CARDIAC TRANSPLANTATION

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As a consequence of improved management in acute coronary syndromes and improved longevity of the population, the number of patients with heart failure is growing. The prevalence and incidence in industrialised countries are estimated to be around 1% and 0.15% of the population, respectively.[w1] Up to 10% of people with heart failure are at an advanced stage, amounting to 300 000 patients in the USA and 60 000 in the UK. In parallel, research [w2–5] has led to the concept of cardiac replacement by transplantation. Following the first successful heart transplantation in 1967 in the Groote-Schuur-Hospital, Kapstadt, South Africa,[w6] the first successful US heart transplant was performed in 1968 at Stanford University. In the same year, an ad hoc committee at Harvard University established the criteria of brain death.[w7] More than 55 000 cardiac transplants have now been performed in more than 200 hospitals worldwide (www.ishlt.org). The combination of good surgical success rates and the presence of a growing number of well equipped cardiac transplant programmes has created an enormous flux of heart failure patients towards these centres. Since the annual cardiac transplantation rate will likely remain below 4500 worldwide, with < 3000 in the USA and < 300 in the UK, it is evident that cardiac transplantation will continue to play only a very limited quantitative role in the treatment of the advanced heart failure syndrome.[1] Yet, its importance will continue to reside with its role as the option of last resort for patients with advanced heart failure, offered within centres with a complete spectrum of medical and surgical treatment options. The aim of this review is to outline a contemporary perspective on cardiac transplantation with respect to recipient and donor management, as well as an appropriate organisational policy. For further background reading, excellent material is available.[w8–15]

▶ EMERGING TREATMENTS IN ADVANCED HEART FAILURE

There has been progress in medical treatment including angiotensin converting enzyme (ACE) inhibitors [w16] and β blockers.[2] Surgical therapies including coronary artery bypass grafting with or without surgical anterior ventricular endocardial restoration,[w17] mitral reconstruction in cardiomyopathy patients with severe mitral regurgitation,[w18] combined with partial left ventriculectomy in idiopathic dilated cardiomyopathy,[w19] and left ventricular assist device therapy[3] [w20–24] are evolving. The current status of surgical therapies for advanced heart failure has recently been reviewed in this series.[w25] Antiarrhythmic heart failure therapy with implantable defibrillators has also improved survival.[w26]

CURRENT SURVIVAL BENEFIT WITH CARDIAC TRANSPLANTATION

The appropriate identification of heart transplant candidates is based on the expected gain in survival and quality of life compared to all organ conserving medical and surgical treatment options in advanced heart failure. Selection criteria have been addressed in expert consensus guidelines.[4] They are a matter of increasing controversy. The assumption of a survival benefit across the entire spectrum of advanced heart failure may not be valid any longer because of two opposing trends. One trend is the increasing survival with emerging organ saving treatments. The other trend is that outcomes after cardiac transplantation have not consistently improved, due to listing of more critically ill patients, use of so-called marginal donor hearts from an extended donor pool,[1] and the initiation of new heart transplantation centres with an inevitable learning phase.[w27]

The death rates of advanced heart failure patients on the waiting list of the United Network for Organ Sharing (UNOS), the US organisation in charge of organ transplantation (www.unos.org), have decreased dramatically over time, from 432.2 per 1000 patient years in 1990 to 172.4 per 1000 patient years in 1999. For patients with advanced medical urgency status (status 1A, defined as haemodynamic instability requiring ventricular assist device implantation or high dose intravenous inotropes) in 1999, it was 581.9 per 1000 patient years, as compared with 204.7 per 1000 patient years for medical urgency status (status 1B, defined as requirement of low dose intravenous inotropes) and 130.7 per 1000 patient years for regular urgency status (status 2, defined as stable outpatient condition) registrants. In comparison to waiting list outcomes, for the 1997-98 UNOS heart transplant cohort the one year post-transplantation survival rate was 86%. Recipients

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Table 1	Cardiac transplantation indication criteria
1. Accepted	Heart Failure Survival Score (HFSS, Aaronson 1997[6]) high risk
	Peak V_{O_2} <10 ml/kg/min after reaching anaerobic threshold
	NYHA class III/IV heart failure refractory to maximal medical treatment
	Severely limiting ischaemia not amenable to interventional or surgical revascularisation
	Recurrent symptomatic ventricular arrhythmias refractory to medical, ICD, and surgical treatment
2. Probable	HFSS medium risk
	Peak V_{O_2} <14 ml/kg/min and severe functional limitations
	Instability of fluid status and renal function despite good compliance, daily weights, salt and fluid restriction and flexible diuretics
	Recurrent unstable ischaemia not amenable to revascularisation
3. Inadequate	HFSS low risk alone
	Peak V_{O_2} >15–18 ml/kg/min without other indications
	Left ventricular ejection fraction <20 % alone
	History of NYHA class III/IV symptoms alone
	History of ventricular arrhythmias alone

ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association; V_{O_2}, oxygen consumption.

in medical urgency status 1 at the time of transplant had slightly lower one year post-transplantation survival rates (mean (SD) 84.8 (0.7)% *v* 87.5 (1.0)%) than those in status 2 at the time of transplant.

The International Society for Heart and Lung Transplantation (ISHLT) Registry (www.ishlt.org) indicates an improvement of one year survival after cardiac transplantation from 74.4% between 1980-86 to 85.6% between 1996-99. It does not provide data on waiting list mortality. Thus, the survival benefit with cardiac transplantation cannot be estimated from the ISHLT registry data.

The COCPIT (comparative outcomes and clinical profiles in transplantation) study by the German Transplantation Society and Eurotransplant International Foundation (www.eurotransplant.org)[5] found in a complete national cohort of all 889 adult patients listed for a first heart transplant in Germany in the year 1997 that patients with a predicted high risk of dying from heart failure according to the Heart Failure Survival Score (HFSS), using heart rate, mean blood pressure, aetiology, QRS duration, serum sodium, left ventricular ejection fraction, and peak oxygen uptake,[6] experienced not only the highest risk of dying on the waiting list (32%, 20%, 20% for high, medium, and low risk patients, respectively; p = 0.0003), but were the only group that had a survival benefit from transplantation. Limitations of this cohort study included a short observation period, and incomplete data in the HFSS which was in part a result of the fact that the COCPIT data collection was started before the HFSS was published.

All data currently available suggest that the survival benefit from cardiac transplantation is greatest in those patients who are at highest risk of dying from advanced heart failure without transplantation.

IMPROVEMENT OF MANAGEMENT COUNTERBALANCES SICKER PATIENT COHORT
Consistent with this trend, a shift toward more severely ill patients undergoing cardiac transplantation has been observed during the last 10 years.[w28] With an increasing fraction of patients undergoing orthotopic heart transplantation after previous cardiac surgery, intraoperative management has become more challenging.[w29 w30] The surgical challenges have specifically increased with an increasing fraction of patients undergoing ventricular assist implantation as bridge to transplantation.[w31 w32] Furthermore, traditional contraindications for transplant listing are being questioned—for example, with respect to a history of Hodgkin or non-Hodgkin lymphoma,[w33] elevated pulmonary vascular resistance requiring sophisticated medical bridging,[w34] increased pretransplantation panel reactive antibody (PRA) concentrations,[w35] and left ventricular

assist device (LVAD) use [w36 w37]—implying that advances in transplantation management have offset the increasing severity of transplant recipients.

CURRENT INDICATIONS/CONTRAINDICATIONS AND EVALUATION PROCEDURE
Current indication criteria are a modification of the 1993 American College of Cardiology Bethesda guidelines,[4] mainly based on the availability of the HFSS[6] (table 1). Conditions considered contraindications for cardiac transplantation, based on evidence of reduced short term and long term survival benefit after transplantation, are listed in table 2.

Patients are evaluated for transplantation after referral by a cooperating cardiologist. At the initial evaluation, a mutual long term working relationship between patient, relatives, and the team is established. The evaluation includes the tests summarised in table 3. The listing decision involves a recommendation by the team and decision by the patient. The complexity of the evaluation process mandates a team approach. For the patient with permanent contraindications the team offers continued care with the same intensity as for a transplant candidate, in conjunction with the primary care physician and cardiologist. At the time of listing, the patient and family are informed about the peculiarities of the waiting time, the perioperative period, the long term maintenance medication, and the rules of living with the new heart. A flexible schedule of outpatient appointments constitutes the cornerstone of waiting time surveillance. Deteriorating heart failure may precipitate organ failure. The bridging of organ function is part of the management of heart transplant candidates. If irreversible organ dysfunction ensues, the termination of life support must be considered, incorporating the patient's preferences. The patient must know that in case of a donor organ offer, acceptance of the organ depends on the judgment of donor organ quality by the donor surgical team.

