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Indications and Outcome in Adult Heart Transplantation: A Review

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2019

INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR

UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

Indications and Outcome in Adult Heart Transplantation: A Review

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JUNHO 2019

Assinatura do Estudante

Assinatura Orientador

7 de Junho de 2019

Resumo

Introdução: O transplante cardiaco tem sido o tratamento gold standard para os doentes com insuficiência cardiaca em estadio terminal nos últimos anos. A mortalidade diminui nas últimas décadas e os doentes mostram uma melhoria da sua qualidade de vida, tendo uma sobrevida superior a 12 anos. O objective nesta revisão é dar a conhecerr alguns dos mais recentes avanços nos resultados a curto e a longo prazo, mais propriamente, na Vasculopatia Cardiaca do Enxerto, tempo de isquemia do enxerto, rejeição, suporte circulatorio mecánico e na imunossupressão e comprender como é possivel ajudar ainda mais estes doentes.

Métodos: Foram pesquisados artigos no PubMed e foram acedidos ao report e guidelines do ISHLT, Eurotransplant, ACCF/AHA, UNOS e ESC tendo sido selecionados 81 artigos para esta revisão.

Resultados: Nos últimos anos temos observado uma mudança na imunossupressão com o uso de Micofenolato de mofetil e Tacrolimus a aumentar e o uso de Ciclosporina e Azatioprina a diminuir. O Everolimus apresenta bons resultados na manutenção da função renal apesar de aumentar o risco de rejeição. A rejeição tem diminuido de incidência nos últimos anos mas o seu diagnóstico precoce e o follow up mostra-se incerto. A Vasculopatia Cardiaca do Enxerto é a causa mais importante de comorbilidades a longo prazo sendo o diagnosticada através da angiografia coronária.

Discussão: Nos últimos anos temos observado um aumento da idade do recipiente e do dador o que pode afetar os resultados nestes doentes. É preciso ainda considerer esta mudança e o seu efeito na sobrevivência. É necessário mudar os criteria de exclusão de dadores já que as politicas atuais se mostraram bastante restritas. São necessário mais estudos sobre a etiologia da CAV, a sua prevenção e o diagnóstico de forma mais precoce. O uso de TCMS é importante no tratamento da disfunção do enxerto ou como ponte para o transplante apresentando bons resultados.

Conclusão: São necessários mais estudo sobre os doentes com indicação para transplante cardiac e sobre os novos agentes imunossupressores. A vasculopatia cardiaca do enxerto e a rejeição necessitam de testes com maior precisão de diagnóstico para melhorar a sobrevivência dos doentes transplantados.

Abstract

Introduction: Heart transplantation represents the gold standard treatment for patients with end-stage HF in the last years. Mortality after transplant decreased in the last decade and patients show improvement in their quality of life. The objective is systematically reviewing the advances in the outcome, more exactly in Cardiac Allograft Vasculopathy, allograft ischemic time, rejection, mechanical circulatory support and immunosuppression and understand how we can help more these patients.

Methods: PubMed and guidelines/report from ISHLT, UNOS, *ACCF/AH, Eurotransplant,* and ESC were researched, and 81 articles selected for this revision.

Results: In the last years we observe a change in the immunosuppression with the use of Mycophenolate Mofetil and Tacrolimus instead of Ciclosporin and azathioprine. Everolimus presents great results in the manutention of renal function but increase the risk of rejection. In the last years the rejection becomes less common but the early diagnostic and the follow-up of patients still uncertain and difficult. The Cardiac Allograft Vasculopathy still the most important cause of late graft dysfunction and the best approach to diagnostic is the coronary angiography.

Discussion: In the last years we observe an increase in the age of donors and recipient, what cause a change in the outcomes of this patient. Is important to consider that this change and the effect in the survivor. Is necessary to change the criteria of exclusion for non-use of donors because they are very restricted. Is necessary more study's about the Cardiac Allograft Vasculopathy to understand how we can prevent and make the correct diagnostic. The use of mechanical circulatory support is important for the treatment of graft dysfunction or to make the bridge until transplant with excellent outcomes.

Conclusion: Is necessary more studies about the population that need a transplant and about the new option for immunosuppression. CAV and rejection need a more efficient test for diagnoses.

Keywords:

Heart Transplantation, therapeutic use, patient selection, treatment outcome;

Abbreviations

HT: Heart Transplantation

HF: Heart Failure

UNOS: United Network for Organ Sharing

CCMP: Chemotherapy-induced Cardiomyopathy

RT-CMP: Radiotherapy-induced Cardiomyopathy

NICMP: Non-ischemic Cardiomyopathy

IVUS: Intravascular Ultrasound

MIT: Maximal Intimal Thickness

CNI: Calcineurin Inhibitor

TAC: Tacrolimus

CsA: Ciclosporin

EVR: Everolimus

SIR: Siromilus

mTOR: Mammalian Target of Rapamycin Inhibitors

AR: Acute Rejection

EMB: Endomyocardial Biopsy

AZA: Azathioprine

MMF: Mycophenolate Mofetil

MPA: Mycophenolic Acid

ACR: Acute Cellular Rejection

AMR: Antibody-mediated Rejection

LR: Late Rejection

HLA: Human Leukocyte Antigen

PRA: Panel Reactive Antibody

DSA: Donor-specific Antibodies

PGD: Primary Graft Dysfunction

EGF: Early Graft Failure

CPR: Cardiopulmonary Resuscitation

ACS: Acute Coronary Syndrome

ASP: Attenuated-signal Plaque

GEP: Gene Expression Profiling

FFR: Fractional Flow Reserve

IMR: Index of Microcirculatory Resistance

LVGLS: Left Ventricular Global Longitudinal Strain

LVFP: Restrictive Left Ventricular Filling Pattern

MACE: Major Adverse Cardiovascular Event

OCT: Optical Coherence Tomography

LFP: Layered Fibrotic Plaque

NFCP: Nonfatal Cardiac Allograft Vasculopathy Progression

CFR: Coronary Flow Reserve

CA: Coronary Angiography

LVAS: Left Ventricular Assist System

DCA: Adriamycin

OCS: Organ Care System

PPV: Positive Predictive Value

NPV: Negative Predictive Value

CAD: Coronary Artery Disease

ATG: Anti-thymocyte Globulin

GFR: Glomerular Filtration Rate

CAV: Cardiac Allograft Vasculopathy

CMV: Cytomegalovirus

EBM: Endomyocardial Biopsy

MCS: Mechanical Circulatory Support

LVAD: Left Ventricular Assist Device

VAD: Ventricular Assist Device

ECMO: Extracorporeal Membrane Oxygenation

VA-ECMO: Veno-arterial Extracorporeal Membrane Oxygenation

RVAD: Right Ventricular Assist Device

DSE: Dobutamine Stress Echocardiography

OHT: Orthotopic Heart Transplantation

LVH: Left ventricular Hipertrofy

LVEF: Left Ventricular Ejection Fraction

PSI: Proliferation Signal Inhibitors

IECA: Isolated Eosinophilic Coronary Arteritis

ARB: Angiotensin Receptor Type I Blocker

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Introduction

The first successful HT in humans occurred in 1967 in South Africa [1]. Fifty years later a lot has changed, becoming the gold standard treatment for patients with end-stage HF [2] and the only one that allows the recovery of approximately 70% of their quality of life [1]. In the 2018 ISLHT report, transplant patients have an average life expectancy greater than 12 years, one of the biggest achievements of this procedure [1]. Despite a negative trend in the volume of transplants performed at the beginning of the 21st century, due to the decrease in organ supply and the increase in demand, the most recent data show a positive evolution in the last decade, with more than 3000 transplants in the USA in 2017. [1, 3-5]

The latest ISLHT report in the USA observes an increase in older donors, an increase in the average age of recipients (55 years old), and in recipients over 70 years old without affecting long-term survival. The main indications for HT in adults were non-ischemic dilated cardiomyopathies and ischemic cardiomyopathy, which had the highest long-term survival rates. Retransplantation continues to represent a small part (2.2%) of transplants and presents a low survival rate overall [1].

