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FEATURES

Cardiac transplantation

JOHN F. GOODWIN, M.D., F.R.C.P., F.A.C.P., F.A.C.C.

IN 16 YEARS, cardiac transplantation has changed from a high technology adventure to what has recently been described as a "service" need.[1] At the end of 1984, there were at least 10 American programs, with 15 more in preparation.[1] Now there are a total of 72 centers in the United States and at least 27 in other countries performing cardiac transplantation.

Results from the Stanford program indicate that survival is 83 ± 3.6% at 1 year and nearly 76 ± 4.5% at 2 years.[2] Similar results are reported from the two United Kingdom programs at Harefield and Papworth.[3,4] The world registry reported a survival rate at 1 year of 80% and at 4 years of 70%, excluding death in the first 30 days after operation, with use of cyclosporine.[5] Most recently, in November-December 1985, Heimbecker[5] reported an actuarial rate of 80% in London, Ontario, at 4.5 years.

The striking improvement in results has been attributed mainly to the reduction in acute ejection achieved with cyclosporine (75% survival with, but only 58% without, at 2 years[1]), but other factors are also involved, such as more critical selection of patients, early detection of rejection by repeated endomyocardial biopsy, and improved postoperative care and management of infection. More expert handling of antilymphocytic serum and improved myocardial preservation during the operation are also important.[1]

The marked improvement in cardiac performance and status reflects the excellent function of the transplanted heart that is not suffering from rejection. Despite denervation, the heart demonstrates normal contractility and contractile reserve. In addition, an exaggerated chronotropic response to a catecholamine challenge occurs, perhaps due to "up-regulation" caused by differences in density numbers or binding affinity of β-adrenergic receptors.[6]

The effect of transplantation on quality of life can be dramatic. In terms of cardiac status, improvement from NYHA class IV clinical condition to class I was evident in 97% (of 106) of the patients who survived 1 year or more at Stanford, and most of them had returned to work.[7]

Other aspects of the quality of life after transplantation have been studied intensively in the United Kingdom with the Nottingham Health Profile.[4] Results of questionnaires based on six aspects of life (physical mobility, pain, sleep, energy, social isolation, and emotional reactions) showed dramatic improvement after the operation. But in the United States, psychological and social problems have been prominent in transplant patients.

Selection of recipients must be based on both sound positive criteria (the need for the operation and the result to be expected) and negative criteria (absence of contraindications). The majority of suitable recipients have either coronary disease or cardiomyopathy. Patients with end-stage rheumatic heart disease are apparently presenting for consideration only rarely now. Occasionally, patients with obscure inoperable congenital heart disease but with normal pulmonary vascular resistance may be considered.[7]

Patients with cardiomyopathy tend to be particularly suitable candidates because they are usually young adults who are otherwise healthy. Dilated cardiomyopathy is the most suitable type because it is usually a diffuse myocardial disease, other organs are healthy, and the prognosis is very poor, with around 50% of the patients dying within 2 years after diagnosis. Symptoms of intractable heart failure make life insupportable.

In 1974 I wrote that transplantation should be considered "in desperate cases."[8] Now, 12 years later the prognosis of dilated cardiomyopathy is only a little better than it was, but the results of transplantation have improved so dramatically that patients should be considered before they become "desperate," always

Dr. Goodwin is Emeritus Professor of Clinical Cardiology, Royal Postgraduate Medical School, London.

Address for correspondence: Dr. John F. Goodwin, 2 Pine Grove, Lake Road, Wimbledon SW19 7HE, United Kingdom.

bearing in mind that some patients improve spontaneously, so that all effective medical treatment should be tried first. Poor hemodynamic performance and clinical relapse or continuing deterioration are bad omens.

Patients with hypertrophic cardiomyopathy are much less suitable candidates for transplantation than those with dilated cardiomyopathy because the prognosis for life is often good and the symptoms are mild in many patients. But patients with intractable arrhythmias or heart failure will need consideration. Restrictive cardiomyopathy, especially that caused by endomyocardial fibrosis in the late stages where endocardial resection and atrioventricular valve replacement have been unsuccessful, could be a possible indication for transplantation. But those patients who have the hypereosinophilic syndrome with involvement of other organs present special problems because of the likelihood of underlying disease being transferred to the donor heart. Amyloid heart disease may be in the same category, although one patient has received a transplantation in the United Kingdom, so far with an excellent result.

Age under 50 years, a tough, mature, and resilient psyche, and an intuitive supportive family are useful predictors of a successful result.

