INTRODUCTION

Heart transplantation is an effective option in certain patients with end-stage heart failure.1 In 1984, the first heart transplantation in Spain was performed, and since then, both the number of centers with an active heart transplant program and the number of procedures have greatly increased. Currently, more than 5000 heart transplantations have been performed in 18 Spanish centers.1,3

The Spanish Society of Cardiology’s working group on heart failure, heart transplantation, and associated therapies organized a consensus conference on heart transplantation that was held in Seville, Spain in June 2005 and to which all Spanish heart transplant teams were invited. The aim was to evaluate, discuss, and reach a consensus on the most important and controversial topics in different areas of heart transplantation today: organization, recipient selection, donors, rejection, immunosuppression, allograft vasculopathy, long-term complications, and pediatric heart transplantation. This report summarizes the working group’s recommendations, and reports the level of evidence supporting each recommendation.

Key words: Heart transplantation. Consensus conference.

Conferencia de Consenso de los Grupos Españoles de Trasplante Cardiaco

La Sección de Insuficiencia Cardiaca, Trasplante Cardiaco y Otras Alternativas Terapéuticas de la Sociedad Española de Cardiología desarrolló en Sevilla, en junio de 2005, una Conferencia de Consenso sobre trasplante cardiaco (TC) a la que fueron invitados a participar todos los grupos españoles de TC. El objetivo fue determinar, discutir y consensuar los aspectos más relevantes y/o controvertidos de diferentes áreas del TC en la actualidad: organización, selección del receptor, donantes, rechazo, inmunosupresión, enfermedad vascular del injerto, complicaciones a largo plazo y TC pediátrico. Este documento reúne las recomendaciones del grupo de trabajo, incluido el grado de evidencia con que se respalda cada una.

Palabras clave: Trasplante cardiaco. Conferencia de Consenso.

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The Spanish Consensus Conference on Heart transplantation (SCCHT) is a project of the Spanish Society of Cardiology’s working group on heart failure, heart transplantation, and associated therapies. The aim of the conference was to review, discuss, and reach a consensus on the most important topics in different areas of heart transplantation today in Spain and to draft guidelines useful for making diagnostic or therapeutic decisions in clinical practice. This is not intended to be a textbook but rather a document that focuses on some of the most controversial aspects. All the centers that perform heart transplantations in Spain were invited and more than 60 participants attended.

The project was launched in December 2004 and was divided into 8 chapters. Each chapter was drawn up by a working group, which reviewed the scientific evidence available. The 2 coordinators of each working group along with the general coordinator (Editorial Board) were
CHAPTER 1. ORGANIZATION OF HEART TRANSPLANTATION IN SPAIN

Organization on a National Level

Number of Centers and Allocation

The current number of centers in Spain (n=18) is considered appropriate for the actual level of activity, that is, up to 300 heart transplantations per year. The most advisable approach is to keep the number of transplantation centers constant and not open more centers.1

The ideal allocation would be according to number of inhabitants but given that Spain is organized politically in autonomous regions, the allocation to centers should be divided into 6 zones. The NTO, as an independent organization, should defend the equity and rights of the patients over the interests of the centers.

Elective transplantation: Patients who do not meet the requirements for emergency 0 transplantation are considered elective transplantation patients. The criteria for assigning organs take into account AB0 blood group compatibility and body surface area (the donor’s body surface area should not be more than 25% larger than that of the recipient) as well as other criteria of the autonomous regions. There is a rotation among the different hospitals that takes into account geographic regions to thus reduce ischemia times and facilitate transport. If the hospital where the organ was extracted is also where the transplantation is to be done, the decision is guided according to whether the donor and recipient are of the same blood group or compatible blood groups. If the hospital is not where the transplantation is to be performed, and several hospitals with heart transplant programs are present in the same city, the offers will be made according to compatibility criteria and only when no compatible recipient is found will a recipient be sought within the same autonomous region.
Emergency transplantation (emergency 0): In order to apply uniform criteria for identifying which recipients can be included on a waiting list for heart transplantation as emergency 0, the Spanish Society of Cardiology’s working group on heart failure, heart transplantation, and associated therapies, along with the NTO, has established a series of conditions that the patient must meet to be considered for emergency transplantation (Table 1). These conditions can be revised on a yearly basis according to the outcomes of these transplantations and the appearance of new cardiac support techniques.

From an operational point of view, and to guarantee good coordination and total transparency in the interaction between the NTO and other heart transplantation centers, if a patient is included on the waiting list as an emergency 0 case, a specific protocol is used (Table 2).

It is considered necessary to have a category of emergency transplantation to resolve critical situations of patients in critical condition, but external audits are recommended in this patient group to verify that the patients are indeed in critical condition.

**LOCAL ORGANIZATION**

**Heart Failure Clinics**

Patients who are candidates for heart transplantation should be assessed by a multidisciplinary team in the heart failure clinic. This clinic should be responsible for carrying out complete and integrated treatment of heart failure patients. The following patients should be attended in such clinics:

- Patients being evaluated as candidates for heart transplantation.
- Patients on the waiting list for heart transplantation.
- Patients in the immediate postoperative period after heart transplantation. Collaboration with physicians of the intensive care unit while the patient is in that unit.
- Patients in the late postoperative period with scheduled admissions: endomyocardial biopsies, annual check-up.
- Patients with complications after transplantation (rejection, infections, others).

**Organizational Structure of a Heart Transplant Program**

It is recommended that the technical management of a heart transplant program is the responsibility of 2 individuals (2 team leaders), a cardiologist belonging

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**TABLE 1. Emergency 0 Level in 2007**

<table>
<thead>
<tr>
<th>Level I</th>
<th>Patients needing retransplantation due to primary graft failure in the initial period (in the first 48 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level II</td>
<td>Patients in cardiogenic shock and with ventricular or cardiopulmonary support with ECMO in the case of infant recipients</td>
</tr>
<tr>
<td>Level III</td>
<td>Patients in cardiogenic shock who require vasoactive drugs and invasive mechanical ventilation</td>
</tr>
<tr>
<td>Level IV</td>
<td>Patients in cardiogenic shock with intra-aortic balloon counterpulsation</td>
</tr>
</tbody>
</table>

*ECMO indicates extracorporeal membrane oxygenator.

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**TABLE 2. Specifications for Considering Patients for Emergency Transplantation: Year 2007**

1. The National Transplant Organization should be notified by fax of the cause of heart failure. This fax should also include the data corresponding to criteria normally used to include a patient on a waiting list. The fax will specify whether the patient needs intra-aortic balloon counterpulsation, the duration of such a technique, venricular support, ECMO, invasive mechanical ventilation, and catecholamines (type and dose) and will be signed by 1 of the team leaders. If applicable, the fax will also include the characteristics of the donor (age, weight, sex, etc) that the team is prepared to accept

2. The following offers will be made:

<table>
<thead>
<tr>
<th>Donor</th>
<th>Recipient</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>for 0 and B</td>
</tr>
<tr>
<td>B</td>
<td>for B and AB</td>
</tr>
<tr>
<td>A</td>
<td>for A and AB</td>
</tr>
<tr>
<td>AB</td>
<td>for AB</td>
</tr>
</tbody>
</table>

3. Should an appropriate offer become available to a team, whether from 1 of their own donors, the same province, or autonomous region, zone, or because it is the general turn of the hospital for an elective recipient, and that team has notified an emergency 0, it will be left to the team to establish appropriate internal priorities for the patients in an emergency situation

4. The turn will correspond to the team that does an emergency heart transplantation

5. Should several emergency patients coincide, priority will be given according to the levels described (I, II, III, IV). If 2 or more patients have the same level, the order of inclusion on the waiting list will take precedence, unless the donor and recipient are in the same hospital

6. If 2 emergencies occur—one in a pediatric recipient and the other in an adult recipient—priority will be given to the pediatric recipient if a donor of the same characteristics is required

*ECMO indicates extracorporeal membrane oxygenator.
to the heart failure clinic and a heart surgeon from the transplant team.

There should be a coordinator for each of the following services directly or indirectly implicated in the transplant program: Resuscitation, coronary or intensive care unit, anatomic pathology, microbiology and immunology, and nursing service.

**Definition of the Heart Transplantation Process**

1. Selection of candidates for heart transplantation. This procedure consists of a series of measures and actions aimed at selecting the patients who are considered suitable for this treatment. Ideally, the procedure should be undertaken by members of the heart failure clinic. Initially, the patients are evaluated by their cardiologist (or another specialist), who belongs to the service or to another referral center and who, after considering the patient to be a candidate for heart transplantation, will then contact the heart failure clinic or cardiology service of the transplantation center. Subsequently, it will be decided whether the patient is assessed in an outpatient setting or in hospital. This decision will depend on the characteristics of the patient, the degree of emergency, the place of residence, etc.

2. Heart Transplantation. Heart transplantation includes the following procedures:

   - Evaluation and acceptance of the organ: Done in collaboration between cardiologists and heart surgeons.
   - The availability of an organ is notified via the transplant coordinator of the hospital or directly to the transplantation team.
   - Selection of the most appropriate recipient: Performed by the cardiologist responsible for selecting candidates and the heart surgeons responsible for removing and implanting the graft.
   - Surgical procedure: According to the corresponding protocol.
   - Immediate postoperative period: In a conventional intensive cardiac care unit. Special heart transplantation units are not considered necessary.
   - Late postoperative period: In a conventional hospital ward, either of the cardiology or heart surgery service.

3. Follow-up program. Chronic patient. Life-long follow-up. A set of measures and actions performed on a recipient of a heart transplantation with the aim of avoiding complications, improving the quality of life, and extending survival. These tasks should generally be performed by members of the transplant program or the heart failure clinic. The endomyocardial biopsies should be done by physicians of the transplant program or by regular members of catheterization laboratories.

After the first year, at least 2 yearly examinations (every 6 months) are considered necessary along with at least 1 annual echocardiogram. In view of the limited evidence in the literature on the treatment and control of graft vascular disease (studied by coronary angiography and intravascular ultrasound [IVUS]), it is impossible to make recommendations, outside of an investigational scenario, about the protocol and the workflow for the clinical management.

**REQUIREMENTS FOR RECOGNITION OF TRANSPLANTATION CENTERS**

**Legal Framework**

A legal framework was established by the Royal Decree 2070/1999 dated December 30, 1999 (published in the Official State Bulletin [BOE] of January 4, 2000;[3];179-90), which regulates the activities of procurement and use of human organs and the coordination between autonomous regions in terms of donors and recipients of organs and tissues.

Official recognition of new centers offering heart transplantation will be granted as part of health policy aimed at ensuring suitable management and allocation of resources, in accordance with the actual needs of the population. At present, this function is carried out by the corresponding health authorities of the autonomous regions. The requirements that organ transplantation centers should meet are specified in articles 15, 16, 17, and 18, and in Annex II of the Royal Decree 2070/1999. In summary, these are divided into minimum general requirements and minimum specific requirements.

Article 15 states that transplants can only be done by recognized centers and with prior written consent of the recipient. It also states that the confidentiality of the donor’s personal data is mandatory.

Article 16 defines the procedures for awarding, renewing, and rescinding authorization for organ transplantation centers.

Article 17 defines the general minimum requirements to be met by the organ transplantation centers to obtain authorization. These requirements are as follows:

   - To be recognized as a center for extracting organs from dead donors, with proof of a sufficient level of activity to guarantee the feasibility and quality of the transplant program.
   - To have a care and operational structure suitable for the intervention requested.
   - To have the health resources necessary to guarantee a suitable follow-up and appropriate management of possible complications associated with the transplantation procedure.
   - Availability of the corresponding medical and surgical unit, with health staff with sufficient and proven
experience in the type of transplantation to be performed.

- To guarantee the availability of specialists with proven experience in the diagnosis and management of complications that arise from transplantation.
- To have the installations and material necessary to guarantee a satisfactory transplantation procedure in the preoperative, peroperative, and postoperative phase.
- Availability of an anatomic pathology service with the technical and human resources for study of the complications associated with transplantation and able to perform post mortems.
- Availability of a microbiology laboratory able to carry out controls for infectious complications that may present in patients.
- A transplantation board and protocols to ensure appropriate selection of recipients, the transplantation procedure, and immediate and long-term postoperative follow-up to guarantee the quality of the entire therapeutic procedure.
- Availability of a unit within the hospital to coordinate the transplantation procedures.
- Availability of a register, with restricted and confidential access, to record the procedures performed with the necessary data for identification of the donors, such that appropriate follow-up of the organs transplanted in the center can be performed.
- Availability of an appropriate register to allow assessment of the activity of transplantation procedures done in the center, as well as the outcomes.
- To guarantee the availability of an immunology laboratory and a histocompatibility laboratory with sufficient technical and human resources to ensure that the required immunological studies to monitor the patient before and after the transplant are done correctly.
- The medical and surgical units involved in the different types of transplant will be constantly adapted to scientific progress made in the field and will follow up-to-date diagnostic and therapeutic protocols in accordance with generally accepted medical practice.

Annex II defines the specific minimum requirements for performing heart transplantation:

- Availability of a cardiology service and heart surgery unit with sufficient staff and proven experience in heart surgery requiring extracorporeal circulation.
- Availability of a catheterization laboratory with the necessary experience in invasive cardiology techniques.

The aim of the above is to guarantee that transplantations are performed satisfactorily and that patients receive adequate treatment of possible complications.

In addition to these legal requirements, any center that aims to be officially recognized as a transplantation center should have a program to develop and promote mechanical circulatory support.

CHAPTER 2. STUDY AND SELECTION OF THE RECIPIENT

Assessment of the Severity and Prognosis of Heart Failure

Mortality remains high despite the substantial advances in treatment of severe heart failure in recent years. Heart transplantation is often the only therapeutic alternative, although not all patients with severe heart failure will benefit from transplantation. When selecting a recipient, the limited number of donors, the high morbidity and mortality associated with transplantation, and the possibility of other alternative therapies should all be taken into account.

Risk Factors for Mortality in Patients With Heart Failure

The clinical course of patients with heart failure varies widely from the prognostic point of view. The annual mortality in unselected populations of patients with heart failure is as high as 40%. However, in patients enrolled in clinical trials who are treated with angiotensin converting enzyme (ACE) inhibitors and ß-blockers, mortality was reduced to 6%-25%, depending on the severity of heart failure. Given that mortality during the first year after heart transplantation is around 15% to 20%, appropriate prognostic stratification is necessary. The COCPIT study found that heart transplantation only improved prognosis in patients with a predicted high risk of death before transplantation. The authors used the Heart Failure Survival Score (HFrSS), a system for calculating prognosis based on the analysis of 7 readily obtained noninvasive variables (ischemic cardiomyopathy, intraventricular conduction defect, resting heart rate, mean blood pressure, left ventricular ejection fraction [LVEF], peak exercise oxygen uptake [VO₂max], and serum sodium levels) with a different weighting for each variable. Briefly, we will review the 4 most important risk groups for heart failure mortality which should be taken into account to establish severity and indication for heart transplantation.

Symptoms or Functional Class

Measurement of functional class using the NYHA classification is not very accurate since it is based on the patients’ subjective perception and physician’s interpretation. Exercise testing can provide a more
objective and reproducible assessment of functional class. Peak exercise oxygen uptake \( >14 \text{ mL/kg/min} \) was associated with a 1-year survival of 94%, which is comparable to that obtained with heart transplantation, whereas survival with \( \text{VO}_{2\max} <10 \text{ mL/kg/min} \) was associated with increased mortality.\(^{18}\) However, medical treatment has improved since this study was published, specially with the introduction of \( \beta \)-blocker therapy, being the approach to interpretation the test results somewhat changed. The cutoff currently recommended for a patient to be considered for inclusion on a waiting list is \( \text{VO}_{2\max} \leq 14 \text{ mL/kg/min} \) in patients intolerant of \( \beta \)-blockers or \( \leq 12 \text{ mL/kg/min} \) in \( \beta \)-blocker treated patients.\(^{12}\) However, the decision to include a patient on a waiting list for heart transplantation should not just be based on the value of \( \text{VO}_{2\max} \). In intermediate circumstances (for example, \( 12<\text{VO}_{2}<14 \text{ mL/kg/min} \)), HFSS, and/or additional clinical evidence of poor prognosis can help in decision-making and determine whether a patient should be included on the waiting list for heart transplantation. Evidence of poor prognosis includes:\(^{12}\)

1. Frequent admission to hospital for volume overload, angina, or arrhythmia;
2. Persistently elevated creatinine or pulmonary vascular resistance;
3. Elevated natriuretic peptide (BNP or NT-proBNP), troponin, or uric acid concentrations; and
4. Resynchronization failure or an implantable cardioverter defibrillator.

**Ejection Fraction**

A very low LVEF (<20%) should not be the only criterion for indicating heart transplantation; prognosis in these patients should also be assessed according to other concurrent risk factors.\(^{26,29}\) The most important of these criteria include severe left ventricular dilation (left-ventricular end-diastolic diameter (LVEDD)<75-80 mm), sustained arterial hypotension, elevated pulmonary capillary wedge pressure (>25 mmHg), and a low cardiac index (<2.5 L/min/m\(^2\)).

**Neurohormonal Activation**

In advanced heart failure, elevated plasma levels of renin, angiotensin, aldosterone, and noradrenaline have been observed. Sodium plasma levels below 130 mEq/L are associated with worse survival. Although the prognostic value of natriuretic peptides has been established, their actual role in the indication of heart transplantation has yet to be defined.

**Ventricular Arrhythmia**

Sustained ventricular arrhythmias are indicative of worse prognosis, but they need to be specifically assessed and managed, something which is beyond the scope of this document.

**Assessment of When to Include a Patient on a Waiting List**

Deciding whether and when to include a patient on a waiting list for heart transplantation is not easy. This decision should be based on knowledge of the natural history of the heart disease and all the alternative treatment options. It is necessary to carefully select potential recipients with the greatest chance of a successful outcome.\(^{14}\) Table 3 shows the indications for heart transplantation.

