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International Society of Heart and Lung Transplantation position statement on the role of right heart catheterization in the management of heart transplant recipients

Hoong Sern Lim, MD^a, Eileen Hsich, MD^b, Keyur B. Shah, MD^c

^aQueen Elizabeth Hospital Birmingham, University Hospitals Birmingham National Health Service Foundation Trust, Birmingham, United Kingdom

^bCleveland Clinic, Cleveland, Ohio

^cThe Pauley Heart Center, Virginia Commonwealth University Medical Center, Richmond, Virginia

Right heart catheterization (RHC) provides direct assessment of cardiopulmonary filling pressures and cardiac function. It has a well-established role in the management of patients with advanced heart failure and assessment of heart transplant candidacy.^{1,2} Data from invasive monitoring of hemodynamics may also influence the management of heart transplant recipients

The 2010 International Society for Heart and Lung Transplantation (ISHLT) Guidelines for the Care of Heart Transplant Recipients did not include the use of RHC.³ The current statement aims to define the role of RHC in the management of heart transplant recipients. The Writing Group has identified 7 clinical scenarios in which the data from RHC may influence the care of heart transplant recipients, and specific recommendations can be made. The peri-operative use of RHC will not be discussed in this document.

The classifications of recommendations used in this document are:

- Class I: conditions for which there is evidence or there is general agreement that a given procedure is beneficial, useful, and effective;
- Class II: conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment;
- Class IIa: conditions for which the weight of evidence/opinion is in favor of usefulness/efficacy;
- Class IIb: conditions for which usefulness/efficacy is less well established by evidence/opinion; and
- Class III: conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful.

The levels of evidence are:

- Level A (highest): multiple randomized clinical trials;
- Level B (intermediate): limited number of randomized trials, nonrandomized studies, and registries; and
- Level C (lowest): primarily expert consensus.

Clinical Scenarios

Clinical scenario 1: RHC is reasonable at the time of surveillance cardiac biopsy in an asymptomatic patient. (Class IIa, 6 months after transplantation; IIb, >6 months after transplantation; Level of Evidence: C)

Cardiac allograft rejection remains a major cause of death in heart transplant recipients, despite advances in immunosuppression therapy. Acute cardiac allograft rejection may be divided into acute cellular rejection (ACR), acute antibody-mediated rejection (AMR), or mixed. Symptoms associated with ACR and AMR are often non-specific or absent until potentially fatal graft dysfunction develops. Hence, endomyocardial biopsies (EMBs) are performed routinely at standard intervals after transplantation as surveillance for acute rejection. However, EMB has significant limitations. Sampling error or non-uniformity of histopathologic changes can result in false-negative biopsy samples.⁴

In addition, the concordance rates between pathologists are modest. The CARGO II study (Cardiac Allograft Rejection Gene Expression Observational II Study) evaluated concordance among pathologists using the 2004 ISHLT grading system for ACR. A panel of 4 independent pathologists assessed EMB samples from participating study centers that had been graded by the local pathologist. The overall agreement between local and panel pathologists was 71% overall, but the concordance rate was poor at 28.4% for samples assigned grade 2R rejection. The concordance rate for AMR on EMB samples may be even worse. Unrecognized and untreated rejection may result in cardiac dysfunction and hemodynamic deterioration that may lead to sudden cardiac death.⁵

RHC provides additional information regarding allograft function that complements other modalities for the diagnosis of rejection, including EMB. Pulmonary hypertension in heart transplant recipients is an independent risk factor for death.⁶ Hemodynamic data from RHC are also vital in tailoring therapeutic interventions independent of the findings on EMB. Objective evidence of hemodynamic impairment on RHC, even without histologic evidence of rejection on an EMB sample, has prognostic significance and may prompt treatment for acute rejection.

Conversely, treatment of acute rejection (e.g., cytolytic therapy) may be deferred or curtailed in the presence of normal hemodynamics, particularly if EMB findings are equivocal. The additional diagnostic information from RHC, when performed at the time of EMB, carries minimal incremental risks and obviates the need for an additional procedure (and associated risks), particularly when diagnostic uncertainty remains after EMB. On this basis, RHC is reasonable at the time of surveillance EMB, especially in the first 6 months after transplantation, because the risk of and death from acute rejection are highest early after transplantation.

