Evaluation of Arteriovenous Shunting in Patients With End-Stage Liver Disease: Potential Role of Early Right Heart Catheterization

M. Nagiub[a], R.T. Stravitz[b], D. Grinnan[c], and W. Moskowitz[a,*]

[a]Division of Pediatric Cardiology, Children's Hospital of Richmond, Virginia Commonwealth University, Richmond, Virginia; [b]Section of Hepatology, Hume-Lee Transplant Center, Virginia Commonwealth University, Richmond, Virginia; and [c]Division of Pulmonary Disease and Critical Care Medicine, Virginia Commonwealth University, Richmond, Virginia

ABSTRACT

Background. In patients with end-stage liver disease (ESLD), the presence of hypoxemia suggests the presence of intrapulmonary oxygen shunting (IPS) and/or transatrial shunting. Early identification of each is imperative to avoid potentially fatal peritransplantation complications and appropriately prioritize patients for liver transplantation (LT). The aim of this work was to compare the sensitivity of transthoracic echocardiography (TTE) and right heart catheterization (RHC) with intracardiac echocardiography (ICE) for identifying the etiologies of resting hypoxemia in patients with ESLD being evaluated for LT.

Methods. Records of 28 patients with ESLD and resting hypoxemia who underwent TTE with bubble study and RHC/ICE were reviewed. Patients with a patent foramen ovale (PFO) were compared with non-PFO patients to determine diagnostic accuracy of TTE with bubble study versus RHC/ICE.

Results. TTE with bubble study diagnosed PFO, IPS, and pulmonary hypertension (PH), respectively, with sensitivities of 46%, 41%, and 25% and specificities of 46%, 45%, and 80% compared with RHC/ICE. Although IPS detected by RHC/ICE was more common in patients without a PFO (92%), 5 patients with a PFO (33%) also had IPS ($P = .002$). Isolated PH was detected exclusively in patients with a PFO (5/15; 33%).

Conclusions. TTE with bubble study is neither sensitive nor specific to exclude a PFO in patients with ESLD. RHC/ICE is a safe and accurate diagnostic/interventional modality in this group of patients and is useful to diagnose other comorbidities, such as IPS and PH, that may coexist and contribute to resting hypoxemia.

IN patients with end-stage liver disease (ESLD), resting hypoxemia represents a frequently encountered dilemma with important clinical implications. To avoid serious perioperative complications around liver transplantation (LT) and to provide maximal priority to wait-listed patients, the presence of arteriovenous shunting within the microvasculature of the lung (hepatopulmonary syndrome [HPS]) must be distinguished from right-to-left interatrial shunting through a patent foramen ovale (PFO) or other atrial septal defect (ASD), flow-through that occurs owing to the coexistence of pulmonary hypertension (PH). It has been estimated that 20%–26% of healthy adults have a PFO [1], which has been associated with an increased risk of cryptogenic stroke or transient ischemic attack [2–4], suggesting that PFO increases the risk of paradoxic embolism. During LT, the presence of PFO may also increase the risk of paradoxic air or fibrin embolism with reperfusion of the graft [5], which may represent an important rationale for closure of the defect during pre-transplantation cardiac evaluation.

Trans-thoracic echocardiography (TTE) with agitated saline solution injection (bubble study) can detect right-to-

*Address correspondence to William Moskowitz, MD, Division of Pediatric Cardiology, Children Hospital of Richmond at Virginia Commonwealth University, 1200 East Broad Street, PO Box 980543, Richmond, VA 23298-0543. E-mail: wmoskowitz@mcvh-vcu.edu

0041-1345/15
http://dx.doi.org/10.1016/j.transproceed.2015.10.033

left shunting, but it can not accurately identify the site of shunting [6,7]. Although transesophageal echocardiography (TEE) with bubble study is considered to be the standard approach to diagnose a PFO [8], insufficient increase in right atrial above left atrial pressure may compromise its sensitivity [7]. TEE with bubble study has also been advocated to diagnose intrapulmonary shunting (IPS) [9]; however, the presence of high-risk esophageal varices is frequently cited as a relative contraindication to TEE [10,11]. In addition, TEE does not directly measure pulmonary pressure, and the finding of elevated right ventricular systolic pressure by means of TEE does not suffice for applying for added wait-list priority for PH according to current Organ Procurement and Transplant Network (OPTN) policy [12]. Finally, TEE is a diagnostic modality without therapeutic capability, and finding a PFO on TEE mandates a 2nd invasive procedure, right heart catheterization (RHC), to close the defect.