### TABLE 3. Indications for Heart Transplantation ACC/AHA Practice Guidelines, 2005\(^a\)

<table>
<thead>
<tr>
<th>Type of Indication</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I. Absolute indications</strong></td>
<td>For hemodynamic deterioration due to heart failure, Cardiogenic shock refractory to treatment, Proven dependency on intravenous inotropic support to maintain sufficient organ perfusion, ( \text{VO}_{2\max} &lt;10 \text{ mL/kg/min} ) having passed the anaerobic threshold, Severe myocardial ischemia that impairs normal activity and that is not amenable to revascularization surgery or percutaneous angioplasty, Symptomatic recurrent ventricular arrhythmias resistant to all therapeutic approaches,</td>
</tr>
<tr>
<td><strong>II. Relative indications</strong></td>
<td>( \text{VO}_{2\max} \leq 11-14 \text{ mL/kg/min} ) (or 55% of predicted) and substantial limitation in functional activity, Unstable and recurrent ischemia not amenable to another intervention, Recurrent instability of fluid balance/renal function not attributable to lack of treatment compliance,</td>
</tr>
<tr>
<td><strong>III. Insufficient indications</strong></td>
<td>Low left ventricular ejection fraction, Prior history of NYHA functional class III or IV, Prior ventricular arrhythmias, ( \text{VO}_{2\max} &gt;15 \text{ mL/kg/min} ) (&gt;55% of predicted) without other indications,</td>
</tr>
</tbody>
</table>

\(^a\)ACC indicates American College of Cardiology; AHA, American Heart Association; NYHA, New York Heart Association; \( \text{VO}_{2\max} \), peak oxygen uptake from exercise testing with gas exchange analysis. Taken from Hunt SA et al.\(^{20}\)

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transplantation proposed in the latest guidelines of the ACC/AHA for assessment and treatment of heart failure. Table 4 shows the recommended examinations and tests for assessing candidates for heart transplantation.

When to include a patient on a waiting list is a complex decision with many factors to consider. The determining factor is severely impaired functional capacity but, given the subjectivity of the NYHA classification, we should use the 6-minute walk test or conventional exercise testing to assess this aspect, either alone or measuring the peak exercise oxygen uptake (VO2max), as this is the best method for assessing functional capacity. If the patient is unable to walk further than 250 meters in the 6-minute walk test or VO2max is below 10 mL/kg/min, that patient should be included on the waiting list without further delay. If VO2max lies between 10 and 14 mL/kg/min, other determinants of prognosis (functional class, etiology of the heart failure, LVEF <20%, ventricular arrhythmias, hyponatremia, syncope, etc) will be used to decide whether to include the patient on the waiting list.

Assessment of Pulmonary Hypertension

Pulmonary hypertension (PHT) is defined as mean pulmonary arterial pressure >25 mm Hg. Pulmonary artery hypertension is a risk factor for acute right ventricular failure after heart transplantation and increased morbidity and mortality. The assessment of PHT before transplantation includes the following hemodynamic variables (Table 5): a) transpulmonary pressure gradient (TPG) calculated as the difference between the mean pulmonary arterial pressure and pulmonary capillary pressure.
TABLE 5. Important Hemodynamic Variables to Study in Potential Candidates for Heart Transplantation

Pulmonary artery hypertension and high pulmonary vascular resistance (PVR) should be considered relative contraindications for heart transplantation when PVR >5 WU or left PVR >6, or TPG >16-20 mm Hg

<table>
<thead>
<tr>
<th>Variable</th>
<th>Calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) wedge pressure (TPG=mPAP-PCWP); b) pulmonary vascular resistance (PVRs=TPG/cardiac output) in Wood units (WU); and c) pulmonary vascular resistance index (PVRI=TPG/cardiac index) in WU/m².</td>
<td></td>
</tr>
</tbody>
</table>

Pathophysiology of Pulmonary Hypertension

In chronic heart failure, end-diastolic pressure increases with left ventricular dysfunction. This increase is transmitted in retrograde direction to the pulmonary vascular bed resulting in increased pulmonary venous pressure and reactive vasoconstriction of the pulmonary bed. This type of PHT is considered reactive. In general, it decreases when the left ventricle is "unloaded" either by pharmacological or mechanical means. However, pathological remodeling of the pulmonary capillary bed may occur, inducing changes of the vessel wall. Thus, cell proliferation with medial hypertrophy and hyperplasia have been described, associated with muscularization of the arterioles and lymphatic vessels, and increased intimal fibrosis. These changes could lead to irreversible PHT manifest through a fixed increase in pulmonary vascular resistance (PVR). In PHT secondary to heart failure, both types may be present and it is important to determine to what extent PHT is reversible. Pulmonary hypertension is considered reversible when it responds quickly to vasodilators and inotropic agents, whereas it is considered irreversible when it does not respond to such drugs. When studying PHT in a candidate for heart transplantation, these 2 types of PHT should be distinguished. The first type can be managed pharmacologically after transplantation, whereas the second will cause acute right ventricular failure of the transplanted heart and increase morbidity and mortality.

Assessment of Pulmonary Hypertension in Candidates for Heart Transplantation

Pulmonary hypertension and right ventricular dysfunction are independent predictors of poor outcome in patients with heart failure. Pulmonary hypertension is also an independent predictor of mortality after heart transplantation, as reflected in the International Heart and Lung Transplantation (ISHLT) registry in which, of the 9640 patients included, survival was worse in those with severe PHT.23,24 Pulmonary vascular resistances show a linear correlation with mortality after transplantation. The risk is significantly higher if TPG >12 mm Hg and PVRs >2.5 WU; a patient is considered high risk if TPG >15 mm Hg and PVRs >5 WU (values considered as contraindications for heart transplantation in most heart transplant programs).

The following drugs are the most widely used ones in the pharmacological test:

- Inotropic agents and/or vasodilators: dobutamine, milrinone and levosimendan, nitroglycerin, and nitroprussate.
- Nonselective vasodilators: intravenous prostanoids (prostaglandin E1 [PGE1] and epoprostenol).
- Selective vasodilators: Nitric oxide (NO), sildenafil, and stable analogues of prostacyclin.25,26

If PHT does not respond to pharmacological therapy, placement of left ventricular support devices to "unload" the left ventricle might be effective in some cases,27 although the number of patients reported in the literature is still small.27

In the perioperative phase of heart transplantation, it is recommended to use aggressive perioperative prophylactic protocols in patients with PHT to avoid right ventricular dysfunction of the transplanted heart.28

The essential points are as follows:

- Optimization of treatment for heart failure before surgery using drugs that reduce PHT.
- Initiation soon after surgery, if possible before removing extracorporeal circulation, of vasodilator treatment (to keep PVR low). Nitric oxide and systemic or inhaled prostanoids have been shown to be beneficial.
- In the postoperative period, it is necessary to monitor for the appearance of right ventricular dysfunction, maintain cardiac output with inotropic support, monitor heart rhythm and manage preload (central venous pressure >10 mm Hg), and reduce PVRs with NO during mechanical ventilation and with sildenafil afterwards to keep PVR low. After heart transplantation, there is a
substantial early decrease in PHT, the right ventricle of the transplanted heart progressively adapts to the residual PHT thereby allowing progressive withdrawal of the vasodilators.

There are however special situations that are hard to manage, such as some adult congenital heart diseases and valve diseases with right ventricular dysfunction in which the extent of PHT can be underestimated.

Assessment of Concurrent Diseases as Risk Factors and Absolute Contraindications

There are increasingly fewer absolute contraindications for heart transplantation and so it is now preferable to talk of conditions that increase post-transplantation morbidity or mortality and that either alone or in combination can advise against transplantation. Ideally, we would have at our disposal a risk assessment that would give us a more objective measure, but there is still insufficient evidence for such a scale. We can however differentiate between absolute contraindications (Table 6), relatively major contraindications (Table 7), and relatively minor contraindications (Table 8).

Heart transplantation is not recommended in the case of 1 absolute contraindication, 2 relatively major contraindications, or 1 relatively major contraindication and 2 relatively minor ones. When 3 relatively minor contraindications coincide, that particular patient would have to be considered on his or her individual merits.

We will now review some of the factors related to major risk after heart transplantation.

Diabetes Mellitus

Diabetes mellitus (DM) affects long-term survival and quality of life of the transplant recipient, as it is associated with organic complications such as nephropathy, neuropathy, and vascular disease. The diabetic recipient usually suffers decompensation with the immunosuppressive therapy given after heart transplantation, and this may occasionally accelerate disease progression. It should be remembered that either alone or in combination can advise against transplantation.

Atherosclerotic disease can also be an absolute contraindication if it is diffuse or distal and not amenable to revascularization. In the case of proximal and localized lesions amenable to revascularization, the risk is increased due to the possibility of an embolic or thrombotic event, but such lesions are not considered an absolute contraindication. Furthermore, after heart transplantation, immunosuppressive therapy with corticosteroids may accelerate disease progression. It should be remembered...
that stroke with sequelae can affect therapeutic compliance and rehabilitation after transplantation.31,32

Neoplastic Disease

If the patient has a history of neoplastic disease, there should be no evidence of residual or recurrent disease, or metastases during a sufficiently long period for the disease to be considered cured. The recommendations of the International Society of Heart and Lung Transplantation (ISHLT)31 require each patient to be stratified according to the risk of recurrence of the tumor in collaboration with the oncologist. Heart transplantation can be indicated when the risk of recurrence is low according to histological typing, treatment response, and lack of metastases. The time necessary for indication of heart transplantation after neoplastic disease in remission varies according to the factors described previously and it is not recommended to establish an arbitrary interval (for example, 5 or 10 years) as had been done in the past.31,34

Active Ulcerous and Diverticular Disease

The presence of active ulcerous and diverticular disease should be considered a relative contraindication. In the case of ulcers, endoscopic evidence of cure should be available before heart transplantation. It is recommended to use H2 antihistamine agents, proton pump inhibitors, or other prophylactic measures in these patients.

Psychosocial Issues

Abusive and addictive consumption of tobacco, alcohol, cocaine, and other drugs of abuse is considered an absolute contraindication. For these patients to be considered for transplantation, an abstinence period of at least 6 months should be documented and a favorable report from a specialist team should be available. Persistent psychopathic diseases, suicidal behavior, severe behavioral disorders, and previously documented lack of therapeutic compliance are also considered absolute contraindications.35

Kidney Failure

Assessment of kidney failure should be done when the patient is in the best possible hemodynamic condition to rule out kidney failure secondary to decreased cardiac output and/or aggressive diuretic treatment. In general, normal sized kidneys, absence of proteinuria, and improvement in kidney function with inotropic therapy suggest that the kidney failure is secondary to heart failure.31,32

When creatinine is assessed as a continuous variable, concentration should not exceed a level associated with a sharp increase in risk. In general, a relative contraindication for heart transplantation is creatinine >2.5 mg/dL or creatinine clearance <50 mL/min, as such findings are associated with greater risk of postoperative dialysis and worse survival at 1 year.35 In patients with kidney disease, the possibility of combined kidney transplant should be considered, or the use of non-nephrotic immunosuppressive therapy.

Liver Failure

Liver failure may be due to liver congestion arising from right ventricular dysfunction secondary to pulmonary hypertension. Persistent abnormalities in liver enzymes despite acceptable improvement in right atrial pressure (<14 mm Hg) indicates intrinsic liver disease. If there is a suspicion of liver disease, the medical history of the patient should be assessed and the cause investigated by imaging techniques and monitoring liver enzymes for a 2-fold elevation in transaminases. The possibility of a secondary coagulation disorder should also be investigated.36 Liver biopsy might be necessary to rule out organic disease. Liver cirrhosis is considered an absolute contraindication for heart transplantation. In certain cases, combined heart and liver transplantation can be considered.

Chronic Lung Disease

Lung disease can prolong extubation and increase the risk of infection in the immediate postoperative period. Therefore, the following are considered absolute contraindications for heart transplantation: forced expiratory volume in 1 second (FEV1) <40% of predicted, forced vital capacity (FVC) <50% of predicted, and carbon monoxide diffusing capacity (DLCO) <40% of predicted in the presence of emphysema or pulmonary fibrosis despite optimum treatment.31,32

Recent pulmonary embolism increases the risk of abscess formation in immunodepressed patients.37 In such cases, depending on the size and site of the embolus, it is necessary to wait between 1 and 3 months.

Infectious Disease

Active infection is a temporary contraindication until the infectious process has resolved satisfactorily.31 Untreatable life-threatening infections are absolute contraindications. Infection with the human immunodeficiency virus (HIV) is a relative contraindication, and each case should be assessed individually according to the organic involvement and the state of the disease.38

Decreased survival in patients with hepatitis B surface antigen has not been shown.39 In any case, it is necessary to rule out liver cirrhosis, with biopsy if necessary, and
to suppress the viral load with antiviral therapy given that there is a risk of reactivation of the disease with immunosuppression after transplantation.

Patients who are positive for hepatitis C virus (HCV) do not seem to have significant additional risk. The viral load in these patients should be quantified. If the virus is not detected, liver function is normal, and the liver biopsy shows that inflammation is minimal, survival after heart transplant appears to be similar to that of any other patient with a positive serologic test for HCV. If circulating HCV is detected (>10^5/mL), the disease is active and the patient should receive treatment to reduce or even eliminate the virus. In these cases, if liver function is normal and no cirrhosis is present in biopsy, 5-year survival is similar to that of other patients without hepatitis; such patients are therefore candidates for heart transplantation. However, abnormal liver function that cannot be explained by heart failure and evidence of cirrhosis in the biopsy should be considered absolute contraindications.

**Mycarditis**

Mycarditis is considered a relative contraindication for heart transplantation given that it is associated with a higher rate of acute rejection and early postoperative mortality. The recommendation is to postpone heart transplantation as long as possible after the acute episode, although there are no data that define the period after which spontaneous improvement is unlikely. In this case, ventricular support would be indicated and heart transplantation carried out only if this measure does not lead to improvement.

**Osteoporosis**

Osteoporosis is considered a relative contraindication after heart transplantation, it does increase long-term morbidity mainly as a result of the side effects of chronic corticosteroid treatment.

**Obesity**

Although obesity has not been shown to be related to a higher risk of mortality, acute rejection, or graft vascular disease, it does increase the risk of hypertension, diabetes mellitus, hyperlipemia, infections, and complications of osteoporosis. Although body weight is a continuous variable and it is hard to establish a cutoff, a body weight >120% of the ideal weight is generally considered a relative contraindication.

**Age**

According to data from the Spanish heart transplantation registry and other series, age over 65 years is associated with increased early and late mortality. However, studies of transplants in carefully selected recipients over 65 years of age have reported findings with similar survival to younger recipients. Although acute rejection is lower in older patients, there is a greater risk of graft vascular disease. We therefore consider that inclusion of patients aged over 65 years on the waiting list should be assessed individually taking into account biological age and comorbidities.

**Uncommon Indications for Heart Transplantation**

Although ischemic heart disease, advanced valve disease, and dilated cardiomyopathy are the most common reasons for heart transplantation (accounting for approximately 90% of the cases), there are other less common indications.

- Symptomatic ventricular arrhythmias were a much debated indication for heart transplantation until a few years ago; nowadays, they are considered an indication provided that they are refractory to medical treatment, treatment with implantable cardioverter defibrillators (ICDs), or surgical treatment.
- Patients with restrictive cardiomyopathy secondary to hereditary or familial amyloidosis can undergo heart transplantation in combination with liver transplantation in the same operation or in separate operations. In other types of amyloidosis such as primary amyloidosis, the outcomes of heart transplantation are poor due to progression of the underlying disease in other organs or recurrence in the transplanted heart; nevertheless, in carefully selected young patients, it can be combined with bone marrow transplantation. In some cases of senile cardiac amyloidosis, good long-term survival has been shown, and so such patients could be considered for inclusion on a waiting list for heart transplantation.
- In patients with restrictive secondary cardiomyopathy secondary to hemochromatosis, acceptable outcomes can be obtained with a combination of liver and heart transplantation in selected cases.
- Neuromuscular disease is a relative contraindication for heart transplantation. However, transplantation should be done after the physical therapist and neurologist have assessed the functional status and prognosis of the patient.

**Indications for Heart Retransplantation**

Heart retransplantation accounts for 2% of all heart transplantations currently performed. The most common reason, accounting for an estimated 65% of all retransplantation procedures, is graft vascular disease. Retransplantation (regardless of the indications for heart disease similar to those for primary transplantation) should be considered in patients with...
severe 3 vessel disease with reduced LVEF and severe symptoms. Before retransplantation, coronary revascularization should be attempted whenever possible.

Acute severe rejection after transplantation and episodes of severe rejection unresponsive to medical treatment are the second most common reasons for heart retransplantation. The indications should be very strict, as these patients are in a very serious condition with prolonged stays in intensive care units (ICUs). They have a very high mortality despite heart retransplantation.

Patients considered for heart retransplantation should undergo the same study as candidates for primary heart transplantation, with particular emphasis on the search for cytotoxic antibodies. If the panel of reactive antibodies is positive, cross testing is required before retransplantation. Before the 1950s, these patients had a worse prognosis, but nowadays overall survival is similar in both patient groups. However, when considering the possibility of heart retransplantation, ethical questions should be addressed according to the underlying philosophy of the program. The indications for urgent and elective heart retransplantation are as follows:

- Emergency retransplantation: acute graft failure; acute, severe, and untreatable cardiac rejection.
- Elective retransplantation: coronary allograft vasculopathy, chronic graft dysfunction, or restrictive graft disease.

Acceptance and Management Criteria for Candidates for Emergency Heart Transplantation

Emergency heart transplantation can be considered for all patients, younger than 65 years, with cardiogenic shock or acute chronic heart failure (awaiting elective heart transplantation), in a life-threatening condition despite optimum treatment for whom no other reasonable surgical options are available.

Established Indications

1. Retransplantation for primary graft failure lasting at least 48 hours.
2. Cardiogenic shock treatable by heart transplantation with ventricular support or intra-aortic balloon counterpulsation, with vasoactive drugs at high doses, and mechanical ventilation.

Criteria for Including a Patient on an Emergency List

In order to select a candidate, appropriate stratification is necessary to exclude patients with unacceptable risks and to ensure optimum resource use. The causes of shock and potentially reversible components, the severity of hemodynamic deterioration, and the duration and the presence of multiorgan failure should all be assessed.

Evaluation and Basic Management


Hemodynamic Assessment

Swan-Ganz catheterization. Arterial catheterization. Coronary angiography (only if it is considered indicated for studying the patient’s heart disease to rule out possible reversible processes).

