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# Cardiopulmonary Disease in the Liver Transplant Patient: The Role of Doppler Echocardiography

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## 1. Introduction

End-stage liver disease and in particular cirrhosis of the liver may have a deleterious effect on all major organ systems. A significant cause of this effect is endothelial cell dysfunction. This dysfunction may be the result of the excessive shear force on the blood vessel wall caused by the typical high flow circulation that is seen in many cirrhotic patients. Inflammatory and vasoactive molecules that are either not cleared by the liver or are released by the diseased liver may also play a significant role in causing this endothelial dysfunction. It is well known that cardiac failure may cause liver dysfunction and damage, also the reverse is true. Cirrhosis of the liver may cause cardiac dysfunction. In fact if closely examined beta-receptor down-regulation may be present in every cirrhotic patient. Because the splanchnic arteriolar vasodilatation and overall reduction in systemic vascular resistance results in an increased cardiac output in the typical cirrhotic patient, a false sense of dynamic cardiac function may be engendered. Clinically significant cirrhotic cardiomyopathy may be present and not recognized.

The effect of liver cirrhosis on the pulmonary vascular endothelium may result in arteriolar vasodilatation and the creation of pulmonary vascular shunts causing hypoxia. This is termed hepatopulmonary syndrome (HPS). If vascular remodeling with proliferation of vascular smooth muscle cells and medial hyperplasia occurs resulting in an increased resistance to blood flow, this causes pulmonary hypertension and right ventricular dysfunction. If this is associated with portal hypertension it is termed portopulmonary hypertension (POPH).

The patient with cirrhosis of the liver presenting for liver transplantation requires careful evaluation preoperatively and intense monitoring perioperatively. The role of the Doppler echocardiogram has now become an essential tool for the successful management of these patients.

## 2. Cirrhotic cardiomyopathy

Typically the cardiovascular changes observed in the patient with liver cirrhosis are that of a hyperdynamic circulation. This is clearly manifested by a very increased cardiac output and a reduced systemic vascular resistance. The peripheral arterial vasodilatation, especially in

the splanchnic bed, is caused by an excessive release of endothelial derived nitric oxide, carbon monoxide and endogenous cannabinoids. (Woitas et al, 1997). In the cirrhotic liver there is an increased hepatic sinusoidal resistance to blood flow due to impaired endothelial nitric oxide production and the fibrotic changes that develop. This results in portal hypertension.

Despite the high resting cardiac output there is a blunted cardiac ventricular contractile response to stress. Cirrhotic cardiomyopathy that was initially thought to only occur in alcoholic cirrhosis or conditions causing iron overload can now be demonstrated in nearly all patients with severe liver cirrhosis. (Lee, 1989). This is well masked in most patients by the reduction in afterload caused by the low systemic vascular resistance. And it may be revealed during times of stress such as liver transplantation or when there is a sudden shunting of venous return to the heart by the performance of a transjugular intrahepatic portosystemic shunt stent placement procedure. (Van der Linden et al, 1996)

Cirrhotic cardiomyopathy is defined as chronic cardiac dysfunction in patients with cirrhosis, and is demonstrated by a reduced contractile response to stress, altered diastolic relaxation, down regulation of beta-adrenergic receptors and electrophysiological changes without other known causes of cardiac disease. This is a high output cardiomyopathy that may result in cardiac failure and pulmonary hypertension when an acute rise in cardiac output occurs such as at reperfusion of a new liver graft. (Ramsay, 2007)

The examination of cardiac function by echocardiography may initially be interpreted as normal cardiac function because of the significant reduction in afterload caused by the low systemic vascular resistance. However on closer examination both systolic and diastolic dysfunction may be demonstrated. The diagnostic features are: an E/A ratio  $< 1$ , a prolonged deceleration time  $> 200\text{ms}$ , a prolonged isovolumetric relaxation time  $> 80\text{ms}$ , enlarged left atrium, overall decreased pattern of contractility, decreased wall motion, increased wall thickness, resting ejection fraction  $< 55\%$ , ratio of pre-ejection period to LV ejection time is prolonged  $> 0.44\text{s}$  (rate corrected). (Zardi et al. 2010). Therefore the clinician has to perform a precise echocardiographic examination or the diagnosis of cirrhotic cardiomyopathy may be missed and a label of a hyperdynamic well functioning heart erroneously applied. The ventricular systolic dysfunction may only be demonstrated after induced stress. This cardiomyopathy worsens with increasing liver failure.

