Perioperative Management of Heart Transplantation: A Clinical Review

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Title Page

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4. Clinical trial number and registry URL: None

5. Prior Presentations: None.

6. Acknowledgments: None

7. Word and Element Counts:
Manuscript: 3850
Number of figures: 1
Number of tables: 4

8. Abbreviated Title (Running Head): Perioperative Management of Heart Transplantation

9. Summary Statement: In this clinical review, the authors summarized the perioperative management of heart transplant patients with a focus on hemodynamics, immunosuppressive strategies , hemostasis and hémorrage, and the prevention and treatment of infectious complications .

10. Funding Statement:
No funding.

11.Conflicts of Interest:

Nicolas Nesseler: declares no competing interests
Alexandre Mansour: received payments made to his institution from i-SEP for consulting fees, and from LFB, Aguettant and Pfizer for lecture fees.
Bernard Cholley: received payments from Orion Pharma, Nordic Pharma, Edwards Life Sciences, and AOP Orphan for participation to advisory boards and lectures at industry symposia.
Guillaume Coutance: declares no competing interests
Adrien Bouglé: received payments from Fresenius and LFB for lecture fees.

Introduction

Heart transplantation remains the treatment of choice for patients with end-stage heart failure allowing high-survival rates and improved quality of life[1]. Worldwide, more than 6000 heart transplantations are performed annually, with one-year post-transplant survival around 85% and median survival now exceeding 12 years[2]. The progressive improvement in post-transplant outcome that has been observed over these years is mostly driven by a dramatic drop in the early post-transplant mortality[2]. However, the first weeks following heart transplantation remain critical with an 8% 1-month mortality in contemporary cohorts[2]. The perioperative period remains at very high risk due to the increasing proportion of candidates bridged to transplant with durable mechanical circulatory supports and an increasing number of sensitized patients[3,4]. In addition, the prioritization of high-risk candidates on ECMO support and the broader eligibility for both recipient- and donor-related risk factors of primary graft dysfunction (older age, comorbidities) also contribute to increase the challenges of the perioperative period[2,5]. The role of the cardiothoracic anesthesiologist-intensivist in the early management of heart transplant recipients is crucial both during surgery and in the ICU[6]. Guidelines focused on the perioperative management of heart transplant recipients are still lacking and the area of knowledge required is vast. This includes the management of hemodynamic instability, transfusion and hemostatic disorders, immunosuppression, infectious complications (prevention and treatment) in addition to acute kidney injury and renal replacement therapy. This review aims at summarizing the latest knowledge in the field of perioperative management of heart transplant recipients in order to guide cardiothoracic anesthesiologist-intensivists.

Hemodynamic management

Vasoplegia

Defining vasoplegia

A refractory vasoplegic syndrome (a persistent low vascular resistance requiring intravenous vasopressors) is observed in 11-60% of heart transplantation patients[7,8]. There is currently no standard consensus on the definition of vasoplegic syndrome after cardiac surgery or more specifically after heart transplantation, but hypotension occurring within 24 h of heart transplantation with a cardiac index (CI) greater than 2.2 L/kg/m^2 and a systemic vascular resistance of less than 800 dyne-s/cm^5 is generally considered characteristic of this situation[7,9]. The pathophysiology of vasoplegic syndrome remains poorly understood, but it could be associated with cytokine release, adrenergic receptor desensitization, increased nitric oxide synthesis, relative deficiency of vasopressin, activation of ATP-sensitive potassium channels, vascular smooth muscle cell membrane hyperpolarization, dysfunction of the renin-angiotensin system, and endothelial glycocalyx alteration[10].

Risk factors

Age, history of thyroid disease or chronic kidney disease, ventricular-assist device prior to transplant, duration of cardiopulmonary bypass and intra operative blood products are associated with this condition[8,11,12]. Treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is associated with vasoplegia after cardiac surgery[13], although this is less well documented after heart transplantation[8]. Nevertheless, the presence of a vasoplegic syndrome may be associated with an unfavorable prognosis in heart transplantation patients[14], and the consequences of the vasoplegia do not appear to differ after heart transplantation and after standard cardiac surgery[15].