Assessment of Possible Contraindications or Risk Factors for Poor Prognosis

In general, the contraindications for emergency transplantation are the same as for elective transplantation. Therefore, despite the critical situation of the patient, we have to have information on the conditions that will increase morbidity or mortality after transplantation and that, alone or in combination, will dissuade us from performing the transplantation.

For this assessment, it is necessary to evaluate possible systemic diseases or dysfunction of other organs which independently limit and reduce quality of life in the context of terminal heart failure. On the other hand, transplantation should be considered before reaching severe and irreversible multiorgan dysfunction.

When the patient needs transfer to a different center for heart transplantation, some aspects can make such a transfer risky or unnecessary:

- Extensive active bleeding.
- Severe hypoxia: PaO$_2$ <50 mm Hg at inspiratory oxygen fraction (FiO$_2$) of 100%.
- Dependence on prolonged dialysis.
- Inappropriate hemodynamic support (mean arterial pressure <50 mm Hg or persistent metabolic acidosis).
- Suspicion of severe and irreversible neurological lesion.
- Patients in critical condition who require transfers lasting more than 5 to 6 hours.

The decision whether to include a patient on a waiting list for heart transplantation is a multidisciplinary action (with the participation of specialists such as intensivists, heart surgeons, cardiologists, and anesthetists) undertaken...
by the reference center. Therefore we should refrain from hasty discussion about transplantation with the patient or patient’s family before the medical team has assessed the feasibility of the procedure. In addition, the timing of transplantation has to be continually revised according to the patient’s condition.19,52-54

Exclusion of Patients From Emergency List Due to Worsening Condition

Heart failure can lead to multiorgan failure, which drastically reduces the chances of a successful outcome in these patients, even though heart transplantation itself is successful (Table 9). Therefore, prevention and management of such failure is an important part of the therapeutic strategy in these patients. Among the particularly useful measures in this context are ventricular support devices which help maintain the vital functions, avoid and/or help recovery from multiorgan damage, and reduce the surgical risk.

Although there are factors predictive of recovery of specific organs, it is difficult to establish strict selection guidelines. It is reasonable to assume that patients with multiorgan failure (defined as 2 or more organs affected simultaneously in addition to the cardiovascular system with progressive deterioration despite intensive support therapy) do not benefit from heart transplantation, especially in cases with suspicion of sepsis.16B

CHAPTER 3. HEART DONOR

Problem; Expansion of Donor Pool; Suboptimal Donors

The shortage of organ donors is a problem that still needs to be solved. The number of patients awaiting HT has progressively increased in the past 10 years; however, fewer HTs are being carried out because the number of donors has not increased.4 In Spain, 10% of recipients on the waiting list die, and a high percentage will never receive a transplant. Therefore, it is necessary to increase the number of heart donors, possibly with a strategy that optimizes the use of “suboptimal” donors, in 3 areas:

1. Liberalize the selection criteria for heart donors.
2. Optimize donor management.
3. Streamline the donation process.

“Suboptimal” donors are defined as those without some of the following characteristics: a) age <40 years; b) no history of cardiac arrest; c) no active infection or neoplasm; d) no heart disease or cardiac trauma; e) normal LVEF; f) absence or low doses of inotropics (dopamine <10 µg/kg/min); g) ABO compatibility; h) donor/recipient weight quotient <25%, and i) ischemia <4 h.

Screening Criteria for Heart Donors

Age

Age is a continuous risk factor.

Trends in Donor Age in Spain. Status in 2004

Over 10 years in Spain, the mean donor age has increased by 11 years and the percentage of donors younger than 45 years has decreased by 23 points: (www.ont.msc.es/donacion/estadisticas/home.htm).

Impact of Increased Donor Age on Heart Transplantation Outcome. Considerations

– An age threshold for acceptance of the heart donor cannot be established as a single assessment criterion.
– It is an independent predictor of mortality after HT.
– It increases the incidence of GV.
– In individual experiences, there was no impact on early or late mortality with the selected use of donors older than 40.
– Mortality of patients on the waiting list is higher than the increase of in-hospital mortality from using donors older than 40.
– When assessing donors over 40 years of age, recent echocardiography should be mandatory.
– The donor pool should be increased by agreeing on “mandatory” use (by creating alternative or complementary lists) of hearts from donors older than 55 who meet the following: a) echocardiogram without structural involvement or segmental contractility abnormalities; b) projected ischemia time <3 h, and c) moderate doses of inotropics.

Cardiac Function

For an accurate assessment of cardiac function, careful donor management is essential to optimize the hemodynamic status (euvolemic state, with normal postloading and mean blood pressure 260 mm Hg) and

TABLE 9. Variables Associated With Late Recipient Death: Spanish Heart Transplantation Registry 1984-2004

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.012</td>
<td>1.004-1.020</td>
<td>.002</td>
</tr>
<tr>
<td>Kidney failure</td>
<td>1.4</td>
<td>1.2-2.0</td>
<td>.004</td>
</tr>
<tr>
<td>Diabetic mellitus (ID)</td>
<td>1.6</td>
<td>1.2-2.8</td>
<td>.001</td>
</tr>
<tr>
<td>Circulatory support</td>
<td>1.5</td>
<td>1.1-1.9</td>
<td>.006</td>
</tr>
<tr>
<td>CMV (R–/D+)</td>
<td>1.5</td>
<td>1.1-1.8</td>
<td>.003</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval; CMV (R–/D+), recipient not infected and donor infected with cytomegalovirus; HR, hazard ratio; ID, insulin dependent.
to correct respiratory and endocrinologic-metabolic imbalances, with as few requirements as for symptomaticimetics (pulmonary catheter if there are high requirements). No clinical determinant alone should dictate the exclusion of a potential heart donor (older than 55 years, DM, HBP, smoker, alcohol consumption, and/or inhaled cocaine, cerebral hemorrhage, carbon monoxide intoxication).55,56 Electrocardiography is always necessary (to rule out left ventricular hypertrophy, necrosis, and arrhythmias). Cardiac enzyme testing is not mandatory, but should be interpreted along with the other variables.

Inotropic drug requirements (dopamine and dobutamine, >10 µg/kg/min, or norepinephrine) imply greater risk of graft dysfunction, but this fact alone should not exclude donation. When contractile function is normal (LVEF >50%), donation should be considered.

Echocardiography is advisable in all donors and an echocardiogram performed in the last 24 hours is mandatory in suboptimal donors (age >40 years, high inotropic doses, left ventricular hypertrophy on the ECG, or chest trauma). Biventricular function should be analyzed. Contractility abnormalities can be reversible, particularly in young donors, and depend on the hemodynamic status.57,58 Mild left ventricular hypertrophy (<13 mm) does not contraindicate transplantation (more so if ischemia is less than 160 min, without HBP, and without ECG criteria). Mild valve problems or a small ostium secundum are not exclusion criteria. When ventricular dysfunction (LVEF <50%) is documented:

- Perform a new assessment after optimizing the donor’s hemodynamic and metabolic management (recovery protocols), particularly in young donors and those with mild dysfunction.57
- Therapy with insulin, corticosteroids, thyrotropin, and arginine, or arginine vasopressin has been shown to improve cardiac function and decrease the needs for inotropics.57,58
- Contemplate the use of donors with moderate systolic dysfunction (LVEF of 40%-50%), taking into consideration lower donor age, favorable recipient characteristics, and short ischemia time.

Coronary angiography should be performed when there are 2 of the 3 following characteristics: DM, age >45 years in men or >50 in women, and other classic coronary risk factors.

For proper assessment of cardiac function before transplantation, the heart should be adequately examined.

**Immunological Compatibility**

ABO compatibility is a requirement, whereas Rh compatibility is not.

The absence of lymphocytotoxic antibodies in the recipient’s serum is a requirement in the pre-transplantation assessment. More than 10% reactivity in a panel of at least 30 cells requires prospective crossmatch test with recipient’s serum and donor lymphocytes.

Greater HLA mismatch between donor and recipient (2 DR or 4 in all) has been associated with a greater risk of rejection and lower survival.59,60 However, HLA-based prescreening is not possible in practice.

**Ischemia Time**

Optimal ischemia is considered to be <180 min. Prolonged ischemia is considered to be >240 min. One-year survival is similar for optimal and prolonged ischemia, although the long-term (10-year) data are insufficient.61 Ischemia at the limiting threshold is considered to be 300 min, with insufficient clinical data after this point. Therefore, this time should not be exceeded, particularly if there are other risk factors such as advanced age.62,63 Available studies that compare various preservation solutions show differences among them, as well as a lack of consensus regarding their basic composition.64-66 Although extracellular solutions appear to be more effective, total agreement about this does not exist.

Transplants with prolonged ischemia should be considered at risk and myocardial protection should be maximized. There should be no additional donor risk factors (eg, age >40 years, cardiovascular risk factors, high inotropic doses). This is the type of transplant in which new preservation solutions should show short-term and long-term clinical benefits.64,65

**Other Variables**62,65-68

- Donor weight <25% of recipient weight is an added risk factor. Individual management is necessary according to other variables (ischemia time, clinical condition, and recipient PHT). Body mass index (BMI) should be considered in extreme weights.
- Female sex is associated with greater early mortality and, therefore, individual assessment is recommended and the other variables (weight, ischemia time, inotropic doses) should be considered.
- Alcohol and inhaled cocaine abuse is associated with a greater risk of graft dysfunction and coronary artery disease in the case of cocaine. Thus, it is necessary to analyze cardiac function and handle each case individually.
- Carbon monoxide intoxication with carboxyhemoglobin above 20% is an absolute contraindication. Lower figures are acceptable if cardiac function is normal.

The assessment of donor neoplastic and infectious disease must be done using the consensus document to

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Recipient-Based Donor Selection

Donor selection should be integrated with recipient selection. Greater clinical deterioration and higher pulmonary resistances in the recipient determine the need for a greater functional reserve in the heart donor. The risk of primary graft failure is higher with the use of suboptimal donors who show a decreased functional reserve (elevated inotropic requirements or contractility abnormalities on echocardiography). Donor age and ischemia time are important in this situation.

TABLA 10. Future Outlook. New Allocation Criteria for Heart Donors

The current status is controversial and requires analysis.

Three possible exclusive general models:
- Maintain current model
- Proposal 1: “Offer to recipient”
- Proposal 2: “Modification of areas”

Creation of “Complementary Lists”:
- Older donor/older recipient
- Suboptimal donor/recipient at limit

Modification of Emergency 0 (pediatric transplantation)

Proposal 1: “Offer to recipient”:
- Single national list per blood group
- Emergencies and source hospital have priority
- Allocation is by weight and time listed
- Advantage: fairer, more equitable
- Problems: more travel, more ischemia, higher costs, no adherence to autonomous community organization of health care

Proposal 2: “Modification of allocation areas”:
- Maintain current emergency criteria, and local, and community donation
- Areas established as concentric 100-km circles around donation point
- Geographic proximity, time, and money savings considered priorities; short ischemia is facilitated

Proposal 2: Example of “allocation areas”:

<table>
<thead>
<tr>
<th>Zone I</th>
<th>Zone II</th>
<th>Zone III</th>
<th>Zone IV</th>
<th>Zone V</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Coruña</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Navarra,</td>
</tr>
<tr>
<td>Albacete</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Madrid, Navarra</td>
</tr>
<tr>
<td>La Rioja</td>
<td>Navarra</td>
<td>Zaragoza, Valladolid</td>
<td>Asturias, Madrid</td>
<td>Barcelona, Zaragoza, Murcia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zaragoza, Valladolid, Cantabria</td>
<td>Asturias, Madrid</td>
<td>Valencia, A Coruña</td>
</tr>
</tbody>
</table>

Creation of complementary lists:
- National lists
- Not considered Emergency 0:
  1. Older donor (55 years or older) with priority for older recipient (65 years or older)
  2. Suboptimal donor not accepted in general turn, for recipient at limit (at least 3 relative contraindications)

Modification of Emergency 0 (pediatric transplantation):
Grades:
Grade I: emergency retransplantation (unchanged)
Grade II: ventricular assist (unchanged)
Grade II:
- Pediatric patient with IABC, induced hypothermia (<34°C), intubation, or amines
- Adult with IABC (unchanged)
Grade IV: intubated adult with amines (unchanged)

*aIABC indicates intra-aortic balloon counterpulsation.*
Future Outlook

The current status of donation in Spain is controversial and requires an in-depth analysis. There was considerable debate about organ distribution, and various proposals for improvement that should be defined in the future were made. Table 10 contains some of the ideas discussed. Figure 1 contains a summary of the recommendations of the Donor Working Group.

CHAPTER 4. CARDIAC ALLOGRAFT REJECTION

Rejection can be understood as the result of the recipient’s immune response to the allograft. The target cells of the transplanted heart include myocytes and coronary vessel endothelial cells, which form the interface between the recipient’s immune system and the transplanted heart.

Pathology of Rejection. Endomyocardial Biopsy

Sample Acquisition and Processing

During endomyocardial biopsy (EMB), the bioptome should be used to obtain at least 4 pieces of myocardium, measuring 3-4 mm each.69,70 These should be sent to the laboratory for analysis, even those which seem fatty and clotted. Each piece should consist of at least 50% myocardium, otherwise the sample is considered substandard.69-71 It is inappropriate to submerge the tissue in physiological saline solution, which produces artifacts in the cells, or to leave the tissue on gauze or filter paper. The usual diagnostic method of choice is optical microscopy (OM). However, special methods can also be of help, such as immunofluorescence staining.

Optical Microscopy

Immediately after acquisition, the tissue is submerged in 10% phosphate-buffered formalin at

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**Figure 1. Summary of Donor Working Group Recommendations**

1. Increase the use of suboptimal donors:
   - No clinical variable alone should determine the exclusion of a potential heart donor
   - Previous echocardiogram and inspection at removal are the most effective methods for assessment
   - A recent echocardiogram is mandatory when age >40 years, high inotropic doses, left ventricular hypertrophy on electrocardiographic, noninvasive cocaine abuse, severe chest trauma, cyanide intoxication, or carbon monoxide with carboxyhemoglobin >20%
   - Enhance donor hemodynamic and hormonal optimization (to decrease catecholamines)
   - Decrease ischemia time by modifying donor distribution according to proposal 2
   - Exceed 240 min of ischemia if the donor is optimal and prioritize myocardial preservation
   - Use of donors with weight <25% or female sex in situations of low allograft ischemia time or recipient without pulmonary hypertension

2. Donor/recipient pool redistribution:
   - Regulated use of older donor (age ≥55 years)
   - Rational use of donors for recipient “at limit”

Creation of national complementary list:
   - Older recipient (age ≥65 years) or “at limit” (at least 3 criteria)
   - No possibility of Emergency 0
   - Exclusively for use in older donor (age ≥65 years)
   - Donor not accepted in general turn
   - Allotment to recipient according to time listed
   - Without acceptance, the turn is not passed
room temperature and taken to the laboratory. Following standard procedures, the tissue samples are embedded in paraffin blocks from which multiple 4-µm sections are taken. Several sections are cut to at least 3 depths, placed on 3 slides, and stained with hematoxylin-eosin (1 with Masson trichrome). If needed, the paraffin-embedded tissue may be analyzed using immunoperoxidase techniques with specific antibodies and PCR to detect opportunistic infections.

**Immunofluorescence**

A fresh sample is set aside in gauze soaked in physiological saline solution, packed in ice and immediately sent to the laboratory. It is frozen in Optimal Cutting Temperature compound (OCT) or isopentane at –20°C. The frozen capsule is submerged in liquid nitrogen and can be stored at –70°C for a long period. This technique is not commonly used, but is sometimes included in some protocols. Most centers only perform immunofluorescence assay when there is clinical suspicion of antibody-mediated rejection and EMB indicates low-grade cellular rejection. Concentrations of IgG, IgM, IgA, C4, and C3 are determined. Currently, C4d and C3d can be determined by immunofluorescence and immunoperoxidase techniques.

With the aim of classifying and simplifying the anatomopathological changes that should be assessed by EMB, the Working Formulation (WF) of the International Society for Heart and Lung Transplantation (ISHLT) drafted some recommendations in 1990 that have guided the scientific community for many years. These guidelines were reviewed in 2004, and some changes were made, mainly to the nomenclature of the grades of rejection (Table 11). The aim was to simplify some diagnostic difficulties of clinical relevance, especially the interpretation of grade 2 rejection, the differentiation between Quilty B lesions and autoimmune lymphoproliferative syndrome, and infection with rejection and lymphoproliferative syndrome. An attempt was also made to classify antibody-mediated rejection (previously called humoral rejection). (Table 12).

### Biopsy Interpretation and Associated Problems

According to the WF, 3 pieces of myocardium are sufficient to detect rejection. Despite this, EMB provides

#### TABLE 11. Classification of Acute Cellular Rejection

<table>
<thead>
<tr>
<th>1990</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>No rejection. Myocardium without lesions</td>
</tr>
<tr>
<td>Grade 1A</td>
<td>Mild focal rejection. Focal lymphocytic infiltrate (perivascular or interstitial) without myocytolysis, in 1 or more parts</td>
</tr>
<tr>
<td>Grade 1B</td>
<td>Moderate focal rejection. Mild diffuse scattered lymphocytic infiltrate without myocytolysis, in 1 or more parts</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Moderate multi focal rejection. Aggressive infiltrate with myocytolysis or distortion of the myocardium. Eosinophils may be present. Normal myocardium between infiltrates</td>
</tr>
<tr>
<td>Grade 3A</td>
<td>Moderate multi focal rejection. Aggressive infiltrates with multifocal myocytolysis in 1 or more parts. Polymorphonuclear neutrophils, eosinophils, and hemorrhage may be present.</td>
</tr>
<tr>
<td>Grade 3B</td>
<td>Severe rejection. Diffuse aggressive inflammation with myocytolysis, endothe litis and vasculitis, hemorrhage, polymorphonuclear neutrophils, and eosinophils</td>
</tr>
</tbody>
</table>

#### TABLE 12. Classification of Antibody-Mediated Rejection

<table>
<thead>
<tr>
<th>1990</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>No signs of humoral rejection</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Absence of cellular infiltrate with positive immunofluorescence, vasculitis, or severe edema</td>
</tr>
</tbody>
</table>

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less information than expected on 2%-15% of clinical rejection episodes.

