Liver Transplant Considerations and Outcomes for the Portopulmonary Hypertension Patient

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The perioperative management of patients presenting for orthotopic liver transplantation who have associated pulmonary hypertension still presents a challenge to the operative team. As a result of the limited amount of accurate data available, and because the conclusions reported are often conflicting, it has not been easy to develop an evidence-based strategy for the safe management of these patients through liver transplantation.[1-13] This failure to reach a consensus opinion may be a result of the fact that patients have very different pathological presentations. When there are various associated comorbidities coupled with a lack of complete hemodynamic and echocardiographic data, it is difficult to make a precise comparative evaluation between transplant candidates.

Typically, patients with advanced liver disease experience a hyperdynamic circulatory state, with increased cardiac output and decreased systemic vascular resistance.[14] In addition, some patients with pulmonary hypertension associated with liver disease have increased venous blood volume due to systemic volume overload, or they may have left, right, or biventricular cardiac dysfunction. Patients with portal hypertension have true portopulmonary hypertension when the measured pulmonary hypertension is accompanied by an increased resistance to pulmonary blood flow, as demonstrated by a calculated (pulmonary vascular resistance is a calculation based on the other measurements) increase in pulmonary vascular resistance, in the presence of a normal pulmonary capillary occlusion pressure or left ventricular end-diastolic pressure.

It is essential, therefore, to accurately characterize the pulmonary hemodynamics in these patients. The required hemodynamic data must be determined from right heart catheterization and must include the following values: mean pulmonary artery pressure (mPAP), cardiac output, pulmonary artery occlusion pressure, and calculated pulmonary vascular resistance, in the stable, resting state. Cardiac output is typically high in this patient group. If a normal or low value is obtained, volume depletion is usually present; however the diagnosis of cardiomyopathy should be considered. If the patient is volume depleted, the volume replenishment needed to restore homeostasis may lead to the demonstration of an even higher mean pulmonary artery pressure than initially measured, although the pulmonary vascular resistance is unlikely to change.

Pulmonary hypertension may be found in up to 20% of patients with cirrhosis of the liver. However, according to some studies, true portopulmonary hypertension has a prevalence of about 5% in patients presenting for orthotopic liver transplantation.[9,1] High cardiac output, cardiac failure, cardiomyopathy, and volume overload account for a number of non-portopulmonary hypertension presentations, and the management of these patients is very different from those with true portopulmonary hypertension. In fact, some degree of cardiomyopathy (downregulation of beta receptors) has been reported to occur in all cirrhotic patients, thereby blurring the lines between true portopulmonary hypertension and pulmonary hypertension secondary to other causes.[15]

Portopulmonary hypertension is defined as the existence of portal hypertension with a resting mPAP >25 mm Hg, a pulmonary artery occlusion pressure <15 mm Hg, and pulmonary vascular resistance > 240 dynes.s.cm^{-5}.

Essential hemodynamic measurements are calculated as follows: mPAP (mm Hg) = pulmonary artery systolic pressure + [(pulmonary artery systolic pressure – pulmonary artery diastolic pressure) / 3]; pulmonary vascular resistance (dynes.s.cm^{-5}) = (mPAP – pulmonary artery occlusion pressure) x 80 / cardiac output. Cardiac index (cardiac output/body surface area) and pulmonary vascular resistance index allow body surface area to be taken into account so that true comparative measurements may be made. However, rarely does the portopulmonary hypertension literature provide this complete information.

The pathological changes in the microvasculature of the lungs of patients with portopulmonary hypertension include plexogenic arteriopathy, medial hyperplasia, thrombosis, and eventually fibrosis, quite similar to those findings found in idiopathic pulmonary arterial hypertension. Concomitant with these changes, vascular dilations and shunt formation may occur, such as that seen in patients with hepatopulmonary syndrome.[21] This observation suggests that these changes may to balance the physiological outcome until one predominates.[22]

The pulmonary vascular abnormalities may progress, even

after orthotopic liver transplantation, unless long-term pulmonary vasodilator therapy is instituted.[1, 23] The shunt formations do resolve after transplantation, however, and this may reveal the underlying pulmonary hypertension. Therefore, transplantation may be considered an effective therapy for hepatopulmonary syndrome, in contrast to portopulmonary hypertension.

