Cardiopulmonary transplantation in children: a reason for optimism?

Heart transplants are now an established mode of treatment for heart failure in adults. Are they justified in children? We believe they are.

The aim is to provide a normal quality of life. However, for some, particularly those with an acute cardiomyopathy, it can be a question of life or death. Long term survival is limited by the development of coronary artery disease (probably as a result of chronic rejection) and post-transplant lymphoproliferative disease (PTLD). However, data from the International Society of Heart and Lung Transplantation (URL <www.ISHLT.org/regist>) shows a one year survival of 80%, five year survival of 70%, and a “half life” of 12.2 years.

So who should be considered? The ISHLT database shows roughly equal numbers of children with congenital heart disease and some form of cardiomyopathy, though this depends on the age group. In those under 1 year of age, over two thirds have congenital heart disease. In the older children (11–17 years of age) the ratio is reversed with most having a cardiomyopathy.

In patients with congenital heart disease, the indication is usually progressive decline in ventricular function although in some it may be intractable arrhythmias. Often it is a subjective decision by the child and their parents based on a poor quality of life. In contrast, patients with a cardiomyopathy may present with an acute episode. Although in most cases it is a dilated cardiomyopathy, patients with hypertrophic or indeed restrictive cardiomyopathies are seen. Bonnet and colleagues in a recent issue of Heart highlighted the rare but important cases which are caused by metabolic disorders—the screening of a child with cardiomyopathy is a very complex issue and is reviewed well by Schwarz and colleagues.

Of the children presenting with a dilated cardiomyopathy, who should be referred for transplantation? The natural history is not well defined, making decisions difficult. This may reflect a disparate aetiology. It has been suggested that in those in whom a viral infection was the initial insult, recovery would be anticipated—the use of the polymerase chain reaction to detect enterovirus in the myocardium is a definite contraindication. However, with the uncertainties involved in assessment of pulmonary vascular resistance, and the fact that the results of heart lung transplantation in children are suboptimal (see later), it is hard to be absolute. With a borderline pulmonary vascular resistance we would aim for an oversized heart or one from a domino procedure (patient undergoing heart lung transplant for cystic fibrosis). At present, we match donor and recipient only for blood group and size—there is no time for HLA matching. In many children, particularly those with a cardiomyopathy, the heart is very enlarged and so there is the opportunity to use an oversized heart from a bigger donor. We have used hearts from donors with a body weight ratio of up to 3:1. We match the heart shadow on the recipient’s chest x ray with a silhouette from the donor chest x ray.

Poor ventricular function

The child who presents acutely with poor ventricular function poses a particularly difficult challenge. Is it acute myocarditis, which might be expected to recover with treatment, or idiopathic cardiomyopathy? The Toronto group used endomyocardial biopsy to identify 36 children with acute lymphocytic myocarditis and concluded that they had a good outcome following treatment with immunosuppression. More recently, McCarthy and colleagues concluded that those with a fulminant form of myocarditis made a better recovery than those with a less severe illness. In contrast, the myocarditis treatment trial in adults did not support routine treatment of myocarditis with immunosuppression. The gold standard for the diagnosis of myocarditis is an endomyocardial biopsy and, although the Dallas criteria for histological classification are well established, their interpretation and application remain difficult. In view of the limited sensitivity and specificity of endomyocardial biopsy we have not found it helpful in the management of these children with an acute illness. In the future it may be possible to identify susceptible children and develop more precise treatment using gene targeting.

Contraindications to heart transplant are few. We have undertaken combined heart and liver or heart and kidney transplants. While there are no anatomical arrangements which preclude a heart transplant, adverse physiology in the form of high pulmonary vascular resistance (> 6 Wood units) is a definite contraindication. However, with the uncertainties involved in assessment of pulmonary vascular resistance, and the fact that the results of heart lung transplantation in children are suboptimal (see later), it is hard to be absolute. With a borderline pulmonary vascular resistance we would aim for an oversized heart or one from a domino procedure (patient undergoing heart lung transplant for cystic fibrosis). At present, we match donor and recipient only for blood group and size—there is no time for HLA matching. In many children, particularly those with a cardiomyopathy, the heart is very enlarged and so there is the opportunity to use an oversized heart from a bigger donor. We have used hearts from donors with a body weight ratio of up to 3:1. We match the heart shadow on the recipient’s chest x ray with a silhouette from the donor chest x ray.

At present some children still die waiting for a heart. Recently two strategies have emerged—“bridging to transplant” and, for infants, an ABO “mismatched” transplant. With an apparent shortage of donors, is “bridging to transplant” ethically justified? Figures from the UK transplant database show that the number of children (under the age of 16 years) undergoing heart transplantation in the UK is small—a range of 22–28 per year over the last six years. We know that in the paediatric age group, in contrast to the adult population, there are more donor hearts offered than there are recipients. However, in 1999, 15 children died on the UK heart transplant waiting list. On the other hand, in 1996–98 only 25% of donor hearts offered in the 0–12 age group were used while only 50% were used in the 12–16 age group. Thus, there are donor hearts available, which are not being used. In conjunction with colleagues at Great Ormond Street Hospital we have begun a programme of mechanical assist using an external biventricular assist device (the Department of Health has just granted supragovernmental funding). This has the advantage over ECMO (extracorporeal membrane oxygenation) of providing pulsatile flow and using the patient’s own lungs, thus reducing the complexity of, and complications from, the circuit. To
date, we have successfully transplanted four patients after “bridging” using the biventricular assist device.

**Transplantation in the neonate**

Heart transplantation in the neonate and young infant, where size matching is more critical, is still limited by the number of donors. The question of diagnosis of brain death in the neonates is a controversial one and the Hoffenberg report in 1987 concluded that the criteria used to diagnose brain stem death in adults should not be applied to neonates in the first seven days of life. ABO matching has to date been sacrosanct. However, it has been suggested recently that because of their immature immune system, newborns can develop tolerance. There have been sporadic reports of inadvertent ABO mismatch transplants performed in the adult population with a universally fatal outcome. However, West and colleagues from the Hospital for Sick Children in Toronto have just published their experience of ABO incompatible heart transplantation in 10 infants with a survival of 80%—the two early deaths were from causes unrelated to the ABO incompatibility. If this is borne out in larger studies (we have recently had success in two ABO mismatched infant transplants), then it becomes a realistic possibility to offer heart transplantation to more infants with complex congenital heart disease.

Finally, what of lung transplantation? The ISHLT Paediatric report 2000 acknowledges that “evidence continues of striking improvement in patient survival post heart transplantation. Unfortunately this same era of striking improvement in patient survival post heart transplantation in the neonate, where size matching is more critical, is still limited by the number of donors. The question of diagnosis of brain death in the neonates is a controversial one and the Hoffenberg report in 1987 concluded that the criteria used to diagnose brain stem death in adults should not be applied to neonates in the first seven days of life. ABO matching has to date been sacrosanct. However, it has been suggested recently that because of their immature immune system, newborns can develop tolerance. There have been sporadic reports of inadvertent ABO mismatch transplants performed in the adult population with a universally fatal outcome. However, West and colleagues from the Hospital for Sick Children in Toronto have just published their experience of ABO incompatible heart transplantation in 10 infants with a survival of 80%—the two early deaths were from causes unrelated to the ABO incompatibility. If this is borne out in larger studies (we have recently had success in two ABO mismatched infant transplants), then it becomes a realistic possibility to offer heart transplantation to more infants with complex congenital heart disease.

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