Management of vasoplegia

As highlighted in the recent guidelines of the International Society for Heart and Lung Transplantation, the first-line choice in the treatment of vasoplegia is norepinephrine[16] (see figure, Supplemental Digital Content 1). However, the management of post heart transplantation vasoplegia is most often extrapolated from the literature related to this condition following standard cardiac surgery, due to the lack of specific data. In a recent Brazilian single center study, Hajjar et al. randomized 330 patients with vasoplegic shock after cardiac surgery to receive vasopressin or norepinephrine[17]. Mortality or severe complications occurred in 32% of patients receiving vasopressin, compared with 49% receiving norepinephrine, but the extrapolation of these findings has been questioned. Moreover, acute renal failure occurred in only 10.3% of patients receiving vasopressin, compared with 35.8% of patients receiving norepinephrine[17]. In heart transplantation patients with vasoplegia syndrome, vasopressin was shown to decrease norepinephrine requirements, but the level of evidence remains low[18]. Similarly, the use of methylene blue, hydroxocobalamin or angiotensin II could be of interest in this population but, up to now, efficacy of these therapies has only been substantiated by cases reports[10,19–23].

Primary graft dysfunction

Defining primary graft dysfunction

The International Society of Heart and Lung Transplant defined primary graft dysfunction after heart transplantation as a failure of the transplanted heart, necessitating high doses of catecholamines and/or temporary mechanical circulatory support to achieve an adequate cardiac index in the recipient, and diagnosed within 24 hours of completion of surgery in the absence of a discernible alternate cause such as hyper acute rejection, pulmonary hypertension or surgical complications[24,25]. Primary graft dysfunction can be further characterized as predominantly left-sided or right-sided, as well as mild, moderate, or severe, depending on the level of cardiac dysfunction and the extent of inotrope and mechanical support required (Table 1). The most recent data suggest an incidence of 10% to 36% with severe primary graft dysfunction occurring in 8 to 18%

of heart transplantation patients. Primary graft dysfunction is associated with increased 30-day and one-year mortality[25].

Risk factors

The risk factors for primary graft dysfunction include factors related to the donor, the recipient, and the surgical procedure itself (Table 2). The RADIAL score was developed from a cohort of 621 heart transplantation patients in which 6 risk factors were identified using multivariable analysis: 1) recipient risk factors include: right atrial pressure ≥ 10 mm Hg, age ≥ 60 years, diabetes mellitus, dependence towards inotropes, 2) donor risk factors: age ≥ 30 years, and length of ischemic time ≥ 240 minutes[26]. The RADIAL score allows heart transplantation patients to be stratified into groups with an incremental incidence of primary graft dysfunction [27]. In patients bridged to heart transplantation with continuous-flow left ventricular assist devices, the RADIAL score did not accurately predict severe primary graft dysfunction. In this group, the risk factors for primary graft dysfunction included: mechanical support duration >1-year, elevated pre-heart transplantation creatinine plasma levels, elevated central venous pressure/pulmonary capillary wedge pressure ratio, and use of amiodarone before heart transplantation[28].

Management of primary graft dysfunction

Despite the lack of high-level evidence supporting their efficacy, inotropic drugs and vasopressors (including dobutamine, dopamine, milrinone, epinephrine, and norepinephrine) remain the first line treatment for primary graft dysfunction. These medications may potentially be combined with vasopressin and inhaled nitric oxide[8] (see figure, Supplemental Digital Content 1). The use of milrinone as a bridge to transplantation has been reported in a few cohort studies, but the data regarding the treatment of primary graft dysfunction using this medication is extremely limited[29,30]. Weis et al. assessed the effect of levosimendan in twelve heart transplantation patients with primary graft dysfunction, with good results on hemodynamic parameters such as cardiac index, mean