A calculated pulmonary vascular resistance >240 dynes.s.cm^{-5} is generally considered pathological, although some authorities[16,17] have defined pulmonary hypertension by a value >120 dynes.s.cm^{-5}. Portopulmonary hypertension is further graded hemodynamically into mild (mPAP 25 to 35 mm Hg) moderate (mPAP >35 to 45 mm Hg) and severe (mPAP >45 mm Hg). Management of the patient with portopulmonary hypertension >35 mm Hg depends on the causative factors. Volume overload may be treated with diuresis or, if renal function is severely impaired, by utilizing continuous venovenous hemodialysis. If this treatment is effective and ventricular function is good, then transplantation may continue without extra risk. If cardiac function is poor as the result of a cardiomyopathy and filling pressures remain elevated, then the patient is at significant risk if transplantation is undertaken, unless significant improvement in cardiac function is achieved with inotropic agents. In most of the liver failure patients presenting for transplantation, pulmonary vascular resistance is low and left ventricular function appears enhanced, such that it takes experience in this group of patients to diagnose even moderate degrees of ventricular dysfunction. If reduced left ventricular function is noticed on echocardiography, it is likely that a severe cardiomyopathy exists and the transplantation should be deferred for further evaluation.

Reactive pulmonary hypertension may respond to anesthesia, adequate ventilation, and pulmonary vasodilators. Patients with fulminant liver disease who also have associated metabolic and respiratory acidosis may well have pulmonary hypertension that will respond to correction of the acidosis and adequate ventilation. Patients diagnosed with portopulmonary hypertension just prior to liver transplantation may respond to acute pulmonary vasodilator therapy. Inhaled nitric oxide (iNO), the prostacyclin analogue iloprost, intravenous milrinone, epoprostenol, and oral sildenafil have all been administered to reduce mPAP with varied responses.[18,19] If the mPAP is lowered to 35 mm Hg or less, the pulmonary vascular resistance is <240 dynes.s.cm^{-5}, and right ventricular function is good, there is no reported increased risk to proceeding with transplantation.[17]

If the mPAP and pulmonary vascular resistance remain elevated, whether the patient will survive liver transplantation may depend on right ventricular function and the added stressors applied to it during the perioperative period. There are reports of successful transplantation in patients with an mPAP of 53 mm Hg and pulmonary vascular resistance as high as 639 dynes.s.cm $^{-5}$. However, other reports demonstrate 100% mortality in patients with an initial mPAP >50 mm Hg.[12,20]

Moderate and severe portopulmonary hypertension places the liver transplantation patient at increased risk of perioperative morbidity and mortality.[17, 20] The data available to date indicate a perioperative mortality of greater than 70% if liver transplantation were carried out with an mPAP of 45 mm Hg or higher and up to 100% if the mean pressure were >50 mm Hg. There is no increase in mortality risk if the mPAP is 35 mm Hg or less.[20] A multicenter, national liver transplant database reported an overall mortality perioperatively of 36% for patients with portopulmonary hypertension undergoing transplantation.[17]

Despite the realization that pulmonary hypertension may increase the morbidity and mortality of patients undergoing orthotopic liver transplantation, and the close attention to the cardiopulmonary system during the patient's pretransplant assessment, it is not uncommon for patients to be diagnosed on the operating table at the induction of anesthesia.[24] This is because the symptoms of end-stage liver disease are similar to those of severe pulmonary hypertension, and the time course for development of pulmonary hypertension is unknown.

The risk to the patient with portopulmonary hypertension is based on two major outcomes that are very dependent on right ventricular function. First an acute increase in pulmonary vascular resistance during transplantation may result in right ventricular dysfunction, which results in an elevation of right heart pressures, causing congestion and failure of the new liver graft. Second, a profound increase in pulmonary vascular resistance, as may be seen following reperfusion of the new liver graft, may cause the right ventricle to fail acutely, with resulting serious morbidity or mortality.

