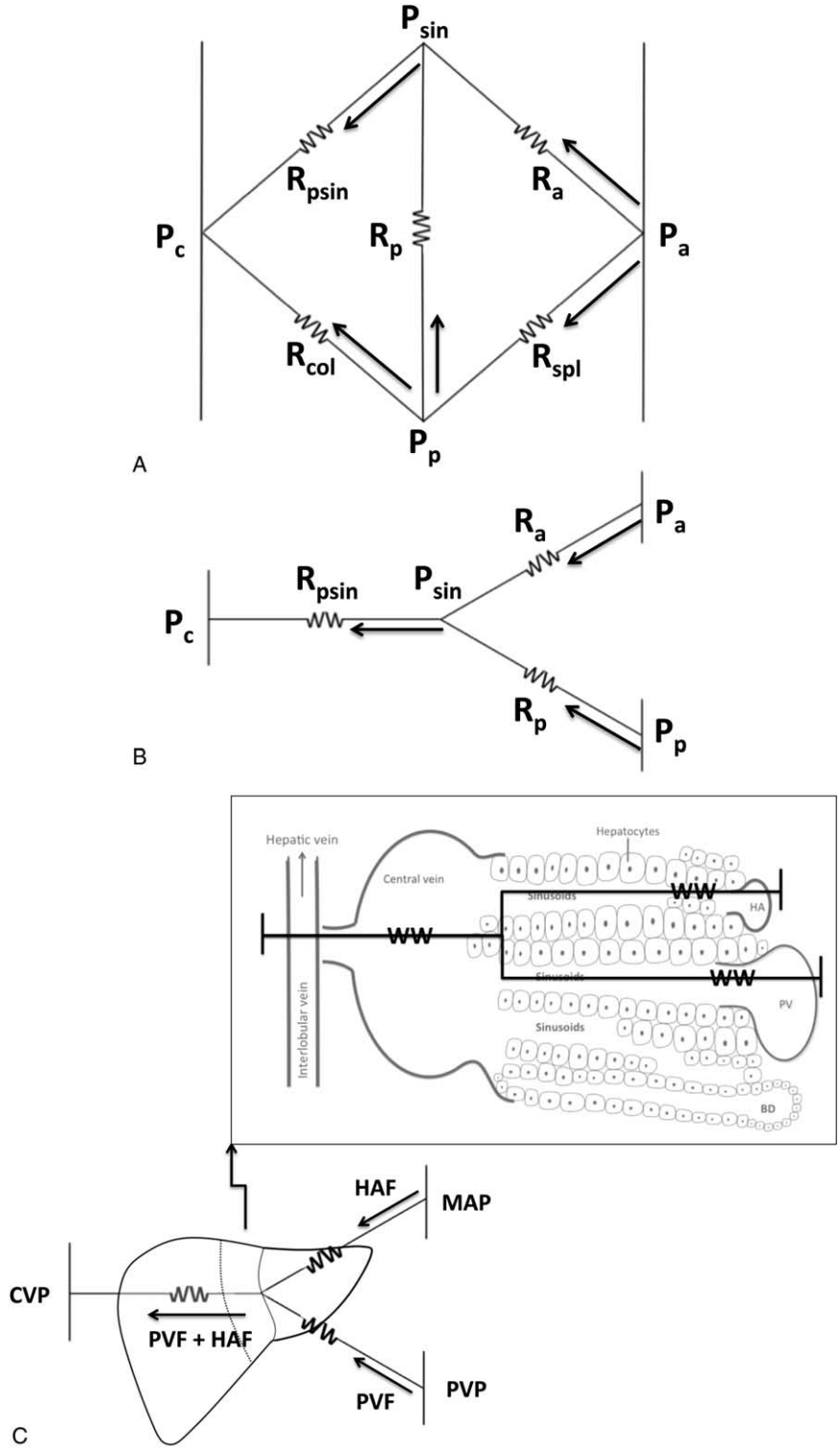

FIGURE 4. A, Bradley's Wheatstone bridge model explaining the complex correlations between flow (arrows), pressure, and resistance. B, The electrohydraulic analogy of our model intraoperatively after graft implantation at equilibrium. C, Incorporation of the electrohydraulic analogy diagram microscopically and macroscopically into the hepatic circuit. In the gross view, the 3 major resistances are taken as a whole and could be calculated as an actual value by applying the hepatokinetic power model (shown in B). CVP = central venous pressure, HAF = hepatic artery flow, MAP = mean arterial pressure, P_a = systemic arterial pressure, P_c = inferior vena caval pressure, P_p = portal venous pressure, P_{sin} = sinusoidal pressure, PVF = portal vein flow, PVP = portal vein pressure, R_a = hepatic arteriolar resistance, R_{col} = collateral resistance, R_p = portal venular resistance, R_{psin} = postsinusoidal resistance, R_{spl} = splanchnic resistance.

Finally, BMI $\leq$24 or $\geq$34 and female-to-female gender match were unique risk factors identified in our study. The impact of obesity on surgical outcomes has been discussed extensively; however, there is still a lack of consensus about its influence on the outcome of major surgical procedures.[34–38] In a recent cohort study, obesity (BMI $\geq 30\,kg\,m^{-2}$) was an independent risk factor for postoperative events.[39] The influence of donor gender in the outcome of LT has not been investigated thoroughly; however, worse outcomes in renal transplantation have been reported with female grafts.[40] Previous studies of various sizes have identified that grafts from female donors transplanted into male recipients result in worse outcomes.[41–46] The possible pathophysiological mechanism is still under investigation. We found that the risk of severe in-hospital complications markedly increased in female patients transplanted with female donor grafts. Further subgroup analysis will be required for assessment of this phenomenon; eg, female recipients were more likely to have hepatitis C as the primary cause requiring transplantation (17/35), as compared to the male recipients (12/68) in our studied population.

There are several limitations in our study. First, we analyzed a relatively small number of cases in a single transplant center. Additionally, we did not perform detailed subgrouping, which might provide valuable information. In fact, the major problem we encountered was that it was difficult to construct a hydrodynamic model mimicking the human liver in vitro; therefore, we will continue verifying this hypothesis in animal models. This study design can only illustrate the effectiveness of this hypothesis through clinical observation; the exact mechanism of hepatokinetic power conversion and the possible pathophysiology is still being explored. In conclusion, the hepatokinetic power model can explain the correlation between systemic and hepatic hemodynamics in a simple and quantifiable manner based on our present clinical observation. Hepatic resistance, as the derivative of the hepatokinetic power gradient, can be calculated as an actual value for the first time, and appears to be clinically significant in predicting severe in-hospital surgical complications.

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