Clinical scenario 2: RHC should be performed in patients with new or worsening cardiac allograft function or symptoms suggestive of acute cardiac allograft rejection. (Class I, Level of Evidence: C)

Assessment of filling pressures and cardiac output/index to determine allograft function is indicated when patients have symptoms or signs of heart failure or a decline in left ventricular systolic function by imaging (i.e., echocardiogram). Deterioration in graft function may be due to acute rejection but should also prompt investigation of other non-immune causes such as pulmonary hypertension and coronary artery disease. The treatment of acute rejection depends on a multitude of factors, including pathologic, hemodynamic, echocardiographic, and clinical findings. RHC, in conjunction with EMB can differentiate patients who are hemodynamically stable from those with significant allograft dysfunction (e.g., elevated filling pressures, depressed cardiac output, or both) and guide therapeutic intervention. Urgent hospitalization and treatment with intravenous corticosteroids, cytolytic therapy, and inotropes/vasopressors is recommended in patients with hemodynamically significant acute rejection. Hence, RHC provides critical prognostic and diagnostic information regarding allograft function that guides complex hemodynamic and immunomodulatory therapies.⁶

Clinical scenario 3: RHC is reasonable in patients with persistent congestion or renal dysfunction to assess filling pressures and cardiac allograft function. (Class IIb, Level of Evidence: C)

Hemodynamic assessment may be necessary to guide medical therapy when intravascular volume is unclear, especially when accompanied by worsening renal function and hypotension (systolic blood pressure < 90 mm Hg or symptomatic low systolic blood pressure). Patients usually undergo heart transplantation for recurrent end-stage heart failure and continue to retain fluid after transplantation. Surgical trauma elicits a neuroendocrine and inflammatory stress response that is characterized by sodium and water retention,⁷ which may be exacerbated by the use of steroids for immunotherapy and/or presence of hypoalbuminemia due to malnutrition. Diuretics are the mainstay of treatment of fluid retention but may be complicated by hypotension or worsening renal function. RHC is reasonable in these clinical situations to elucidate the pathophysiology of congestion and renal dysfunction after transplantation, which may include pre-existing renal dysfunction, the use of calcineurin inhibitors and antibiotics, sepsis, and sub-clinical pericardial tamponade.⁸

Clinical scenario 4: RHC is reasonable in patients with suspected restrictive physiology and allograft vasculopathy. (Class IIb, Level of Evidence: C)

Invasive hemodynamic assessment may identify patients with extensive coronary allograft vasculopathy (CAV) and poor prognosis. The presence of restrictive physiology (high atrial pressures and decreased cardiac index) has been associated with increased myocardial fibrosis in the setting of CAV.⁹ The presence of restrictive physiology in the cardiac allograft identifies patients with a poor prognosis¹⁰ who may warrant intensified surveillance, further clinical investigation, or consideration for retransplantation.

The ISHLT has published clinical guidelines defining the severity of CAV that incorporate hemodynamic parameters in addition to angiographically defined coronary disease.¹¹ The guidelines specify that once a patient is diagnosed with CAV, establishing the presence of restrictive physiology with invasive hemodynamic measurements would reclassify a patient with mild or moderate-grade disease (ISHLT CAV1 or CAV2) into the highest severity group (ISHLT CAV3). These patients would consequently be considered for retransplantation based on the presence of restrictive physiology. Therefore, routine invasive hemodynamic measurement after heart transplantation is reasonable when assessing for CAV.