Some morphological changes can interfere with, and thus block, correct interpretation. These may be due to the procedure (contraction bands in myocytes, distortion due to biotome jaws, vessel invagination, and hemorrhages), to sampling errors (lesions and previous biopsy site, fat, pericardial and mesothelial tissue—indicating perforation—and chordae tendineae) or to uncertain factors (ischemia, necrosis due to vasopressors, edema, internal changes in myocytes, infections, lymphoproliferative processes, myocyte calcification, etc.).75

**Hyperacute Rejection**

Hyperacute rejection is not usually diagnosed by EMB, since its severity and fulminant clinical course prevent this from being performed. Its pathology is known mainly via experimental models and rarely via autopsy. The heart may be hemorrhagic or pale and, edematous. Histological analysis shows massive hemorrhage, margination of polymorphonuclear intravascular leukocytes and microthrombi in the vessels.

**Acute Cellular Rejection**

Under OM, this manifests as inflammatory infiltration, either focal or diffuse, made up of mononuclear cells (predominantly lymphocytes), with or without concomitant damage or myocardial necrosis. The ISHLT classification of histological severity of rejection is shown in Table 11.

**Acute Antibody-Mediated or Humoral Rejection**

The diagnosis of acute antibody-mediated rejection (AMR) remains a matter of controversy and there is no consensus on its definition or histological diagnosis76; as a result, its incidence is difficult to estimate. Diagnosis is generally based on histological features of injury in the myocardial capillaries and the detection of immunoglobulins and/or complement activation on small-vessel walls using immunofluorescence techniques in fresh frozen tissue or by immunohistochemical techniques.

There are few morphological manifestations in the initial stages and these are characterized by mild changes in interstitial cellular cells and myocytes. Hemorrhage and edema are common, but are difficult to assess as they can be caused by several artifacts. When the inflammatory process is already evident, vasculitis with polymorphonuclear leukocytes and macrophages is visualized under OM. Table 12 shows the ISHLT consensus criteria for the diagnosis of AMR.

Clinical suspicion is diagnosed by graft dysfunction without evidence of significant cellular rejection at biopsy.69,73,75

**Other Biopsy Findings**

The 2004 ISHLT Working Formulation system recommends paying particular attention to specific biopsy findings unrelated to rejection: ischemic alterations, Quilty effect, infections, and lymphoproliferative processes.

**Ischemic Alterations**

Early ischemic alterations are characterized by bands of necrosis with coagulation, vacuolization, and fatty necrosis of the myocytes. They frequently extend to the surface of the endocardium. They may be confused with rejection, but here inflammatory infiltration is proportionately greater than the degree of myocyte damage.75 Late ischemic alterations are related to graft vascular disease. These affect the microvasculatization due to myocyte vacuolization which causes microinfarctions. This situation should be considered the prelude to disease in larger vessels and may help to explain the etiology of late graft failure.75

**Quilty Effect**

This is characterized by lymphocyte infiltration in the endocardium. This consists of T and B lymphocytes and can also include plasma cells and macrophages. Infiltration may be limited to the endocardium (Quilty A) or extend to the subendocardium (Quilty B), although this is devoid of clinical meaning. It can sometimes resemble a focus of aggressive infiltration, due to tangential sectioning, and may be confused with acute rejection. In these cases, the guidelines suggest making successive sections until the relationship with the endocardium is clarified. It may be useful to demonstrate the presence of B and T lymphocytes using immunoperoxidase staining, because in rejection there are mainly T lymphocytes and in Quilty effect a significative percentage of B lymphocytes are also present. No relationship to viruses, lymphomas, rejection, or the type of treatment has been demonstrated. Although it has been considered an ambiguous form of rejection, this association remains unclarified. The Quilty effect tends to simply disappear, although it sometimes persists for weeks.75,76

**Infectious Myocarditis**

The myocardium may become inflamed due to infection that can be diagnosed at EMB. The inflammatory infiltrate found in infectious myocarditis can be difficult to distinguish from that found in acute rejection. The former infiltrate tends to be more polymorphic, with plasma cells and eosinophils, unlike that found in rejection which is usually monomorphic.
If the level of necrosis is higher than expected and the infiltrate is polymorphic, a diagnosis of myocarditis should be considered. Infection by cytomegalovirus (CMV) causes cytopathic changes and characteristic intranuclear inclusions. Although they are found in the myocardium, this is rare, and it is easier to find them in other tissues (gastrointestinal, lung).

Toxoplasma gondii cysts may be found. Whole cysts may occasionally be found or broken cysts with inflammation. In any case, infiltrates together with a cyst are rarely observed. Whole Toxoplasma gondii cysts without inflammation can come from the donor heart in areas where this is endemic. Chagas’ disease can also be diagnosed at EMB, which can recur in patients undergoing transplantation due to Chagas’ cardiomyopathy or when this is acquired with the donor organ.

Other cardiomyopathies can recur after transplantation and be found at biopsy: giant cell myocarditis, sarcoidosis, and amyloidosis.7,95

Malignant Neoplasms and Lymphoproliferative Processes After Transplantation

The lymphoproliferative processes following transplantation may include a set of different lymphoid infiltrates, usually B lymphocytes, and several associated with Epstein-Barr virus. The lymphocytes range from small, differentiated and polyclonal lymphocytes to large atypical, monoclonal, and very aggressive cells, identical to nodal lymphomas.91

Diagnosis of Acute Rejection

Clinical Manifestations

Given current immunosuppression regimes, most rejections are asymptomatic and diagnosis is usually made at surveillance EMB. In some cases, there may be associated nonspecific signs of heart failure, such as dyspnea, asthenia, or edema. If these symptoms appear early, they can be difficult to distinguish from the postoperative symptoms themselves, anemia, the side effects of immunosuppressive medication, or a combination of these factors. In any case, the appearance of these symptoms, whether accompanied by clinical signs of heart failure or not, mean that an echocardiogram and/or biopsy must be conducted to rule out possible rejection. (Class I recommendation. Level of evidence: C.)

The prognosis and severity of rejection are directly correlated with the intensity of symptoms and with the grade of heart failure and graft dysfunction. It is essential to distinguish the concept of “anatomopathological rejection,” discovered by chance at protocol biopsy, from “clinical rejection,” with signs and/or symptoms of graft dysfunction (whether confirmed by biopsy or not), since 2 different entities are involved, with radically different evolution and prognosis. Unfortunately, the intensity (grade) of rejection at EMB has very little correlation with the clinical severity of rejection. Patients frequently present severe hemodynamic compromise secondary to rejection, whereas the biopsy may only indicate grade 1-2 rejection, or even the absence of pathological rejection.
Nor is it unusual to find grade 4 rejection in the context of an asymptomatic patient and with normal graft function. Thus, clinical decisions on the intensity and speed of treatment should be based on the clinical situation of the patient, hemodynamic data, and systolic graft function. (Class I recommendation. Level of evidence: C.) Table 13 shows how rejection is treated. Even if empirical treatment of rejection with severe hemodynamic compromise is already underway, performing a control biopsy is still recommended. (Class I recommendation. Level of evidence: C.)

**Endomyocardial Biopsy**

Biopsies have traditionally been considered the only reliable method for the early detection of rejection following heart transplantation, and has been universally accepted almost from the time the transvenous technique was described in 1974. The strategy generally followed is an EMB protocol conducted at predetermined intervals, regardless of the patient's clinical situation, based on the idea that the early diagnosis of rejection using this technique would make it possible to begin treatment before graft dysfunction occurs. Given that the incidence of rejection decreases with time, usually occurring in the first months after transplantation, and is infrequent after the first year, some EMB protocols have been designed which take this into account.

Although the concept of following up rejection after heart transplantation using an EMB-mediated protocol seems clear, the sensitivity and specificity of EMB is not known precisely. There are histological rejection episodes that resolve spontaneously and clinical rejection episodes, ie, graft dysfunction and hemodynamic compromise with normal biopsy or low-grade rejection. Furthermore, the patients with severe rejection and hemodynamic compromise who present low-grade rejection at biopsy seem to have worse evolution than those with more severe grades of rejection at biopsy. Finally, the aim of performing serial biopsies is not always achieved (the prevention of advanced rejection), because the incidence of severe rejection with hemodynamic compromise is 5% of all rejections and ranges from 10% to 15% of all patients.

In any case, although the sensitivity and specificity of EMB are not known with any degree of accuracy, it is the technique of choice for diagnosing and treating rejection. (Class I recommendation. Level of evidence: C.)

**Biopsy Techniques**

Biopsies are normally performed via the right internal jugular vein or deep femoral vein. An specific bioptome is advanced to the apex and septum of the right ventricle. Although fluoroscopy is usually sufficient to orientate the bioptome, echocardiography can also be used.

**Complications of Endomyocardial Biopsy**

The incidence of complications is relatively low but they are often severe. In a series of 3331 biopsies, the percentage of complications was 0.5%. Early complications may include: pelvic hemorrhage (femoral route), superior vena cava dissection (jugular route), perforation of the right ventricle with tamponade, vagal reactions, arrhythmias, and deep vein thrombosis with the risk of pulmonary thromboembolism. A significant complication is the late appearance of severe tricuspid valve regurgitation due to chordae tendinae rupture during the procedure. The prevalence of rupture has been estimated at almost 12% and with surgical indications at 7%.

**Echocardiography**

Echocardiography plays an important role in monitoring, diagnosis, and treatment of rejection. Similar to EMB, its sensitivity and specificity are unknown. However, from a practical standpoint, it can be assumed with reasonable certainty that an asymptomatic patient with good systolic graft function as indicated by echocardiography is not undergoing significant clinical rejection, at that time. In contrast, a patient who develops acute clinical heart failure and general graft dysfunction is undergoing severe rejection with a high degree of probability. The speed and availability of echocardiography are very useful in these cases.

Furthermore, echocardiography has a set of characteristics (availability, simplicity, is non-invasive, provides general information on the graft), that make it indispensable in following up graft function in allograft recipients. (Class I recommendation. Level of evidence: C.)

Rejection with hemodynamic compromise has been reported where the biopsy was negative or only detected “light” anatomicopathological rejection in up to 35% of the patients. In these cases, systolic dysfunction detected via echocardiography can establish the severity of rejection and, thus, the correct response is to initiate rejection treatment without delay and without waiting for the biopsy results. Even if EMB does not indicate rejection the patient should be treated, given the risk of a false negative result.

Thus, echocardiography plays an essential role in the diagnosis and treatment of rejection with hemodynamic compromise. (Class I recommendation. Level of evidence: C.) A possible application of echocardiography in monitoring rejection is to replace the EMB protocol with serial echocardiographic studies; there are some reports in this regard. In the “extreme” cases mentioned (general acute graft dysfunction or absolute normal systolic function), clinical decisions could be made...
without the need to perform a biopsy, whereas EMB would be performed in the intermediate or “doubtful” cases.93

Thus, echocardiography provides reliable information on systolic and diastolic function, and makes it possible, in an appropriate clinical context, to reduce the number of biopsies. (Class IIA recommendation. Level of evidence: C.)

Other Non-Invasive Methods

Numerous non-invasive techniques to detect rejection have been studied with the aim of avoiding the drawbacks and costs of biopsy.94 Intracardiac electrogram monitoring after pacemaker implantation, cytoimmunological monitoring, radionuclide imaging, and magnetic resonance imaging have been used with variable results, although these have not generally been used to replace or reduce the number of biopsies performed in daily clinical practice. Echocardiographic techniques based on Doppler ultrasound have been assessed in nearly all their modalities.95-97 Although the results correlate with those obtained from simultaneous biopsies to varying degrees, they are not normally used in daily clinical practice. The general impression is that these techniques are too sensitive to detect the various parameters of diastolic function and can be easily modified by the varied hemodynamic changes often occurring in the allograft recipient (retention of liquids, arterial hypertension, restrictive pattern, etc.), which means that in practice, they cannot be used to discriminate between these and rejection.

Thus, multiple methods are available for diagnosing rejection. They tend to be labor-intensive, somewhat impractical and with rather low sensitivity and/or specificity. (Class III recommendation. Level of evidence: B.)

Future Prospects

Gene expression has recently been studied for diagnosing rejection. In this regard, a non-invasive method for monitoring the immune response has already been developed for diagnosing cardiac rejection based on gene expression profiling in peripheral blood mononuclear cells (AlloMAP® testing, XDx Inc., San Francisco, U.S.A.). The great advantage is that by means of a peripheral blood sample the risk of rejection and tissue damage can be identified before this occurs, thus reducing the number of EMBs and making it possible to optimally adjust the immunosuppressive medication, with the obvious advantages of reducing the risks involved with these drugs, at a lower economic cost and with improvements in the quality of life due to fewer biopsies.94,95 The Cardiac Allograft Rejection Gene Expression Observational Study (CARGO)96 designed and validated a test for the AlloMAP® in a large-scale, multicenter, prospective study, and found that its main usefulness lies in its high negative predictive value to rule out rejection in patients 6 months post-transplantation. More studies are underway that will clarify whether these methods are of real use when following up allograft recipients.

Risk Factors and the Natural History of Time-Related Rejection

Time Up to First Rejection

The risk of acute cellular rejection decreases with time after heart transplantation.97 Thus, risk is high in the first month after transplantation and decreases over the following months, such that it rarely occurs after 6 months. (Class I recommendation. Level of evidence: B.)

Its occurrence after 1 year is exceptional and is often due to late changes in immunosuppression.98 (Class I recommendation. Level of evidence: C.)

We can assume that half of the clinically significant rejections, that is, those which lead to therapeutic action, occur during the first month and almost all the remaining rejections occur in the following 6 months.

This is a well-established temporal sequence and is the reason why immunosuppressive therapy is initially intense and then later decreased. Similarly, EMB should be more frequent the nearer the time of transplantation, but perhaps is less justified after 1 year unless there is reasonable clinical suspicion of rejection or substantial changes in the immunosuppressive regimen.

The usefulness of EMB during the first week post-transplantation is questionable if the clinical data does not support this. Immediately after transplantation there may be histological alterations that are not caused by rejection, but by injury due to the protection process, which are characterized by disproportionate necrosis in the context of the inflammatory cellular process. These alterations are at their peak in the first week after transplantation.99 Particular strategic problems may still be involved in conducting EMB during this period if the patient remains heavily instrumented.

The consensus EMB schedule in Spain is outlined below.

Elective EMB Schedule


Various circumstances can modify the proposed schedule, mainly due to the frequency and severity
of rejection, changes in immunosuppression, or comorbidities.

**Guidelines for Endomyocardial Biopsies in Cardiac Transplantation**

The following guidelines are proposed for biopsy after cardiac transplantation:
- Programmed biopsies in the first 12 months post-transplantation.
- Clinical suspicion of rejection.
- Monitoring effectiveness of treatment after an acute rejection.  
  (Class I recommendation. Level of evidence: C.)
- Monitoring after corticosteroid therapy.
- Monitoring after concomitant treatment that may have modified the pharmacokinetics of the immunosuppressive drugs and, thus, the degree of immunosuppression in the patient.  
  (Class IIa recommendation. Level of evidence: C.)
- Systematic monitoring in asymptomatic patients 1 year after transplantation.  
  (Class III recommendation. Level of evidence: C.)

**Repeat Rejection**

If a rejection episode has already occurred, a useful method to predict recurrent rejection is to assess the probability of another occurring as a function of time. During the first year after transplantation, approximately 25% of patients will have a new rejection episode in the month following the previous episode. The risk of a new rejection episode peaks at 2 weeks after the previous episode and rapidly decreases after the first month. The risk of recurrent rejection is much lower after the first year following transplantation.97

**Types of High-Risk Rejection**

**Hyperacute Rejection**

This type of rejection carries the greatest risk. It occurs in the first minutes or hours after reestablishing blood flow after transplantation. It may be due to preformed donor-specific anti-HLA antibodies, anti-ABO antibodies (due to blood group incompatibility), or anti-endothelial cell antibodies.104 This form of rejection is rare but severe (often fatal), since the preformed antibodies combine with endothelial antigens in the transplanted heart, with consequent complement activation, acute inflammatory infiltration, and, finally, fibrinoid necrosis of the vessels in the transplanted organ.104 (Level of evidence C.)

**Grade 3R Rejection at Biopsy**

This grade of histological rejection (previous ISHLT grades 3-B and 4) is very aggressive. Fortunately, it is rarely observed in clinical practice. Its incidence, including 3A rejections, fluctuates around 3% of all biopsies.105 In those cases where resolution is not rapid, prognosis considerably worsens. (Level of evidence C.)

**Vasculitis and Evidence of Antibody-Mediated Rejection at Biopsy**

Typical microvascular rejection includes findings of vasculitis (transmural infiltration of lymphocytes and monocytes, with or without neutrophils) at EMB, which often shows elements of cellular rejection. Acute antibody-mediated rejection (humoral) can occur from days to weeks after heart transplantation, although it can also appear in the long-term72 and is initiated by donor-specific anti-HLA antibodies or anti-endothelial cell antibodies.106 This type of rejection is less frequent than cellular rejection and occurs in 10%-20% of the patients.107 Its importance lies in its frequent association with severely depressed ventricular systolic function, probably caused by diffuse ischemia secondary to the loss of coronary vasodilator reserve. Furthermore, although the incidence of cellular rejection seems to have decreased over time due to the new immunosuppressives, humoral rejection remains at the same level.108 The patients at greater risk of AMR include: women, patients undergoing retransplantation, patients with high reactivity to the panel of antibodies or positive cross-match, recipients with positive CMV serology, and OKT3-sensitized recipients.109 In addition to intravenous steroids, treatment for this type of rejection includes therapies designed to minimize antibody concentrations, such as serial plasmapheresis.72,116 Other drugs such as rituximab have recently been proposed,117,118 although there is limited experience. (Level of evidence C.)
**Rejection with Hemodynamic Compromise**

Hemodynamic compromise is observed (clinical signs of low cardiac output, reduced ejection fraction and need for inotropic agents) in approximately 5% of rejection episodes. Its incidence does not seem to vary significantly from the time of transplantation onward.44

The mechanism by which depressed systolic function occurs is not clearly defined, although experimental studies indicate that interleukin (IL)-1, IL-2 and tumor necrosis factor may play a role in graft dysfunction during rejection.50,54,113,114

This type of rejection has been associated with female sex, black recipients, recipient with diabetes mellitus, older donors, black donors, and donors with diabetes mellitus.84 (Level of evidence C.)