EXPANSION OF DONOR CRITERIA
Donor heart acceptance criteria need to be continuously revised in order to responsibly increase the donor pool. These

Table 2 Cardiac transplantation contraindication criteria

Cardiac disease	Irreversible pulmonary hypertension (PVR >6 WU despite standardised reversibility testing protocol)
Other diseases	Active infection
	Pulmonary infarction within the last 6–8 weeks
	Significant chronic renal impairment with persistent creatine >2.5 or clearance <25 ml/min
	Significant chronic hepatic impairment with persistent bilirubin >2.5 or ALT/AST >×2
	Active or recent malignancy
	Systemic diseases such as amyloidosis
	Significant chronic lung disease
	Significant symptomatic carotid or peripheral vascular disease
	Significant coagulopathies
	Recent peptic ulcer disease
	Major chronic disabling disease
	Diabetes with end organ damage and/or brittle diabetes
	Excessive obesity (e.g. >30% over normal)
Psychosocial	Active mental illness
	Evidence of drug, tobacco, of alcohol abuse within the last six months refractory to expert intervention
	Psychosocial instability refractory to expert intervention
Age	> 65 years

ALT/AST, ratio of serum alanine aminotransferase to aspartate aminotransferase; PVR, pulmonary vascular resistance; WU woods units.

Table 3 Cardiac transplant evaluation tests

Laboratory	Creatinine, blood urea nitrogen, electrolytes, liver panel, lipid panel, calcium, phosphorus, total protein, albumin, uric acid, complete blood count with differential and platelet count, thyroid panel, antinuclear antibodies, erythrocyte sedimentation rate, rapid plasma reagin, iron binding, partial thromboplastin time, prothrombin time
	Blood type
	IgG and IgM antibodies against cytomegalovirus, herpes simplex virus, HIV, varicella-zoster virus, hepatitis B surface antigen, hepatitis C antigen, toxoplasmosis, other titres when indicated
	Prostate specific antigen (male >50 years), mammogram and pap smear (female >40 years)
	Screening against a panel of donor antigens (panel reactive antibodies) and human leucocyte antigen phenotype
	24 hour urine for creatinine clearance and total protein, urinalysis, urine culture
	Baseline bacterial and fungal cultures if indicated
Cardiac	12 lead ECG, 24 hour Holter monitor
	Echocardiogram
	Thallium scan if indicated
	Exercise stress test with oxygen uptake measurements
	Right and left heart catheterisation
	Myocardial biopsy on selected cases where aetiology of heart failure is in question
Vascular	Transcranial Doppler
	Peripheral vascular studies
	Carotid Doppler >55 years
Renal	Intravenous pyelogram if indicated
Pulmonary	Chest x ray
	Pulmonary function tests
	Chest computer tomogram >65 years (thoracic aorta)
Gastrointestinal	Abdominal ultrasound >55 years
	Upper gastrointestinal series if indicated
	Barium enema if indicated
	Liver biopsy if indicated
Metabolic	Bone densitometry
Neurologic	Screening evaluation
Psychiatric	Screening evaluation
Dental	Complete dental evaluation
Cardiothoracic surgery	Evaluation
Physical therapy	Evaluation
Social work	Patient attitude and family support, medical insurance, and general financial resources
Transplant coordinator	Education

extended criteria include advanced donor–recipient size match, donor age, donor heart dysfunction, donor heart structural changes, donor malignancies, and donor infection. A normal sized adult male (> 70 kg) donor is suitable for most recipients, despite an increased risk associated with small donor size relative to the recipient. Safe expansion of donor age criteria to >60 years has been reported.[w38] Donors older than 55 years may be used selectively in certain higher risk recipients. Other donor factors such as left ventricular hypertrophy and ischaemic time may synergistically increase the mortality risk.[w39] Donor hearts with myocardial dysfunction can recover after transplantation.[w40] Donors with mild coronary artery disease may be considered for selected higher risk recipients. A small series of donor hearts treated with bypass grafting for obstructive coronary lesions at the time of transplantation with a good long term survival has been reported.[w41] The transplantation of 37 and 363 hepatitis B surface antigen+ donor hearts and anti-hepatitis B core antibody positive donor organs, respectively, based on 13 309 heart transplants in the time period between 1994 and 1999 in the UNOS registry—on the assumption that patients were at similar risk of dying from heart failure—was associated with a similar five year post-transplantation survival.[w42] Current donor contraindications are listed in table 4.