According to 2017 Eurotransplant report, HT is the fourth most performed transplant, with donor numbers slightly declining during the last decade. The average age of the donor has risen in recent years and is close to 45 years old, somewhat different from the American reality [6, 7].

The main causes of mortality in these patients are graft dysfunction in the first 30 days, infectious causes in the first year and in the long-term, renal failure, and CAV. Rejection, ACR and AMR are also important factors in the prognosis of these patients, whose incidence has decreased due to immunosuppressive treatment. The risk of malignancies in the long-term is high, with an incidence of approximately 28%, the most common being skin neoplasia. Despite this, approximately 60% of the patients are not hospitalized during the first year and 80% between the second and fifth year of transplantation [1]. Immunosuppressive therapy has been one of the areas with the most advanced in recent years [1, 4, 8]. The most recent treatments include MMF or MPA and TAC, with a survival rate similar to older regimens with CsA and with fewer side effects [1, 9].

Despite major developments in surgical technique and diagnostic techniques, long-term survival is still limited by CAV, acute rejection, and the side effects of immunosuppressive therapy [4]. Increased donor and recipient age, increased co-morbidities and marginal donors, and

increased use of LVADs make it even more necessary to continue efforts to increase the survival of these patients [8, 10].

Methods

A search was performed on PubMed using the following keyword combinations: “Heart transplantation”, Mortality”, “adult”, “Practice Guideline”, “Patient Selection”, "Treatment Outcome" and “utilization”. 173 studies found using the mentioned keywords were selected to this revision. Inclusion criteria were: written in English or Portuguese, retrospective study, an observational study, prospective study, or guideline and published between 2009 and 2019. Just adult populations were accepted and 19 articles about congenital heart disease are excluded because the main manifestations are in pediatric age. 39 articles are excluded because they are duplicate in the research. 71 articles after the read of abstract and title are excluded because they cover topics not included in this revision (multi-transplant, therapy for end-stage HF, recipient treatment, waiting list, treatment for CAV and rejection, another disease like amyloidosis and adhesion to therapeutic). 10 relevant papers cited in the selected articles were added to the group. 17 guidelines are included from ISHLT, ACF/AHA, Eurotransplant, OPTN/SRTR and Society of critical care medicine, ending up with 81 articles analyzing in this review.

Results

1. Indications

HT is the most commonly used therapy for patients with end-stage HF when they no longer respond to medical therapy [2]. Lenneman *et al* and Oliveira *et al* evaluated the patients undergoing transplantation for dilated cardiomyopathy due to chemotherapy, a growing population, consisting of young female patients with a higher prevalence of breast neoplasia and leukemia [11, 12]. A 10-year survival was higher (P = 0.026) in the Lenneman study [11] and the same in the Oliveira study (P = 0.19) [12]. There was no increase in mortality due to neoplasia or its recurrence. The infection rate was higher in the Oliveira study (P = 0.006) [12]. These patients presented a greater need for right ventricular assist devices prior to transplantation (P = 0.0021) and longer ischemia time (P <0.001) due to their use [12].

Patients with HF are only indicated for transplantation at an advanced stage, which often makes the transplant difficult. With this idea, Lund *et al* evaluated the use of a screening test to identify patients eligible for transplant (SEE-HF, ScrEEning for Advanced Heart Failure) in patients undergoing resynchronisation therapy and with stage III and/or IV HF NYHA and EF <40%, with 1.5% of patients screened being indicated for transplantation and LVAD [13].

The existence of available donors is a determining factor in HT, and in recent years the number of donors has increased [5]. Bombardini *et al* evaluated the use of stress echocardiography to select donors aged >55 or with cardiovascular risk factors and the survival rate after 1 year was 93% and after 3 years 37 of the 43 recipients were alive [14].

In recent years, we have witnessed an increase in the use of marginal donors. Aliabadi-Zuckermann *et al* observed that the 3-year survival rate in Vienna was 79% and the survival of organs accepted by other centres after being rejected by Vienna for non-quality reasons and quality reasons was 73% and 63% (P <0.001), with higher survival in the case of positive virology (77%), high catecholamines (68%), long ischemic time (71%) or low ejection fraction (68%) and lower in the case of hypernatremia (46%), cardiac arrest (21%) and valvular pathology (50%) [15].

In an attempt to improve the selection of recipients, Weiss *et al* created a score, IMPACT (Table 1), with 12 recipient variables, up to 50 points, which is associated to mortality after the first year [16]. According to this score, survival at 1 year with a score between 0 and 2 was 92.5%, between 7 and 9 points was 86.3%, higher than 10 was 74.9% (P <0.001) and with scores higher than 20, mortality was greater than 50% [16]. Trivedi *et al* created a score (Table 2) for mortality based on the donor and the recipient [17]. Based on this score, low-risk recipients (score = 1) were combined with high-risk donors (score ≥3) and survival at 1 and 5 years of age was 89% and 74%,

respectively, and the combination of high-risk donors and recipients (score ≥5) had a survival rate of 62% and 49% [17].

2. Outcome

Mortality after transplant decreased in the last decade [5], is one of the major achievements of HT. Patients show great improvement in their quality of life, however, infections, neoplasias, chronic renal disease, and CAV continue to interfere with long-term survival [18].

Organ preservation evolved greatly, and OCS, a new ex vivo perfusion platform, was studied by Ardehali *et al* in a PROCEED II study and by Chan *et al* in a retrospective study. Survival at 30 days (P = 0.45) [19] and at 2 years (P = 0.38) [20], rejection rates and cardiovascular events were similar to the cold storage group [19, 20]. The mean total preservation was higher and the cold ischemia time was lower [19, 20].

Immunosuppressive therapy has changed greatly in recent years, and the study by Zijlstra *et al* observed that, between 2000 and 2013, immunosuppressive therapy was TAC and/or MMF, received statins early on and renal function remained stable over 5 and 10 years (P = 0.001 and 0.002). The transplant group from 1984-1999 had younger patients, a lower donor percentage >50 years, and an immunosuppressive treatment consisting of CsA and AZA. Despite the increase in donor and recipient age and comorbidities, the most recent era presented a higher survival rate at 10 years (80% vs 60%) [9].

A randomized clinical study, SCHEDULE, by Andreassen *et al,* evaluated the introduction of EVR between the 7^{th} and 11^{th} week in maintenance therapy with MMF and steroids. EVR presented higher GFR after the first year (P <0.001), reduction in the incidence of CAV (P = 0.003), lower MIT (P = 0.03), lower incidence of CMV infection (P <0.001), but higher incidence of acute rejection (P = 0.03) [21]. This study was continued for a further 3-year period and GFR was higher (P <0.001) and MIT lower (P = 0.019), with EVR and the incidence of CAV and acute rejection similar to CsA group (P = 0.104, P = 0.483) [22]. Authen *et al* evaluated the effect of EVR and CsA on quality of life before, 12 and 36 months after HT and found no differences between immunosuppressive agents and the 3 questionnaires (p<0,01) [23]. A retrospective substudy of SCHEDULE by Nelson *et al* in 2017 found that GFR was greater in the EVR group at 1 and 3 years (P = 0.0004 and P = 0.03), as was the ratio of albumin/creatinine in urine (ACR) (P = 0.002) [24]. Helmschrott *et al* observed that eGFR, serum creatinine and the incidence of ACR were similar between mTOR/CsA and mTOR/TAC (P >0.05), and repeated measurement of eGFR showed a similar decrease in the 2 groups [25]. Kaczmarek *et al* observed that survival at 5 years was similar between TAC/MMF, SIR/MMF and TAC/SIR (P = 0.31, P = 0.47, P = 0.86) [26]. The rejection free period was lower such as the incidence of CAV in SIR/MMF [26]. The longest free period for CMV infection occurred with