On electrophysiological examination a prolongation of the QT interval ( $> 0.44\text{s}$ ) is frequently seen and this may be associated with the degree of liver dysfunction. It is associated with an increased risk for ventricular tachyarrhythmias and may be an important diagnostic indicator of cirrhotic cardiomyopathy. The sudden onset of atrial fibrillation may also be an indicator of underlying cardiomyopathy.

The beta-adrenergic receptor impairment seen with cirrhosis may be an early sign of cardiomyopathy. (Lee et al. 1990). There is a decrease in chronotropic and inotropic responses to beta-adrenergic receptor stimulation. This maybe due to a reduction in both receptor density and function and is found in all patients with cirrhotic cardiomyopathy. Cardiac contractility in cirrhosis is impaired especially when exposed to stress. Other contributing factors include ventricular overload from the hyperdynamic circulation and volume overload, circulating humoral factors and cardiac cellular membrane changes.

The cirrhotic cardiomyopathy does improve after liver transplantation with disappearance of diastolic dysfunction, and normalization of the cardiac response to stress.(Liu & Lee,

2005). The key to diagnosis of cirrhotic cardiomyopathy when baseline ventricular function may appear normal or hyperdynamic is to stress the heart and reveal the cardiac contractile impairment.

### 3. Hepatopulmonary syndrome

Hepatopulmonary syndrome (HPS) is characterized by pulmonary arteriolar endothelial dysfunction associated with liver disease, resulting in intrapulmonary vascular dilatations. These vascular dilatations result in a shorter transit time for red blood cells to traverse alveolar capillaries and therefore create a shunt causing an increase in alveolar to arterial (A-a) oxygen gradient. The alveolar oxygen being unable to completely traverse the dilated alveolar capillary, resulting in some deoxygenated blood reaching the systemic circulation, further increases the ventilation perfusion mismatch. If the size of the A-a gradient is  $> 15$  mmHg the criteria for HPS are met. Clinically the hypoxemia may range from mild to being very severe requiring supplemental oxygen. The shunts most commonly are found diffusely throughout the lung (Type 1 HPS) but occasionally a discrete arteriovenous malformation may develop (Type 2 HPS), bypassing the alveolar capillaries completely. This type of discrete shunt will not pick up extra oxygen if supplemental oxygen is provided as it completely bypasses the alveoli. The more diffuse pathology will respond to supplemental oxygen.

The diagnostic criteria for HPS are: (Rodriguez-Roisin & Krowka, 2008).

1. The presence of liver disease usually with portal hypertension and cirrhosis.
2. An A-a oxygen gradient  $> 15$  mmHg.
3. Pulmonary vascular dilatation demonstrated by:
  - a. A delayed, contrast enhanced (agitated saline) echocardiogram showing contrast in the left heart chambers 4 to 6 cycles after their appearance in the right heart chambers.
  - b. Brain uptake  $> 6\%$  following  $^{99m}\text{Tc}$  macroaggregated albumin lung perfusion scan.

The screening test for all liver transplant candidates should be pulse oximetry in the sitting position followed by contrast enhanced transthoracic Doppler echocardiography if hypoxemia (hemoglobin saturation  $< 92\%$ ) is detected. If there is delayed appearance (over 4 to 6 cardiac cycles) of contrast in the left heart then HPS should be considered. If contrast appears immediately in the left heart then there is probably a direct communication and transesophageal echocardiography should be performed to determine the diagnosis.

If a discrete arteriovenous shunt exists it may be ameliorated by coiling in interventional radiology. Hepatopulmonary syndrome is a progressive disease and is an indication for liver transplantation. It resolves in approximately 6 months after liver transplantation. The clinical signs and symptoms that develop with HPS include digital clubbing, cyanosis, spider angiomas, exertional dyspnea and platypnea (a worsening of dyspnea on moving from lying to standing). This is the complete opposite to most other causes of dyspnea where the patient is more comfortable breathing sitting up. Frequently the patient will also develop a more severe hypoxemia on sitting up (orthodeoxia).

Hepatopulmonary syndrome is found in approximately 30% of liver transplant candidates. In a recent study where patients were screened with contrast enhanced echocardiography 46% of patients had pulmonary vascular dilatations but had not developed hypoxemia. (Fallon et al. 2008). There may be other reasons for hypoxemia in the liver transplant candidate, and these reasons may also increase the severity of hypoxemia in HPS patients.

These may include hydrothorax, intrinsic lung disease, atelectasis and other ventilation diffusion perfusion abnormalities. The early use of Doppler echocardiography can facilitate the diagnosis of HPS. Following liver transplantation intensive respiratory therapy may be necessary to prevent further hypoxia developing because of atelectasis, fluid overload, aspiration and other pulmonary complications. (Gupta et al, 2010). However liver transplantation is the only therapy that will cure HPS and therefore it is indicated for this condition. (Swanson et al. 2005).

