12-24-2020

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Hepatic Vein Flow Index During Orthotopic Liver Transplantation as a Predictive Factor for Postoperative Early Allograft Dysfunction

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Objectives: The authors devised a hepatic vein flow index (HVFi), using intraoperative transesophageal echocardiography and graft weight, and investigated its predictive value for postoperative graft function in orthotopic liver transplant.

Design: Prospective clinical trial.

Setting: Single-center tertiary academic hospital.

Participants: Ninety-seven patients who had orthotopic liver transplant with the piggy-back technique between February 2018 and December 2019.

Measurements and Main Results: HVFi was defined with HV flow/graft weight. Patients who developed early graft dysfunction (EAD) had low HVFi in systole (HVFi sys, 1.23 v 2.19 L/min/kg, p < 0.01), low HVFi in diastole (HVFi dia, 0.87 v 1.54 L/min/kg, p < 0.01), low hepatic vein flow (HVF) in systole (HVF sys, 2.04 v 3.95 L/min, p < 0.01), and low HVF in diastole (HVF dia, 1.44 v 2.63 L/min, p < 0.01). More cardiac death, more vasopressors at the time of measurement, more acute rejection, longer time to normalize total bilirubin (TIME t-bil), longer surgery time, longer neohepatic time, and more packed red blood cell transfusion were observed in the EAD patients. All HVF parameters were negatively correlated with TIME t-bil (HVFi sys R = −0.406, p < 0.01; HVFi dia R = −0.442, p < 0.01; HVF sys R = −0.44, p < 0.01; HVF dia R = −0.467, p < 0.01). The receiver operating characteristic curve analysis determined the best cut-off levels of HVFi to predict occurrence of EAD (HVFi sys < 1.608, HVFi dia < 0.784 L/min/kg), acute rejection (HVFi sys < 1.388, HVF dia < 1.077 L/min/kg), and prolonged high total bilirubin (HVFFi sys < 1.471, HVF dia < 1.087 L/min/kg).

Conclusions: The authors’ devised HVFi has the potential to predict the postoperative graft function.

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Key Words: early allograft dysfunction; piggy-back technique; orthotopic liver transplant; hepatic vein flow; transesophageal echocardiography

LIVER TRANSPLANTATION (LT) continues to be the gold standard for treating end-stage liver disease (ESLD), and the piggy-back technique has been widely used for orthotopic LT (OLT) since its introduction in 1989, mostly because of more stable intraoperative hemodynamics.1,2 Outflow obstruction of the liver graft is a well-reported complication of the piggy-back technique, and may lead to allograft dysfunction, graft loss, and death.2,3

Intraoperative anesthetic management in LT can be challenging due to preoperative medical comorbidities, significant...
intraoperative hemodynamic changes, and periodic unexpected findings, such as intracardiac thrombi or pulmonary emboli; and the usefulness of intraoperative transesophageal echocardiography (TEE) has been discussed in previous publications. Although TEE use during LT can aid in the diagnosis and management of hemodynamic instability and is recommended in the practice guidelines from the American Society of Echocardiography (ASE)/Society of Cardiovascular Anesthesiologists (SCA) and the American Association for the Study of Liver, its routine intraoperative use has limited scientific support. Actually, TEE is relatively contraindicated in grade 3 or recently bleeding esophageal varices, which are common in ESLD, and the possibility for complications should not be ignored. However, the biggest argument is that TEE findings can provide only a clinical impression, which is subjective to interobserver variability, although there is no doubt TEE provides important hemodynamic information. An increasing number of reports show the usefulness of TEE to detect procedure-related complications, such as graft hepatic vein (HV) or inferior vena cava (IVC) stenosis. However, no published study has performed the quantitative assessment of graft flow using intraoperative TEE. Because HV can be assessed with TEE, TEE-derived HV flow parameters have a potential to detect early allograft dysfunction (EAD) sooner and guide therapy to optimize the graft function. HV is the outflow of graft flow and can be an index of graft perfusion. Also, HV flow can be calculated using intraoperative TEE measurements. The authors’ group recently demonstrated that hepatic vein flow index (HVFi), which was defined as TEE-measured HV flow/graft weight, potentially had good predictive value for postoperative EAD in piggy-back OLT patients. The current study used the same methodology for calculating HVFi as the authors’ previous retrospective study. The differences were (1) the current study was a prospective design, whereby HVFi was calculated before outcome data collection, and (2) the current study sought to demonstrate reproducibility of the HVFi score by means of intra-rater and inter-rater variances.