TAC/SIR (89.7%) [26]. GFR remained stable in SIR/MMF (P = 0.045) [26]. The discontinuation of medication was higher with TAC/SIR (P = 0.034) and with SIR/MMF (P = 0.003) [26]. Guethoff *et al* observed that survival at 1, 5 and 10 years was similar between TAC/MMF and CsA/MMF (P >0.05), however, the free period without AR was higher with TAC/MMF (P = 0.004), just as the CAV-free period at 5 and 10 years (P = 0.003) [27]. In a randomised prospective study from 2015, Guethoff *et al* found that the rejection-free period and incidence of CAV was not different between low-TAC/SIR and TAC/MMF (P = 0.100, P = 0.922), just as the value of creatinine and survival at 5 and 8 years (P = 0.957, P = 0.957, P = 0.138) [28]. Kobashigawa *et al* showed that after 1 year, the increase in MIT was lower in EVR (P <0.001), as was the incidence of CAV (P = 0.018) and the incidence of CMV infection (P <0.001) compared to MMF [29]. Watanabe *et al* studied the replacement of MMF with EVR 2 years after HT and EVR presented a low increase in plaque volume (P = 0.004) and a decrease in lumen volume (P = 0.017) [30].

Rejection is one of the problems that continue to interfere with patient survival [8]. Soderlund *et al* showed that ACR ≥2R in the 1st year is more common in the EMB per clinic (P <0.05) between 1988-1999 (P <0.05) and between 16-52 weeks (P <0.05) [31] and that ACR≥2R after the 1st year is also more common in the EMB per clinic (P <0.05) [32]. Imamura *et al* observed that patients with PRA + (P = 0.042) presented LR earlier [33]. The risk factor for LR was PRA + (P = 0.020) whereas for ACR it was sex mismatch (P = 0.042) [33]. Farrero *et al* observed that patients with DSA post-transplant had a higher incidence of ACR (P < 0.001) and AMR (P <0.001), especially in C1q + patients [34]. Survival in DSA + was lower due to high acute rejection mortality (P = 0.031) but there was no difference between the C1q + and – groups [34]. In 2015, Kobashigawa *et al* evaluated, in the IMAGE trial, the use of GEP instead of EBM and, after 18 months, no differences were observed in the level of mortality, retransplantation rate, rejection, graft dysfunction (P = 0.44), MIT increase (P = 0.944), echocardiographic study and satisfaction level [35].

The use of MCS has been increasing in the last years, whereas VAD is the most used [1]. Tran *et al* observed that the use of ECMO due to graft dysfunction results in lower mortality (P = 0.02), while patients requiring CPR have a high mortality rate (P = 0.01), especially when CPR> 30 min (P = 0.001) and EF> 35% (P = 0.001) [36]. Tchantchaleishvili *et al* showed that the use of MCS decreased survival at 30 days (P = 0.01) and at 1 year (P <0.001), with RVAD or VA ECMO presenting the highest survival rates (P = 0.055) [37]. Johnston *et al* 2016 created a score, TRIP-MCS (table 3), to assess mortality in the first year after HT, after the use of MCS [38]. It is a score of up to 57 points, with 13 donor's and recipient's variables. The first-year mortality rate predicted through this model was similar to the observed values (P <0.001), with one point increasing mortality by

8.3% [38]. Patients were divided into risk groups: low (0 to 10), intermediate (11 to 20) and high (> 20) with a mortality of 8.6%, 12.8% and 31%, respectively [38].

CAV is one of the major causes of mortality in the long-term [1] and its diagnosis is done with CA [39]. Okada *et al* observed that patients with increased ASP had a higher incidence of ACR (P = 0.006), such as plaque volume (P = 0.07) and an even higher mortality and retransplantation rate (P = 0.0005) [40]. In 2016, Yang *et al* evaluated several physiological indicators of coronary heart function such as FFR and IMR, whereas an IMR ≥20 after 1 year (P = 0.01) and FFR <0.90 (P = 0.03) shortly after transplantation are predictors of mortality in the long-term (P = 0.009) [41]. The decrease in IMR in the first year post-transplant is related to increased patient survival (P = 0.03) [41]. In 2016, Clemmensen *et al* found, in a prospective study, that the LVGLS ultrasound marker is a good predictor of MACE in patients with or without CAV (P <0.0001, P <0.05) and of mortality (P <0.0001) [42]. LVFP is a predictor of MACE in patients with CAV (P <0.01) [42]. The combination of both markers makes them predictors of MACE and mortality (P <0.0001, P <0.0001) [42]. In 2017, Clemmensen *et al* evaluated the coronary microcirculation through OCT and the area of the intima increased (P <0.0001), the lumen decreased in only 2% (P <0.01), the LFP increased more than 5 times (P <0.001) as well as the bright spots (P <0.001), while plaque lipids (P = 0.78) and calcification (P = 0.37) remained stable [43]. In another study, Clemmensen *et al* observed that LFP was the most prevalent CAV lesion in the OCT and is related to its severity (P <0.01) [44]. LFP (P <0.0001) and bright spots (P <0.001) were predictors of NFCP and were also combined (P <0.0001) [44]. Rutz *et al* studied the contrast echocardiography and its markers, rBV, indicative of microvascular density, lower in the group with CAV (P = 0.0157) and β, indicative of coronary conduction, higher in patients with CAV (P = 0.0410) [45]. rBV is inversely related to the intimal thickening detected by the IVUS and an rBV <0.14 predicts a CAV, with a sensitivity of 75% and a specificity of 90% (P = 0.004) [45]. Sade *et al* observed that 9 patients with CAV were diagnosed through CA, 10 through DSE and 14 through CFR [46]. DSE has a sensitivity of 55.6% and a specificity of 64.3%, a PPV of 50% and an NPV of 69.2% [46]. CFR has a sensitivity of 100%, a specificity of 64.3%, a PPV of 64.3% and an NPV of 100% [46]. The combination of both allows an increase in specificity to 87.2% [46]. In the study by Peled *et al*, 47% of patients received aspirin during the first month and had a lower incidence of CAV (P <0.001) and mortality (P <0.0001) [47]. The use of aspirin decreased mortality by 84% (P <0.001) and CAV by 68% (P <0.0001) [47]. The risk factors associated with CAV and mortality were CMV (P = 0.02), smoking (P = 0.008) and history of rejections (P = 0.0038) [47]. In the study by Kim *et al*, 49% of patients received aspirin up to 6 months post-transplant and the incidence of CAV was lower in this group (P = 0.04) [48]. Tremblay *et al* observed that patients between 1983-1998 presented a higher incidence of

smoking, renal dysfunction, alteration of levels of LHDL, higher incidence of rejection, young donors, CA ($P < 0.001$) and prevalence of CAV ($P = 0.005$) [49]. Independent factors for progression of CAV were the young age of the recipient ($P = 0.013$) and early-stage transplantation ($P = 0.049$) [49].