arterial pressure, or mean pulmonary artery pressure[31]. In this cohort of patients with primary graft dysfunction, survival at day-30 was 93%. When cardiac output remains inadequate despite high doses of inotropes and/or vasopressors, the use of temporary mechanical circulatory support is needed to provide systemic perfusion and oxygenation, allowing the graft to recover and maintaining the other organs. For patients needing a temporary mechanical circulatory support, veno arterial ECMO seems to be associated with shorter assistance duration, lower incidence of major bleeding, of renal failure requiring renal replacement therapy, and reduced mortality compared with patients supported with a continuous-flow external ventricular assist device[32]. The ideal timing for ECMO implantation in patients with primary graft dysfunction is not known. However, as with the timing for ECMO implantation in post cardiotomy cardiogenic shock, it can be assumed that early implantation is beneficial. Thus, in a cohort of 347 patients assisted with post cardiotomy veno arterial ECMO, including 59 primary graft dysfunction patients, postoperative implantation of veno arterial ECMO was independently associated with an increased risk of Kidney Disease Improving Global Outcomes stage 3 acute kidney injury[33]. In a retrospective study involving 135 primary graft dysfunction patients including 66 assisted with veno arterial ECMO, delayed initiation of veno arterial ECMO was independently associated with in-hospital mortality[34]. Thus, veno arterial ECMO implantation appears to be an efficient strategy for the management of severe primary graft dysfunction, in spite of a significant impact on long-term quality of life[35]. Finally, although there is data pointing to a beneficial effect of left ventricle unloading in patients assisted by veno arterial ECMO, there is little specific evidence in transplant patients[36]. Indeed, in a recent study from the Extracorporeal Life Support Organization registry on the association between left ventricle unloading and in-hospital mortality, transplantation was an exclusion criterion[36].

Right heart failure / Pulmonary Hypertension

Right heart failure remains a frequent and potentially severe complication after heart transplantation and contributes significantly to morbidity and mortality. When a discernible cause

can be identified, right heart failure is related to a secondary graft dysfunction. Usual etiologies include hyper acute rejection (see dedicated paragraph), known surgical complication, or pulmonary hypertension. As the presence of pre-transplant pulmonary hypertension in heart recipients increases the risk of post-transplant right heart failure, the selection of transplant recipients and their pre-transplant hemodynamic optimization is essential. A single-center retrospective study reported an incidence of 5.9% for severe right heart failure after heart transplantation, while increased pulmonary capillary wedge pressure and mean pulmonary arterial pressure were identified as risk factors[37]. The International Society for Heart and Lung Transplantation suggests that a pulmonary vasodilator challenge with inhaled (nitric oxide or prostacyclins) or intravenous (nitroglycerin or nitroprusside) vasoactive agents should be administered when the systolic pulmonary artery pressure is ≥ 50 mmHg and when the transpulmonary gradient is ≥ 15 mmHg or the pulmonary vascular resistance is > 3 Wood units. Meanwhile, systolic arterial blood pressure should be maintained above 85 mmHg. Although the right and left filling pressures decrease within weeks following heart transplantation, an elevated mPAP after transplantation is an independent prognostic factor for long-term mortality[38,39].

The management of right heart failure relies on the preservation of coronary perfusion through the maintenance of an adequate mean arterial pressure using norepinephrine infusion, optimization of the right ventricle preload with careful monitoring to avoid congestion, reduction of the right ventricle afterload by decreasing pulmonary vascular resistance and limitation of pulmonary vasoconstriction through ventilator settings (avoiding hypoxia and hypercarbia)[40] (see figure, Supplemental Digital Content 1). Inhaled nitric oxide is unique in that it allows selective pulmonary vasodilatation and is effective in improving stroke volume as a result of right ventricle afterload reduction[41]. However, there is currently no clear evidence that this medication may improve long-term outcome in patients and the cost/benefit ratio is questioned[42]. Finally, it was recently suggested, in a retrospective cohort of cardiac surgical patients with pulmonary hypertension or

right ventricular failure, that the combination of inhaled milrinone and epoprostenol was associated with beneficial effects on hemodynamics[43].

The severe forms of primary graft dysfunction are traditionally managed with veno arterial ECMO, but up to 45% of patients with primary graft dysfunction have isolated right ventricular dysfunction[27]. In these patients, percutaneous right ventricular support, for example through the Protek Duo cannula or with the Abiomed Impella RP device, could be particularly useful, allowing mechanical support of the right ventricle without the detrimental effects of veno arterial ECMO (non-physiological circulation with reduced pulmonary flow, risk of intravascular pulmonary thrombosis, increased left ventricular afterload)[44,45].