#### 4. Portopulmonary hypertension and pulmonary hypertension

The pulmonary vasculature is highly distensible and can accommodate the hyperdynamic circulatory state usually seen in patients with advanced liver disease with only a minimal increase in pulmonary artery pressures. The endothelial dysfunction that occurs with liver disease may present in the pulmonary circulation as predominantly vasodilatory causing HPS, but alternatively hyperplasia of the media may be found together with vascular smooth muscle proliferation, vasoconstriction, intimal proliferation and eventual fibrosis, all presenting as an obstructive pathology causing an increased resistance to flow. This may result in pulmonary hypertension and if associated with portal hypertension it is termed portopulmonary hypertension (POPH).

The diagnostic criteria for POPH include a mean pulmonary artery pressure (mPAP) > 25 mmHg at rest, and a pulmonary vascular resistance (PVR) > 240 dyn.s.cm<sup>-5</sup>. The transpulmonary gradient (TPG) > 12 mm Hg, (mPAP - PAOP [pulmonary arteriolar occlusion pressure]) reflects the obstruction to flow and distinguishes the contribution of volume and resistance to the increase in mPAP.

The right ventricle (RV) is a thin wall chamber with little muscle power to overcome an increased resistance to forward flow. In the presence of a cirrhotic cardiomyopathy, volume overload and an increased *afterload* the RV will become dysfunctional, dilate and may fail. If the RV begins to fail the central venous pressure will rise and the liver will become congested. In better circumstances if the increase in PVR develops slowly the RV may hypertrophy and be able to cope with the increased workload. Survival of the patient and also the liver graft in the transplant recipient depends on the ability of the RV to cope with the increased workload. Therefore in the patient presenting for liver transplantation with POPH a careful assessment of RV function by Doppler echocardiography is essential.

Portopulmonary hypertension has been classified into mild (mPAP 25-35 mmHg), moderate (mPAP >35 and < 45 mmHg), and severe (mPAP > 45 mmHg). Mild POPH is not associated with an increased mortality at liver transplantation although the immediate recovery period may be challenging if there is a significant increase in cardiac output after reperfusion of the new graft. Moderate and severe POPH are associated with significant mortality at transplantation. The key factor is not the mPAP but the RV function.

All patients being assessed for liver transplantation should be screened for pulmonary hypertension. Approximately 20% of candidates will have pulmonary hypertension but this is usually the result of volume overload, cirrhotic cardiomyopathy, cardiac failure and the high output circulation. These patients will have a normal PVR and TPG. True POPH is found in approximately 5% of transplant candidates, and it is essential for it to be diagnosed prior to the start of the transplant procedure.



The assessment screen is as follows:

1. All potential transplant candidates screened with transthoracic Doppler echocardiography.
  - a. Right ventricular systolic pressure (RVSP) > 50 mmHg a right heart catheterization required to characterize the pulmonary hemodynamics.
  - b. If diagnosed in the operating room just prior to the start of transplant surgery the RV function must be assessed by TEE. Only proceed if RV function good and withstands a stress test.
2. mPAP < 35 mmHg
  - a. PVR < 240 dyn.s.cm<sup>-5</sup>
  - b. Good RV function
  - c. Place on transplant waiting list and start pulmonary vasodilator therapy
  - d. Reassess every 6 months
3. mPAP 35-40 mmHg
  - a. PVR > 240 dyn.s.cm<sup>-5</sup>
  - b. Good RV function that withstands stress test consider placing on transplant list
  - c. Start pulmonary vasodilator therapy
  - d. If RV dilated and function poor do not list until effective therapy has allowed RV to improve.
4. mPAP > 40 mmHg
  - a. Assess RV function but even if good do not list until patient has undergone a period of vasodilator therapy.
  - b. If RV function poor do not transplant. Allow time to improve with therapy.
  - c. Consider a liver bilateral lung transplant.
5. All patients with POPH should be reassessed by TEE every 6 months.

Transthoracic Doppler echocardiography is a good assessment screening tool but it does require the presence of a tricuspid regurgitant jet to make the estimate of RVSP. This jet may not be present in 10 - 20% of patients. The RVSP is calculated from the peak tricuspid regurgitant velocity (TRV) using the modified Bernoulli equation and estimating right atrial pressure (RAP):

$$RVSP = 4(TRV)^2 + RAP$$

This algorithm has a 97% sensitivity and a 77% specificity for diagnosing moderate and severe POPH. (Kim et al. 2000).