Methods

Study Design

This study was approved by the Henry Ford Health System Institutional Review Board (IRB #12156), and written consent was obtained before enrolling the patients. Also, this study was registered in ClinicalTrials.gov (NCT03814031).

This was a prospective, observational study of a cohort of adult patients who underwent OLT using the piggy-back technique between February 2018 and December 2019 at the Henry Ford Hospital in Detroit, Michigan. TEE data were collected from intraoperative TEE images as part of a prospective echocardiographic protocol measuring two-dimensional TEE-calculated hepatic vein flow (HVF) using transgastric modified HV view (Fig 1). In order to obtain the transgastric modified HV view, insert the probe into the stomach, find the transgastric basal view, rotate the probe right, identify the IVC as a...
large vascular structure in the liver, withdraw the probe to image drainage of the IVC into the right atrium, and adjust the omniplane angle (0°-40°) to image the HV as it drains into the IVC.

The patients’ demographics, perioperative clinical information, and postoperative outcomes were collected from the authors’ computerized patient database.

**Patient Cohort**

Inclusion criteria were adult patients undergoing the OLT piggy-back technique with TEE-measured HV flow between February 2018 and December 2019. Exclusion criteria were patient refusal to participate in the study, absolute TEE contraindication, inability to acquire appropriate images for HV flow measurement, or unavailability of a cardiac trained anesthesiologist.

All patients received general anesthesia with endotracheal intubation, standard American Society of Anesthesiologists monitoring, arterial blood pressure monitoring, central venous pressure monitoring, pulmonary artery pressure monitoring, and comprehensive TEE examination with designated protocol. Intraoperative anesthetics, mechanical ventilation, vasopressor, inotropic, and fluid/transfusion management were performed based on department protocol such as to maintain mean arterial pressure >65 mmHg, tidal volume 6-8 mL/ideal body weight (kg), positive end-expiratory pressure at 5-to-7 cmH2O.

**Data Collection**

TEE images were collected intraoperatively by National Board of Echocardiography-certified advanced perioperative echocardiographers using an iE33 echocardiographic machine with an X7 TEE probe (Philips Medical Systems, Andover, MA), and were stored in Syngo Workflow (Siemens Medical Solution, Malvern, PA). Timing for acquiring TEE modified transgastric HV view was in the neohepatic phase before fascia closure. To obtain HV flow, the pulsed-wave Doppler (PWD) sample volume was set in the graft HV just distal to IVC-graft anastomosis where an acceptable flow envelope was obtained.

**Echocardiography Parameters**

Three investigators (A, B, and C), who were also National Board of Echocardiography-certified advanced perioperative echocardiographers, measured HVF in systole and diastole independently using TEE images, which were acquired by a single cardiac anesthesiologist (advanced TEE boarded). The authors calculated HVF as follows: HVF (L/min) = HV area (cm²) x HV max velocity (cm/s) in systole and diastole x 60/1000, where HV area (cm²) = square of HV radius (cm) x 3.14, and HV max velocity (cm/s) was measured by TEE PWD with sample volume selected in the HV (Fig 1), where diameter of HV was measured as well. Efforts were made to align PWD and HV. The authors defined HVFi as HVF/donor liver weight (kg). The authors adjusted HVF with graft weight because recently it is more common to assess graft flow with graft size.\(^{18}\) To minimize selection bias, all the investigators were blinded to the hypothesis of the study.

**Outcomes**

The primary outcome was EAD, which was defined by the presence of one or more of the following: total bilirubin (t-bil) ≥10 mg/dL (171 µmol/L), or INR ≥1.6 on day 7, and ALT/AST >2,000 IU/L within the first seven days.\(^{19,20}\) The secondary outcome was acute rejection within six-to-eight weeks after transplant, prolonged (>seven days) time to normalize total bilirubin (TIME t-bil), prolonged (>seven days) time to normalize INR (TIME inr), and prolonged (>seven days) time to normalize platelet count (TIME plt).