The negative aspects of selection (contraindications) include age over 55 years, widespread vascular disease, pulmonary vascular resistance over 10 units, diabetes mellitus, recent pulmonary infarction, active infection, and neoplastic disease. Active peptic ulcer may also constitute a contraindication.

The cost of transplantation has been analyzed in some depth. In 1984 it was $67,000 in the United States[1] and £15,000 in the United Kingdom.[7] Now the costs in the United Kingdom have been reduced further, to £11,000 to £12,000, but the costs in the United States may have increased. Thus it seems that transplantation is at least four times more expensive in the United States than in Britain. The reduced costs in the United Kingdom may be attributed to the use of cyclosporine and the consequent reduction in length of the hospital stay and to fewer early rejection episodes.

Complications are principally those of rejection and infection. Problems of acute rejection have been dramatically reduced by cyclosporine; moreover, when rejection does occur, it is slower and more indolent, myocardial edema being absent in the presence of myocardial infiltration and even necrosis.[1] This has made management of rejection much easier. However, striking atherosclerosis and myocardial fibrosis have occurred later. Late complications other than atherosclerosis are renal damage, hypertension, and lymphoma.[5] Certainly hypertension and renal damage result from cyclosporine, but lymphoma is a well-recognized complication that may be related to immunosuppressive drugs in general rather than to cyclosporine in particular. Smaller doses of immunosuppressive agents may reduce the incidence of malignancy. Measures aimed at preventing chronic coronary artery disease include rigorous selection of donors, use of antiplatelet agents, low animal fat diet, and avoidance of cigarettes.

Although cyclosporine is a remarkably effective immunosuppressive agent, the complications of renal impairment, hypertension, and lymphoma are not to be minimized. Hypertension can be controlled easily, but renal deterioration and the possibility of tumor formation are serious disadvantages. Furthermore, the development of severe atherosclerosis in the donor heart is yet to be fully understood and prevented. What part does rejection play? Could cyclosporine, by frustrating early rejection, open the way to chronic and less easily managed late rejection? If so, then the long-term results of cardiac transplantation may be compromised.

The need for cardiac transplantation has been assessed in the United States and in the United Kingdom. In the latter, the British Cardiac Society report[7] estimated that there would be 750 possible cases annually and 400 to 500 likely patients. In the United States[1] the need would be around 1000 to 5000 annually. Since there appears to be an increasing number of patients who might be suitable heart transplant donors because of brain death (around 2000 per year in 1984),[1] these figures suggest that the need for donor hearts may be met in the United States unless the indications for transplantation are widened,[1] but reservations have been expressed in the United Kingdom.[7]

Transplantation inescapably raises many issues of morality, ethics, spirituality, and wisdom. There are those (physicians among them) who believe sincerely that transplantation offends against nature and morality, mainly because of the distressing circumstances surrounding donor hearts and fear of traffic in organs for profit, whether intellectual or financial. Some people are repelled by the need to remove the heart while it is still beating, feeling that death cannot be assured until the heart has stopped and that removal of the heart is gross violation.

However, the concept of brain death is now well established. As long age as 1974, recognition of brain death in California resulted in legal permission to remove the beating heart from donors with brain death. This judgment was reinforced in the United Kingdom at the Conference of Royal Colleges and Faculties and

by a letter to all physicians from the Chief Medical Officer of the Department of Health and Social Security. Now the concept of brain death is accepted as equivalent to total death by the public, and the importance of removing the heart before it stops beating is understood.

The morality of asking relatives for permission to remove the heart for transplantation has been widely discussed. Those who feel uneasy about requesting organ transplantation may gain comfort from the knowledge that many, if not most, bereaved people gain solace from the fact that the death of one they love has not been in vain and that the heart can be used to save another life. In Britain, doctors can be unwilling to ask relatives so that opportunities are missed. Advice requiring permission to be sought as part of the death certification procedure could be considered in order to reduce doctors' reluctance and to make their task easier. I respect, although I cannot agree with, the view that despite all arguments, the removal of the heart from a person who has recently died in tragic circumstances is a violation of Christian ethic and principle.

Other arguments have been raised against cardiac transplantation, such as the need for frequent hospital visits, the dependence of the patient for long periods, perhaps permanently, on complex follow-up procedures and tests, the risks of infection, uncertainty about future malignancy, the undesirable side effects of long-term immunosuppression, and the risk of dangerous effects of other drugs that are used. All these concerns are valid, but in my view do not outweigh the most tangible evidence of the benefits of transplantation in severely stricken cardiac invalids.

