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*Original Article*

# Lung and heart-lung transplantation

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Increased understanding and awareness of congenital cardiac disease has allowed early identification of these children. Advances in surgical techniques, anesthesia, and medical treatment have rendered the majority of forms of congenital cardiac defects treatable. Therefore, the incidence of pulmonary hypertension related to the Eisenmenger syndrome should decrease. However, some patients need treatment for pulmonary hypertension despite repair of defects. Heart-lung[1] and lung transplantation[2] remain the therapeutic options when medical therapy fails.

According to the registry of the International Society for Heart and Lung Transplantation, 25% of heart-lung and less than 1% of lung transplants have been performed for adult patients with congenital cardiac disease.[3] Similarly, more than 40% of heart-lung and 5% of lung transplants have been performed in children with congenital cardiac anomalies.[4] The objective of this session is to address four major points: the cost-benefit and risk-benefit issues for lung or heart-lung transplantation versus currently available medical treatments, the allocation policies for these patients, the risk-benefit issue for lung versus heart-lung transplant, and the use of ventricular assist devices in patients with biventricular failure as to allow successful isolated heart transplantation following improvement of pulmonary hemodynamics.

## Lung or heart-lung transplantation versus medical treatment

In comparison with idiopathic pulmonary arterial hypertension, the natural history of patients with pulmonary hypertension associated with congenital cardiac disease is considerably better, with a greater than 60% survival rate being reported 20 years following diagnosis. It has been also suggested that adults with the Eisenmenger syndrome have a more favorable hemodynamic profile and prognosis than adults with the idiopathic form,[5] with an 80% and 40% survival respectively five and 25 years following diagnosis. Furthermore, the Columbia University group recently reported that long-term infusion of epoprostenol improves hemodynamics and the quality of life in patients with pulmonary hypertension associated with congenital cardiac defects.[6] In contrast, the survival after lung or heart-lung transplantation is approximately 50% at five years,[3] but it continues to decrease thereafter, as opposed to heart transplant where survival at one year is fairly predictive of rates observed at five and ten years. The Papworth group evaluated the potential survival benefits by reviewing 653 patients accepted for lung transplantation.[7] Among them, 76 subjects had the Eisenmenger syndrome. They reported that lung transplantation confers a significant survival benefit for patients with various lung diseases except for the Eisenmenger syndrome. However, these data primarily reflect outcomes in adolescents and adults. Although post-transplant outcomes are comparable, survival without transplant in pediatric patients is likely to be worse, as in a large single center series, 25% of patients were on mechanical ventilation at transplant.[8]

While survival is the most important measure for the success of transplantation, improving the recipient's quality of life is another important objective of the procedure. Several studies have shown improved quality of life after lung and heart-lung transplantation.[9,10] Gains diminish, however,

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with the onset of complications such as bronchiolitis obliterans syndrome.[11,12] No studies have investigated the impact of transplantation on the quality of life specifically for patients with congenital cardiac disease and pulmonary hypertension.

The issue of cost-effectiveness must be analyzed taking the quality of life into account, in particular in view of the lifetime cost of care for the lung transplant recipient estimated at about $425,000 in the United States[13] and $180,000 in the United Kingdom.[14] Investigators have attempted to determine the cost per year adjusted for the quality of life.[15,16] The emerging picture is that although the lifetime follow-up of lung transplant recipients is associated with high costs, it remains cost-effective in view of the gain in terms of quality of life as compared with standard care without transplantation. The lowest gain, however, has been observed for secondary pulmonary hypertension.[15] Thus, although no clear survival benefit has been demonstrated for patients with congenital cardiac disease, recipients with advanced symptoms appear to benefit in terms of the quality of life, but at considerable cost. There may be a survival benefit in pediatric patients who require mechanical ventilation. Development of more effective therapies for bronchiolitis obliterans may also lead to a survival benefit.

*Patients with congenital heart disease and advanced pulmonary vasculopathy presenting with severe class IV symptoms should be counseled that quality of life benefit is likely. With the exception of those patients requiring mechanical ventilation or until more effective therapies for bronchiolitis obliterans are available, the impact of transplantation on survival and the cost-benefit relationship remain unclear.*

*Class: IIa. Level of evidence: C.*

## Indication and allocation for lung and heart-lung transplantation

The timing of referral is particularly difficult in patients with congenital cardiac anomalies because they are not a homogeneous group. Regarding the Eisenmenger syndrome, some centers would follow guidelines for idiopathic pulmonary arterial hypertension proposed by the International Society for Heart and Lung Transplantation,[17] but it should be emphasized that there is no general agreement on this, as others would refer only patients with advanced class IV symptoms.

*Referral*

- New York Heart Association functional class III or IV, irrespective of the ongoing therapy
- Rapidly progressive disease.

*Transplantation*

- Persistent class III or IV symptoms on maximal medical therapy
- Low (less than 350 meters) or declining six-minute walk distance
- Cardiac index of less than 2 liters/min/$m^2$
- Right arterial pressure exceeding 15 mmHg.

Similar recommendations for children with the Eisenmenger syndrome were included in a consensus statement from major pediatric lung transplant centers.[18] The same document recommends immediate referral for children with specific anomalies (i.e. pulmonary venous stenosis) because of poor response to medical therapy.