**Statistical Analysis**

For continuous variables, the normality test was performed using the Kolmogorov-Smirnov test. Continuous variables with normal distribution were displayed as mean ± standard deviation, and those with non-normal distribution were displayed as median and interquartile range. Categorical variables were presented as proportions and absolute numbers. The differences between the two groups were investigated using unpaired and paired Student t tests or the Mann-Whitney U test. The Chi-square or Fisher exact test was used for categorical variables. A correlation analysis was performed for HVFi and the times including TIME t-bil, TIME inr, and TIME plt (Spearman as non-normal distribution). Also, Youden’s index was used for receiver operating characteristic (ROC) curve analysis to evaluate the appropriate cut-off value of HVFi for predicting EAD, acute rejection, and prolonged TIME t-bil (>seven days). The authors also performed subgroup risk adjustment analysis in the cardiac death group with bivariate analysis. Intrarater and inter-rater reliability analyses of HVFi were performed using intraclass correlation coefficient (ICC).\(^{21-23}\) The authors randomly picked 30 images and obtained consistency ICC for interobserver variability using all 3three investigators (A, B, and C) and absolute-agreement ICC for intraobserver variability using investigator C, who measured all images twice with an interval of six-to-eight weeks.\(^{23}\) For interobserver variability, three investigators post hoc determined HV diameter, peak systolic flow, and peak diastolic flow based on the PWD signal. All statistical analyses were performed using R (The R Foundation for Statistical Computing, Vienna, Austria. ver 4.0.2). All p values of less than 0.05 were considered statistically significant.

**Sample Size Calculation**

Assuming incidence of EAD was 23.2% (range of incidence was 2%-23%).\(^{19,20}\) 70 patients in control and 21 patients in EAD were needed at the power of 80% and alpha 0.05 with achieving at least 0.7 for area under curve in ROC analysis. To be conservative and account for potential problems with imaging analysis, 97 patients were enrolled.
Results

Of the 120 eligible patients, 97 participated in the study (patient refusal to participate in the study: two patients, absolute TEE contraindication: five patients, damping of the HVs images: six patients, and technically challenging to obtain appropriate views for HVF measurement: ten patients). No turbulent flow was observed in HV in the authors’ cohort. The characteristics of these 97 patients are shown in Tables 1 and 2. No significant gastrointestinal bleeding was reported in the authors’ study. The median HVFi in the EAD group was significantly lower than the median HVF in the non-EAD group. In addition, the best cut-off levels to predict EAD for HVFi sys was 1.608 and HVFi dia 0.784. Patients who developed EAD had low HVFi in systole (HVFi sys, 1.23 v 2.19 L/min/kg, p < 0.01), low HVFi in diastole (HVFi dia, 0.87 v 1.54 L/min/kg, p < 0.01), low HVFi in systole (HVFi sys, 2.04 v 3.95 L/min/kg, p < 0.01), and low HVFi in diastole (HVFi dia, 1.44 v 2.63 L/min/kg, p < 0.01). More cardiac death, more vasopressors at the time of measurement, more acute rejection, longer TIME t-bil, longer surgery time, and more packed red blood cell transfusion were observed in the EAD patients (Table 1). Correlation coefficients between HVFs and graft function index, such as TIME t-bil, TIME inr, and TIME plt, are shown in Table 3. All HVF parameters were correlated negatively with TIME t-bil (HVFi sys R = -0.406, p < 0.01; HVFi dia R = -0.442, p < 0.01; HVF sys R = -0.44, p < 0.01; HVF dia R = -0.467, p < 0.01). The scatter plot is shown in the EAD and non-EAD groups in Figure 2. The ROC curve analysis and Youden criterion determined the best cut-off levels of HVFis to predict occurrence of EAD (HVFi sys <1.388, HVF sys <1.077 L/min/kg; Fig 3, A), acute rejection (HVFi sys <1.388, HVF sys <1.077 L/min/kg; Fig 3, B), and prolonged high t-bil (HVFi sys <1.471, HVFi dia <1.087 L/min/kg; Fig 3, C). HVFi was superior to HVF in terms of predicting these outcomes. Subgroup risk adjustment by bivariate analysis in the cardiac death group is shown in Table 4. The authors chose donor age, model for end-stage liver disease (MELD), cold ischemic time (CIT), and warm ischemic time (WIT) as references based on previously reported risk factors for EAD.19 The ICCs for the inter- and intraobserver analyses (WIT) as references based on previously reported risk factors (MELD), cold ischemic time (CIT), and warm ischemic time (WIT) were reference based on previously reported risk factors (Table 5).