Table 4 Donor contraindications

Finding	Rationale
Age >55–60 years	Reduced allograft function
Diffuse coronary artery disease	
Documented myocardial infarction	
Documented other heart disease	
Refractory ventricular arrhythmias	
Malignancies (except CNS)	Tumour spread in recipient
Refractory generalised infection	Infection spread in recipient

CNS, central nervous system.

DONOR MANAGEMENT PRINCIPLES

Optimal management of the haemodynamic, metabolic, and respiratory status of the donor is essential in order to maximise the yield of suitable thoracic donor organs.[7] Specifically, this has been advocated by the group at Papworth Hospital in Cambridge, UK.[w43] Brain death is associated with an "autonomic and cytokine storm". The release of noradrenaline (norepinephrine) leads to subendocardial ischaemia. Subsequent cytokine release results in further myocardial depression. This is accompanied by pronounced vasodilation and loss of temperature control. Vasodilation and myocardial depression are compounded by changes in volume status, specifically by relative hypovolaemia which is usually a consequence of aggressive diuretic treatment used to minimise donor cerebral oedema. Optimal donor haemodynamic management includes a pulmonary artery catheter to achieve the goals of euvolaemia and normal cardiac output, minimising the use of α agonists.[8] Metabolic management aims at correcting

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Table 5 Effect of denervation on cardiac pharmacology

Substance	Effect on recipient	Mechanism
Digitalis	Normal increase of contractility; minimal effect on AV node	Direct myocardial effect; denervation
Atropine	None	Denervation
Adrenaline	Increased contractility; increased chronotropy	Denervation hypersensitivity
Noradrenaline	Increased contractility; increased chronotropy	Denervation hypersensitivity
Isoproterenol	Normal increase in contractility; normal increase in chronotropy	No neuronal uptake
Quinidine	No vagolytic effect	Denervation
Verapamil	AV block	Direct effect
Nifedipine	No reflex tachycardia	Denervation
Hydralazine	No reflex tachycardia	Denervation
β Blocker	Increased antagonist effect	Denervation

AV, atrioventricular.

acid-base imbalances and hormonal perturbations. Substitution of insulin, corticosteroids,[w44] triiodothyronine,[w45] and arginine vasopressin [w46] has been shown to be of benefit. A committed transplantation coordination network such as developed in Australia contributes to optimal donor management and recruitment.[w47]

GENERAL PRINCIPLES OF POST-TRANSPLANTATION MANAGEMENT

The post-transplantation management serves a fourfold purpose: control of allograft rejection, minimisation of side effects of immunosuppressants, coping with the transplantation process, and reintegration of the patient into society. The main challenges in the early postoperative period are the management of rejection and infection. In the long term course after transplantation, the main challenges are management of vasculopathy and malignancies. The denervation physiology characteristic of orthotopic cardiac transplantation requires a distinct modification of pharmacotherapy (table 5).

Allograft rejection

The alloimmune response of the recipient leads to destruction of the allograft (fig 1). The differentiation of this alloimmune response is orchestrated by a subtle regulation of soluble immune mediators, called cytokines.[w48] An understanding of acute allograft rejection requires an appreciation of complex, adaptive networks like the interdigitated inflammatory, immune, and physiologic processes that are at work in transplanted allografts.[w49]

Rejection management by immunosuppression

The three drug regimen of cyclosporine, azathioprine, and usually corticosteroids has been the mainstay of immunosuppression for patients undergoing cardiac transplantation since the early 1980s. However, this regimen has some inherent toxicities and does not prevent graft coronary artery disease. Thus there has been a widely perceived need for the introduction of improved immunosuppressive agents. The most commonly used drugs, their targets, selectivity, and main side effects are summarised in table 6.

Recently several new immune pharmacological agents have become available. For induction therapy beyond the polyclonal antithymocyte globulin or monoclonal OKT3, antibody preparations which specifically bind to the interleukin 2 (IL2) receptor, basiliximab and daclizumab, are being evaluated. The new maintenance immunosuppressive drugs are either inhibitors of de novo synthesis of purine or pyrimidine nucleotides, or are immunophilin binding drugs that inhibit signal transduction in lymphocytes. The newer inhibitors of de novo nucleotide synthesis include mycophenolate mofetil, mizoribine, brequinar, and leflunomide. The immunophilin binding drugs are cyclosporine, tacrolimus, and rapamycin. Out of these, four agents have been introduced recently into clinical cardiac transplantation. Mycophenolate mofetil is used as a substitute for azathioprine and has been shown to result in lower mortality and rejection rates in heart transplant recipients.[9] Tacrolimus can be used as a substitute for cyclosporine.[w50] Specific blockade of the high affinity IL2 receptor (CD25) with the human IgG1 monoclonal antibody daclizumab reduces the frequency and severity of cardiac allograft rejection during the induction period.[10] Rapamycin/sirolimus has been shown to reverse refractory cardiac allograft rejection.[w51]