Arrhythmias

The mechanisms for arrhythmogenesis in heart transplant patients are related to several factors including: surgical technique, graft ischemia duration, autonomic denervation, immune rejection, cardiac allograft vasculopathy, and graft dysfunction. The loss of parasympathetic input from the vagus nerve results in a higher resting heart rate for transplant patients (90-100 bpm) and a significantly reduced heart rate variability. Graft ischemia exceeding 240 minutes and the bi-atrial surgical technique are associated with increased rates of post-operative atrial fibrillation. Atrial fibrillation, atrial flutter, and supra ventricular tachycardia are the most common post-transplant arrhythmias and are associated with decreased long-term survival[46,47]. Despite their frequency, atrial arrhythmias occur in heart transplant recipients at a much lower rate (2-4%) than in other post cardiac surgery patients (overall incidence of 26.7%, from 22.9% for CABG to 45.2% for combined procedures[46,48]. The majority of atrial fibrillation episodes occur within two weeks of transplantation, whereas atrial flutter most commonly presents after the first two weeks. Atrial fibrillation and flutter may be associated with acute rejection and/or cardiac allograft vasculopathy, particularly when arrhythmias persist beyond the post-operative period[46,47]. Ventricular arrhythmias and sudden cardiac arrest represent 10% of deaths after heart transplantation, with an incidence of 1.30 per 100

person-years[49,50]. Treated rejection and cardiac allograft vasculopathy were described as risk factors for sudden cardiac death in heart transplant patients[51]. The management of atrial fibrillation after heart transplantation is similar to that of other cardiac surgery patients. A treatment strategy of rate versus rhythm control is determined by the presence of symptoms and the effect of atrial fibrillation on systolic function. Rate control may be achieved with β-blockers, with short half-life drugs being preferred at the onset of treatment in this setting to ensure tolerance. Rhythm control may consist in electrical or pharmacological cardioversion[52]. It should be remembered, however, that treatment of the recipient with amiodarone before heart transplantation is a well-established factor for primary graft dysfunction[45,53,54]. Finally, as these patients are frequently on inotropes, it may be strategic to decrease the inotropes and to look for other pharmacologic methods for rate or rhythm control. There are no specific guidelines for anticoagulation after heart transplantation, and a decision should be made after considering the CHA_2DS_2-VASc score according to current guidelines[55]. Sinus node dysfunction and atrioventricular block requiring pacemaker implantation are present in 2 to 15% of heart transplant patients[56–58]. In addition to the bi-atrial surgical technique, risk factors for early pacemaker implantation (less than 3 months) are donor age, ischemic time, cellular rejection and amiodarone use before heart transplantation[59]. Late pacemaker implantation (more than 3 months) risk factors include donor age and cardiac allograft vasculopathy[60].

Tricuspid regurgitation

Tricuspid regurgitation is the most common valvular abnormality after heart transplantation (19-84%), and has been associated with increased morbidity and mortality[61,62]. The risk of mortality is greater in case of tricuspid regurgitation due to primary graft dysfunction or rejection[63]. Therefore, if the effects of sub-clinical tricuspid regurgitation remain controversial, the more severe forms could be associated with chronic fluid congestion, lower extremity edema, liver congestion and finally renal failure[64].

Whether there may be other factors that could be responsible for a functional tricuspid regurgitation (allograft rejection, pre-operative abnormal transpulmonary gradient and vascular resistance), the main risk factor seems to be the bi-atrial surgical technique[65]. Hence, Aziz et al. observed a higher incidence of tricuspid regurgitation among patients who underwent bi-atrial surgical technique versus patients who underwent a bi-caval approach (41% at 1 month, 52% at 24 months vs. 15% at 1 month and 30% at 24 months)[66]. Tricuspid regurgitation can also be the consequence of the anatomic disruption of the sub-valvular apparatus. Specifically, endomyocardial biopsy, performed to detect allograft rejection, is a procedure particularly at risk of creating valvular lesions. Although the majority of patients are asymptomatic, moderate to severe tricuspid regurgitation can induce progressive right ventricle cavity enlargement, elevated right-side pressures and eventually symptoms of right heart failure. Diuretics remain the cornerstone treatment for patients with tricuspid regurgitation. However, a surgical intervention could be indicated in refractory cases to prevent ventricular failure and the systemic consequences of severe tricuspid regurgitation[67].

Perioperative management of immunosuppression

Allograft rejection remains an important cause of graft dysfunction, patient mortality and morbidity after heart transplantation[68]. The immunosuppressive regimen must balance the risk between allograft rejection and the complications of over-immunosuppression, particularly infectious complications occurring early after heart transplantation.