Right ventricular function should be assessed by echocardiography, whether the diagnosis of portopulmonary hypertension is made preoperatively or on the operating room table. Preoperatively, right ventricular systolic pressures >50 mm Hg and/or abnormal right ventricular chamber size, wall motion, or septal movement toward the left ventricle, require further analysis of hemodynamic data by right heart catheterization. The pulmonary vascular resistance that is calculated from the right heart catheter is very dependent on cardiac output. Typically elevated in cirrhotic patients, cardiac output is found to increase in most patients following reperfusion of the new liver graft. In a majority of patients, this increase in cardiac output $_{is}$ in the range of 5% to 10%. However, the increase is unpredictable and may reach 300% or greater in a small number of patients (3.8%).[24] This massive unpredictable increase may stress a marginal right ventricle. Therefore, the key to survival in this patient population is good right ventricular function, and this must be assessed carefully before transplantation and during the procedure.

How rapidly portopulmonary hypertension can develop is uncertain, as reports vary from 3 weeks to 5 years.[24,25] Pulmonary thromboembolism may be the cause of an acute presentation of portopulmonary hypertension. As mentioned above, routine transthoracic contrast-enhanced echocardiography (CE-TTE) should be performed as part of the pretransplantation work-up. The symptoms of portopulmonary hypertension are too similar to those of end-stage liver disease to be able to differentiate without CE-TTE.

Echocardiographic findings of abnormal right ventricular function provide an indication for right heart catheterization, it

can be used to monitor the effectiveness of pulmonary vascular therapy, and it can be used as an assessment tool for determining the ability of the right ventricle to compensate for the increased pulmonary vascular resistance.[26,27] If the right ventricle can adjust to the increased afterload over time by hypertrophying, this may provide a better chance of decreasing morbidity and mortality during transplantation. Perioperative risk to the patient is not only related to the absolute value of the mPAP and pulmonary vascular resistance but is also a function of the condition of the right ventricle. Once portopulmonary hypertension has been diagnosed, follow-up screening by CE-TTE to assess effectiveness of therapy and right ventricular function should occur at least every 6 months.

Right heart catheterization is the gold standard for the diagnosis of pulmonary hypertension, including portopulmonary hypertension.[28] It not only provides accurate assessment of portopulmonary hypertension, pulmonary hypertension, and ventricular function, it can help sort out the differential diagnosis of hyperdynamic circulation, volume overload, and increased afterload. It also allows an evaluation of acute vasoreactivity and can be used to monitor the effectiveness of therapeutic interventions.

Up to 60% of patients with portopulmonary hypertension may not have their condition detected until reaching the operating room, undergoing the induction of anesthesia prior to liver transplantation.[24] If diagnosed for the first time in the operating room, once an accurate diagnosis has been made and right ventricular function has been assessed by transesophageal echocardiography (TEE), a decision has to be made whether to proceed with surgery or delay transplantation to a future date after effective vasodilator therapy. Acute vasodilator testing should be considered when a diagnosis of moderate portopulmonary hypertension (mPAP >35 to 45 mm Hg) has been made. In the immediate preoperative setting, iNO, inhaled nitroglycerin, or inhaled iloprost are best suited to effect an immediate response. Intravenous vasodilators such as milrinone are somewhat limited by the systemic vasodilation that these agents may cause. The response to iNO is variable, with some patients responding well and others showing no vasoreactivity at all.[18,19,29-32] Liver cirrhosis is associated with excessive production of endogenous nitric oxide and this may explain this unpredictable response to iNO. [33]