A more accurate screening algorithm has been reported by measuring the increased PVR utilizing the ratio of peak TRV to the RV outflow tract velocity time integral (VTI<sub>RVOT</sub>). The sensitivity and negative predictive values are reported at 100%. (Farzaneh-Far et al. 2008)

An accurate assessment of RV function as determined by TEE is essential to the management of the liver transplant recipient. The success of the transplant will depend on the RV maintaining good function during and after the procedure despite all the increases in cardiac output, volume and PVR. If RV dysfunction or failure occur then graft congestion with possible failure and serious morbidity including mortality may occur. The intraoperative course can be more optimally managed under TEE guidance.

The role of liver transplantation in the management of POPH is not well defined. Some patients will reverse quickly after transplant, others may require months or years of ongoing

vasodilator therapy. Still other patients may continue to progress and eventually develop RV failure. There are even patients who will develop pulmonary hypertension after liver transplantation. Liver transplantation offers the best outcome to patients with POPH that is responsive to vasodilator therapy.

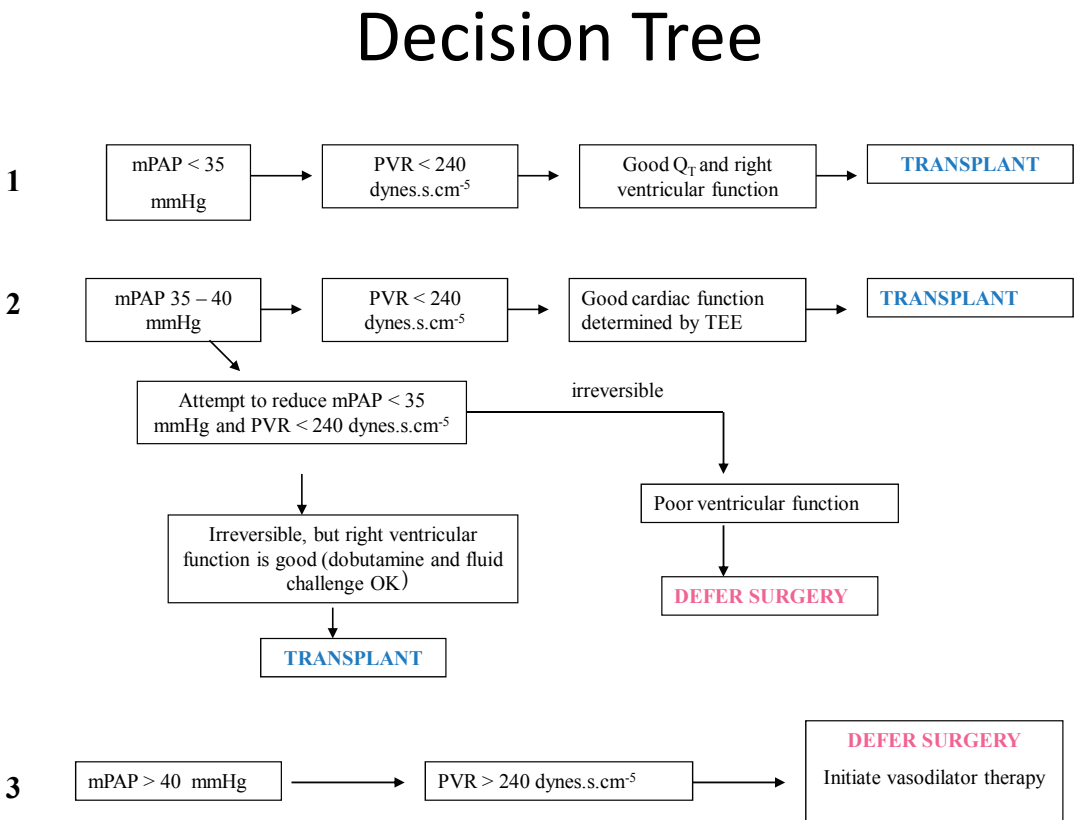
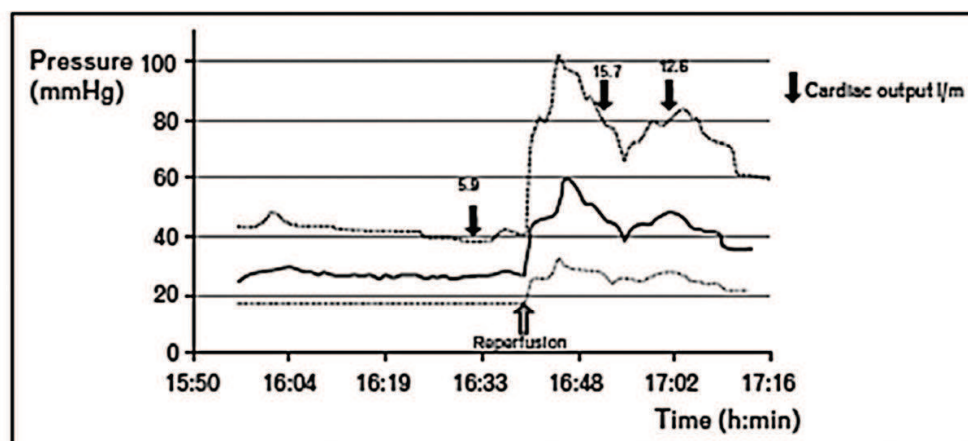