Induction therapy

The principle of an induction therapy is to induce a profound and rapid immunosuppression to lower the risk of rejection. Three approaches are widely used (sorted by the level of immunosuppression required): (i) no induction therapy, (ii) non-depletive monoclonal induction using IL-2 receptor antagonists and (iii) polyclonal induction with anti-thymocyte globulins (T-cell depletion therapy).

The practice is variable across centers and countries[68]. No study ever proved a survival benefit of one strategy over another at the population level[69]. The benefit-risk ratio of each approach should be discussed for every patient at the time of listing. Table 3 summarizes the doses, side effects and monitoring of each drug.

Perioperative management of allosensitization

Allosensitization represents a major barrier to heart transplantation. The presence of antibodies to human leukocyte antigens (HLA) is associated with increased risk of waitlist mortality. The proportion of allosensitized patients awaiting heart transplantation continues to increase, possibly due to the increasing exposition to procedures prior to transplant, including durable mechanical circulatory support, homografts, and blood products[4].

Virtual crossmatches at the time of organ proposal (i.e., the analysis of the immunological compatibility of the donor and the recipient: comparison of anti-HLA antibody developed by the recipient to the HLA antigens of the donor), allow an accurate and early evaluation of the immunological risk of rejection. The exclusion of grafts from donors with HLA antigens against which the recipient has developed donor-specific antibodies helps avoiding hyperacute rejection of the transplanted organ. In addition, donor-specific antibodies might induce acute and chronic injuries due to antibody-mediated rejection, or cardiac allograft vasculopathy[70,71]. The downside of this selection process is that the higher the number of unacceptable antigens, the narrower the donor pool[3]. The definition of what is an unacceptable antigen is therefore essential but remains highly controversial (level of Mean Fluorescence Intensity, in vitro complement fraction C1q binding, dilution)[72].

Since heart transplantation is a vital therapeutic option, some centers opt to cross HLA barriers and manage donor specific antibodies subsequently[73]. A peri-operative combination of plasmapheresis and high-dose intravenous immunoglobulins can be used to reduce donor-specific antibodies plasma levels in patients at moderate immunological risk. For higher-risk patients, an intensification

of the immunosuppression may be required. The early inhibition of the complement cascade is an attractive approach due its major implication in antibody-related acute allograft injury.

Maintenance immunosuppressive therapy

The early maintenance immunosuppressive therapy usually relies on a triple drug regimen: calcineurin inhibitor (tacrolimus, cyclosporine), cell-cycle inhibitor (mycophenolate mofetil, mycophenolic acid) and corticosteroids[16]. Table 3 summarizes the doses, side effects and monitoring of each drug with a particular focus on short-term management in the ICU.

Treatment of cardiac allograft rejection

The pathologic evaluation of endomyocardial biopsies remains the gold-standard to monitor, diagnose and classify heart allograft rejection. The International Society for Heart and Lung Transplantation working formulations classifies acute cellular rejection from 0R to 3R according to the importance of lymphocytes infiltrates and signs of myocyte injury (Figure 1A) and antibody-mediated rejection from 0 to 3 according to the presence of histologic (microvascular inflammation) and immunopathologic (complement C4d deposition in capillaries, presence of intravascular macrophages) signs of antibody-mediated rejection (Figure 1B)[74,75].

This international classification is the guide to rejection therapies. The presence of an acute allograft dysfunction is always considered as a marker of the severity of an ongoing rejection and should prompt aggressive immunosuppressive strategies. While the treatment of acute cellular rejection is well described and consensual (corticosteroids , anti-thymocyte globulin in the case of severe graft dysfunction)[16], the treatment of antibody-mediated rejection—remains controversial[76]. Plasmapheresis and high-doses of intravenous immunoglobulins represent the first-line therapy but a more aggressive immunosuppressive strategy may be required, particularly in case of allograft dysfunction[77,78] (Table 3).