Rejection monitoring

Several methods of rejection monitoring have evolved over the last decades (table 7). The endomyocardial biopsy has long
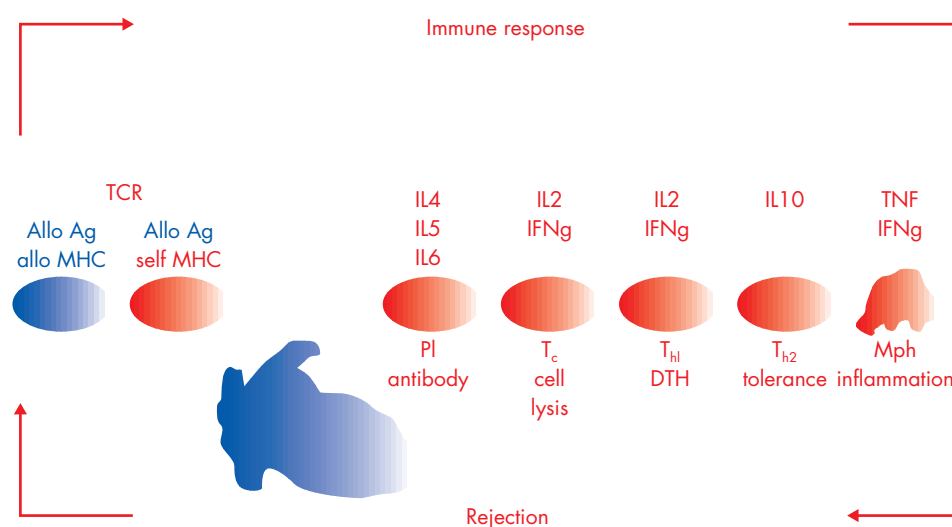
Figure 1 The alloimmune response consists of antigen (Allo Ag) presentation in the context of major histocompatibility (MHC) molecules either by donor cells or by recipient cells to the recipient's T cells via T cell receptor (TCR). This leads to T lymphocyte differentiation to CD4 T cells of T helper1 (Th1) or T helper2 (Th2) phenotype, CD8 cytotoxic T cells (Tc), and B lymphocyte development into plasma cells producing specific clones of antibodies. These immunocompetent cells destroy the allogeneic graft cells. In addition, an inflammatory response by the innate immune system involving macrophages (Mph) participates in this networked alloimmune response. Cytokines (IL2-10, TNF, IFng) play an important role in this orchestrated response. The Th2 subset may favour graft acceptance.

Table 6 Commonly used immunosuppressive drugs: targets, main side effects, and selectivity

Method	Target	Major side effects	Selectivity
Steroids	Lymphocytes/RES	Osteoporosis, diabetes, psychosis, infection, obesity	+
Azathioprine	Lymphocytes	Marrow suppression, hepatopathy	++
Polyclonal antithymocyte globulin	T lymphocytes	Infection, malignancies	++
Monoclonal CD3 antibodies	CD3+ T lymphocytes	Infection, malignancies	+++
Mycophenolate	De novo purine synthesis in lymphocytes	Gastrointestinal	++++
Cyclosporine	IL2 inhibition in T lymphocytes	Nephropathy	++++
Tacrolimus	IL2 inhibition in T lymphocytes	Nephropathy	++++
Daclizumab	IL2 receptor antibodies	None	++++

RES, reticuloendothelial system.

been the preferred technique for monitoring the rejection status of the cardiac allograft,[w52] based on the ISHLT cardiac allograft rejection grading system.[11][w53] Different non-invasive algorithms for cardiac allograft rejection monitoring have been proposed. Early after cardiac transplantation, raised concentrations of inflammatory cells and soluble inflammatory molecules and lower concentrations of immunocompetence markers are associated with impaired allograft function in the absence of cellular rejection. Based on this, an algorithm incorporating clinical status, graft function, mononuclear cell subset analysis, and endomyocardial biopsy has been proposed.[12] Use of an algorithm combining endomyocardial biopsy, lymphocyte growth assays, and anti-HLA antibody measurements enables prospective stratification of cardiac transplant recipients into risk categories for progression to high grade rejection. Low risk individuals require fewer biopsies, moderate risk individuals require an ongoing schedule of surveillance biopsies, and high risk individuals require rational organisation of interventional strategies aimed at preventing rejection.[13]