Mortality is high after rejection with severe compromise (30% at 1 month and 50% at 12 months following the episode).84 Fifty percent of such cases involve acute cellular rejection (biopsy ≥3A); early mortality is common in these patients, but if this does not occur, prognosis is good and ventricular function is completely recovered. The other 50% involve humoral rejection (biopsy ≤2), with worse prognosis, especially in the medium term, and incomplete or late recovery of ventricular function.84,115 (Level of evidence C.)

**CHAPTER 5. IMMUNOSUPPRESSION**

**Induction Treatment in Heart Transplantation**

Despite the broad experience of induction treatment (IT) in HT, the preventive, early application of this cytolytic treatment remains controversial. Estimates put the number of HT patients receiving IT at more than one in three, with a trend towards less frequent use due to the potential risk of increased infections, tumors and cytokine release syndrome.41,110,113 Large-scale, controlled, prospective clinical trials that would facilitate the inference of definitive results on the use of IT have yet to be conducted. All conclusions have been drawn from retrospective analysis of databases. According to the ISHLT (2005) registry, 47% of HT centers do not use induction of any kind.108

**Induction in Heart Transplantation? A Good Question**

The following treatments have been used: Muromonab-CD3 (OKT3), antithymocyte globulin (ATG), antilymphocyte globulin (ALG), antithymocyte serum (ATS), and more recently, IL-2 receptor blockers.

Efficacy is determined from incidence of acute myocardial rejection, infections and tumors, and overall survival. Acute myocardial rejection remains a substantial cause of early death post-HT. The use of IT reduces incidence of acute myocardial rejection and, consequently, reduces the number of deaths from rejection. This is more marked in younger patients. Induction treatment has been seen to negatively influence on overall survival in populations with little risk of rejection, possibly due to the increase in deaths from infection.115

Centers usually decide to use IT because of clinical preferences or established protocols. When these do not exist, IT is indicated in situations of kidney failure in order to delay administering calcineurine inhibitors (CNI). In general, and according to the consensus meeting, 90% of participants consider that IT must be individualized to suit patient characteristics. (Class IIa recommendation. Level of evidence C for use of IT.)

**Comparative Analysis of Approaches to Induction Treatment**

The use of IL-2 receptor blockers adds a new concept to IT. They have no direct cytolytic effect, which adds undoubted advantages in perioperative clinical management. Two IL-2 receptor CD25 chain antibodies are currently administered: daclizumab and basiliximab. Daclizumab is a humanized monoclonal antibody that, added to conventional triple therapy with cyclosporin A (CsA), mycophenolate mofetil (MMF), and prednisone, has demonstrated its efficacy in reducing acute rejection in a 3-month follow-up in short series.123-124 (Class IIa recommendation. Level of evidence B for IT with daclizumab.)

Basiliximab is a (human/murine) chimeric monoclonal antibody that specifically links to the IL-2 α chain (CD25).125-127 It is administered twice using 20 mg doses, on days 0 and 4 post-HT. A controlled study of Spanish groups has shown its efficacy in acute rejection.124 Basiliximab is safe and better tolerated than OKT3 in combination with CsA, MMF, and prednisone. By comparison with OKT3, administration does not lead to lymphocyte release syndrome. The infection rate is low. One-year survival of patients receiving basiliximab was 94%, although the population size was not designed for this purpose. (Class IIa recommendation. Level of evidence B for IT with basiliximab.)

Despite recent studies, IT continues to be empirical, but a marked tendency exists towards abandoning classical cytolytic therapy in favor of IL-2 receptor blockers (anti-CD25 antibodies) due to their greater tolerability, derived from their safety, efficacy, and the absence of cytokine release syndrome. Induction therapy
Calcineurine Inhibitors in Heart Transplantation

The calcineurine inhibitors CsA and tacrolimus (Tac) are used post-HT in combination with antiproliferative agents and steroids. Specifically and irreversibly, CNI inhibit the early phase of T-cell activation. Their greatest limitation is the adverse effects that depend on its plasmatic concentrations. The drug of reference post-HT has been CsA. The original oil-based (standard) formula was later replaced by a new microemulsion formula (Neoral). Classical CsA monitoring was by analyzing valley values (C0). However, the best predictor of total exposure currently seems to be measuring concentrations 2 h after dose administration (C2). Although several methods of determining drug concentrations exist, use of a single method is recommended (TDx). At the time of writing, the MOTOWN study is soon to be published. The authors have studied 3 different C2 intervals in the first 6 months post-HT. Currently, most Spanish heart transplant centers (80%) do not systematically determine C2, principally due to problems of hospital logistics.

Tacrolimus was introduced in HT in the late 1990s and has progressively been incorporated as a CNI in place of CsA, especially in patients with CsA intolerance or as a rescue rejection therapy. (Class I recommendation. Level of evidence B.)

Two randomized, multicenter studies, 1 in Europe and another in the US, compared the formula of standard oil-based CsA with Tac in association with azatioprine and steroids. The 2 CNI proved equally effective at preventing rejection and death at 1 year post-transplant. (Class I recommendation. Level of evidence A for use of CsA or Tac in patients with de novo HT.)

However, lower incidence of hypertension and hyperlipidemia has been found with Tac than with CsA. A multicenter, 18-month follow-up study of Tac versus microemulsion CsA (Neoral) combined with azathioprine and steroids showed Tac was better at preventing rejection (central biopsy assessment), with no difference in survival. Incidence of HTA and dyslipidemia was lower in patients assigned to Tac and incidence of DM was lower in those assigned to CsA. Currently, a European multicenter study (PANEUHTX) is comparing CsA Neoral and Tac in combination with MMF and steroids. As well as efficacy in preventing acute rejection, they will determine efficacy in preventing graft vascular disease (GVD) (determined by IVUS). Results will help clarify which of these 2 CNI is better in regimens with MMF.

Recently, hopes for immunosuppression of HT have been raised by the combination of CNI and proliferation signal inhibitors (PSI) (sirolimus and everolimus). A large, randomized, multicenter study of CsA in combination with everolimus and steroids has shown its greater efficacy than the combination with azathioprine and steroids in reducing both cellular rejection and GVD incidence and progression. However, the combination of everolimus and CsA associates with greater incidence of kidney failure, possibly due to ignorance as to the true exposure to CsA when administered in these combinations. Similar benefits were observed in another multicenter study comparing CsA+sirolimus and steroids with CsA, azathioprine and steroids for rejection and GVD, together with a worsening of renal profile. (Class IIa recommendation. Level of evidence A for the combined use of mTOR-inh or PSI with CsA vs a combination of CsA with Azathioprine.)

Antiproliferative Agents: Mycophenolate Mofetil, Sodium Mycophenolate, and Azathioprine

Azathioprine (AZA) was the first antiproliferative immunosuppressors used in solid organ transplants and facilitated reduced rejection rates when in combination with corticoids and, later, in triple therapy with CsA, until the appearance of MMF. Use of MMF, a potent antiproliferative agent, has grown following publication of the first double-blind, randomized, multicenter trial with MMF or AZA. This study reported a significant reduction in 1-year mortality in patients administered MMF, reduced need for rejection treatment and increased incidence of opportunistic infections. (Class I recommendation. Level of evidence B for use of MMF with CNI and steroids in patients with de novo HT vs use of CNI+Azathioprine and steroids.)

In the HT maintenance phase, replacement of AZA by MMF also demonstrated MMF achieved a greater reduction in the number of rejections needing treatment. The greater immunosuppressive potency of MMF versus AZA has led to a reduction in CNI dosage in patients with HT and kidney failure, achieving improved kidney function parameters (creatinine and creatinine clearance). The value of monitoring mycophenolic acid to control the efficacy and adverse effects of MMF is still controversial. (Class IIb recommendation. Level of evidence C.)

The value of monitoring mycophenolic acid to control the efficacy and adverse effects of MMF is still controversial. (Class IIb recommendation. Level of evidence C.)

Following initial studies, MMF was found to have a protective role with respect to AZA regarding IVUS-diagnosed GVD (Class IIa recommendation. Level of evidence C.)

Recent studies have reported on sodium mycophenolate, a new antiproliferative with a profile for efficacy and safety similar to MMF.
Evidence on the Use of Corticoids in Heart Transplantation

Corticoids have many secondary effects that can prejudice quality of life, morbidity, and progression of GVD. They continue to be part of all immunosuppression regimens in de novo HT although the trend is towards withdrawing them as early as possible. However, few publications report on the safety and efficacy of this strategy. Studies do show that, in the acute phase of HT, triple therapy (CsA, AZA, and corticoids) is more efficient than double therapy (CsA and AZA) at preventing fatal rejection. Keogh et al randomized 112 patients with HT to double or triple therapy and found that actuarial survival and systolic function were similar in both groups, as was the proportion of secondary effects. However, incidence of rejection at 3 months was inferior in the group receiving triple therapy. Among patients with double therapy, 47% were converted to triple therapy due to persistent rejection or kidney failure. (Class I recommendation. Level of evidence B for use of steroids in patients with de novo HT.)

After the appearance of potent immunosuppressive drugs like CsA and in order to minimize the secondary effects of corticoids, progressive reduction and/or withdrawal of these in the maintenance phase of HT has been promoted, with disquieting results. The clinical benefits of steroid withdrawal are especially important in patients at low risk of rejection and with at least 1 of the following conditions: DM, osteoporosis, obesity, and repeated infections. However, a potential risk of rejection exists and the risk/benefit of this strategy is not well known. In fact, according to the ISHLT registry, more than 60% of long-term patients receive steroids. (Class IIb recommendation. Level of evidence B for progressive reduction and/or withdrawal of steroids in the maintenance phase.)

mTOR Inhibitors in Heart Transplantation

Also known as proliferation signal inhibitors (PSI), mTOR inhibitors (mTOR-inh) like everolimus and sirolimus, act on the proliferation of T- and B-lymphocytes and vascular smooth muscle cells in a late phase of the cellular cycle. Both drugs have been shown to reduce episodes of acute rejection in de novo patients treated with CsA and steroids versus AZA at the risk of worsening kidney function and with no differences in survival. (Class IIa recommendation. Level of evidence A.) To date, comparison of mTOR-inh+CNI versus mTOR-inh+MMF has not been reported.

Everolimus and sirolimus have shown a protective effect on the development of IVUS-determined GVD at 1 year, and at 2 years post-HT for everolimus (Class IIa recommendation. Level of evidence A.) In human and animal experimental models, the use of these drugs has been shown to have a beneficial effect on GVD. Evidence for this has facilitated the current authorization of everolimus for use in HT. However, less is known about the effect of these drugs on established GVD. In 1 study, the long-term introduction of sirolimus seems to help slow the progression of established GVD. In Spain, RAPASTAT analyzed chronic patients with IVUS-diagnosed GVD, finding that the change to sirolimus with low-dose CsA and steroids versus CsA with AZA or MMF and steroids, led to a significant reduction in coronary lesion size. (Class IIa recommendation. Level of evidence C on conversion to mTOR-inh drugs in patients with established GVD.)

Management of secondary effects of mTOR-inh is not well-defined. One severe complication is pulmonary infection in the form of interstitial pneumonitis. Less serious infections include hypertiglycericemia, which responds well to statins, hematopoietic alterations (especially thrombocytopenia), edemas, bacterial infections, skin disorders, delayed healing of wounds, oral ulcers, and diarrhea.

Due to its improved nephrologic profile, mTOR-inh is a strong contender as an alternative to CNI, whether as a replacement or associated with very low doses in patients with kidney failure. Conversion studies have shown its greater benefit when administered to patients with non-advanced stages of kidney failure parameters. (Class IIa recommendation. Level of evidence B.) In several experimental studies, like sirolimus and everolimus, mTOR-inh has shown an antineoplastic effect. Based on this clinical and experimental evidence, several HT centers convert to mTOR-inh in patients with specific neoplasias, given the adversity of their prognosis. (Class IIa recommendation. Level of evidence C.)

Immunosuppression Strategies in the Face of Complications After Heart Transplantation

In this section, we present a summary review of the immunosuppressive drug combinations best suited to each of the following problems.

Dyslipidemia. Several of the drugs used are hyperlipidemic through various mechanisms (steroids, CNI, mTOR-inh). Comparative studies including CNI indicate a more favorable profile for Tac than CsA, although no firm scientific evidence exists to justify making changes in immunosuppression.

High blood pressure. The European and US comparative studies of (oil-based) CsA and Tac both found incidence of HTA was greater in the CsA group. In patients with HTA that is difficult to control, replacing...
CsA with Tac can help, as can withdrawal or reduction of steroid dosage.

**Diabetes mellitus.** Corticoids that induce resistance to insulin are strong predictors of the appearance of DM post-transplant, so their withdrawal benefits patients. In kidney transplantation, comparison with CNI indicates an estimated 5-fold greater risk of developing DM in the Tac group than in the CsA group. In HT, differences between Tac and CsA are not statistically significant, probably due to insufficient sample size, although it seems more likely that Tac would propagate diabetes. All of this leads us to believe that the free combinations of steroids, possibly with CsA as CNI, may be the last likely to promote diabetes. (Class IIa recommendation. Level of evidence B.)

**Hyperuricemia.** The hyperuricemic effect of CsA, often observed above all in kidney transplants, is well-known. Some studies report improvement in gout crises on changing to Tac. However, authors consider observed hyperuricemia is more closely related with kidney dysfunction and frequent use of diuretics than with the effect of CsA as such.

**Graft vascular disease.** Together with tumors, GVD is the principal cause of mortality at >1 year post-transplant. Recent studies report mTOR-inh associated with CNI may help prevent or slowing progression of GVD (comparative studies with AZA). These studies found no improvement in survival although they do report improved nephrotoxicity for CNI. To date, no information on comparison with MMF is available.

**Kidney failure.** Substantial differences in the nephrotoxic profiles of the 2 CNI available have not been clearly established. Use of MMF permits association with lower quantities of CNI than with AZA. In patients with kidney failure, another strategy is to withdraw CNI and convert to mTOR-inh.

**Neoplasias.** Neoplasias are a growing problem in the long-term evolution of patients with HT. Recently hopes have been raised about the use of mTOR-inh given it mediates in the intracellular signaling of various tumorous cells.

**Neurotoxicity.** Multiple adverse neurologic and psychiatric manifestations have been described with the use of CNI. These are more frequent with Tac. Reducing CNI dosage often leads to improvement, although permanent effects have been described despite the suspension of treatment. An alternative could be the combination of MMF and mTOR-inh in patients with considerable neurotoxicity.

**Myelotoxicity.** Immunosuppressors like AZA, MMF, and mTOR-inh are myelotoxic. In AZA, myelotoxicity is more marked if it is administered in combination with allopurinol.

### CHAPTER 6. GRAFT VASCULOPATHY

#### Definition and Current Situation

Graft vasculopathy (GV) is the main cause of graft failure and death after the first year following heart transplantation (HT). Graft vascular disease is a type of accelerated atherosclerosis characterized by diffuse, concentric intimal thickening in the epicardial and intramural arteries. At 5 years following HT, 42% of patients present angiographic evidence of GV. When IVUS is used, however, significant intimal thickening is detected in 58% of patients already in the first year after the procedure. The clinical manifestations of this condition can include angina, myocardial infarction, or sudden death, but the most typical in the advanced phases is heart failure.

Following the diagnosis of GV, the incidence of death or retransplantation at 1 and 3 years is 36% and 80%, respectively. Nevertheless, in the last decade mean survival after the diagnosis has increased from 2 to 4.2 years. The pathogenesis of GV is unknown, but it seems to be a manifestation of a chronic immune response, in which other nonimmune factors also play a part. The number, severity, and late occurrence of acute rejection episodes has been associated with the development of GV. In fact, even mild recurrent rejection during the 3 months following HT is related with increases in intimal thickness as measured by IVUS.

Included among the nonimmune recipient factors are DM, peripheral vascular disease, dyslipidemia, and the ischemic etiology of the heart disease for which transplantation was indicated. Total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides are independent variables related with GV on IVUS evaluation. However, the parameter most closely related with progression is LDL-C. Cytomegalovirus infection has been associated with GV in experimental and clinical studies, although the precise implication of this infectious agent has not been definitely demonstrated.

Donor-transmitted atherosclerotic disease follows a pathological course different from that of GV. A certain degree of atherosclerosis is detected in 50% of donors.
over 40 years of age. On IVUS examination, 36% of implanted hearts present donor-transmitted lesions. These lesions progress in 50% of recipients during the first year of follow-up, but are rarely a cause of ischemic events.

Utility of Noninvasive Diagnostic Procedures

Noninvasive tests for the detection of GV are less sensitive than invasive testing and the degree of acceptance of these techniques varies according to the center. Dobutamine stress echocardiography has the highest sensitivity (79%-95%) for detecting GV. The specificity of this technique is lower (55%), but reaches 95% when only advanced forms are considered (Stanford grades III and IV). Dobutamine stress echocardiography is useful for establishing the risk of experiencing cardiologic events. It is, however, an operator-dependent technique and the contractility alterations occurring in HT can be misinterpreted as ischemia.

The various modalities of myocardial perfusion studies have a sensitivity of 22%-100% and a specificity of 55%-100%. Electron beam computed tomography study has shown that calcification of the arterial wall correlates with the development of cardiac events. The sensitivity of the calcium score is high for predicting coronary stenosis and the degree of intimal proliferation in HT, nonetheless, a percentage of GV patients do not develop detectable calcification.

Perfusion studies with magnetic resonance (MR) imaging, which are under clinical development, allow quantification of the myocardial perfusion reserve (MPR) following adenosine administration. The endomyocardial/epimyocardial perfusion ratio is decreased in patients with GV. A ratio of >1.3 in the absence of prior hypertrophy or previous rejection suffices to exclude GV without the need for other invasive studies or hyperemic tests.

Recommendations for Noninvasive Procedures

- Dobutamine stress echocardiography: yearly follow-up in asymptomatic patients. (Class Ib recommendation. Level of evidence C.)
- Perfusion studies, electron beam computed tomography, and MR: these procedures are not currently recommended for diagnostic study of GV in transplant recipients.