Discussion

1. Indication

The assessment of patients with end-stage HF for their selection for transplantation should be done by a multidisciplinary team and based on the guidelines [4]. Both AHA [2] and ESC [50] present indications for HT. But in 2016, ISHLT, the world's largest transplant organization, presented an update on indications and contraindications for transplant candidates (Table 4) [51, 52] and these are the most commonly used. Fragility was included in these guidelines due to its high prevalence in the elderly population, given that it is associated with the gradual and natural physiological decline that occurs with aging [53-55], aggravates the prognosis, the results with the use of LVAD and the need for hospitalizations [54]. Its presence may contraindicate the performance of the transplant [51, 55]. There is little consensus regarding the evaluation method and the type of tools that should be used in patient assessment [51]. Another change is the reference that highly sensitized patients have a high priority on the waiting lists due to increased difficulty in finding a compatible donor [51], due to the increased risk of rejection [56].

Despite high early mortality and low long-term survival [1, 51, 57, 58], retransplantation is an option for patients with chronic symptomatic or asymptomatic CAV with LV or graft dysfunction and no evidence of acute rejection [51, 58] or, in the case of primary graft failure as well [58]. In the 2014 ISHLT report on the subject, and although the number of retransplantations remains constant since 1982 (between 2% and 4%), it is highlighted that the increase in the long-term survival of recipients increases the likelihood of future retransplantation [58], whereas these results need to be improved.

Both the donor and the recipient have characteristics that are different from those of 50 years ago, the median age of the recipient went from 40 years old in 1982 [57] to 55 years old in 2018, with an increase in recipients >60 years old [1]. Although the age of the recipient is related to increased mortality [57], after an individual risk assessment, the recipients >70 years old may undergo transplantation [59-61]. In the Zilstra study in the Netherlands, it was observed that, despite the increase in the recipient's age, long-term survival also increased, due to improved long-term care [9]. With the increase of the recipient's age and the incidence of end-stage HF, transplantation is increasingly important as the only therapeutic option with gain in quality of life for the patient.

In the 2016 review, Bianco *et al* referred an increase in recent years of transplants by CCMP or RT-CMP, whereas these pathologies have gained greater recognition and a correct classification [62]. CCMP affects approximately 10% of patients and 2-4% of patients will present end-stage HF [12] and, according to UNOS, between 1987 and 2011, 0.8% of transplants had CCMP and RT-CMP

[62]. The increase in cancer and drug exposed survivors contributes to the increase in transplanted patients [11, 12, 62]. Anthracyclines, cyclophosphamide, trastuzumab and tyrosine kinase inhibitors are examples of agents that cause cardiomyopathy [12]. The higher risk of cardiomyopathy occurs in breast cancer, which accounts for the greater number of young and female patients in the studies by Oliveira and Lenneman [11, 12]. There is no free interval defined between cancer and transplantation [11, 63] and, according to the ISHLT guidelines, cancer is no longer a contraindication for transplantation [52]. Although OHT has been questioned in the past due to the risk of recurrence and infections, today it is a safe therapeutic option for these patients [12]. Due to the increase in cancer survivors, it is important to pay more attention to these patients, since they require special attention due to poorer results with VAD due to the thoracic adhesions.

Patients are referred to transplantation at an advanced stage, and the use of a screening test is a promising approach. Most patients undergoing transplantation or LVAD are in stage IV, the inclusion of the NYHA classification and the EF value increased the diagnostic value of the Lund screening [13]. It allows the identification of patients who may benefit from HT or LVAS at an earlier stage, even before the symptoms worsen, alert the physician to the possible benefit of transplantation in the patient and work with the patient on the advantages of transplantation [13].

The stagnation in the number of donors, in relation to the number of recipients [1] led to the use of marginal donor organs [14], increasing the pool of donors and the number of transplantations performed [64]. Marginal or high-risk donors are donors of advanced age (over 40 years old) or with cardiovascular risk factors [14, 65]. It is necessary to find a balance between the expansion of donor selection criteria and maintenance of the high survival of the recipients and the risk of graft dysfunction [64]. In a report on the use of marginal donors in France, limitations for the use of these donors are referred (Table 5) [64]. The use of donor organs between ages 40 and 55 presents a greater benefit, increased survival, in relation to the risk of CAD and LVH [65], which means their organs may be used [64]. The transthoracic echocardiogram, a non-invasive exam, evaluates cardiac motility and the LVEF of the graft [64]. According to the Bombardini *et al* study, the use of dipyridamole or dobutamine echocardiography allows the exclusion of grafts with motility alterations, both during rest and in stress [14]. The good medium-term results for survival and death similar to “normal” donors [14] are in line with the widening of donor age to >55 years as the exclusion criterion in the USA in 2015 (table 6) [66]. One of the consequences of the use of older donors is the increasing diagnosis of donor CAD [65]. Donor CAD increases the risk of early graft failure [14] but not of CAV [67]. It is diagnosed through CA (stenosis

≥50%) or IVUS (≥0.5 mm) after transplantation [67]. In the USA, CA is recommended in all donors over 40 years of age or donors with risk factors [66]. Thus, the increased use of marginal donors should be done with caution, and further studies are needed to evaluate the use of donors between the ages of 55-70 in the long-term [64].

Weiss and Trivedi created a score for mortality, both of which allow correct allocation of organs [16, 17]. Patients with a score of ≥20 on the IMPACT score present high mortality [16] and do not benefit from the use of marginal donors. The same line of thought can be applied to the Trivedi score, but with the advantage that it included data from the donor and allows a search for the best donor for the recipient in question, a very useful tool in the case of high-risk recipients, where it is possible to decrease the waiting period [17]. Through the Trivedi score, it is also possible to deduce that the use of high-risk donors in low-risk recipients is safe, which is important for better allocation of organs, without impairing long-term survival [17].

In recent years we have witnessed an expansion of organ acceptance criteria, both in the USA [66] and in Europe [15], as was observed in the Aliabadi-Zuckermann study in a center in Vienna. This center presented a lower organ acceptance rate (31.8%) than the European medium (38%), due to its stricter selection criteria [15]. This study showed that the center could broaden its donor acceptance policy without affecting short and long-term survival [15]. Positive virology, high level of catecholamines and low LVEF, all the factors related to the donor had the highest survival rates in other centers, which means that these should be the criteria to be changed [15]. The fact that all the factors are related to the donor, show the greater importance of the recipient in post-transplantation results [64].

2. Outcome

2.1 Allograft Ischemic time

Addressed by ISLHT in 2017, allograft ischemic time refers to the period in which the graft does not present blood supply, from the cutting of the aorta to the coronary reperfusion in the recipient [3]. In 2017, its value was 3.2 hours in the USA and >4 hours in Europe, and it has been decreasing since 2000 [3]. A value of >4h is associated with lower survival, both in the short and long-term, but with higher mortality risk in the immediate post-transplantation period [3] and is associated with PGD [68]. High values are associated with the risk of rejection, but unrelated to CAV [3] and are acceptable in younger recipients [3].

Despite the evolution of organ preservation in recent years [8, 19, 20] cold storage, where the organ is maintained in a cold environment, is still the most used technique [19, 20]. It presents a higher risk of allograft ischemic time, a longer cold ischemia time [19, 20]. Another technique, ex vivo perfusion, of which the Organ Care System (OCS) platform is an example, allows transport in

an environment similar to the normal physiological state (continuous perfusion of nutrients and oxygen in a warm environment that maintains the heartbeat) [19, 20]. The need for graft instrumentation and evaluation increased the total mean time for preservation, the time elapsed since the heart stopped until the reperfusion in the recipient but decreased the cold ischemic time, the period during which the organ remains in a cold environment, in the studies by Chan and Adehali [19, 20]. Survival at 30 days [19] and at 2 years [20] was similar to cold storage. The rejection of 5 organs in the Ardehali study [19] raises some questions regarding the OCS, due to the risk of lactate accumulation. Although it is not statistically important, the incidence of CAV is lower in the OCS group due to the shorter cold ischemic time [20], and further studies on the long-term results of this technique are required. In spite of this, the use of OCS allows the increase of the donor pool, the resuscitation of unacceptable organs, pre-transplant pharmacological or genetic use, the increase in organ availability and transportation between long distances [19]. With the use of marginal donors, the use of LVAD and previous cardiac surgeries on the rise, allograft ischemic time will increase [3, 34], and the OCS will be able to overcome this obstacle.