Heart-lung transplantation is indicated for severely symptomatic patients who are unlikely to have a successful repair of congenital cardiac defects, and patients with severely depressed left ventricular function (left ventricular ejection fraction less than 35%).[8,19] German groups, however, have performed heart-lung transplantation as the procedure of choice for these patients, resulting in similar outcomes.[20,21] Again, it should be emphasized that other groups would not support this approach. In the United States, the United Network for Organ Sharing allocates lungs to adolescents and adults based on a multi-factorial analysis of the waiting list and transplant mortality.[22] Children aged less than 12 years old continue to be allocated lungs based on time accrued on the waiting list. There has been increased allocation to recipients with idiopathic pulmonary fibrosis and cystic fibrosis, and decreased allocation to recipients with emphysema and pulmonary hypertension.[23] In the United States, heart-lung candidates receive first priority for lungs when allocated the heart and priority behind Status 1A heart candidates when allocated the lungs. The heart priority is unlikely to increase, as the waiting list mortality for heart-lung transplant candidates is comparable to lung candidates and much lower than Status 1A or 1B heart candidates.[24]

*Patients with advanced pulmonary hypertension associated with congenital heart disease should be referred and listed for lung or heart-lung transplantation if they persist with class IV symptoms (New York Heart Association) despite maximal medical therapy. In particular, heart-lung transplantation should be considered for patients who are unlikely to have a successful repair of the congenital cardiac defects.*

*Class: IIa. Level of evidence: C.*

## Lung versus heart-lung transplantation

There are three transplant options for end-stage patients; single lung transplantation with repair of

the cardiac defect, bilateral lung transplantation with repair of the defect, and heart-lung transplantation. Theoretical advantages with single lung transplantation include shorter bypass time, thoracotomy instead of sternotomy, less bleeding, and organ sparing.[25] It is well recognized, however, that single lung transplantation for pulmonary hypertension involves a potentially difficult post-operative course and high mortality.[19] Cardiac repair with bilateral lung transplantation[8,26] appears to be associated with a better post-operative course, but carries potential morbidity associated with longer cardiopulmonary bypass. Heart-lung transplantation[20,21] is a simpler operation as compared to bilateral lung transplantation, but requires allocation of two organs from the scarce donor organ supply, adds risk of cardiac graft coronary vasculopathy and is less tolerant of ischemic time.

Several reports have shown similar survival between bilateral lung transplantation and heart-lung transplantation for pulmonary hypertensive patients.[8,19,27] No single center has, however, transplanted a large enough number of patients with Eisenmenger syndrome. The Toronto group analyzed the International Society for Heart and Lung Transplantation and United Network for Organ Sharing Joint Thoracic Registry database which included 69, 106 and 430 single-lung, bilateral-lung and heart-lung transplantations respectively.[28] This analysis suggests that heart-lung transplantation appears to offer a survival benefit for pulmonary hypertensive patients with ventricular septal defects and should be considered as the operation of choice. Regarding pediatric patients with congenital cardiac disease and advanced pulmonary vasculopathy, the number of transplants reported by the International Society for Heart and Lung Transplantation[4] is quite limited (less than 100) and the major experience has been reported by the St. Louis group. They reported that despite the complexity of combined cardiac repair with bilateral lung transplantation in 35 cases, and the resulting perioperative morbidity, patients had similar outcomes as compared with 16 patients who underwent heart-lung transplantation.[8]

## Ventricular assist devices and patients with pulmonary hypertension and congenital cardiac disease

Some patients with congenital cardiac disease have altered pulmonary hemodynamics with increased vascular resistance partly or totally related to left ventricular dysfunction. Outcomes for isolated cardiac transplantation are often poor in this scenario, so that levels of pulmonary vascular resistance above 6 Wood units $\cdot$ m$^2$ or a transpulmonary gradient exceeding 15 mmHg are routinely considered as exclusion criteria for this procedure. In these instances, heart-lung transplantation appears as a therapeutic option.[29] Recent reports of normalization of elevated pulmonary vascular resistance in adults treated on a long-term basis with ventricular assist devices[30] raise the possibility that similar improvement can occur in children. Recently, the use of Berlin pediatric device in two patients initially referred for heart-lung transplant allowed isolated heart transplant with successful outcome.[31] Further studies are obviously required before this approach can be recommended.

*Bilateral lung transplantation with repair of the cardiac defects is favored over heart-lung transplantation for patients with congenital heart disease and advanced pulmonary vasculopathy.*

*Class: IIb. Level of evidence: C.*

Alternatively, recipients with preoperatively increased pulmonary vascular resistance might benefit from short-term or long-term treatments with drugs such as continuous intravenous epoprostenol, enteral sildenafil, etc. started peri-operatively and maintained for months. This approach has been successfully attempted more than several times, and appears to be promising in terms of avoiding heart-lung transplantation. This would increase the likelihood of getting a donor, as heart transplant would be carried out alone instead of waiting for a heart-lung block. The potential impact of this approach on outcomes warrants further investigation.

*Patients with congenital heart disease associated with left-sided failure and elevated pulmonary vascular resistance not responsive to an acute pulmonary vasodilator challenge should be considered for heart-lung transplantation if pulmonary hemodynamics cannot be improved by medical therapy or if medical therapy cannot be administered for any reasons. The role of ventricular assist devices to improve pulmonary hemodynamics requires further investigation.*

*Class: IIb. Level of evidence: C.*

## Conclusion

Because of statistical impossibility to demonstrate a clear survival benefit, lung and heart-lung transplantation remain a procedure of last resort for patients with advanced pulmonary vasculopathy associated with congenital cardiac disease. Ongoing development of therapies to improve pulmonary hemodynamics in these patients will likely reduce the numbers of patients requiring transplant in the future. At present, lung and heart-lung transplant should be considered in order to improve the quality of life in selected patients.

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