We have recently adopted a different strategy for evaluating and managing hypoxemic patients with ESLD undergoing LT evaluation. Patients with hypoxemia and a bubble TTE suggestive of right-to-left oxygen shunting have undergone RHC, intracardiac echocardiography (ICE) [13], measurement of right heart pressures, and closure of the PFO, if present, during the same procedure, bypassing TEE. We hypothesized that this approach would: 1) more accurately identify the presence of a PFO than TTE; 2) allow the identification of coexisting PFO and IPS; 3) directly measure the degree of PH; and 4) allow closure of a PFO during a single procedure. The following pilot study demonstrates the poor diagnostic accuracy of TTE and emphasizes the potential feasibility of this algorithm as time and possibly cost saving.

METHODS

Institutional Review Board approval was obtained for this retrospective observational single-center study. Records for 28 patients undergoing LT evaluation from 2009 to 2014 were reviewed. There were 2 primary inclusion criteria. First, patients must have had resting hypoxemia, which we defined as a PO_2 on room air of $\leq$70 mm Hg. Second, patients must have demonstrated evidence of right-to-left shunting by means of TTE with bubble study, most of which were indeterminate for the site of shunting as assessed by the number of heart beats to detect microbubbles in the left heart. During TTE, incorporation of the peak tricuspid regurgitant jet velocity into a modification of the Bernoulli equation was used to estimate the right ventricular systolic pressure, as previously reported. A peak right ventricular systolic pressure $\geq$35 mm Hg was defined as PH [27].

The potential complications of right heart catheterization, intracardiac echocardiography, and device closure of PFO include infection, thromboembolism, vessel damage, bleeding, arrhythmias, and device embolization. Antibiotics were given before device implantation, followed by 2 additional doses over 24 hours. Heparin was administered and guided by activated clotting time, and venous access sites were closed with the use of Cardiva III devices (Cardiva Medical, Sunnyvale, California). In patients with significant thrombocytopenia and/or significantly prolonged international normalized ratio, platelet infusions and/or fresh frozen plasma infusions, respectively, were given immediately before the procedure.

RHC was performed on all patients, and ICE assessment was performed to evaluate anatomy and degree and direction of shunting with the use of standard protocols [9,13–15] using an 8-F ICE catheter with a 5–10-MHz multiple frequency transducer (Acunav; Siemens, Erlangen, Germany). ICE data collected included the presence or absence of a PFO, presence or absence of fenestration [16], and the presence or absence of IPS [17], which was detected with the use of selective right and left pulmonary artery (PA) injections of agitated saline solution (ICE bubble study). IPS at RHC/ICE was defined as the presence of left atrial microbubbles after injection of agitated saline solution into the PAs. Concomitantly, right heart and PA pressures were obtained in all patients. If a PFO was detected at RHC, closure of the defect was performed with the use of Cardio Seal/Helex devices. Patients who underwent PFO closure received cefazolin intravenously for 24 hours as well as clopidogrel for 3 days and aspirin for 6 months.

All renal failure patients underwent scheduled hemodialysis periprocedurally, either before or after cardiac catheterization, to optimize hemodynamics or assist in handling the extra volume related to blood product infusions. No contrast was used for any of the RHC patients including kidney failure patients. Aspirin dose was adjusted according to guidelines [18].

Statistical Analysis

Descriptive statistics were generated to characterize the study population on demographic and clinical variables. The Mann-Whitney test was used to detect differences between groups. TTE findings were compared with ICE findings to detect sensitivity, specificity, positive predictive value and negative predictive value in patients with and without a PFO. P values $<.05$ were considered to be significant.

RESULTS

The performance of TTE compared with criterion-standard RHC/ICE is depicted in Table 1. Overall, TTE with bubble

Table 1. Performance of Transthoracic Echocardiography With Bubble Study (TTE) Versus Right Heart Catheterization With Intracardiac Echocardiography (ICE) in Detecting Patent Foramen Ovale (PFO), Intrapulmonary Oxygen Shunting (IPS), and Pulmonary Hypertension (PH)

Catheterization Results	TTE Positive for PFO	TTE Negative for PFO	Total
ICE positive for PFO	7	8	15
ICE negative for PFO	7	6	13
Total	14	14	28
	TTE positive for IPS	TTE negative for IPS	
ICE positive for IPS	7	10	17
ICE negative for IPS	6	5	11
Total	13	15	28
	TTE positive for PH	TTE negative for PH	
PA mean $\geq$25 mm Hg	2	6	8
PA mean $<$25 mm Hg	4	16	20
Total	6	22	28

Abbreviation: PA, pulmonary artery.