2.2 Immunosuppression

It encompasses induction therapy that covers the immediate post-operative and maintenance therapy that accompanies the patient throughout his/her life [4]. Induction therapy is only used in 50% of patients [1] and can be done with polyclonal antibodies, more specifically ATG in patients at high risk for rejection [8]. The maintenance therapy used in approximately 75% of cases in 2018 is TAC/MMF and corticosteroids during the first year, a triple regimen [1, 30], presenting low rejection rates and the improvement of renal function, which is the regimen recommended by ISHLT [8]. PSI can replace CNI starting at 6 months to reduce the risk of renal injury, and should not be introduced before due to the risk of non-healing of the surgical wound [8].

In recent years, the use of the CsA+AZA+prednisolone regimen decreased and the use of TAC+prednisolone+MMF increased, as observed in several studies [9, 31, 49]. The use of TAC is beneficial in relation to CsA, presenting a lower incidence of AR and CAV, without increasing overall survival [27]. ISHLT is consistent with these results and recommends the use of TAC instead of CsA [8]. The use of MMF, purine synthesis inhibitor [26, 29], presents greater survival when compared to AZA, lower AR rates [27] and no effects on renal function [26]. The use of MMF can cause diarrhea and leukopenia [25].

TAC and CsA are CNI [27] and, although they decrease the rate of AR [28], they present nephrotoxic effects, which decrease long-term survival [21-27]. In 2004, with the introduction of mTOR, EVR, and SIR, with antiproliferative effects (PSI) on hematopoietic and non-hematopoietic

cells [29] and neutral effect on renal function [21, 22, 24-26, 28]. These drugs decrease the risk of CMV infection and malignancies [25, 26, 69]. The use of mTOR is promising, by reducing the nephrotoxic effect of CNI, but is associated with the appearance of proteinuria as reported in Nelson's study and his use is contraindicated in patients with prior proteinuria due to the failure rate [24]. This study found no relationship between the value of GFR and proteinuria and the absence of regression of proteinuria with IECA or ARB show that the aldosterone or renin does not interfere in this framework [24]. The use of a regimen without CNI in high-risk patients does not require induction therapy due to the risk of rejection [26]. The elimination of CNI increased lateral effects such as poor healing of the surgical wound or pleural effusions [21, 22, 26], as previously mentioned in the ISHLT guidelines [8]. Patients recover their quality of life with the transplant but, due to the side effects of immunosuppressive therapies and the complications of the transplantation, they will present a lower quality of life than the general population [23]. Despite the benefits at the renal level, EVR may be associated with more severe psychological effects due to the risk of rejection [23].

The SCHEDULE study showed that the use of EVR introduced early on improves renal function and reduces CAV, in both the short and intermediate term [21, 22]. Despite increased rejection in the first year, its use may bring long-term benefits [21, 22]. Given that only low-risk patients were used in these studies since high-risk patients were excluded, the early use of EVR is safe in this group [22]. The Kaczmarek study revealed that treatment without CNI (SIR/MMF) maintains GFR during 5 years and increases the CAV-free period, but is poorly tolerated by the patient and increases the incidence of rejection [26]. The Imamura study found no association between EVR in the absence of CNI and late ACR [33], such as the Kaczmarek study [26]. Patients with side effects caused by CNI or MMF, with episodes of rejection, CAV or malignancies may benefit from the use of mTOR with low doses of CNI, which reduces CNI nephrotoxic potential and the risk of rejection of mTOR, however, the Helmscroot study showed no difference in eGFR and ACR between mTOR/CsA and mTOR/TAC [25]. One disadvantage of this study is that it did not indicate that mTOR was used, nor when it was introduced. In 2015, Guethoff showed that low-TAC/SIR showed no difference in the incidence of ACR, CAV, renal function and survival with TAC/MMF, and the benefit in renal function was not maintained during the 8 years [28]. This study had an 8-year follow-up, the largest of the studies with mTOR/mTOR, thus allowing the evaluation of their long-term effects. Unlike the SCHEDULE study, it did not present any benefit in renal function, just as the Helmscroot study, which shows that the protective effect of mTOR is not maintained in the long-term. These studies use different methods to evaluate renal function, from serum creatinine to GFR and eGFR, which makes it impossible to extrapolate their results and

compare them. Further clinical trials are important, in order to elucidate the long-term effects of mTOR despite its good short-term results. Studies in this field involve small populations with the intensification of studies such as Guethoff and Kaczmarek with mTOR, which present high discontinuation rates due to lateral effects, making it difficult to draw conclusions from these studies. Another point still to be clarified is when the introduction of mTOR should be made, and a balance must be found between the risk of rejection and the reduction of CNI exposure.

2.3 Rejection

Its strict monitoring is done through EMB during the first year [8]. After this high-risk period, high-risk patients should perform an EBM every 6 months, otherwise, the patient does not justify its performance and may opt to use ventricular evoked potentials [8].

Sensitization, presence of autoantibodies, decreases compatibility with the donor, or post-transplantation (DSA) is associated with rejection [33], CAV and decreases long-term survival [56]. Female recipients are more likely to be previously sensitized, due to pregnancies and a higher incidence of autoimmune diseases [33]. The use of LVAD or previous surgeries increases the risk of sensitization [70]. PRA value >10% detects the risk of sensitized patients and should be performed prior to transplantation [56, 71]. In 2018, a new recipient allocation system (table 7) entered into force at UNOS, which included 6 zones, one of them for sensitized recipients [72], to decrease the waiting list of these patients and following the ISHLT recommendations [5].

In the Soderlund study, the highest number of EBM was recorded between 1988 and 1999, which can be explained by the development of induction and maintenance immunosuppressive therapy [31]. The highest number of EMBs was between week 16 and 52, due to poor therapeutic control and decreased use of immunosuppressants during this phase [31, 33] indicating that this period requires more vigilance through EBM. According to Soderlund, high-risk patients (patients with sex mismatch and history of ACR in the first year) should perform EMBs periodically [32], as recommended by the ISHLT guidelines [8]. The Imamura study is in line with this suggestion, showing that patients with a history of ACR in the first year and PRA + present a high risk of LR, requiring greater follow-up with EBM [33]. Patients without ACR and PRA - may see the number of EMBs reduced, thus avoiding the complications associated with this technique [33].

GEP is a non-invasive and economical procedure, based on the analysis of 20 genes [35]. Based on previous studies, a value ≥30 between the 2nd and 6th month and ≥34 after 6 months is indicative of ACR, leading to the performance of a biopsy [35]. In the Kobashigawa study, no differences in ACR, survival, and IVUS parameters between the use of GEP and EBM post-transplantation were found [35]. This study showed the efficacy and safety of GEP in low-risk populations, given that high-risk patients were excluded from this study [35]. A high number of

biopsies lead to an increase in side effects (hemorrhage, pericardial perforation) because it is an invasive technique, and GEP is important for stratifying patients according to the risk of rejection and to decrease the use of EBM [35]. However, more long-term studies on the use of GEP are needed.

In the Farrero study, the existence of a high immune response explains the high rejection mortality rate in the group with de novo DSA [34]. This study also showed that a blood test looking for autoantibodies may stratify patients according to their risk for rejection [34]. It was the first study to show the importance of C1q, which assesses the ability of antibody complement binding to DSA and AMR [34], thus being another tool for monitoring patients and improving their long-term follow-up and monitoring, and decreasing the use of EBM.