Infectious complications

Infections are the leading cause of death within the first year after heart transplantation and justify targeted prophylaxis[79]. The development of infection can be facilitated by the level of immunosuppression, drug-induced leukopenia or immunomodulation by viral infection such as cytomegalovirus[80]. A classic timeline describes 3 distinct periods of infection after solid organ transplantation: 1) the postoperative period within the first month is characterized by nosocomial and donor-derived infections (cytomegalovirus, Epstein-Barr virus or Toxoplasma spp.), 2) the second period, up to 6 months after surgery, with opportunistic infections, and 3) after 6 months, community-acquired or rare infectious agents are expected. However epidemiologic data are scarce, not recent (>10 years), with various methodologies and from a limited number of centers which makes generalization difficult. The two most recent cohorts, with a follow-up comprised between 3 months and one-year, found a high incidence of infection (60 to 80%) after heart transplantation with the highest rate within the first month[81,82]. Among infectious agents, bacteria were the most frequently involved (>50%), viruses were also frequent (30%), whereas fungal infection accounted for only 13-14%. The predominant pathogens were Enterobacteriaceae and Herpesviruses. Multidrug resistant bacteria were frequent (15-20% of the cases). Respiratory tract and bloodstream were the most frequent bacterial infection sites, whereas viral infections were mostly mucocutaneous and respiratory. Although less represented, surgical site infections may be more prevalent (9-10%) following heart transplant than other cardiac surgeries[81,83,84]. Interestingly, cannulation site infection may be a frequent complication (37%) in patients supported by ECMO after heart transplantation[85].

Preventive strategies based on pharmacological prophylaxis according to serologic status of the donor or recipient are recommended by the International Society of Heart and Lung Transplantation guidelines for the care of heart transplant recipients[16], and are summarized in Table 4. Prophylaxis against *Pneumocystis jirocevi* and *Toxoplasma gondii* is recommended during the early postoperative

period, usually with Trimethoprime/Sulfamethoxazole, if not contraindicated. Anti-fungal prophylaxis to prevent mucocutaneous candidiasis or aspergillosis is not routinely recommended but may be considered in case of specific risk factors for aspergillosis. High risk patients for cytomegalovirus infection (seronegative patients with seropositive donors), should benefit from antiviral prophylaxis (ganciclovir or valganciclovir) within 10 days after the transplantation for at least 3 months[86]. Seropositive patients may benefit from antiviral prophylaxis or from a preemptive strategy according to the center preference[87]. In the latter, cytomegalovirus viral load is quantified by nucleic acid amplification testing at least weekly in the whole blood, and an antiviral treatment is initiated only when a predetermined threshold is achieved. However, no specific threshold can be recommended given the inter-assay and patient-related factors variabilities. A preemptive strategy might prevent late cytomegalovirus infection, drug toxicity, and reduce cost. Conversely, universal prophylaxis is easier to implement, prevents other herpes virus infections and may prevent opportunistic infections or graft rejection[86]. Antimicrobial prophylaxis before the surgery with activity against skin flora, including *Staphylococcus aureus* is recommended to prevent surgical site infections[16]. If a chronic infection of ventricular-assist device, pacemaker or defibrillator is present, a perioperative antibiotic therapy based on known microbiologic susceptibilities should be initiated after consultation of an infectious disease specialist. Non-pharmacologic strategies range from standard precaution to protective isolation. Standard precautions are recommended for all patient care and include hand hygiene, personal protective equipment in case of possible exposure to infectious material, respiratory hygiene, adequate environment cleaning, adequate handling and disinfection of patient care equipment and instrument, and safe injection practices. Despite the lack of evidence protective isolation seems very frequent in heart transplant centers across the world with an important variability in the measures used, high-touch surface disinfection, private rooms and daily linen change being the more frequent measures used[88].

Hemostasis and transfusion management

The treatment of postoperative hemorrhage and transfusion protocols following transplantation are poorly described. Furthermore, these patients are largely under-represented and seldom studied in prospective trials investigating bleeding and transfusion in cardiac surgery[89–93]. In the absence of specific data and guidelines, perioperative hemostasis and transfusion management in heart transplantation should probably follow current guidelines for cardiac surgery, including preoperative management of antithrombotic drugs, cardiopulmonary bypass optimization, algorithm-guided therapy for perioperative bleeding, use of viscoelastic testing[94,95]. A suggested perioperative bleeding management protocol is provided (see figure, Supplemental Digital Content 2).