Prophylaxis and treatment of infection

Opportunistic infections after transplantation continue to constitute a challenge for management (table 8). Cytomegalovirus (CMV) remains the most important infection affecting heart transplant recipients. In the prevention of CMV disease, those at risk of primary disease (donor seropositive, recipient seronegative) should receive prophylaxis.[w54] In many units, oral ganciclovir is now the preferred route of prophylactic treatment. To monitor activity of CMV infection, assessment of viral load has become a valuable tool. *Legionella pneumophila* may cause pneumonia of variable severity after cardiac transplantation. Chlorination and heating of water is an important preventive measure. Specific cultures in outbreak situations should be considered to identify less frequent *L pneumophila* serotypes and the non-pneumophila *Legionella* species.[w55] *Pneumocystis carinii* pneumonia,[w56] tuberculosis,[w57] toxoplasmosis,[w58] pulmonary aspergillosis,[w59] and other fungal infections[w60][w61] continue to constitute challenges for the immunocompromised heart transplant recipient. Sulfamethoxazole/trimethoprine is used in most units for *P carinii* pneumonia prophylaxis.

Transplant vasculopathy

Cardiac allograft vasculopathy (CAV), an unusually accelerated and diffuse form of obliterative coronary arteriosclerosis, determines long term function of the transplanted heart and is the major cause of death in the long term after cardiac transplantation. CAV is a complicated interplay between immunologic and non-immunologic factors resulting in repetitive vascular injury and a localised sustained inflammatory response.[w62] Dyslipidemia, oxidant stress, immunosuppressive drugs, and viral infection[w63] appear to be important contributors to disease development. Endothelial dysfunction is an early feature of CAV and progresses over time after transplantation. Early identification of CAV is essential if long term prognosis is to be improved. Annual coronary angiography is performed for diagnostic and surveillance purposes. Intravascular ultrasound is a more sensitive diagnostic tool for early disease stages and has revealed that progressive luminal narrowing in CAV is in part caused by negative vascular remodelling. Because of the diffuse nature of CAV, percutaneous and surgical revascularisation procedures have a limited role. If annual coronarograms demonstrate rapid progression, retransplantation may be considered. Prevention of CAV progression is a primary therapeutic goal.[w64] Unfortunately,

Table 7 Methods of cardiac allograft rejection monitoring

Method	Delay	Serial assessment	Costs	Indication of rejection	Sensitivity	Specificity
History	None	Yes	+	Dyspnoea, weight gain, discomfort	+	+
Physical exam	None	Yes	+	Arrhythmia, S3, crackles, JVD, oedema	+	+
ECG	None	Yes	+	Atrial arrhythmias, low voltage	+	+
Pacemaker	Telemetry	Every night	+++	Voltage ↓ 7%	+++	+++
Echo	30 mins	Yes	+++	Isovolumic relaxation time ↓, fractional shortening ↓	+++	+++
Biopsy	24 hours	Max 1/week	+++	Cell infiltrates, haemorrhage	+++	+++
Myosin scan	24 hours	Max 1/3 month	+++	Heart/lung ratio >1.6	+++	+++
MRI	1 hour	Max 1/week	+++	Signal ↑ due to oedema	+++	+++
Immune monitoring	4 hours	Yes	+++	CD4/CD8↑, HLA-DR+/CD14 ↑, IL2↑	+++	+++

JVD, jugular venous distension.

Table 8 Management of opportunistic infections after cardiac transplantation

Organism	Test	Treatment
Cytomegalovirus	IE-Gene, PCR, IgM	Gancyclovir, if severe additional CMV antibodies
Herpes simplex virus	IgM	Aciclovir
Varicella-zoster virus	IgM	Aciclovir
Hepatitis B virus	IgM	Lamivudine
Legionella species	Urine antigen, *x* ray	Erythromycin
Mycobacterium tuberculosis	Ziehl-Neelson	Rifampicin, isoniazid, myambutol
Nocardia asteroides	Brain CT	Sulfamethoxazole/trimethoprim
Pneumocystis carinii	*x* ray	Sulfamethoxazole/trimethoprim
Toxoplasma gondii	*X* ray, IFT, CFT, IgA, IgM	Pyrimethamine + sulfadiazine, folic acid
Candida albicans	Direct	Fluconazole, itraconazole
Aspergillus fumigatus	*X* ray	Itraconazole, amphotericin B, flucytosine
Cryptococcus neoformans	Brain CT	Itraconazole, amphotericin B, flucytosine, or fluconazole
Listeria monocytogenes		CNS: ampicillin + gentamycin

CMV, cytomegalovirus; CT computed tomography; IFT immunofluoresence test; CFT, complement fixation test.

conventional preventative measures have limited effects. Several pharmacological agents, including the calcium channel blocker diltiazem [w65] and statins such as pravastatin[14] or simvastatin,[w66] have been shown to be effective.