The goal of vasodilator testing in the portopulmonary hypertension patient is to bring the mPAP down to 35 mmHg or less and to reduce pulmonary vascular resistance to <240 dynes.s.cm^{-5}. An accurate assessment of right ventricular function by TEE is also an essential part of patient examination. If acute vasodilator therapy is not effective, then surgery is postponed and long-term vasodilator therapy such as intravenous epoprostenol or in some centers oral bosentan is started. The use of bosentan, a dual endothelin receptor antagonist (A and B), is generally not recommended in portopulmonary hypertension as it may cause a rise in hepatic enzymes, although it has a potential advantage because it does not require long-term intravenous access. Most pulmonary artery hypertension experts are wary of using bosentan for portopulmonary hypertension patients because in a large multicenter study that excluded patients with liver disease at least a threefold upper limit of normal elevation of liver aminotransferases (ALT and AST) occurred in about 11% of patients, accompanied by elevated bilirubin in a small number of cases. Epoprostenol generally produces a greater increase in cardiac output than does iNO. It is also a powerful systemic vasodilator that reduces systemic as well as pulmonary vascular resistance. It can be administered only by continuous intravenous infusion (central venous access via portable infusion pump) since its half-life in circulation is brief (3 to 5 min). Common adverse effects attributable to epoprostenol include jaw pain, headache, diarrhea, flushing, leg pain, and nausea or vomiting. More serious complications may occur because of the delivery system (catheter-related infections or thrombosis). Sildenafil has been used in managing portopulmonary hypertension, but no trials have been reported studying its efficacy in that condition.

Those patients with portopulmonary hypertension who undergo liver transplantation have a varied survival rate and change in pulmonary hemodynamics. One study reported a mortality of 71% at 36 months after transplantation in patients with portopulmonary hypertension who did not receive postoperative epoprostenol.[1] The same group reported 100% survival in a group of patients with portopulmonary hypertension treated acutely with iNO followed by epoprostenol.[23] Normalization of pulmonary pressures occurred in all patients, but took between 2 days and 18 months of postoperative epoprostenol therapy.[23]

Reassessment of the patient at frequent intervals by repeat echocardiography can provide information not only on the progress of therapy but also on the condition of the right ventricle. With time, conditioning of the right ventricle may occur, and a widely dilated chamber may develop into a hypertrophied and well-contracting ventricle. If this occurs, then the patient may tolerate liver transplantation with a higher mPAP.[34]

If pulmonary hypertension is diagnosed on the operating room table just before starting surgery, a decision has to be made to proceed or defer the procedure. This decision needs to be made rapidly, as another recipient may need to be admitted. The decision to proceed should be based on the level of the mPAP and systemic vascular resistance, the reversibility of the mPAP and systemic vascular resistance, and the condition of the right ventricle, as evaluated by TEE. It must include a careful rechecking of the hemodynamic data to ensure its accuracy and the elimination of other diagnoses, such as fluid overload, cardiomyopathy, and respiratory acidosis. The reversibility of the increased mPAP can be rapidly tested by the administration of iNO or another pulmonary vasodilator (see above). The function of the right ventricle may be evaluated by TEE surveillance while a one liter fluid bolus and a dobutamine infusion are administered. If the mPAP reduces to <35 mm Hg, pulmonary vascular resistance falls below 240 mm Hg, and right ventricular function is not severely impaired, a reasonable expectation exists that surgery can proceed safely. Inhaled nitric