Clinical scenario 5: RHC should be performed in all patients undergoing assessment for heart retransplantation. (Class I, Level of Evidence: C)

Heart retransplantation is indicated in selected patients with significant allograft vasculopathy and dysfunction. High pulmonary artery pressure, transpulmonary gradient, and pulmonary vascular resistance that are refractory to medical therapy may be contraindications in primary heart transplantation.¹² These hemodynamic parameters should be assessed in retransplantation, particularly because retransplantation is associated with poorer short-term and long-term outcomes compared with primary heart transplantation. Therefore, RHC should be performed on all adult candidates in preparation for listing for heart retransplantation and periodically until retransplantation, in keeping with current recommendations for the assessment of patients for primary heart transplantation.¹

Clinical scenario 6: RHC is reasonable in patients with suspected complications related to EMB or immunosuppression. (Class IIb, Level of Evidence: C)

EMBs are typically performed via the internal jugular and femoral veins. Complications associated with EMB occur in about 3% of patients,¹³ and most are related to central venous cannulation. However, serious complications, such as damage to the tricuspid valve and cardiac perforation, may occur, and the latter may result in cardiac tamponade. Echocardiography is often used, but with central venous access already established, a RHC study can be performed promptly without additional discomfort to the patient to confirm the diagnosis of tamponade physiology or severe tricuspid regurgitation. Pericardial effusions are common after transplant, and tamponade physiology may develop insidiously. Immunosuppression therapy may also contribute to the development of pericardial effusions. In a clinical trial of everolimus vs mycophenolate mofetil, 13% of patients receiving everolimus developed large pericardial effusions at 12 months after transplant.¹⁴ RHC is reasonable as part of the assessment of patients with pericardial effusions to determine whether they have cardiac tamponade physiology and guide interventions.

Clinical scenario 7: RHC is reasonable for the management of heart transplant recipients with pulmonary hypertension. (Class IIa, Level of Evidence: B)

Pulmonary hypertension after transplantation has been associated with increased mortality.^{6,15,16} There are many possible underlying causes, including pulmonary hypertension before transplantation. Sildenafil and bosentan have been used to treat pulmonary hypertension, and several hospitals have demonstrated with careful hemodynamic monitoring sustained reversal of pulmonary pressures after heart transplantation and excellent survival.^{17–20} In one study that included 31 patients treated with sildenafil before heart transplantation for

severe pulmonary hypertension, serial hemodynamic monitoring after transplantation enabled discontinuation of sildenafil 3 months after surgery, with 1-year survival of 93% and 3-year survival of 84%.¹⁷ In another study of 15 patients with severe pulmonary hypertension, sildenafil therapy was weaned off all patients after heart transplantation, except for 2 who needed therapy to control elevated pulmonary vascular resistance.¹⁸ This last study demonstrates the importance of active RHC surveillance in heart transplant patients with pulmonary hypertension.

Complications of RHC

Complications related to RHC are associated with central venous cannulation, the catheterization procedure itself, and catheter residence. The most serious complications of RHC are related to catheter residence, including pulmonary artery rupture, thrombophlebitis, venous or intracardiac thrombus formation, pulmonary infarction, line infections, and endocarditis, which are largely obviated by the removal of the catheter at the end of the procedure. Therefore, the incremental risks associated with RHC at the time of EMB are likely to be minimal.

Conclusion

RHC is a vital tool in the management of heart transplant recipients (Table 1). The value of hemodynamic data from RHC in the diagnosis of clinically significant acute rejection is underlined by the poor concordance rates of EMB results for ISHLT Grade > 2R rejection (when it is most needed), the vagaries of symptom status, and the multitude of diagnostic confounders. The wealth of diagnostic information offered by RHC is associated with minimal incremental risks, particularly when performed at the time of EMB.

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Table 1**The Role of Right Heart Catheterization in 7 Clinical Scenarios**

No.	Clinical scenario	Class of recommendation	Level of evidence
1	At the time of surveillance cardiac biopsy in an asymptomatic patient 6 months after transplantation >6 months after transplantation	IIa IIb	C C
2	New or worsening cardiac allograft function or symptoms suggestive of acute cardiac allograft rejection	I	C
3	Persistent congestion or renal dysfunction to assess filling pressures	IIb	C
4	Suspected restrictive physiology and allograft vasculopathy	IIb	C
5	Assessment for heart retransplantation	I	C
6	Suspected tamponade related to endomyocardial biopsy or immunosuppression	IIb	C
7	Management of pulmonary hypertension in heart transplant recipients	IIa	B