ACR involves a cellular response and its incidence decreases thanks to immunosuppressive therapy and improved diagnosis [8, 56]. It continues to account for 10% of mortality in the 1st year [31], decreased overall survival [32, 33] and the main cause of graft dysfunction during the first year post-transplantation [26]. ACR has a higher incidence during the first 3 months post-transplantation and after the first year of transplantation, the risk decreases progressively without ever disappearing [31], as was observed in the Soderlund study [32]. Risk factors are sex mismatch, CMV infection, HLA-mismatching, young recipients and donors and long ischemia time [31]. The existence of DSA also increases the risk of ACR, given that these antibodies act as a trigger [34]. Insufficient immunosuppressive therapy also increases the risk of ACR [8]. CsA and TAC are the most efficient in preventing ACR episodes whereas early weaning, before 6 months, increases rejection rates [69].

AMR results from the existence of autoantibodies against class I and II HLA in the graft, activating the complement or the mTOR pathway in the immunoglobulin membrane [56]. In recent years, new antibodies have been implicated in this process, such as the anti-angiotensin type 1 receptor antibody. The appearance of these autoantibodies results from transient ischemia or trauma during surgery, leading to an autoimmune response after graft antigen release. Antibodies act in synergy creating a “perfect storm” and the appearance of AMR [73, 74]. AMR is an indicator of poor prognosis and is more common in sensitized patients [70]. Its study can be done through immunohistochemistry using paraffin sections with C4d or CD68 screening or the immunofluorescence of frozen sections with C3d and C4d study and the study of capillary HLA when possible [75]. EBM should be initiated 2 weeks post-transplantation and may be anticipated in sensitized patients [75]. The frequency of EBM should be performed according to the local transplantation center and the results obtained in the first 2 biopsies [75]. The complement study allows more efficient identification of those at high risk, and patients with C1q + positive in more

than 2 consecutive samples are associated with AMR. It is also important to note that patients with HLA class I or class I and II antibodies are more likely to present positive C4d immunofluorescence and develop rejection when compared to patients without DSA [56]. Detection of de novo DSA in 2/3 of the patients prior to AMR is important for the formation of autoantibodies involved in rejection, whereas the complement (C1q), in this case, acts as an adjuvant for inflammation, as observed in the Farrero study [34], which may be a new marker for EMB.

2.4 Mechanical Circulatory Support

The use of mechanical circulatory techniques such as VAD provides an improvement in the patient's condition while waiting for transplantation [1, 13, 38], with VAD use increasing from 9.1% in 2006 to 32.6% in 2017 [5]. The use of TCMS is indicated as a bridge for transplantation [1, 36, 38] or, in the case of ACS, postcardiotomy failure, decompensated IC and primary arrhythmia [36]. VAD and ECMO present a poor prognosis when used in patients with CPR >30 min or with EF >35% [36]. There is a new generation of MCS which present a lower risk of thrombosis [5], which may improve the outcomes of these patients.

ISHLT refers to the use of mechanical circulation as the possibility of reversing some comorbidities, such as neoplasia, where it is possible to perform the treatment before transplantation [51]. Regarding obesity, it allows weight loss and can be combined with bariatric surgery to make weight loss more efficient [76, 77], but the continuous-flow devices are associated with weight gain, which places these patients at a disadvantage [78, 79].

The use of MCS before transplantation may help predict mortality after the transplant, as indicated by the Johnston study [38]. The TRIP-MCS score (table 3) encompasses donor and recipient variables, whereas mortality was similar between the validation and derivation group [38]. It allows the stratification of patients according to the risk of mortality after the first year and allows the assessment of which patients will benefit from the transplantation or the use of VAD [38].

In a study conducted in the Netherlands, the use of VAD as a bridge for transplantation increases the ischemia time due to the creation of adhesions [9]. The increase in donor age increases the incidence of graft dysfunction, associated with an increased ischemic period, such as the increase in the age of the recipient due to associated pathologies [9, 68].

PGD, most importantly related to mortality (27.1%) in the first 30 days post-transplantation [68, 80], has like etiology the donor-recipient incompatibility and an ABO incompatibility [68]. It can be divided into primary dysfunction without a known cause, or secondary dysfunction with a known cause, such as hyperacute rejection, pulmonary

hypertension, among others [68]. Its diagnosis can be made through echocardiographic data (LVEF) and the level of ionotropic support, essential for its classification (table 8) [80]. Adequate treatment allows a similar survival for patients without dysfunction [68], and the use of MCS is recommended, with the venoarterial extracorporeal membrane (VA-ECMO) being the most used [68]. The use of MCS presents a worse prognosis according to the Tchantchaleishvili study [37] and the use of ECMO presents a good prognosis [36, 37].

In 2015, ISHLT refers to EGF, severe PGD, with death or retransplantation associated with severe graft dysfunction up to 30 days post-transplantation [81]. Both donor factors (advanced age, cause of death non-head trauma and long duration of ischemia) and recipient factors (disease severity, dialysis history, use of amiodarone, creatinine or high pulmonary resistance, ventilator or MCS use) are associated with EGF [81]. Thus, PGD may increase in the next years and it is important to increase its recognition and correct treatment.

2.5 Coronary Allograft Vasculopathy

CAV is the main cause of long-term mortality and the most common form of chronic rejection [29, 45, 49]. According to ISHLT, CAV has a prevalence of 8% in the first year and 50% in 10 years [51]. It results from the proliferation of the endothelial and smooth muscle layers, activation of the immune system and consequent inflammatory response and platelet activation [46, 48], with diffuse and progressive thickening of the intima layer of the epicardial arteries [40, 41, 43, 44, 48]. As risk factors, we have male gender, advanced age of donor and recipient, the prior ischemic disease in the recipient, metabolic syndrome, smoking, CMV infection, donor CAD and rejection episodes [29, 47-49]. The classification is based on angiographic findings, such as the degree and the location of the stenosis and based on the ejection fraction of the diastolic dysfunction (table 9), classified as mild (CAV1), moderate (CAV2), and severe (CAV3) [39].

Tremblay's study of CAV over the last 30 years has shown a reduction in its incidence, due to the control of risk factors such as dyslipidemia, smoking, kidney disease, use of statins, MMF and TAC, control of rejections, prophylaxis for infection by CMV. The use of angiography has decreased in recent years, and the use of non-invasive techniques, such as the echocardiogram, has increased [49]. This reflects the new trend in the diagnoses of CAV.

According to ISHLT, regarding CAV, the diagnosis should be made through coronary angiography, stenosis value or by IVUS, through thickening of the intima (MIT), due to its high negative predictive value [39]. The use of IVUS greatly simplifies CAV by only detecting intimal proliferation and the CA normally underestimates CAV. The IVUS presents diagnostic value for the early phase of CAV, due to the alteration of the microvasculature [46], but also diagnostic value in the late phase [44]. The difficulty of the angiography in detecting CAV is due to its diffuse and