Invasive Diagnosis of Graft Vasculopathy: When and How

Conventional coronary angiography is the method most often used for assessing GV. The main limitation of this test is that diffuse forms, which do not alter the luminogram, cannot be detected.

Intravascular ultrasound allows several parameters of the coronary vessels to be determined, but maximum intimal thickening is the 1 most often used. Progression of intimal thickening is mainly produced during the first year following transplantation. The most widely accepted prognostic parameter (surrogate marker) is intimal thickness ≥0.5 mm in the first year after transplantation as a predictor of severe GV, clinical events, and mortality at 5 years. In physiological assessment of coronary flow, an abnormal response to acetylcholine is related with the development of intimal thickening, accelerated progression of GV, and a poor prognosis.

Recommendations for Invasive Studies

Coronary Angiography

- Baseline (first months following transplantation) to rule out donor-transmitted atherosclerosis. (Class IIa recommendation. Level of evidence C.)
- When GV is suspected on clinical criteria. (Class I recommendation. Level of evidence C.)
- When a noninvasive test yields a positive result. (Class IIa. Level C.)
- Although there is no consensus as to its utility or frequency of use, coronary angiography is recommended at some time during the follow-up of an asymptomatic transplant recipient. (Class IIa. Level C.)

Intravascular Coronary Ultrasound

- At the end of the first year of follow-up to assess prognosis. (Class Ib recommendation. Level of evidence B.)
- When GV is suspected and coronary angiography is normal. (Class IIa. Level B.)

Physiological Study of Coronary Flow

The usefulness of this procedure is unknown; hence, it is not recommended for the follow-up of HT patients.

Useful Pharmacological Measures Other Than Immunosuppressive Drugs for the Prevention of Graft Vasculopathy

Cardiovascular risk factors, which are present in a larger percentage of the transplant population than in the general population, have been related to a higher risk of developing GV. Although adequate control of these risk factors (hypertension, smoking, DM, and obesity) is reasonable, there are no data demonstrating the efficacy of this measure for preventing GV. Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (ARA-II) are the drugs of choice for
microvascular endothelial function.259 A recent study has documented a benefit of Tac on antiplatelet agents (acetylsalicylic acid, ticlopidine, or clopidogrel).254,255 The HMG-CoA reductase inhibitors (pravastatin, simvastatin, lovastatin, and atorvastatin) are effective for reducing cholesterol and intimal proliferation (independently of the hypolipidemic effect), improving survival, and reducing episodes of hemodynamic deterioration in the first year following transplantation.86,256,257

**Recommendations for the Prevention of Graft Vasculopathy**

As a general measure it is recommended to advise against smoking, optimize metabolic monitoring of DM, and provide adequate hypertension control by administering an ACE inhibitor, ARA-II, or calcium antagonist. (Class I recommendation. Level of evidence C.)

Early use of statins is advocated, regardless of the cholesterol levels. (Class I recommendation. Level of evidence B.)

Scientific evidence supporting the use of antiplatelet therapy in established GV is not available, but one can assume that it will have the same benefits as those seen in patients with arteriosclerosis who have not received a heart transplant (Class IIa recommendation. Level of evidence C.)

**Initial Immunosuppression and Graft Vasculopathy**

The use of immunosuppressive induction therapy with antibodies (polyclonal, monoclonal, or anti-CD25) does not have an impact on the development of GV. Nor have calcineurin inhibitors demonstrated a significant action on this condition. There is no difference between CsA and Tac regarding GV prevention,142,143 although a recent study has documented a benefit of Tac on microvascular endothelial function.270

Mycophenolate mofetil (MMF) has a mild antiproliferative capability, reduces episodes of acute rejection with hemodynamic deterioration, improves survival, and reduces the progression of intimal thickening as compared to azathioprine (AZA).140,190,264 The new antiproliferative drugs, everolimus and sirolimus, clearly reduce the progression of intimal proliferation, and the beneficial effect persists at 2 years following transplantation. Nevertheless, as compared to AZA, everolimus, and sirolimus enhance CsA nephrotoxicity and do not result in increased survival.142,143

**Recommendations for Initial Immunosuppression in Relation to Graft Vasculopathy**

There is no evidence to recommend a specific immunosuppressive induction therapy aimed at preventing GV. Nor is there evidence to recommend a particular calcineurin inhibitor for GV prevention.

Initial immunosuppression based on the use of mTOR inhibitors (sirolimus and everolimus) together with CsA and prednisone is effective in reducing and delaying the initial forms of GV when compared with AZA use, but it is unknown whether there is a benefit from this treatment as compared to MMF. (Class IIa. Level of evidence B.)

**Pharmacological and Nonpharmacological Treatment for Established Graft Vasculopathy**

Graft denervation, which results in an asymptomatic course of GV up to the terminal phase, and the multifactorial etiopathogenesis of the disease makes it improbable that the use of isolated therapeutic measures will control its development. Because of the diffuse and rapidly progressive nature of GV, the classic methods of revascularization are not very effective.265

**Pharmacological Treatment for Established Graft Vasculopathy**

- Secondary prevention: control of immune-related and nonimmune risk factors implicated in the development of GV may be useful.
- Immunosuppressors: sirolimus and everolimus are more effective than AZA for preventing the initial phase of GV.142,143 Although reported data have shown favorable results,140,264 the efficacy of these drugs is less certain in the established forms of GV.

**Nonpharmacological Treatment**

Percutaneous transluminal coronary angioplasty (PTCA) has been used for treating cases of GV in which the anatomy is favorable for this procedure.79,248 The results show an initial successful outcome of 90%, mortality of 1%-2%, and restenosis rate of 25%-55%. Implantation of stents, particularly drug-eluting stents, has been associated with a reduction in restenosis.269,270 Surgical revascularization has high operative mortality (25%-33%).275,276 When distal segments are favorable, measurement of the coronary flow reserve can help in the selection of suitable candidates.275,276 The definitive treatment in the terminal phase is retransplantation91,270,271.

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however, the recurrence rate of GV (50% at 30 months) and the scarcity of donors have made this indication controversial.3

Recommendations for the Treatment of Established Graft Vasculopathy

– Strict control of cardiovascular risk factors. (Class I. Level of evidence C.)
– A change of immunosuppressors should be considered in patients with renal dysfunction. However, the efficacy of this treatment remains controversial. (Class IIa. Level C.)
– A change of immunosuppressors treatment that could provide some benefit for established GV is the use of sirolimus or everolimus. Nonetheless, because of their profile of adverse effects, the decision should be made on an individual basis and not be limited to more solid evidence. (Class IIa. Level C.)
– Surgical revascularization by PTCA is recommended:
  1. In anatomically favorable cases with signs or symptoms of ischemia, with the use of drug-eluting stents. (Class I. Level of evidence C.)
  2. In anatomically favorable cases at a high risk (main artery or multivessel lesions that include the proximal left anterior descending artery [LAD], or left ventricular dysfunction), with the use of drug-eluting stents. (Class IIa. Level of evidence C.)
  3. In lesions unrelated to the signs and symptoms of ischemia, when there is no high risk or unfavorable anatomy. (Class IIb. Level of evidence C.)
– Surgical revascularization is recommended:
  1. In highly selected cases, such as high-risk lesions (main artery or multivessel disease with proximal LAD involvement) related with signs and symptoms of ischemia or ventricular dysfunction that cannot be treated by percutaneous techniques and with no involvement of the distal segments. (Class IIa. Level C.)
  2. In the remaining cases, surgical revascularization is not advisable. (Class III. Level of evidence C.)

Retransplantation

Because of the suboptimal outcome and ethical problems related to retransplantation, this option should always be decided by consensus. According to current practice, retransplantation should be indicated in patients with terminal GV (generally defined by heart failure and systolic graft dysfunction) in whom the above measures are not applicable or have not obtained favorable results more than one year following the initial HT, age >65 years, and no important comorbid conditions. (Class IIa recommendation. Level of evidence C.)

CHAPTER 7. LONG-TERM COMPLICATIONS

Renal Failure After Transplantation

Renal failure is a common complication after heart transplantation and the incidence of this condition has risen in parallel to the increased survival of these patients.283,284 Renal dysfunction after transplantation is related to the use of CNI, although there is some degree of individual susceptibility and other factors may have an impact, such as, recipient age, degree of renal function deterioration before transplantation, ischemic etiology of the underlying heart disease, and development of risk factors such as HBP, dyslipidemia, or DM.

There is no effective treatment for renal failure after transplantation and, therefore, it is essential to prevent progression toward terminal stages through the following:

– Identification of patients at high risk for end-stage renal disease: older age, renal function before transplantation, and risk factors for atherosclerosis.
– Strict monitoring of cardiovascular risk factors (HBP, dyslipidemia, and DM).148 The drugs of choice for hypertension are calcium antagonists, ACE inhibitors, and ARBs.
  – Avoid the use of nephrotoxic drugs (eg, nonsteroidal anti-inflammatories [NSAIDs] and radiocontrast material).
  – CNI dose adjustment, particularly in the first months after HT,149 accompanied by intensification of non-nephrotoxic immunosuppression (MMF as concomitant immunosuppressive). In this regard, the use of relatively low doses of CNI along with mTOR inhibitors (sirolimus, everolimus) has not proven to be effective for renal protection over more conventional protocols.150
  – In chronic patients, conversion to sirolimus has shown to be effective in improving chronic renal failure after HT,148 although this improvement appears to be limited to patients with moderate dysfunction (plasma Cr <2.5 mg/dL). In patients with more severe renal failure, conversion could prevent progression toward terminal stages, although more data are needed to confirm this hypothesis. However, there is some reported experience in de novo HT with CNI-free, sirolimus-based immunosuppression, which indicates a possible benefit in preventing rejection and preserving renal function. The safety and efficacy of this regimen have not been proven.

Hypertension After Transplantation

Following the introduction of CsA, hypertension is probably the most common complication after HT and, although the traditional risk factors of hypertension have played a role, the use of CNI is directly related to the development of HBP after transplantation.283,284 Tacrolimus has similar effects to those of CsA, although the prevalence of hypertension in Tac-based regimens is lower than with CsA.285

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As in essential high blood pressure, 1 of the purposes of the treatment is regression of the ventricular hypertrophy and prevention of renal function deterioration. Normalization of high blood pressure in a previously hypertensive patient (with no changes in therapy) would indicate ventricular dysfunction due to ischemia or acute rejection.

Treatment includes nonpharmacological (eg, salt restriction) and pharmacological measures. A decrease in the steroid dosage and/or early withdrawal of these drugs, as well as reduction of CNIs, would be desirable, although these measures are usually not feasible (in terms of safety) due to the risk of rejection. More than one hypotensive drug is typically needed in more than 50% of patients, of which the most commonly used are calcium antagonists, ACE inhibitors, and ARBs. Calcium antagonists (eg, diltiazem), which have been widely used, alter the pharmacokinetics of CsA (reduce the required dose of CsA, since they increase its blood concentration) and, therefore, close monitoring of blood CsA concentrations is required when these drugs are started and discontinued.\textsuperscript{291} ACE inhibitors have also shown efficacy in the control of hypertension and are, along with calcium antagonists, the drugs of choice for treating this condition; no difference has been found in a comparative study.\textsuperscript{292} Calcium antagonists and ACE inhibitors is a commonly used drug combination; ARBs, alpha blockers, and central vasodilators are also useful, although there is less clinical experience with these drugs. Beta blockers have always been avoided in transplanted patients due to their negative chronotropic effect; however, there is increasing experience in their use, in particular, with carvedilol.

**Neoplasms After Heart Transplantation**

Together with GV, neoplasms are the most common cause of limited long-term survival after solid organ transplantation.\textsuperscript{293} The incidence varies, according to the series consulted. National Registry data from Spain indicate that tumors are the cause of late mortality in 15% to 20% of cases.\textsuperscript{3}

The origin of neoplastic disease following HT may be recurrence of a preexisting condition,\textsuperscript{294,295} donor transmission, or de novo neoplasms.\textsuperscript{296,297} To prevent the first 2 cases, a comprehensive study of both the donor and recipient is needed, as well as strict adherence to the guidelines in terms of contraindications due to previous neoplasms, in both donors and recipients, because even patients with supposedly cured tumors with no evidence of recurrence after 5 years have a higher probability of a new neoplasm.

The incidence of de novo neoplasms in transplanted patients is 3 to 4 times higher than that of the general population. The most common are skin tumors. Classically, the second most common type of tumor has been lymphoproliferative syndromes (LPS), followed by other solid organ tumors, in particular, lung cancer. The onset of the first 2 is earlier, usually within 18 months, whereas cancer of the lung or other solid organs is later.\textsuperscript{298} However, the type of neoplasm appears to be changing. According to data from the Spanish transplant registry, the most common tumors are skin tumors, followed by neoplasms of nonlymphoid origin. The incidence increases with recipient age, and is higher in men than women. The prognosis of noncutaneous tumors is poor, with a 1-year mortality of almost 50% from the time of diagnosis.\textsuperscript{299}

As in the nontransplanted population, the pathophysiology of cancer in patients with HT involves multiple factors, although it differs in several aspects, such as chronic antigenic, immunoregulation abnormalities, and oncogenic virus.

**Skin Cancer**

More than half the patients have a pre-transplantation history of neoplastic or premalignant lesions. Unlike no transplanted patients, squamous cell carcinoma is more common than basal cell carcinoma in the transplant population. There is a higher incidence of melanoma in HT recipients than in patients with other organ transplants. The following are risk factors: sun exposure, age, male sex, blue eyes, and fair skin. As preventive measures, immunosuppression should be minimized and the use of AZA should be avoided.\textsuperscript{298}

**Lymphoproliferative Syndromes**\textsuperscript{300}

Lymphoproliferative syndromes are related to Epstein-Barr virus (EBV) infections.\textsuperscript{293,296} CMV disease, and use of OKT-3 at doses >70 mg during the clinical progress.\textsuperscript{113} The clinical presentation of these conditions can vary considerably, with involvement of almost any organ or system. As a therapeutic measure, besides of conventional oncological treatment, immunosuppression should be reduced.

**Kaposi Sarcoma**

Kaposi Sarcoma is almost 500 times more common in immunosuppressed patients than in persons without immunosuppression. It has been associated with herpesvirus 8 infections.\textsuperscript{302,303}

**Lung Cancer**

Lung cancer is the most common solid organ cancer and is closely related to a history of smoking. The disease progresses rapidly and despite frequent periodic check-ups, patients are usually diagnosed in
advanced stages that cannot be treated with surgical resection.304

Treatment
As a general rule, immunosuppression should be reduced; the problem is to know how to do it and how much. It is recommended that the CNI dose be reduced to half and that AZA be discontinued. The appearance of immunosuppressants with an antiproliferative effect (sirolimus and everolimus) offer new possibilities for the treatment of neoplasms, particularly skin tumors, in transplanted patients, but long-term results are needed to confirm the promising expectations.305

Prevention
In the interim, the best approach is to prevent risk factors (smoking, sun exposure), treat viral infections, monitor EBV viral load, and detect any neoplasms as early as possible by a complete physical examination and additional tests during follow-up.

Arrhythmias: Bradyarrhythmia, Tachyarrhythmia, Sudden Death

Early Bradyarrhythmia
Bradyarrhythmia is common during HT postoperative, with an approximate incidence of 20%.306,307 The condition manifests as sinus bradycardia or absence of sinus activity with atrioventricular (A V) junctional rhythm; A V blockade is rarer. Clinical progress is usually favorable, such that at 3 months it has normalized in 50% to 75% of the cases, and in 90% after 1 year.308 Treatment in the initial stage consists of isoproterenol or atrial pacing. Treatment with theophylline enhances recovery of normal sinus rhythm.309,310

The need for a definitive pacemaker has generally ranged between 2% and 20%, and is presently around 2%, probably due to greater use of the dual-chamber technique. In persistent symptomatic bradyarrhythmia, implantation of a definitive pacemaker is indicated. It may also be indicated in asymptomatic patients with persistent junctional rhythm and in those who have mild bradyarrhythmia at less than 50 bpm 2 to 3 weeks after transplantation, since these patients are more likely to require permanent pacing in the future.311 Ideally, pacing should be dual-chamber or atrial if AV conduction is normal.311

Late Bradyarrhythmia
Late bradyarrhythmia (beyond 5 months) is rare in HT, with an approximate incidence of 1.5%.308 About half the cases could be secondary to acute rejection and would be solved with treatment. When symptomatic bradycardia or an episode of AV blockade develops, acute rejection or GV should be ruled out. If no reversible cause is seen, implantation of a definitive pacemaker and close follow-up are indicated.

Tachyarrhythmia
Atrial arrhythmia. Transient, asymptomatic atrial tachyarrhythmia is frequent after HT, with an incidence of 25% to 50%,313,314 and does not require treatment. The most common sustained atrial tachyarrhythmia during follow-up in transplanted patients is atrial flutter. When detected, biopsy is indicated to rule out acute rejection, since arrhythmia can revert with treatment. Once rejection is ruled out, patients can be treated with overstimulation or electrical cardioversion, although the treatment of choice would currently be electrophysiological study of the arrhythmia and ablation because of the high incidence of recurrence.315 The incidence of atrial flutter or atrial fibrillation reported after HT varies considerably from 9% to 15% in some series316 and below 3% in others.317

Ventricular arrhythmia. Occasional ventricular extrasystole during the postoperative period has been described in up to 65% of patients.313 In the long-term, nonsustained ventricular tachycardia (NSVT) is extremely rare318 and when it is detected, rejection and GV should be ruled out.

Sudden Death
Sudden death is common in patients with HT,313 accounting for 10% of the 257 deaths analyzed in the series from Patel et al.43,44,319 It is usually related to coronary disease, as well as acute rejection in the first year. Ischemia can induce bradyarrhythmia, asystole, tachyarrhythmia, and electromechanical dissociation.

Diabetes: Incidence and Management
Diabetes mellitus of new onset and impaired glucose tolerance (IGT) are some of the most common long-term complications of HT, with an estimated 5-year incidence of 32%.320,321

Characteristics of diabetes mellitus in HT patients are similar to those of type 2 DM in the general population and the ultimate purpose of management for this condition is identical: close control of blood glucose through diet, exercise, and medication.