Malignancies

Malignancies play a major role as cause of death after cardiac transplantation. In the long term course after cardiac transplantation, the risk of malignancies occurring is 1–2% per year. This risk is 10–100 fold higher than the risk in an age matched control population. Malignant tumours of the skin and lymphomas are the most frequent types, but any solid organ tumour may occur. The incidence of post-transplant lymphoproliferative disorder with a cyclosporine based immunosuppressive regimen is estimated to be around 2–4%[w67] (www.ctstransplant.org) and is a frequent and often fatal complication of organ transplantation. It most often results from an Epstein-Barr virus transformed B cell clone, which expresses B cell surface markers such as CD20. While these lymphomas may respond to reduction of immunosuppression, they may be successfully treated with the CD20 antibody rituximab.[w68]

TRANSPLANT CENTRE PRACTICE AND INFRASTRUCTURE

Improvements in perioperative and post-transplantation care have permitted a safe expansion of both the donor pool and recipient criteria for transplantation in experienced individual centres,[w69] and in multicentre registries such as the Cardiac Transplant Research Database.[w70] At large centres including Columbia University where more than 1200 cardiac transplants have been performed since 1977, with a one year survival rate of approximately 90% and a five year survival rate of approximately 75%, an extensive experience with recipients bridged to transplantation by mechanical assist devices has evolved.[w71] The increasing challenge of providing advanced heart failure care founded on evidence based practice patterns requires reliable outcome data including identification of between centre variability and its causes.[w72] There are only a few reports on this subject. Early data suggested an effect of centre volume,[15] potentially as a surrogate for centre experience.[w27] Recently, a total of 662 patients listed between 1992 and 1995 as UNOS status 1 for heart transplantation by four adult US cardiac transplant centres in an organ procurement organisation were analysed. These cardiac transplant centres demonstrated significant variability in the likelihood of transplantation and survival for patients listed as UNOS

status 1.[w73] In Europe, prompted by results from the German COCPIT study,[5] a Eurotransplant wide analysis of centre specific heart transplant outcomes is currently being undertaken, applying empirical Bayes methods.[w74]

ALLOCATION BASED ON MEDICAL URGENCY VERSUS WAITING TIME

The discussion on the respective roles of medical urgency and waiting time in the listing and allocation cascade was started a decade ago following the finding that the survival benefit of transplantation decreases as the waiting time lengthens.[16] Improvements in medical treatment and identification of risk factors for early mortality may make it possible to defer or avoid transplantation in many patients with advanced heart failure [w75] while selecting those patients for transplantation who are at high risk of dying from heart failure without it. To test the hypothesis that cardiac transplantation confers a higher survival benefit in patients with a high risk of dying from heart failure, randomised clinical trial designs have been discussed.[17] [w76–79] If evidence in support of this hypothesis can be established, an allocation policy may either restrict the waiting list to high risk patients from the beginning or accept all potential candidates on the waiting list and subsequently prioritise according to medical urgency, thereby decreasing the impact of waiting time in the allocation algorithm for cardiac transplantation. The latter change has been suggested by the German Transplantation Society[w80] and the US Department of Health and has been reinforced by the Institute of Medicine of the US National Institutes of Health.[18] As an example for a national allocation system incorporating medical urgency, the UK is divided into donor zones with the size of the zone allocated to each transplant centre based on their activity. Each centre then has local autonomy for allocation of donors within their zone to patients on their waiting list. In addition, approximately 15% of the donor hearts in the UK are allocated through a national high urgency system into which each centre can place a fixed number of patients depending on their transplant activity. The quota mechanism helps prevent abuse of the urgency waiting system (http://www.exeter.nhsia.nhs.uk/products/core/donor/donor.asp).