concentric attainment and preference for the end vessels and the stenoses which occur at a later stage, reducing the sensitivity of CA for CAV in an early phase [46]. Several ultrasound markers were proposed for the diagnosis of CAV. The CFR presents high sensitivity for the microvasculature dysfunction, presenting itself as an early marker for detecting CAV [46]. Because it is an invasive and costly procedure and is not available at all hospitals, Sade proposes the performance of CFR and DSE together, on an annual basis, due to high sensitivity, in order to stratify patients according to the risk of CAV, and if both tests are positive, a CA should be performed to study the patient, decreasing the side effects of CA [46]. The IMR reveals microvascular dysfunction, and IMR ≥20 is due to decreased cardiac output and is related to ventricular dysfunction and rejection [41]. FFR is related to myocardial ischemia, and when its value is >0.90 post-transplantation, it is indicative of the presence of donor-related atherosclerosis [41]. In his study, Yang found that both the IMR and FFR are related to mortality [41], and their use in the echocardiogram helps stratify the patient and improve their follow-up. The ASP evaluates the necrotic nucleus, fibrous tissue, and microcalcification existing in the CAV, presenting itself as a marker of plaque instability and inflammation [40]. The presence of a necrotic nucleus and plaques increases the risk of cell rejection and progression to CAV. The serial use of ASP allows the identification of patients at high-risk post-transplantation, compared to classical methods [40]. The LVGLS depends on the longitudinal contraction of the myocardial fibers being affected by CAV, which reaches the epicardial vessels, decreasing LVGLS [41]. LVFP's etiology is myocardial fibrosis caused by immunosuppressive treatment. The combination between LVGLS, which evaluates the VE systolic deformation, and LVFP, which evaluates the diastolic function, presents a synergetic value which allows the identification of patients at high risk for mortality [41]. OCT presents a high spatial resolution and allows the characterization of tissue fibrosis, calcium and lipid components [43]. LFP is an organized lesion resulting from the healing of a thrombus and the bright spots reflect the inflammatory component of CAV [43], the latter having an important role in CAV, as shown by its high prevalence in OCT [44]. The indicators of atherosclerosis, such as calcification and lipid component, remained stable throughout this study, which makes its role in CAV unimportant [43]. The use of OCT complements CA, being useful for patient stratification and subsequent therapeutic approach, but it is an invasive procedure and requires contrast. However, more extensive studies are needed in order to clarify the use and prognostic value of OCT [44]. The diagnosis of CAV through CAV is not sufficient, and the use of dobutamine and CFR echocardiography is the best means for diagnosis, with greater sensitivity thus reducing complications associated with angiography and improving results in the long-term. The use of

other echocardiographic markers also seems promising, however, more randomized studies are needed in order to understand its prognostic value.

Immunosuppressive treatment, statins, BCC, glycaemic control, CMV prophylaxis and the use of antioxidants (vitamin C and E) are essential for prevention [29, 47, 48]. mTOR inhibits the phosphatidylinositol 3-kinase pathway, an important step in CMV replication, thereby decreasing its incidence [28]. In addition, it inhibits the proliferation of smooth and endothelial muscle cells [25, 28-30, 49, 69] but increases the value of lipids which may favor the onset of CAV [29]. In the Guethoff study, no relationship was found between the use of mTOR and CAV, due to the low concentrations of this drug [28]. In the 2013 Kobashigawa study, the replacement of MMF with EVR showed that the increase in MIT was lower with EVR [29]. The Watanabe study presented the same result, even after switching to EVR 2 years post-transplantation [30]. Thus, EVR shows satisfactory results in CAV, however, long-term studies are needed, in order to determine if this effect is prolonged.

According to the Clemmensen study, inflammation and platelet activation are important factors in the etiology of CAV [43, 44]. For this purpose, the use of aspirin was studied and introduced in the Peled study during the first-month post-transplantation, presenting a reduction in the risk of CAV and mortality [47]. Long-term use is safe, and in this study, only one episode of hemorrhaging was reported. The 2010 ISHLT guidelines do not refer to the use of aspirin, which is more commonly used in patients with risk factors for CAV, as seen in the Kim study (male patients, smoking, and ischemic disease) [48] which may induce some effect on the results obtained in these studies. Despite this, the use of aspirin presents a strong protective effect of CAV and its use is practically universal, but clinical trials are still needed to clarify its use.

Key Learning Points

Indications:

- There is a clarity lack of evidence of study´s in this area about the main indication for HT;
- Medium age of donor and recipient have increased in the last years and is uncertain the effect an outcome like the of use of marginal donor, special with advanced age;
- Increased in the transplantation by CCMP or RT-CMP and OHT is safe but the use of MCS presents worst outcomes;
- Screening test in HF patients needs more criteria to increase is power;
- Scores for recipients and/or donors looks promising and can help the correct heart allocation but needs more evidence and long-term studies;
- Is urgent change the donor exclusion policy to increase the number of transplantations;
- Is necessary improve the long-term results of retransplantation and find more solutions to offer to this group of patients;

Outcome:

- OCS present great intermediate outcomes but is necessary a long-term evaluation;
- mTOR is associated with proteinuria, risk of AR and severe psychological effects. More clinical trials are needed to evaluate his long-term effects on renal function;
- A low dose of CNI in high-risk patients can be beneficial but no difference was found in renal function between mTOR/CsA and mTOR/TAC
- The first year after transplantation needs more vigilance through EBM due to poor therapeutic control;
- High-risk patients should perform EMBs periodically after the first year of transplantation; Patients with low risk can see their number of EMBs reduced, avoiding complications associated with the realization of EMB;
- GEP, DSA de novo after HT and C1q is important for stratifying patients according to the risk of rejection and to decrease the use of EBM;
- MCS is indicated as a bridge for transplantation and can reverse some comorbidities; The treatment of PGD included MCS and VA-ECMO IS the most used;
- CAV is the main cause of long-term mortality and CA is the gold standard for the diagnostic but the IVUS is the most used. Some ultrasound markers show great results for CAV but are necessary more clinical validation. Inflammation is an important factor on etiology of CAV and Aspirin should be offered for all patients to prevent CAV;

Conclusion

The reality of heart transplantation has changed tremendously in the last 50 years. A major change occurred with immunosuppression, with the most commonly used drugs being TAC and MMF, and with mTORs presenting good results in maintaining renal function and CAV, but with uncertain long-term results. In addition, the diagnosis of CAV presented several changes, whereas the use of CA may be replaced by the use of non-invasive methods such as echocardiography in low-risk patients. Despite this, the diagnosis of CAV is still not consensual, requiring more long-term studies and the search for a more sensitive test, with early detection. The prevention of CAV with aspirin has shown good results, but further long-term studies are needed.

We currently have a high rate of recipients of advanced age and with a high rate of comorbidities, which may compromise the long-term results of HT. Thus, we must continue to work in improving the survival rate that has stagnated in recent years. The approach of these patients will need to be reviewed so that transplantation remains the gold standard therapy, and it is also necessary to address the age of the patient and their comorbidities.

In this review, there is a lack of information regarding the indications for transplantation, and more studies are also necessary here, in order to understand what type of patients we have as candidates and how we can reduce the waiting time by creating more scores adjusted to the reality of these patients. MCS as a therapeutic bridging aid also requires further investigation regarding the effects on survival.

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Annexes

Table 1: IMPACT Score adapted from Weiss et al 2011 [16]

	Points assigned
Age >60 years	3
Bilirubin	
1-1,99	1
2-3,99	3
≥4	4
Creatinine Clearance	
30-49 mL/minute	2
<30 mL/minute	5
Dialysis between listing and transplant	4
Female sex	3
Heart Failure etiology	
Ischemic	2
Congenital	5
Other	1
Infection	3
IABP	3
Mechanical ventilation prior to transplant	5
Race	
African American	3
Temporary circulatory support	7
VAD	
Older gen pulsatile	3
New Gen continuous	5
Total points possible	50

Legend: IABP: intra-aortic balloon pump;

Table 2: Score adapted from Trivedi et al 2016 [17]

	Points assigned
Donor factors	
Donor age (years)	
50-55	1
>55	2
Ischemic time >4 hours	2
Gender mismatch	1
Diabetes	1
Total donor allowed	6
Low risk: 0 points Intermediate risk: 1,2 points High risk: ≥3 points	
Recipient Factors	
Age> 65 years	1
BMI kg/m^2	
30-35	1
≥35	2
Mean pulmonary artery pressure >30	2
Total bilirubin	
1,5-1,9	2
>1,9	2
Creatinine	
1,5-2,0	1
>2,0	2
Previous transplant	2
Previous cancer	2
Ventilator	2
Mechanical circulatory support	2
Total recipients allowed	16
Very low risk: 0 points Low risk: 1 point Intermediate risk: 2 points High risk: 3,4 points Very high risk ≥5 points	