Discussion

The authors’ presented prospective observational study showed that HVFi and HVF obtained from intraoperative TEE were related to the postoperative graft function of OLT. HVF and HVFi were lower in patients with EAD and negatively correlated with the time to bilirubin normalization after the procedure. Lower HVFis were risk factors for EAD after adjustments with donor age, MELD, CIT, or WIT. ROC analyses revealed the cut-off values of HVFis to predict EAD, acute rejection, and prolonged high t-bil with fair sensitivity and specificity. HVFi was superior to HVF regarding these predictions because graft weight adjustment might have led to assess blood flow in each segment.18

In addition to intraoperative TEE’s widely recognized purpose as a hemodynamic monitor in OLT, the benefits of assessing graft anastomosis patency with TEE qualitatively also have been reported.6,10,15,16 This study was novel in that the authors quantitatively assessed HV flow and its correlation with postoperative graft function in the piggy-back technique. TEE is not without associated complications in ESLD, which include

<table>
<thead>
<tr>
<th>Table 1: Patient Demographics in EAD and Non-EAD Group</th>
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</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Age (y)</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>DCD</td>
</tr>
<tr>
<td>Liver weight (kg)</td>
</tr>
</tbody>
</table>

Abbreviations: CIT, cold ischemic time; DCD, donor of cardiac death; DM, diabetes mellitus; EAD, early allograft dysfunction; EBL, estimated blood loss; FFP, fresh frozen plasma; HCC, hepatocellular carcinoma; HTN, hypertension; MELD, model for end-stage liver disease; NASH, nonalcoholic steatohepatitis; PRBC, packed red blood cells; UOP, urine output; WIT, warm ischemic time.
esophageal varices and coagulopathy, and its benefits and risks should be weighed on a case-by-case basis.6,7 The ASE/SCA now recommends that images of the IVC and HVs be obtained as part of a comprehensive perioperative assessment,8 and its value has been corroborated in several case reports6,10,16,24-26 The modified HV view described in this study is not part of the basic TEE certification endorsed by the ASE/SCA,8,27 and its utility has not been investigated widely in OLT. The authors believe that this is partly because of transplant anesthesiologists’ unfamiliarity with obtaining this view. At the authors’ institute, three out of the six transplant anesthesiologists are cardiac trained and readily available for acquiring necessary images, which might have led to a greater percentage of success in obtaining this view.

In previous studies, assessment of HV mostly has been done with perioperative transabdominal Doppler ultrasound, but mostly on waveform assessment. Britton, et al. reported damping of the HV signal, with Doppler ultrasound, as the first indication of rejection after pediatric LT.28 The authors observed damping of the HV images in six patients, three of whom had acute rejection. Recently, Vetrugno et al. reported the importance of paying attention to HV-flow Doppler waveform by referring to detailed explanations on HV Doppler waveform.10,29 Although Doppler ultrasound has the advantage of being able to identify flows in each HV, TEE comprehensively is able to assess HV flow, volume status, and cardiac function.

Table 2
Hepatic Vein Parameters in EAD and Non-EAD Group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EAD (n = 26)</th>
<th>No EAD (n = 71)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HV flow systolic index (L/min/kg)</td>
<td>1.23 [0.85, 1.73]</td>
<td>2.19 [1.28, 3.70]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HV flow diastolic index (L/min/kg)</td>
<td>0.87 [0.62, 1.32]</td>
<td>1.54 [1.07, 2.34]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HV flow systolic (L/min)</td>
<td>2.04 [1.38, 3.03]</td>
<td>3.95 [2.02, 6.40]</td>
<td>0.0035</td>
</tr>
<tr>
<td>HV flow diastolic (L/min)</td>
<td>1.44 [1.02, 2.20]</td>
<td>2.63 [1.69, 4.13]</td>
<td>0.0015</td>
</tr>
<tr>
<td>Portal vein flow (L/min)</td>
<td>1.27 [1.1, 1.5]</td>
<td>1.5 [1.2, 1.78]</td>
<td>0.34</td>
</tr>
<tr>
<td>Hepatic artery flow (L/min)</td>
<td>0.32 [0.2, 0.44]</td>
<td>0.35 [0.21, 0.59]</td>
<td>0.51</td>
</tr>
<tr>
<td>MAP at the time of measurement (mmHg)</td>
<td>65 [56.25, 70.25]</td>
<td>67 [62.0, 76.5]</td>
<td>0.16</td>
</tr>
<tr>
<td>CI at the time of measurement (L/min/m²)</td>
<td>4.86 [3.8, 5.85]</td>
<td>4.6 [3.28, 5.52]</td>
<td>0.587</td>
</tr>
<tr>
<td>More than 1 vasopressor at the time of measurement</td>
<td>22 (84.6%)</td>
<td>38 (53.5%)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

NOTE. Vasopressors include vasopressin (0.01-0.03 unit/min) or norepinephrine (0.02-0.08 μg/kg/min).
Abbreviations: CI, cardiac index; EAD, early allograft dysfunction; HV, hepatic vein; MAP, mean arterial pressure.