Preoperative Vitamin K antagonists (VKA) should be reversed during surgery using vitamin K and INR-guided four-factor prothrombin complex concentrates[16,96]. In the situation where a direct oral anticoagulant (DOAC) is preferred over VKA, it is appropriate to choose dabigatran rather than anti-Xa DOACs, in combination with a protocol for reversal using idarucizumab[97]. While aspirin can safely be continued, uninterrupted P2Y12 inhibitors might increase postoperative bleeding and should be avoided in patients awaiting heart transplantation[16,98]. In the case of a formal indication for dual antiplatelet therapy, thienopyridines (clopidogrel, prasugrel) should be preferred due to the inefficacy of platelet transfusion in neutralizing ticagrelor when the last intake is less than 24 hours before surgery[99]. Antiplatelet agents' reversal using platelet concentrates should be considered in case of severe perioperative bleeding and may be guided by platelet function testing [99].

Overall, heart transplant seems to be associated with a risk of severe perioperative bleeding and a high exposition to allogeneic transfusion, especially in the setting of redo surgery and bridge to transplantation using ECMO or ventricular assist device support[100–103]. In accordance with cardiac surgery guidelines, post-operative bleeding should be managed using a tailored goal-directed hemostatic protocol, in coordination with the hemostasis specialist (see figure, Supplemental Digital Content 2). Special attention should be paid to patient supported by ECMO or ventricular assist device, which are associated with platelet function defects and acquired von Willebrand syndrome,

although little evidence is available regarding the impact of platelet transfusion or von Willebrand factor concentrate in this setting[104,105].

In the absence of specific data, a restrictive erythrocyte transfusion strategy (hemoglobin threshold between 7.5 and 8 g/dL) should probably be used for heart transplantation, potentially tailored to tissue perfusion/oxygenation values, including central venous oxygen saturation[94,106]. As for patients with chronic heart failure, including those awaiting heart transplantation, postoperative anemia and iron deficiency warrant particular attention and may justify intravenous iron therapy in case of significant bleeding and/or postoperative iron deficiency[107,108].

Heart transplantation patients are at increased risk of venous thromboembolism and should receive pharmacological prophylaxis, primarily using low molecular weight heparin[109]. Antiplatelet therapy using low-dose aspirin is usually initiated early after surgery and would seem to be associated with a reduction of cardiac allograft vasculopathy[110].

Mechanical Ventilation

In the absence of specific data in heart transplantation patients, ventilation strategies recommendations can be inferred from cardiac surgery literature. Intraoperative protective ventilation with tidal volume between 6 to 8 mL/kg of predicted body weight and PEEP at 5 cmH_2O may be recommended according to studies performed in non-cardiac major surgery[111]. However, open-lung ventilation with higher PEEP and lung recruitment maneuvers or ventilation during bypass remain controversial to date[112–114]. Interestingly, mechanical ventilation prior to heart transplantation is strongly associated with increased mortality[115]. Early extubation within 6 hours of ICU admission should be achieved whenever possible[116]. Importantly, extubation may be also achieved safely in patients on veno arterial ECMO with clinical benefit[117].

Acute kidney injury

Early post-operative acute kidney injury is frequent in the first seven days after heart transplantation, with an incidence between 40% to 76% according to Kidney Disease: Improving Global Outcomes classification. Renal replacement therapy is required in 7% to 19% of patients[118–120]. Furthermore, recent studies demonstrate a trend toward an increased incidence of all Kidney Disease: Improving Global Outcomes stages of acute kidney injury over time[118,119]. The preoperative factors independently associated with early acute kidney injury include higher body mass index, diabetes and chronic kidney disease[118,119,121,122]. In addition, longer cardiopulmonary bypass time, postoperative hemodynamic instability, ECMO support, severe bleeding and early initiation of calcineurin inhibitors are independent predictors of early acute kidney injury[118,119,121]. The pathogenesis of heart transplantation-associated acute kidney injury mainly involves type 1 and type 2 cardiorenal syndrome[123]. Among potential mechanisms, a close attention should be paid to right heart hemodynamics, especially preoperative pulmonary hypertension, postoperative right ventricular failure and renal congestion, which appears as a strong predictor of early acute kidney injury[120,124–126]. Severe postoperative acute kidney injury is associated with a higher incidence of chronic kidney disease, rejection and mortality at 1-year after heart transplant[118,119,127]. Although there is no single pharmacological treatment, heart transplant patients might benefit from early prediction and recognition of postoperative acute kidney injury and multimodal bundle implementation[120,128,129]. Specific actions might include postponing calcineurin inhibitors, providing both left and right ventricle support (inotropes, pulmonary vasodilators, circulatory support) and minimizing renal congestion.