Legend: BMI: body mass index;

Table 3: TRIP-MCS score adapted from Johnston et al 2016 [38]

	Points allocated
Recipient Variable	
Age>60 yrs	7
BMI, Kg/m^2	
25-34	5
≥34	10
Total bilirrubin >1,0 md/dL	5
Estimated GFR <50 mL/min/1,73 m^2	10
Any dialysis since listing	6
Mechanical ventilation at the time of transplantation	10
Admitted to ICU at time of transplantation	3
Recently treated infection	4
Type of circulatory support	
Other anatomic position than LVAD or additional support, excluding ECMO	3
Donor Variables	
Age > 40 yrs	3
Sex mismatch with the recipient	4
Inchemic time > 4h	5
Estimated GFR < 50 mL/min/1,73 m^2	5
Total possible score	15

Table 4: Indications and contraindications adapted from ISHLT-WF 2006 and 2016 [51, 52]

	2006	2016
Acceptable Candidates		
	VO2≤14mL/Kg/min;	Continuing approval without change;
	Respiratory Exchange Ratio >1,05 with the achievement of anaerobic metabolism;	Continuing approval without change;
	-	HF prognosis score (SHFM<80% and HFSS in the médium/high risk);
	-	Signficant CAV without evidence of rejection (retransplant);
Probable Candidates		
	Age>70 years should be considered other programs;	Age>70 years should be considered, carefully
	Pre-existing malignancies should be considered when tumor recurrence is slow based on tumor type, response to therapy, and negative metastatic work-up;	Continual approval without change;
Absolute Contraindication		
	BMI >30 Kg/m^2;	BMI >35 Kg/m^2;
	-	Clinical severe symptomatic cerebrovascular disease;
	-	Frailty (3 of 5 symptoms: unintentional weight loss of ≥4,5 Kg within the past year, muscle loss, slow walking speed and low levels of physical activity);
	Active smoker (<6 months since quitting) and active substance abusers (including alcohol);	Continuing approval without change;
Relative Contraindication		
	Diabetes with end-organ damage other than nom-proliferative retinopathy, HbA1c>7,5%;	Diabetes with end-organ damage other than nom-proliferative retinopathy, HbA1c>7,5% or 58 mmol/mol;
	GFR <40 mL/mim/1,73 m^2;	GFR <30 mL/mim/1,73 m^2;
	Peripheral vascular disease;	Continuing approval without change;
	Clinical severe symptomatic cerebrovascular disease;	-
	Mental retardation or dementia;	Mental retardation, dementia or insufficient social support;
	Pulmonary artery hypertension and elevated PVR;	Continuing approval without change;

Legend: BMI: Body mass Index; HbA1c: glycosylated hemoglobin; PVR: pulmonary vascular resistance;

Table 5: Marginal heart donors: criteria for non-use in France (France) adapted from Dorent et al 2018 [64]

Age > 70 years;
Unknown cause of brain death;
Myocardial Contusion;
Intractable ventricular arrhythmias;
Hemodynamic Instability with high-dose of inotropes;
Catecholamine support advice aggressive hemodynamic management;
Persistent LVEF<40%;
Diastolic left ventricular Wall thickness ≥16 mm;
Severe valvular/Congenital lesions;
Obstructive coronary artery disease in any major coronary artery;

Table 6: Exclusion criteria for Donor selection in the USA based on guidelines from Society Critical Care Medicine [66]

Presence of functional and morphologic cardiac disease;
Advanced donor age (>55 years);
Mismatch of donor/recipient size;
Previous cardiac arrest (>20 min);
Significant thoracic trauma;
LVH (Wall thickness >1,4 cm);
Echocardiography and CA in patients > 40 years or young donors with risk factors for CAD;

Table 7: Current status codes for heart transplant allocation adapted from UNOS [72]

Status 1	VA-ECMO; Nom-dischargeable, surgically implanted, nom-endovascular LVAD; MCSD with life-threatening ventricular arrhythmia
Status 2	Nom-dischargeable, surgically implanted, nom-endovascular LVAD; IABP; MCSD with device malfunction/mechanical failure; BiVAD, RVAD or VAD for single ventricle patients; Percutaneous endovascular MCSD
Status 3	Dischargeable LVAD for discretionary 30 days; Multiple inotropes or single high-dose inotrope with continuous hemodynamic monitoring; VA-ECMO after 7 days; percutaneous endovascular circulatory support device or IABP after 14 days; Non-dischargeable, surgically implanted, non-endovascular LVAD after 14 days; MCSD with one of the following: device infection, hemolysis, pump thrombosis, right heart failure, mucosal bleeding, and aortic insufficiency;
Status 4	Dischargeable LVAD without discretionary 30 days; Inotropes without hemodynamic monitoring; Retransplant; Diagnosis of one of the following: congenital heart disease (CHD), ischemic heart disease with intractable angina, hypertrophic cardiomyopathy, restrictive cardiomyopathy, and amyloidosis;
Status 5	On the waitlist for at least one other organ at the same hospital;
Status 6	All remaining active candidates;

Legend: BiVAD: biventricular assist device; IABP: intra-aortic balloon pump;

Table 8: Classification of PGD adapted from ISHLT-WF 2014 [80]

PGD- Left ventricle (PGD-LV)	Mild PGD-LV: one of the following criteria must be met:	LVEF ≤40% by echocardiography, or: CI<2,0 L/min/m^2 (lasting more than 1 hour) requiring low-dose inotropes;
	Moderate PGD-LV: must meet one criteria from I and another criteria from II	I. One criteria from the following: Left ventricular ejection fraction ≤40%, or Hemodynamic compromise with RAP>15 mm Hg, PCWP>20 mm Hg, CI<2,0 L/min/m^2, hypotension with MAP<70 mm Hg (lasting more than 1 hour); II. One criteria from the following: High dose inotropes; Newly placed IABP;
PGD- Right Ventricle (PGD-RV)	Severe PGD-LV Diagnoses requires either both i, ii or iii alone:	Dependence on left or biventricular mechanical support including ECMO, LVAD, BiVAD, or percutaneous LVAD. Excludes requirement for IABP. i. Hemodynamics with RAP>15 mm Hg, PCWP<15 mm Hg, CI<2,0 L/min/m^2 ii. TPG<15 mm Hg and/or Pulmonary artery systolic pressure < 50 mm Hg, or iii. Need for RVAD

Legend: BiVAD: biventricular assist device; CI: cardiac index; IABP: intra-aortic balloon pump; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; TPG: transpulmonary pressure gradient;

Table 9: CAV classification adapted from 2010 ISHLT-WF [39]

CAV_0 (Not significant)	No detectable angiographic lesions;
CAV_1 (Mild)	Angiographic left main (LM) <50% or primary vessel with maximum lesion of <70% or any branch stenosis <70% (including diffuse narrowing) without allograft dysfunction;
CAV_2 (Moderate)	Angiographic LM <50%; a single primary vessel ≥70% vessel, or isolated branch stenosis ≥70% in branches of 2 systems, without allograft dysfunction;
CAV_3 (Severe)	Angiographic LM ≥50%, or two or more primary vessels ≥70% stenosis, or isolated branch stenosis ≥70% in all 3 systems; or ISHLT CAV2 or CAV 2 with allograft dysfunction (defined as LVEF ≤45% usually in the presence of regional wall motion abnormalities) or evidence of significant restrictive physiology;