FUTURE DIRECTIONS

Cell transplantation and regrowth of heart muscle

The concept of regenerating the failing heart is in the experimental stage. Several approaches including transplantation of embryonic cardiomyocytes,[w81] cryopreserved [w82] or bioengineered fetal cardiomyocytes,[w83] neonatal cardiac

myocytes, skeletal myoblasts,[w84] autologous smooth muscle cells,[w85] and dermal fibroblasts [w86] have been proposed. Current problems include chronic rejection in allogeneic cells, lack of intercellular gap junction communication, and differential patterns in excitation–contraction coupling in skeletal and cardiac myocytes. Alternatively, lineage negative bone marrow cells[19] or bone marrow derived endothelial precursor cells with phenotypic and functional characteristics of embryonic haemangioblasts have been proposed. The latter can be used to directly induce new blood vessel formation after experimental myocardial infarction, associated with decreased apoptosis of hypertrophied myocytes in the peri-infarct region, long term salvage and survival of viable myocardium, reduction in collagen deposition, and sustained improvement in cardiac function.[20]

Xenotransplantation

Xenotransplantation theoretically provides an unlimited supply of cells, tissues, and organs. The immunological challenge is that the favourite source animal of choice, the pig, and the human recipient were separated in their evolution 90 million years ago, during which time biological characteristics such as anatomy, physiology, and immunology have drifted far apart. The potential individual benefit of a xenograft has to be counterbalanced against the collective risk of xenozoonoses. Ethically, all three monotheistic religions and Hinduism support the idea of saving and improving human life with the help of an animal organ.[w87] According to a committee of the ISHLT, the current experimental results do not presently justify initiating a clinical trial, but because of the immense potential, research in xenotransplantation should be encouraged.[21]

Mechanical circulatory support

Mechanical circulatory support systems are used nowadays frequently to support patients with severe heart failure to transplantation, to recovery, or as destination therapy. While the early totally artificial hearts and ventricular assist devices were mainly driven from an external pneumatic drive unit, the current generation of assist devices are electrically powered, ultracompact, totally implantable, and have small wearable drive/control consoles, allowing patients to return to their daily activities.[w88] Successful bridging to recovery with ventricular support systems has been reported in postcardiotomy cardiogenic shock, acute myocarditis, and in the peri-infarction period. Benefit is related to reduction of left ventricular myocardial wall stress.[w89] Since the REMATCH (randomized evaluation of mechanical assistance for the treatment of congestive heart failure) trial demonstrated a survival benefit from mechanical circulatory support therapy compared to all other options in non-transplant candidates,[3] this will undoubtedly lead to a redefinition of its role in potential cardiac transplantation candidates in the near future.

Smaller rotational[w24] and completely implantable systems[w90] are under evaluation. In order to facilitate evidence based decision making in advanced heart failure therapy with mechanical circulatory support devices, the ISHLT recently inaugurated an International Mechanical Circulatory Support Device Database. This database provides the opportunity for online data entry via the internet and, as a service and motivation for every centre wordwide to participate, continuous centre specific outcome analyses enabling every participating centre to access its own data and view them in relation to the aggregate database (http://www.ishlt.org/regist_mcsd_main.htm).[22]

> ## Cardiac transplantation: key points
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> ▸ Advanced heart failure is an increasing epidemiological problem wordwide
> ▸ Cardiac transplantation has become the gold standard treatment in selected patients during the last 20 years
> ▸ The numerical disparity between donors and recipients requires equitable solutions
> ▸ Cardiac transplantation is increasingly restricted to patients at greatest risk of dying
> ▸ Alternative treatments include neurohormonal blockers and mechanical support devices

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CONCLUSION

A little more than three decades after the successful implementation of cardiac transplantation, this revolutionary concept of advanced heart failure treatment has gained tremendous momentum and is considered the gold standard treatment in selected patients. More specific modalities of immunosuppression continue to decrease the impact of acute and chronic rejection and immunosuppression related side effects. The success of cardiac transplantation has led to a widespread initiation of transplant programmes and an enlargement of cardiac transplantation waiting lists. The increasing numerical disparity between waiting list size and number of donor organ supply has stimulated research to identify those patients who benefit most from cardiac transplantation, as well to develop alternative treatments for advanced heart failure. The success of these new options, specifically the comprehensive blockers of the renin–angiotensin system and adrenergic system, defibrillators, and mechanical circulatory support devices creates the new challenge for cardiac transplantation to define its contemporary role. Against this background of established advanced heart failure management, organ saving surgical approaches (revascularisation, valve repair, ventricular restoration) and new paradigms such as cell transplantation and xenotransplantation must be tested using appropriately designed studies.

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