It is most important that centers contemplating the introduction of cardiac transplantation programs should conform to the important guidelines already laid down on both sides of the Atlantic: a satisfactory cardiac surgery program already established, experience with immunosuppression, and an active donor program.[1] To this list should be added three riders: first, that a transplantation policy should not interfere with the existing surgical program; second, that the needs of transplantation justify a new program; and third, that all data should be carefully documented and stored for future advances and that active research should be carried out. At all costs the "mountain syndrome" should be avoided (Why climb the mountain? Because it's there. Why do the operation? Because it can be done.)

Heart and lung transplantation, while promising, may cause other problems. By May 1985, 23 heart and lung transplants had been carried out at Stanford[2] and smaller numbers in the United Kingdom and elsewhere. The early mortality of 26% had been reduced, but the long-term problems of atherosclerosis in the graft and obliterative bronchiolitis in the lung remain unsolved. Combined heart and lung transplantation is indicated in patients with intractable pulmonary vascular disease, especially that due to primary pulmonary hypertension and the Eisenmenger syndrome. But patients with lung failure as well who might be considered for lung transplantation might be accepted for the combined procedure if cor pulmonale is present.

Certainly the results of combined heart and lung transplantation are better than those of lung transplantation alone, presumably because the problems of preserving and storing the lung intact have not been solved. Pulmonary infection and edema can occur early in patients with brain death.

The artificial heart at the present time would seem to be essentially a bridging device to keep the patient alive until a suitable donar heart can be found rather than a long-term alternative to transplantation.

The use of animal hearts as donor organs bristles with difficulties. Official national guidelines are needed before any policy decisions are reached.

Innovative cardiac surgery and high technology investigation and treatment have been the topic of much discussion in the recent past. Cardiac transplantation entails much complex technology. I have been extremely privileged to have been closely involved since 1946 in the evolution of cardiology and participated in its golden age. Having worked with cardiac surgeons for over 30 years, I can only praise their initiative and courage, and I can find also only praise for the pioneers of invasive cardiac investigation in the 1940s; the high technology of their time. Cardiology would not have advanced if there had been no innovators with the courage of their convictions and the determination to succeed. The pioneer work of Richards, Cournand, McMichael, and Wood made cardiac surgery possible, and the cardiac surgeons provided the stimulus for further investigation of heart disease. Where would the march of research in congenital heart disease be without the work of Blalock and Taussig? Where would modern cardiac surgeons be without the pioneer work on cardiopulmonary bypass of Lillehei, Kirklin, and Melrose? I thoroughly approve of innovative cardiac surgery, but I also agree with Shinebourne[10] that new operations should not be introduced haphazardly without comparing the new treatment with existing treatment and carefully assessing indications and selecting patients.

Decisions to undertake radical new forms of treatment involving delicate ethical and moral issues should not be made exclusively by physicians and surgeons. These decisions could be regarded as too important to be left to doctors alone, and peer review may not be enough. The enthusiasm to advance knowledge and help the patient may obscure the wider aspects of the approach to such decisions. Although a decision on an individual patient cannot be made by a committee, guidelines to follow the principles can and should be. A committee could be composed of wise lay individuals such as lawyers and clergymen as well as physicians and surgeons. The acceptability of new and radical innovative procedures depends on the willingness of the public to understand their wider implications. Heart transplantation should no longer be considered a radical new form of treatment; it has passed this stage. But as future advances occur, heart transplantation should not be exempted from moral, social, and scientific debate.

High technology has made great advances possible in diagnosis and treatment of cardiovascular disease and is an important part of any cardiac surgical program. Furthermore, linked to clinical skills, noninvasive high technology investigation can sometimes obviate the need for invasive investigation.

There is no antithesis between compassionate clinical care and high technology management; indeed, the reverse is true because high technology complements the clinical approach. But the clinician must not use it in place of clinical expertise and so cut corners with machines. High technology activity has to be paid for, and this may entail a risk of funds being diverted to the minority who can pay from the majority who cannot. It has sometimes been suggested that high technology investigation and treatment deliberately deflect funds away from the preventive needs of cardiology. This is nonsense; of course, funds are needed for prevention of disease, but prevention and treatment are not antithetic; both must be catered to.

Conclusions. The gratifying results of cardiac transplantation in terms of reduced risk and increased benefit suggest an important role for the operation in the next decade. Advances should not blind us to the problems still remaining and uncertainties in the future. Cardiac transplantation has proved itself as dramatic treatment in the short and medium term for irreversible twilight heart disease in selected patients. Work must continue and more experience must be gained to provide the knowledge needed to solve problems still outstanding and to consolidate the long-term results of the procedure.

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