Fig. 1.

### 5. The role of Doppler echocardiography during liver transplantation

Many patients undergoing liver transplantation have varying degrees of cirrhotic cardiomyopathy, volume overload and significant stresses on the cardiovascular system. The addition of TEE to routine monitoring provides much essential information that can assist in patient management. The transgastric view may not be always available because of the placement of surgical retractors but the 4-chamber view can give a good assessment of preload, cardiac function and detection of air emboli and clot emboli. The filling pressures are not an accurate measure of preload especially if there is diastolic dysfunction present.

The postreperfusion syndrome following the opening of the blood supply to the new liver may be severe and better managed with the information provided by the TEE. The effects of acute acidosis, hyperkalemia and hypothermia compounded by an ischemia/reperfusion injury may result in severe arrhythmias, hypotension and cardiovascular collapse. (Ramsay, 2008).



PA2-S, pulmonary artery pressure-systolic; PA2-D, pulmonary artery pressure-diastolic; PA2-M, pulmonary artery pressure-mean. Reproduced with permission from [2]. ..... PA2-S; —, PA2-D; ..... PA2-M.

Fig. 2. Increase in cardiac output with concomitant increase in pulmonary artery pressures at reperfusion of the liver graft

End-stage liver disease is associated with increased risk of coronary artery disease. (Ehtisham, 2010). The incidence of coronary artery disease in liver transplant candidates over the age of 50 years has been reported as high as 28%. (Carey et al, 1995). Patients with risk factors for coronary artery disease should be screened pretransplant and if indicated they should be revascularized. The safety of percutaneous bare metal stent placement in this patient population has been demonstrated. (Azarbal et al, 2011). The dobutamine stress echocardiography has been advocated as the assessment tool of choice in this patient group. (Plotkin et al. 2000). The positive predictive value of this test has been questioned as many of these end-stage liver patients are receiving beta adrenergic blockers and cannot achieve the maximum predicted heart rate and rate pressure product. However there has been demonstrated a high negative predictive value of this test. (Umphrey et al. 2008).

## 6. Conclusion

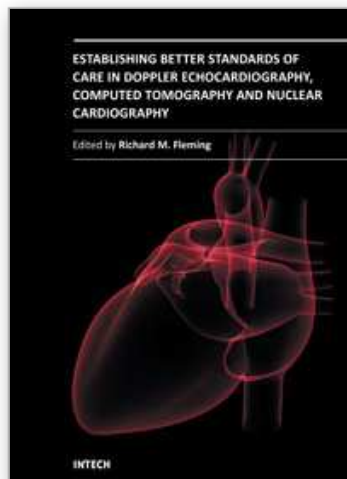
The Doppler echocardiograph technology provides for a better assessment and management of the liver transplant patient. Its routine use in this patient population is to be recommended.

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**Establishing Better Standards of Care in Doppler  
Echocardiography, Computed Tomography and Nuclear  
Cardiology**

Edited by Dr. Richard M. Fleming

ISBN 978-953-307-366-8

Hard cover, 260 pages

**Publisher** InTech

**Published online** 13, July, 2011

**Published in print edition** July, 2011

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Michael Ramsay (2011). Cardiopulmonary Disease in the Liver Transplant Patient: The Role of Doppler Echocardiography, Establishing Better Standards of Care in Doppler Echocardiography, Computed Tomography and Nuclear Cardiology, Dr. Richard M. Fleming (Ed.), ISBN: 978-953-307-366-8, InTech, Available from: <http://www.intechopen.com/books/establishing-better-standards-of-care-in-doppler-echocardiography-computed-tomography-and-nuclear-cardiology/cardiopulmonary-disease-in-the-liver-transplant-patient-the-role-of-doppler-echocardiography>

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