Table 3
Spearman’s Correlation Coefficients Between HVF and Graft Function Index

<table>
<thead>
<tr>
<th>TIME t-bil (d)</th>
<th>TIME inr (d)</th>
<th>TIME plt (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVFi syst/C0</td>
<td>0.406 (p &lt; 0.01)</td>
<td>0.143 (p = 0.177)</td>
</tr>
<tr>
<td>HVFi dia/C0</td>
<td>0.442 (p &lt; 0.01)</td>
<td>-0.142 (p = 0.179)</td>
</tr>
<tr>
<td>HVF syst</td>
<td>-0.44 (p &lt; 0.01)</td>
<td>-0.15 (p = 0.157)</td>
</tr>
<tr>
<td>HVF dia</td>
<td>-0.467 (p &lt; 0.01)</td>
<td>-0.139 (p = 0.189)</td>
</tr>
</tbody>
</table>

Abbreviations: HVF, hepatic vein flow; HVFi dia, hepatic vein flow index in diastole; HVFi syst, hepatic vein flow index in systole; TIME inr, time to normalize INR; TIME plt, time to normalize platelet; TIME t-bil, time to normalize total bilirubin.

Fig. 2. Scatter plot distribution of HVF index in EAD and non-EAD group. (A) HVF systolic index grouped by EAD presence. (B) HVF diastolic index grouped by EAD presence. Note that each red box shows median 25 percentile and median 75 percentile in each group. Abbreviations: EAD, early allograft dysfunction; HVF, hepatic vein flow.
HV flow assessment would be important in predicting graft function given that inflow of the new graft includes the hepatic artery and portal vein, and outflow includes only the HVs. Suboptimal outflow may be due to suboptimal inflow or graft congestion, both of which are ominous signs for postoperative graft function. Previous correlation studies between intraoperative flow assessment of hepatic artery or portal vein and postoperative graft function were unable to show consistency in their correlation.30-32 Takahashi et al. reported that this inconsistency between flow and graft function might be because of a
lack of consistency in the timing of measurements, and

Intrarater HVFi syst 0.998 (0.997, 0.999)
Inter-rater HVFi syst 0.997 (0.995, 0.998)

Table 5
ICC for HVFi sys and HVFi dia

<table>
<thead>
<tr>
<th>Group</th>
<th>ICC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inter-rater</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HVFi sys</td>
<td>0.997</td>
<td>(0.995, 0.998)</td>
</tr>
<tr>
<td>HVFi dia</td>
<td>0.993</td>
<td>(0.988, 0.996)</td>
</tr>
<tr>
<td>Intrarater</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HVFi sys</td>
<td>0.998</td>
<td>(0.997, 0.999)</td>
</tr>
<tr>
<td>HVFi dia</td>
<td>0.998</td>
<td>(0.996, 0.999)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HVFi dia, hepatic vein flow index in diastole; HVFi sys, hepatic vein flow index in systole; OR, odds ratio.

Table 4
Multivariable Logistic Regression for EAD

<table>
<thead>
<tr>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVFi syst</td>
<td>0.313 (0.125-0.783)</td>
</tr>
<tr>
<td>Donor age</td>
<td>1.040 (0.998-1.090)</td>
</tr>
<tr>
<td>CIT</td>
<td>1.010 (0.998-1.010)</td>
</tr>
<tr>
<td>HVFi dia</td>
<td>0.136 (0.0285-0.646)</td>
</tr>
<tr>
<td>Donor age</td>
<td>1.050 (0.996-1.110)</td>
</tr>
<tr>
<td>CIT</td>
<td>1.010 (0.998-1.020)</td>
</tr>
</tbody>
</table>

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The authors hope that this study will encourage transplant anesthesiologists to pay attention to graft flows with TEE in OLT.

References