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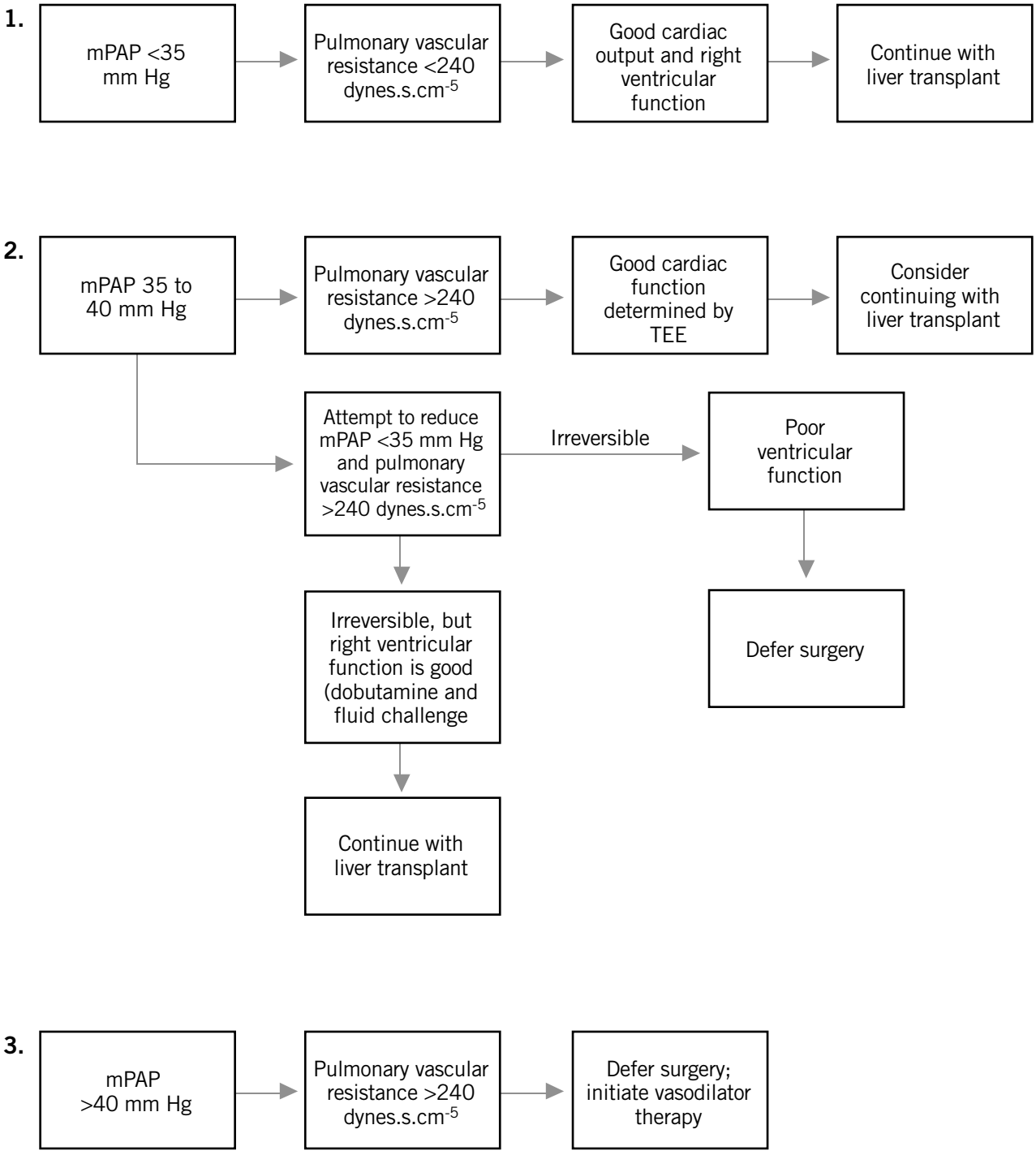
Decision Tree: Management of Pulmonary Hypertension Diagnosed at Induction of Anesthesia for Liver Transplantation.



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oxide may assist in the management of transient acute rises in pulmonary artery pressures associated with reperfusion of the new graft.[35]

An increase in cardiac output is frequently seen (5% to 18% of patients) after reperfusion of the new graft and is typically in the range of 5% to 10%. If there is a significant resistance to pulmonary blood flow, then the laws of physics dictate that the pressure must increase. Occasionally (3.7% of patients), an increase in Q_T of more than 100% of baseline may be seen (**Figure**).[24]

This massive increase in cardiac output with a fixed pulmonary vascular resistance may cause the development of systemic pulmonary artery pressures in patients with preexisting pulmonary hypertension and lead to acute right ventricular failure. Since this massive increase in cardiac output is unpredictable, it is prudent to reduce mPAP to a mild (>35 mm Hg) level before undertaking liver transplantation.

The increase in cardiac output is probably the result of the removal of the obstruction to portal blood flow by the extraction of the diseased liver, together with the systemic vasodilatation caused by the washout of acid metabolites and other vasodilator substances from the new graft. Why some patients have such an increase in cardiac output is not known, but if this occurs it clearly adds to the risk for the patient with pulmonary hypertension. The patient with the relatively fixed pulmonary vascular resistance can react to the increased flow only by an acute increase in pulmonary artery pressure and potential right heart failure.