Medical treatment is similar to that of patients with type 2 DM and should follow a progression.320-322 Non-pharmacological measures are started, and obviously include general measures for cardiovascular risk
prevention, such as weight control, light aerobic exercise, and no smoking. The patient is then switched to monotherapy with oral antidiabetic agents, then to combined oral therapy, and finally to insulin with or without oral drugs. The oral antidiabetic must be chosen based on safety. The possibility of tissue hypoxia and lactic acidosis with metformin and hypoglycemia with sulfonylureas should be considered, particularly in patients with renal failure. Meglitinides are safe drugs in case of renal failure, useful when creatinine clearance >15 mL/min and the treatment of choice in elderly patients who require lower doses. However, there are no randomized studies that compare the action of the various drugs in patients who have received transplants.

In DM after HT, a series of specific measures should be considered: low or less diabetogenic immunosuppressant regimens (dose decrease or steroid withdrawal, CsA instead of Tac, or CNI-free protocols), although this is not always possible because of the risk of rejection.

Infection Prophylaxis in Chronic Patients. Impact of New Immunosuppressants

In HT, perioperative prophylaxis is usually given for infection of the sternotomy wound and against *Pneumocystis jiroveci*, CMV, and *Mycobacterium tuberculosis*.

Co-trimoxazole prophylaxis, for which several dosages are used, all of them effective (1 tablet per day or on alternate days or 2 tablets 3 times per week, or 2 tablets on Saturdays and Sundays) is done in all HT recipients. It is very effective in the prevention of *P. jiroveci* pneumonia, reduces the risk of infection due to *Toxoplasmosis gondii*, *Listeria monocytogenes*, and *Nocardia asteroides*, and is safe and well tolerated. Prophylaxis is indicated for the first 6 to 12 months after transplantation. In chronic patients, it may be reasonable to prolong prophylaxis with co-trimoxazole if they receive extra doses of immunosuppressants.

Cytomegalovirus prophylaxis is advisable in high-risk patients, particularly seronegative recipients with CMV-seropositive donors. Oral valganciclovir during the first 100 days after HT is effective for preventing early CMV disease, but may increase the risk of late disease that can be due to ganciclovir-resistant CMV. Treatment of severe or corticosteroid-resistant rejection with OKT3 or ATG is a risk factor for CMV disease; therefore, prophylaxis with ganciclovir is an established recommendation. There are no data to recommend prophylaxis outside of these indications. The strategy of preemptive therapy, which consists of antiviral treatment (ganciclovir, valganciclovir) in risk situations, as defined by laboratory data (CMV antigenemia, PCR), epidemiological data (CMV serological status of recipient and donor), or clinical situations (eg, treatment of rejection), has been shown to lower the incidence of CMV disease in some series.

Prophylaxis for tuberculosis infection consists of isoniazid (300 mg/day) for 6 to 12 months in patients with positive tuberculin testing (induration ≥5 mm) in the pre-transplantation study and in whom the disease was ruled out. Antifungal prophylaxis with nystatin, itraconazole, or amphotericin and herpes simplex virus prophylaxis with acyclovir are administered in some HT programs, but their efficacy has not been shown.

Is Endocarditis Prophylaxis Necessary?

Apparently, the risk of endocarditis in HT recipients is not high, according to the limited data on this complication. Although the current international guidelines do not specifically recommend antibacterial prophylaxis for infective endocarditis in HT recipients, it is known that many institutions recommend it because some cases have been reported.

Bone Complications: Osteoporosis

The incidence of osteopenia or osteoporosis is as high as 50% in patients with severe HF and 5% present vertebral fractures. After transplantation bone loss is accelerated, as resorption is increased (mainly due to CNIs) and bone formation is inadequate due to steroid-induced osteoblastic inhibition. Up to 20% of bone mass can be lost in the first year, with an incidence of vertebral fractures of up to 35%. Prevention

A bone metabolism study is done before transplantation. If osteopenia is documented, calcium and vitamin D therapy should be started unless contraindicated. In the case of osteoporosis or vertebral fractures, it would probably be useful to add bisphosphonates to inhibit bone resorption. After transplantation, therapy should continue for at least the first year and be assessed later according to clinical symptoms and bone densitometry. There are various studies on the use of bisphosphonates in patients with HT that reflect a clear increase in bone density, although there is less evidence regarding a decrease in fractures. Calcitriol (1,25-hydroxyvitamin D) also reduces bone loss, with a benefit similar to that of alendronate; however, the use of this agent is more complex. Calcitonin may be useful if there is intolerance to bisphosphonates, and raloxifene is useful in postmenopausal women. Physical exercise is important in those patients with bone complications.
problems, once it has been provided that there is no risk of rejection.

CHAPTER 8. PEDIATRIC HEART TRANSPLANTATION

Indications

The major indication for pediatric HT is end-stage HF of any origin in which there is no possible medical, interventionist, or surgical option. The most common indications are cardiomyopathy and congenital heart disease, which generally have already been treated surgically, and, in rare cases, untreatable arrhythmias and unetectable tumors. Among the cardiomyopathies, dilated cardiomyopathy (DCM) is the one that most frequently requires transplantation. In DCM which commences with acute severe HF, HT is recommended when the patient requires intravenous isotropic support, mechanical ventilation, hypothermia or circulatory assistance, or is in an unacceptable functional class, after 2 weeks of optimal medical therapy. In chronic DCM, with optimal medical therapy, the inclusion criteria are: acute deterioration requiring intravenous isotropic support, mechanical ventilation, hypothermia, or ventricular assistance; progression to a functional class unacceptable for normal social and/or school activity; a history of more than 2 years with a shortening fraction <15% or left ventricular end-diastolic pressures >20 mm Hg with pulmonary congestion; growth failure; inability to walk 300 meters in the six-minute walk test or oxygen consumption levels, neoplasms, PVRI >4 WU/m^2 and TPG >15 mm Hg following a reversibility study, slow recovery from the clinical and physiological sequelae of the surgically treated heart disease, heterotaxia and psychosocial factors. In patients with restrictive cardiomyopathy and HF refractory to medical treatment, it should be carried out prior to the development of PHT, which contraindicates isolated HT.

During the immediate postoperative period following surgery for congenital heart disease, HT is indicated when it is impossible to disconnect the extracorporeal circuit or when, after disconnection, persistent cardiogenic shock develops, requiring placement of a mechanical assist device. The absence of treatable residual lesions and a period of at least 5 days of mechanical assistance are considered indispensable for inclusion. Once survival beyond the immediate postoperative period has been achieved, patients with surgically treated congenital heart disease with residual lesions are being included in transplant series in increasingly larger numbers. The operations include biventricular anatomical or physiological corrections (Mustard, Senning or Rastelli procedure) or univentricular correction (Norwood, Glenn or Fontan procedure), with structural or functional lesions (systemic ventricular failure) in which medical, interventional and conventional surgery have been ruled out. There remain few centers that recommend HT as the initial option for treatment in congenital heart disease. Currently, the majority of the most complex heart diseases (including variants of left heart hypoplasia or other univentricular hearts) are being treated conventionally. A case-by-case analysis may lead to an indication for transplantation under specific circumstances.

Contraindications

Currently, HT is absolutely contraindicated only when the anatomical features impede its performance for technical reasons (extremely hypoplastic pulmonary arteries or veins) or in the presence of physiological conditions, such as irreversible PHT when the PVR are >6 WU/m^2 and nonreactive to pulmonary vasodilator testing. In addition, it should not be indicated in the case of certain genetic or biochemical abnormalities related to fatty acids, amino acids, the mitochondrial respiratory chain, glycogen, or polysaccharides due to the involvement of other organs or irreversible diseases of the lung, liver, kidney (in which transplantation is ruled out) or nervous system, or in cases of prematurity of less than 32 weeks gestational age. Relative contraindications (or factors that increase the morbidity or mortality rate) include acute or chronic infections, chronic HBV or other immunodeficiencies, hepatitis B or C virus, increased antilymphocyte antibody levels, neoplasms, PVRI >4 WU/m^2 and TPG >15 mm Hg following a reversibility study, slow recovery from the clinical and physiological sequelae of the surgically treated heart disease, heterotaxia and psychosocial factors. Chromosomal aberrations require individualized analysis and depend on the course of their functional prognosis.

Donor Evaluation

The first steps are to obtain general data (ABO blood group, cause and duration of brain death, eventual cardiac arrest, and related clinical history), assess the hemodynamic conditions (inotropic intervention, urinary flow rate), and calculate the approximate ischemia times. Indispensable additional tests are those related to infections (serology for HBV, toxoplasma gondii, rubella virus, cytomegalovirus, herpes simplex virus [TORCH],...
hepatitis B and hepatitis C; cultures), and ECG and especially echocardiography (carried out by experts) are recommended, as is coronary angiography if the donor is over 40–45 years of age.

Donor Selection Criteria

Cold ischemia of 4 hours is acceptable, and up to 5 if the donor is a child and receives low doses of inotropic agents. The donors can be adults, but organs from individuals over 50 years of age are associated with an increase in the transmission of coronary artery disease and the mortality rate. The size in relation to the weight can be up to four-fold greater in the newborn infant and very young child but, in general, the acceptance of hearts from donors of lower weight (maximum: 20% lower) is not recommended, especially if the recipient presents elevated PVR.

The cardiac functional status (ejection fraction <40%) and the doses of inotropic agents are not contraindications, nor are minor heart defects (atrial septal defect [ASD], restrictive ventricular septal defect [VSD], or bicuspid aortic valve).

Marginal Donors and Special Situations

The acceptance of ABO-incompatible donors has been reported, but, at the present time, the Spanish National Transplant Organization (ONT) does not consider it an option; an elevated level of cytotoxic antibodies requires modified immunosuppression protocols that include previous plasmapheresis, exchange transfusions, and antiproliferative agents, as well as testing of all the donor sera against those of the recipient (which prolongs the ischemia time).

Preservation

The donor must be maintained hemodynamically stable with proper medical treatment, avoiding high doses of catecholamines, prior to harvesting. Myocardial protection is accomplished with different potassium-rich solutions, either commercially available products or those prepared in each center; the purpose is to achieve an effective electromechanical arrest and maintain conditions suitable for cold storage. The cold ischemia time can be minimized by means of continuous warm blood cardioplegic reperfusion throughout implantation.

Harvesting Technique

The technique should be chosen taking into account the underlying disease of the recipient. The most complex situations are: situs inversus, which requires oversized hearts, with the entire axis of the vena cava, up to the jugular veins, and as much of the inferior vena cava as possible; in previous cavopulmonary surgeries, both venae cavae should be preserved, as should be the greatest possible length of the pulmonary artery branches; and in left heart hypoplasia/aortic arch repair, the maximum possible length of aortic arch should be harvested to extend the repair to the recipient descending aorta. The harvesting procedure does not differ from that employed in adults (heparinization, emptying prior to clamping and clamping; ventricular distension must be avoided and uniform cooling must be ensured). The final step, the section of special structures as needed, requires coordination with other organ procurement teams.

Surgical Technique

There is no agreement with regards to the best surgical technique for the venous anastomoses, either atrial anastomoses or bicaval anastomoses, although the latter is preferred since it facilitates the correction of the nearly invariable disproportion between the donor and recipient hearts; moreover, advantages in terms of hemodynamic function and rhythm have also been reported. The timing of the surgical procedure depends on the previous status of the recipient. When he or she is on a waiting list as an outpatient, it is recommended that the family live within 150 km or 2 hours of the hospital. In order to minimize the ischemia time, the recipient should be prepared prior to the arrival of the donor heart. The recipient heart should not be harvested until the donor organ is in the operating room. For the bicaval technique, cardiopulmonary bypass (CPB) is established using the high approach to cannulation of ascending aorta and venous return is achieved by cannulating both venae cavae independently, with the superior vena cava at the level of the brachiocephalic trunk; as an alternative, in repeat operations, cervical or inguinal cannulation can be employed. A drain is placed in left ventricle and a cannula is inserted in superior right pulmonary vein. Once the intervention is over, the latter can be used for monitoring left ventricular filling pressure. With the CPB established, systemic cooling to an esophageal temperature of 28°C is begun. The decrease in the temperature is adapted to the technical needs; for example, a tympanic temperature of 16°C and total circulatory arrest are achieved in cases of concomitant aortic arch reconstruction. The pericardial reflections are dissected at the level of both venae cavae, and an electric knife is used to extensively mobilize the aorta and main pulmonary artery. Under conditions of extreme asepsis, the organ is removed from the transport cooler and is placed in the operating theater in a vessel with crushed ice, avoiding their direct contact. The heart is inspected to rule out patent foramen ovale and cardioplegia is again administered.
The great arteries are dissected and the posterior wall of left atrium is cut open and all the pulmonary veins are joined together. It is necessary to suture the left atrial appendage if simultaneous lung harvest has been carried out with antegrade pulmonary perfusion. The aorta is clamped and atriotomy is begun at the level of the base of right atrial appendage, keeping close to the AV groove; the heart is raised and left atrial wall is cut open at the level of the AV groove, after which the interatrial septum is sectioned; the great arteries are cut at the level of the sigmoid valves. Both venae cavae are sectioned at the level of their junction with right atrium, leaving a bridge of posterior tissue to facilitate anastomosis.156 The left atrium is resected up to 3 mm from the entrance of the pulmonary veins. Implantation begins in the left atrium, with the alignment of the left superior pulmonary vein with the origin of left atrial appendage using a running polypropylene suture until completion of the anastomosis. The length of the pulmonary artery is determined and its anastomosis is initiated in the posterior wall, after which it is anastomosed to the aorta; the order of these steps can be reversed to shorten the ischemia time. The procedure continues with the anastomosis of the inferior vena cava (hemostatic control of the Thebesian veins is important) and, finally, the length of the superior vena cava is determined and end-to-end anastomosis is performed at a distance from its junction with the right atrium (usually with the aorta unclamped). Prior to unclamping, reperfusion of between 5 and 10 minutes, depending on the graft ischemia time, should be carried out. Asystole is maintained, the myocardium is gradually rewarmed, the pressure is kept low and the heart, unloaded. Cardiopulmonary bypass is discontinued, temporary pacing electrodes are placed in atria and ventricles and the sternum is closed.

**Perioperative Management**

Prior to transplantation, all patients should have had optimal medical, antiarrhythmic, anti-PHT, interventional, and surgical treatment and, in some cases, advanced life support.156,157 Maintenance in critically ill patients requires special emphasis on the need to preserve hemodynamic stability; optimal gas exchange; the evaluation of infection and the initiation of antifungal prophylaxis; vigilance of the toxicity of the drugs when administered in adequate doses, once the specific immunosuppressive protocol has been initiated; and monitoring of signs of rejection and organ dysfunction. Pediatric patients differ from adults with respect to the specific perioperative complications that it is necessary to be on the alert for.157 In those cases in which the donor is larger than the recipient, it may be necessary to leave the sternum open, and small hearts frequently develop pericardial effusion.150 It is necessary to rule out obstruction of the systemic venous return due to persistence of prosthetic material (Fontan procedure),148 the need to interpose foreign materials/conduits (situs inversus)151 or, in newborn infants treated by means of the bivacal technique, obstruction of the systemic outflow tract (previous aortic arch surgery) or the persistence of venovenous, or bronchial collateral circulation. Supraventricular arrhythmias are associated with the classical implantation technique. Hypertension due to large hearts can be controlled with beta blockers, ACE inhibitors, and calcium antagonists (usually with amlodipine).

Therapy with inhaled nitric oxide (NO) and isoproterenol should be initiated systematically in the operating room because of the usual association of PHT and the difficulty inherent in the diagnosis of right ventricular dysfunction. Respiratory complications are also more common with organs from larger donors, which produce bronchial compression, with atelectasis and pleural effusion. Chylothorax or recurrent lesion can develop in complex heart diseases that have previously been treated surgically. Other complications to be ruled out are hypomagnesemia (associated with tacrolimus) and subclinical hypothyroidism. Previous severe malnutrition requires greater nutritional support, with restrictions on water intake and caloric, multivitamin and mineral supplementation. Bleeding complications are more severe in patients who have undergone combined surgical treatment, those receiving anticoagulants or antiplatelet agents, cyanotic patients, or those with collateral vessels; likewise, cyanotic patients or those with protein C and protein S deficiency (Fontan procedure) are at higher risk for thrombosis. The diagnosis and treatment of infections should be immediate, especially in previously immunocompromised patients (asplenia, DiGeorge syndrome), and it is necessary to take into account the common viral diseases in pediatrics.

**Immunosuppression**

Immunosuppressive therapy should prevent acute rejection, minimizing the risk of infection, malignant transformation, and toxicity.157,158 The drugs employed in pediatric HT are similar to those of adults, both for IT and maintenance (corticosteroids, CNI, antimetabolites, antiproliferative agents). The protocols have varied over time and from 1 institution to another, and none of them have proved to be superior to the rest. Tacrolimus appears to be more successful in preventing persistent and recurrent rejection than CsA. Mycophenolate mofetil has been found to be more effective than AZA. In comparison to AZA, the new
antiproliferative agents, the mTOR inhibitors (sirolimus, everolimus), have shown greater efficacy in preventing GVD and reducing the incidence of CMV infection, while they are also effective in preventing acute rejection. Induction therapy is used to delay the action of the CNI and avoid renal dysfunction during the immediate postoperative period. Anti-CD25 monoclonal antibodies (basiliximab, daclizumab) have practically replaced classical agents, like thymoglobulin, ATGAM, and OKT3, because they are better tolerated. As maintenance therapy, a number of combinations are utilized and accepted in pediatric HT341,350; initially, triple therapy with a CNI associated with AZA or MMF, and corticosteroids is administered. After 6 months with no evidence of rejection, the corticosteroids should be discontinued and double therapy is maintained, generally with MMF as the second drug. In some cases it is possible to achieve a reduction to monotherapy, the most extensive experience being with Tac alone. Sirolimus and everolimus are employed in renal insufficiency due to nephotoxicity, malignancy, and/or GVD (together with a reduction in or even discontinuance of CNI). The future perspectives point toward the use of everolimus or sirolimus, associated with CNI, from the moment of transplantation. A number of multicenter studies are underway to demonstrate that they prevent acute rejection and GVD and reduce the incidence of CMV infection. New strategies for immune tolerance in the attempt to withdraw chronic immunosuppressive therapy are in the experimental phase.