Nutrition

Nutritional status is crucial but often underestimated in heart failure patients. Yet, cachexia and sarcopenia may occur in at least 10% to 20% of ambulatory patients with systolic heart failure[130].

Therefore, the Heart Failure Society of America proposed in a recent consensus statement a nutritional evaluation and counseling for patients with heart failure proposed for heart transplantation[130]. In the postoperative period, early enteral nutrition is recommended including also patients receiving extracorporeal membrane oxygenation[131]. Oral intake should be the preferred route whenever possible. In patients with uncontrolled shock, enteral feeding must be delayed but low dose of enteral nutrition can be started as soon as shock is controlled. However, in case of low cardiac output requiring inotropic support, the risk of acute mesenteric ischemia requires cautious enteral nutrition introduction, or even delayed introduction[132]. In addition, heart transplantation is frequently associated with hyperglycemia in both diabetic and non-diabetic patients, requiring continuous insulin infusion in ICU to maintain glycemic control[16,133].

Conclusion

Early postoperative mortality following heart transplantation remains high despite substantial improvements over recent years. Therefore, optimal perioperative management of these patients is crucial. Unfortunately, most of the evidence supporting the current recommendations is mainly based on retrospective studies with limited sample size or is adapted from general cardiac surgery practices. Therefore, collaborative research networks at the international level should be strongly encouraged to improve the knowledge and, hopefully, the outcome of heart transplant patients.

Acknowledgments

The authors express their gratitude to Mary Regan, M.D., for proofreading.

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Legends to figures

Figure 1: **Summary of the management of the heart transplant patient over time**. ICU: intensive care unit, CO: cardiac output, TTE: trans-thoracic echocardiography, TEE: trans-esophageal echocardiography, VTE: venous thromboembolism

Supplemental Digital Content 1: **Suggestion of summarized postoperative shock assessment and management.**

[a] usually not found in vasoplegic syndrome characterized by warm extremities, normal capillary refill time and preserved Cardiac Index

[b] In addition, right ventricle failure management include preservation of coronary blood flow via systemic blood pressure maintenance, preload optimization and avoidance of pulmonary vasocontriction via ventilation settings

[c] Epinephrine, Angiotensine II or Methylene Blue (single dose) might be considered in refractory vasodilatory shock, but the level of evidence is low.

CI: Cardiac Index, ECMO: ExtraCorporeal Membrane Oxygenation, MAP: Mean Arterial Pressure, NO: Nitric Oxide, PAC: Pulmonary Artery Catheter, PiCCO: Pulse Contour Cardiac Output, RVAD: Right Ventricular Assist Device, SBP: Systolic Blood Pressure, TTE: TransThoracic Echocardiography, TEE: TransEsophageal Echocardiography

Supplemental Digital Content 2: **Suggested perioperative bleeding management protocol**.

[a] The neutralization of $P2Y_{12}$ inhibitors requires higher platelet concentrates dose (≥2 x standard dose). Platelet transfusion is unable to neutralize ticagrelor when the last intake is less than 24 hours.

[b] Platelet transfusion may be indicated despite platelet count > 100G/L if there is a known exposure to platelet inhibitors (especially $P2Y_{12}$ inhibitors) and/or platelet dysfunction diagnosed using laboratory or point-of-care platelet function tests.

ICU: intensive care unit, iCa^{2+}: ionized calcium, Hb: hemoglobin, CTR: clot time ratio, FCS: fibrinogen contribution to clot stiffness, PCS: platelet contribution to clot stiffness, CTH: heparinase clot time, CT_{IN}: INTEM clotting time, CT_{HEP}: HEPTEM clotting time, $A10_{FIB}$: FIBTEM amplitude after 10 minutes, $A10_{EXT}$: EXTEM amplitude after 10 minutes, C_{EXT}: EXTEM clotting time, R_{CKH}: citrated kaolin with heparinase reaction time, R_{CK}: citrated kaolin reaction time, MA_{CFF}: citrated functional fibrinogen maximum amplitude, MA_{CRT}: citrated rapidTEG® maximum amplitude, R_{CKH}: citrated kaolin with heparinase reaction time, UFH: unfractionated heparin, INR: international normalized

ratio, DDAVP: deamino D-arginine vasopressin, VWF: von Willebrand factor, ECMO: extracorporeal membrane oxygenation, LVAD: left ventricular assist device.