If an acute elevation in mPAP occurs intraoperatively, an evaluation is made as to the etiology: increase in volume, increase in cardiac output, and increase in pulmonary vascular resistance or cardiac failure. Appropriate treatment is initiated. If right heart failure occurs, the new graft is immediately compromised, and the survival of the patient may be in jeopardy. If conventional measures fail, atrial septostomy and the insertion of a right ventricular assist device may be lifesaving.

Conditioning of the right ventricle has been seen in two of our patients who were awaiting orthotopic liver transplantation and were being treated with epoprostenol. The first was diagnosed on the operating room table with an mPAP of 49 mm Hg, pulmonary vascular resistance of 384 dynes.s.cm^{-5}, and a cardiac index of 3.6 L/m^2. The TEE revealed a markedly dilated right ventricle and atrium, the left ventricular ejection fraction was 55% to 60%. An iNO response test reduced mPAP to 45 mm Hg. Liver transplantation was postponed. An epoprostenol infusion was started and the patient tolerated a maximum dose of 8 ng/kg/min. One year later, the patient was receiving epoprostenol at 34 ng/kg/min and mPAP was 47 mm Hg with a cardiac index of 6.9 L/m^2. At reevaluation after further therapy for 4 months, mPAP was 34 mm Hg with a cardiac index of 6.2 L/m^2. Finally, after another 8 months, the patient was admitted for liver transplantation. The mPAP was 39 mm Hg, systemic

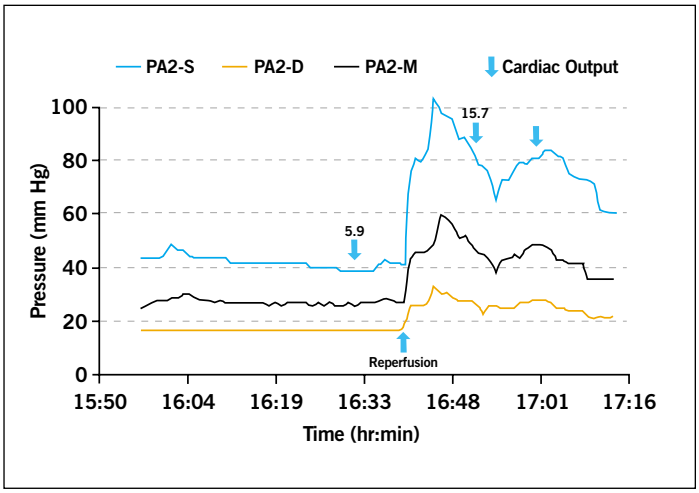

Fig.—Reperfusion of liver graft in patient with pulmonary hypertension.

vascular resistance 130 dynes.s.cm^{-5}, and cardiac index 5.1 L/m^2. On TEE, the right ventricle was now noted to be hypertrophied and contracting well; therefore transplantation was undertaken. At reperfusion there was an increase in cardiac output with a concomitant increase in mPAP to a peak of 55 mm Hg but the patient's right ventricle tolerated this well. The patient recovered well and is continuing treatment with epoprostenol. The experience with the second patient was similar.[34]

Summary

The intraoperative management of pulmonary hypertension in the liver transplant recipient requires an accurate diagnosis of the etiology in order to classify the type of pulmonary hypertension that exists, which determines the subsequent course of action. A clear comprehension of the hemodynamic data and cardiac function is paramount. A TEE is essential in assessing the risk factors. Patients with an mPAP >35 mm Hg and pulmonary vascular resistance >240 dynes.s.cm^{-5} are at particular risk for orthotopic liver transplantation, and should undergo the procedure only after careful individual assessment of all these parameters. The available data provide a compelling reason to postpone transplantation when a patient is found to have an mPAP >35 mm Hg, and these data suggest that attempts be made to improve hemodynamics and right ventricular function. This may be accomplished in the operating room prior to transplantation or may require a prolonged (and sometimes indefinite) course of vasodilator therapy.

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