Acute Rejection

The pathophysiology of cardiac rejection differs with respect to that of adults in that there is indirect evidence that the immune response to the graft is less marked in neonates and infants. Children under the age of 1 year require less immunosuppression. Acute rejection occurs most frequently during the first year after transplantation. However, following that period, there is also an incidence of 25% of late acute rejection, the major risk factor of which is rejection during the first year. This circumstance increases the long-term mortality rate (25% of the patients who experience late rejection die).361

The diagnosis of rejection362 based on the EMB follows the same classification as in adults. The procedure is carried out via femoral or jugular vein, with few complications in experienced centers.361 It is performed less frequently in small children because of the need for general anesthesia, hospital stay and the potential loss of a venous access. It is not systematically carried out during the first year in recipients of less than 1 year of age unless there is a high index of suspicion. In older children, although controversial, the calendar for EMB recommends to carry them out more frequently during the first 3 months, and then at 6 months and 1 year, with subsequent performance of annual EMB with coronary angiography.364 It is recommended that EMB be carried out seven to 15 days after a rejection episode to confirm its resolution and after corticosteroid administration has been definitively discontinued. The clinical features of rejection are nonspecific: irritability, discomfort, loss of appetite and fever, as well as nonspecific changes in rhythm or decreased ECG voltages. Although it is uncommon, rejection having a severe hemodynamic impact, with signs of low output or marked changes in contractility on echocardiography, requires antirejection therapy even without EMB. Serial echocardiography is highly useful for the detection of rejection,365 and there are parameters to be monitored, such as an increase in left ventricular mass, deterioration of systolic, and diastolic functions, new onset pericardial effusion and greater or newly developed mitral insufficiency. Clinical and echocardiographic criteria can help both to limit and to indicate biopsy. Other methods being investigated are electromyographic recordings and lymphocyte gene expression assays (Genzyme).

High-dose corticosteroids are the first-line agents for rejection treatment.366 In episodes occurring during the first 3 months after transplantation, in grade 3B rejection or higher and in rejection with hemodynamic deterioration, intravenous methylprednisolone is administered at a dose of 10 to 15 mg/kg body weight once a day for 3 to 5 days. This is followed by prednisone at 1 mg/kg/day, which is gradually reduced until the prerejection dose is reached. The remaining cases can be treated in the ambulatory setting with oral doses of 2 to 3 mg/kg once a day for 3 days, followed by a gradual reduction to, or direct restoration of, the previous corticosteroid dose. In the case of recurrent or persistent rejection with hemodynamic deterioration, polyclonal antibodies (ATGAM, thymoglobulin), or monoclonal antibodies (OKT3) can be added to the treatment with corticosteroids. With persistent or recurrent rejection or rejection accompanied by hemodynamic deterioration, a change in the baseline immunosuppression should be considered: adjustment of the CNI, a change from CsA to Tac or vice versa, a change from AZA to MMF and/or association of sirolimus or everolimus; in addition, corticosteroids should be maintained or reintroduced. Other alternative therapies for resistant or persistent acute rejection include total lymphoid irradiation367 and plasmapheresis associated with intravenous immunoglobulin or cyclophosphamide.110 This combination has also been used to treat humoral rejection.116 Table 14 shows the doses and concentrations of the immunosuppressive agents employed in pediatrics.118,363-371

Long-Term Complications

Graft Vascular Disease

Graft vascular disease is characterized by diffuse, progressive thickening of the arterial intima, occurring...
both in epicardial and intramyocardial coronary arteries. It is the major cause of morbidity and mortality both in children and adults after the first postoperative year. It causes 19.1% of the mortality between 1 and 3 years after transplantation, 36.7% between 3 and 5 years, and 28.1% after 5 years. Coronary angiography is the standard diagnostic method. This should be performed yearly, especially in older children and during the first years of follow-up. The incidence of angiographic GVD in adults is 10% and 50% 1 and 5 years after transplantation, respectively. The incidence in children is 7.5% and 25%, respectively. The ISHLT pediatric registry reports an incidence of 10.9% at 5 years and 12.8% at 8 years. Intravascular ultrasound has become the most sensitive and reliable diagnostic method. The experience in children is very limited for technical reasons; as in adults, the incidence is much higher when IVUS is employed as the diagnostic method instead of angiography: 38% and 74% at 3 and 5 years versus 11% and 23%, respectively. The incidence in patients who undergo transplantation during the first year of life appears to be lower than that reported in older children. The risk factors that have been related to GVD are time elapsed since transplantation, history of rejection within the first year after transplantation, development of late rejection episodes, CMV infection, and hypercholesterolemia. The utilization of statins has also been related to a decrease in

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Concentration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine A (Sandimmune Neoral capsules and oral solution)</td>
<td>At the time of HT: 0-3 months: 250-300 ng/mL</td>
<td>C2 determination (2 h after administration); better dose adjustment</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Concentration: 100-150 ng/mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maintenance: 4-10 mg/kg/day every 12 h</td>
<td>Increasingly widespread use</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus suspension (0.5 mg/mL) and 0.5 mg, 1 mg and 5 mg tablets</td>
<td>At the time of HT: 0.3 mg/kg/day every 12 h</td>
<td>Hospital-prepared (suspension)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Concentration: 5-10 ng/mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maintenance: 0.05-0.3 mg/kg/day every 12 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine (tablets 50 mg)</td>
<td>At the time of HT: 2-3 mg/kg/day every 24 h</td>
<td>No determinations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maintenance: 1-2 mg/kg/day every 24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycophenolate mofetil (suspension and 250/500 mg tablets)</td>
<td>Dose: 600 mg/m²/day every 12 h or 25-50 mg/kg/day every 12 h</td>
<td>Variable absorption. Greater efficacy than azathioprine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Concentration: 2-5 ng/mL (difficult to achieve in infants and small children)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sirolimus (suspension and 1 and 2 mg tablets)</td>
<td>Dose: 1-3 mg/kg/day every 24 h</td>
<td>Hospital-prepared. Compassionate use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Concentration: 5-10 ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everolimus (pills and tablets)</td>
<td>Dose: 0.8 mg/kg/dose (maximum 0.75 mg) every 12 h</td>
<td>Same indications as for sirolimus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Concentration: 3-8 ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basiliximab</td>
<td>Dose: 12 mg/kg², (maximum 20 mg) iv, days 0 and 4 post-HT</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(maximum 0.75 mg)</td>
<td>Growing use. Preferred over daclizumab (greater convenience and more economical)</td>
<td></td>
</tr>
<tr>
<td>Daclizumab</td>
<td>1 mg/kg/dose iv weekly (5 dose)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Thymoglobulin</td>
<td>1.5 mg/kg/dose iv infusion 5-7 days</td>
<td>Treatment of rejection</td>
<td></td>
</tr>
<tr>
<td>ATGAM</td>
<td>15 mg/kg/day iv infusion 5-7 days</td>
<td>Treatment of rejection</td>
<td></td>
</tr>
</tbody>
</table>

HT indicates heart transplantation.
the incidence of GVD in children, and many groups employ them systematically. The mortality rate in patients with GVD is high, whether due to progressive ventricular dysfunction or to sudden death. At the present time, there is no uniform approach to severe coronary lesions; some groups recommend retransplantation if the lesions are severe, due to the high incidence of sudden death in this group, and others, only if they are associated with evidence of graft dysfunction or inducible ischemia.

The most promising noninvasive technique for the detection of ischemia is dobutamine stress echocardiography. In preliminary studies, it has also been demonstrated that, in children, a positive result is predictive of a complicated course (development of serious events during follow-up). The early detection of GVD by means of noninvasive tests would make it possible to introduce changes in the treatment that could contribute to improving the prognosis in these patients.

Although the only effective treatment for established GVD is retransplantation, the utilization of alternative immunosuppressive regimens might slow its progression. On the other hand, given the diffuse nature of the lesions, the role of interventional procedures is limited. A lower incidence of GVD has been reported in series of adults treated with combinations of calcineurins with MMF or sirolimus, or everolimus instead of AZA. Studies to compare Tac/CsA and MMF or everolimus are underway.

Renal Failure

Data from the ISHLT registry show an incidence of alterations in renal function (RF) of 9.9% at 5 years and of 10.3% at 8 years, with a rate of serious conditions (Cr >2.5 mg/dL) of 0.8% and 0.6%, respectively. Dialysis is required by 1.5% of the patients and, after 8 years of follow-up, 0.6% have had to undergo renal transplantation. Follow-up studies of transplant recipients of more than 10 years duration have reported a risk of having a Cr level >2.5 mg/dL of 0.8% to 1%, respectively. The change in RF is related to the use of calcineurins. Late RF alterations have been associated with the CsA concentration during the initial months after cardiac transplantation. The Cr level is not a reliable marker of renal failure, and Cr clearance should be determined if renal failure is suspected. The best indicator of the probability of late renal failure is almost certainly Cr clearance 1 year after transplantation. The aim of the strategies for treating children with renal failure is to reduce the doses of calcineurins and associate MMF or sirolimus/everolimus.

Diabetes

In general, the incidence of DM is low if immunosuppressive regimens with CsA are employed. The incidence is higher with treatments involving Tac, especially when combined with corticosteroids.

Tumors and Lymphoproliferative Syndromes

Data from the ISHLT registry show that over 90% of the recipients are tumor-free 7 years after transplantation. The most common tumors are those associated with LPS related to primary Epstein-Barr virus infection; thus, the incidence is higher in children than in adults. Up to 63% of the primary infections can culminate in a LPS, versus 5% in patients who were previously seropositive. In half the patients, the disease is located in the head and neck and the histological features are those of plasmacytic hyperplasias, with a benign course and a good response to therapy in the majority of cases. Polymorphic and monomorphic B-cell lymphomas, generally with systemic involvement, are other more serious forms of LPS. The recommended treatment is the reduction of the immunosuppressive therapy and introduction of antiviral therapy with ganciclovir or acyclovir. Either everolimus or rituximab can be of use in these cases.

The role of Epstein-Barr virus infection in the development of LPS indicates the need for a diagnostic protocol, especially in seronegative recipients. Patients who undergo seroconversion should be tested for active infection using PCR, and screening studies for tumors that include assessment of ears, nose and throat and abdominal computed tomography should be carried out.

Growth and Bone Complications

There is little data on linear growth, adult stature and peak bone mass in children who undergo HT. In pediatric solid organ transplant recipients, there are predictors of retarded growth, such as height at the time of transplantation or chronic disease with severe malnutrition or renal dysfunction following transplantation. Marked changes in bone status, such as fractures or avascular necrosis, are uncommon. Osteopenia is difficult to evaluate, and densitometry (DEXA) should be carried out, although, in pediatrics, its interpretation has its limitations, as well as serial studies of the RF and calcium, phosphorus, magnesium, vitamin D, and parathyroid hormone metabolism. The most widely recommended prophylactic measures involve encouraging physical activity, reducing, or discontinuing steroid intake, avoiding renal failure secondary to calcineurins following transplantation and prescribing calcium and vitamin D supplements (according to analytical studies and if corticosteroid therapy is maintained). The use of bisphosphonates requires further research.

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Hepatitis B<sup>a</sup> (HBsAg-mothers [-]) HB<sup>b</sup> HB<sup>b,c</sup> HB<sup>b,c</sup> HB<sup>b</sup> HB<sup>b</sup>

Diphtheria, tetanus, pertussis<sup>e</sup> DTaP DTaP DTaP DTaP dTpa

Polio virus<sup>f</sup> IPV IPV IPV IPV

H influenzae<sup>h</sup> Hib Hib Hib Hib

Meningococcus C<sup>h</sup> MC MC MC<sup>c</sup> MC<sup>c</sup>

Measles, rubella, mumps TV TV

Varicella<sup>j</sup> Var Var

Pneumococcus<sup>k</sup> PCV7 PCV7 PCV7 PCV7

### Immunization Schedule of the Spanish Pediatric Association for 2005

**Vaccine Advisory Committee**

**Figure 2. Vaccines. Immunization schedule of the Spanish Pediatric Association for 2005.**

1. Administration of the hepatitis B vaccine at 0-2-6 months of life.
2. Administration of the hepatitis B vaccine at 2-4-6 months of life.
3. Administration of the varicella vaccine (Var) for healthy children at the age of 12-15 months; beyond this age, selective immunization for susceptible children is performed. It is administered in a single dose or two doses separated by 4-8 weeks.
4. Administration of the diphtheria, tetanus, pertussis (DTaP) vaccine with each dose. Fourth dose administered at the age of 6 years.
5. Administration of the inactivated poliovirus vaccine (IPV) with each dose. Four doses are sufficient.
6. Administration of the conjugate vaccine against Haemophilus influenzae type b (Hib).
7. Administration of the conjugate vaccine against Neisseria meningitidis group C (MC). The most recent epidemiological data indicate that it is advisable to administer a booster dose in the second year of life, regardless of the doses received in primary immunization; this is controlled by 2 doses of Nice-Ig or 3 doses of Menites<sup>h</sup>. This booster immunization is also recommended for adolescents and young adults.
8. Administration of the heptavalent pneumococcal conjugate vaccine (PCV7) 2-4-6-month protocol with a booster vaccine in the second year of life.
9. Administration of the tetanus, diphtheria, pertussis vaccine (Tita) 2-4-6-16 years protocol with a booster vaccine in the second year of life.
10. Administration of the tetanus, diphtheria, pertussis vaccine (Tita) 2-4-6-16 years protocol with a booster vaccine in the second year of life.

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**Notes:**

- Either of 2 immunization protocols can be employed: a) starting at birth and continuing at the age of 2 and 6 months; b) starting at the age of 2 months and continuing at 4 and 6 months. The children of women with hepatitis B virus in serum positive (HbsAg) should receive 1 dose of vaccine (HB) combined with 0.5 mL of hepatitis B immunoglobulin at different anatomical sites within the first 12 hours of life. The second dose is administered at the age of 1 month and the third at 6 months. When the HBsAg status of the cord is unknown, the doses should be vacinated at birth and the mother should undergo testing to determine whether she is positive, in which case, the hepatitis B immunoglobulin should be administered within the first week of life.

- Administration of the varicella vaccine (Var) for healthy children at the age of 12-15 months; beyond this age, selective immunization for susceptible children is performed. It is administered in a single dose or two doses separated by 4-8 weeks.

- Administration of the pertussis-diphtheria-tetanus (DTPa) vaccine with each dose. Fourth dose administered at the age of 6 years.

- Administration of the inactivated poliovirus vaccine (IPV) with each dose. Four doses are sufficient.

- Administration of the conjugate vaccine against Haemophilus influenzae type b (Hib).

- Administration of the conjugate vaccine against Neisseria meningitidis group C (MC). The most recent epidemiological data indicate that it is advisable to administer a booster dose in the second year of life, regardless of the doses received in primary immunization; this is controlled by 2 doses of Nice-Ig or 3 doses of Menites<sup>h</sup>. This booster immunization is also recommended for adolescents and young adults.

- Administration of the heptavalent pneumococcal conjugate vaccine (PCV7) 2-4-6-month protocol with a booster vaccine in the second year of life.

- Administration of the tetanus, diphtheria, pertussis vaccine (Tita) 2-4-6-16 years protocol with a booster vaccine in the second year of life.

- Administration of the tetanus, diphtheria, pertussis vaccine (Tita) 2-4-6-16 years protocol with a booster vaccine in the second year of life.
Immunization

Due to the limitations that develop after HT, immunization must be carried out prior to transplantation. This strategy should be extended to the entire family and other members of the household, whose immunization schedules should be checked and updated, if necessary.

Prior to Transplantation

The usual immunization schedule recommended by the Spanish Pediatric Association should be updated and completed at least 14 days before transplantation. A rapid immunization protocol can be employed with combinations of vaccines to reduce the number of injections. Serological studies, including antibody titers against parotitis, measles, rubella, varicella, and hepatitis B, should be performed in children over 12 years of age.

The child should be vaccinated against varicella (Varilrix), a measure that is not required in all the Spanish autonomous regions. This vaccine should be administered at least 4 weeks before transplantation to children with negative serology who have not been immunized previously. The trivalent vaccine should also be administered 1 month in advance to children who have not had at least 2 prior doses or who have negative serology. The risk of severe pneumococcal infection (Pn) is high, even more so than in splenectomized patients. The heptavalent pneumococcal conjugate vaccine (PCV7) is utilized in children under the age of 2 years and a single dose of the 23-valent pneumococcal polysaccharide vaccine (PPV23) (for those over the age of 2). Revaccination against hepatitis B will be carried out if pretransplantation serology is negative. Hepatitis A vaccination is also recommended. The influenza vaccine can be administered in seasons of higher risk and all older children should be revaccinated with conjugate vaccines against Haemophilus influenza type b (HiB) and Neisseria meningitides group C (MC).

Posttransplantation

In those recipients who were not immunized prior to transplantation, vaccination will begin following the reduction of the immunosuppressive therapy (6 months for vaccines against hepatitis B, Pn, MC, HiB, and diphtheria-tetanus-pertussis [DTP], and the tetanus-diphtheria [TD] and inactivated poliovirus [IPV] vaccines, and 1 year for influenza), with the limitation that the protective response is weaker. In specific cases (hepatitis B), serological studies should be performed. Thereafter, the usual schedule (Figure 2) is generally followed according to age, except for live vaccines (trivalent and oral poliomyelitis, which has been replaced in the usual schedule by the IPV).

Prophylaxis with the humanized monoclonal antibody, palivizumab, is recommended to prevent respiratory syncytial virus infection in children under the age of 2 years during the season of higher risk (October to March), both before and after transplantation. Prophylaxis against CMV is based on the use of ganciclovir or valganciclovir in CMV-negative recipients of hearts from donors with CMV or undetermined CMV status. Polyclonal antibodies (Cytotect) can also be added in special situations. This same combination would appear to play a role in the prevention of Epstein-Barr virus infection. In case of contact with varicella, if the child has not been vaccinated and does not have antibodies to the virus, a varicella-specific gamma globulin (20 mg/kg/day in 4 doses for 5 days) will be administered.

ACKNOWLEDGEMENTS

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A comparison of bisphosphonates and vitamin D.  


A comparison of bisphosphonates and vitamin D.  


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