Anesthesia for cardiac transplantation: A practical overview of current management strategies

A. Koster, C. Diehl, A. Dongas, T. Meyer-Jark, I. U. Lüth

Institute for Anesthesiology, Heart and Diabetes Center NRW, Bad Oeynhausen, Ruhr University of Bochum, Germany

Abstract

Although being a standard surgical procedure since decades, heart transplantation remains a challenge for the cardiac anesthetist as it requires a sophisticated monitoring and management of circulation, ventilation and homeostasis.

Right ventricular failure is the main contributor to early graft failure in heart transplantation. Particularly after prolonged ischemia and reperfusion injury, the donor heart often can not easily adapt to the increased pulmonary artery pressure and pulmonary vascular resistance of the recipient. Therefore, the special task of anesthesia for heart transplantation is to measure and calculate the actual pressures, resistance and transpulmonary gradient in the pulmonary artery bed of the recipient, initiate strategies to reduce pulmonary artery pressure and resistance and to augment right ventricular contractility.

After induction of anesthesia and placement of monitoring lines, a pulmonary artery catheter should be forwarded into the pulmonary artery and measurements performed. These data give important information in how far the patient will be at risk for an increased afterload of the right ventricle and concomitant right ventricular failure. Besides basic ventilation strategies to reduce pulmonary artery resistance such as hyperoxygenation and moderate hyperventilation are compulsory. Inhalation of selective pulmonary artery vasodilators such as nitric oxide or aerosolized prostaglandins should be initiated in case of an increased pulmonary artery pressure and resistance. Inotropic support of the right ventricle is achieved by a combination of beta-adrenergic drugs and phosphodiesterase-3 inhibitors. The effect of the therapy is monitored by measurement of cardiac output, left and right atrial filling pressures and pulmonary artery pressures and continuous monitoring of right and left ventricular function by online transesophageal echocardiography. If the left ventricular preload remains unsatisfactory during this therapy, a vasoconstrictor should be infused to achieve adequate systemic arterial (diastolic) pressures providing adequate coronary artery perfusion. If even these strategies fail to achieve adequate cardiac output the calcium channel sensitizer levosimendan and/or replacement of triiodthyronine (T3), which plasma levels are often decreased during longer periods of cardiopulmonary bypass, are additional pharmacological options. If pharmacological therapy remains unsatisfying to establish a stable circulatory condition, mechanical support must be established.

Severe hemorrhage is not a rare condition especially in patients with previous heart surgery and will be managed with replacement of coagulation factor concentrates and/or infusion of fresh frozen plasma and transfusion of platelet concentrates. Current monitoring assays such as the ROTEM device help to guide specific therapy. In case of uncontrollable hemorrhage infusion of recombinant coagulation factor VIIa is an ultimate option.

Key words: right heart failure, pulmonary artery hypertension, nitric oxide, iloprost, coagulation factor VIIa

Abbreviations

VAD	ventricular assist device
CPB	cardiopulmonary bypass
PAVR	pulmonary artery resistance
PAP	pulmonary artery pressure
TPG	transpulmonary gradient
TAPSE	tricuspid anular plane systolic excursion
MPI (Tei-index)	myocardial performance index
NO	nitric oxide
RV	right ventricle
RVFAC	right ventricular fractional area change
LV	left ventricle
PEEP	positive endexpiratory pressue
TEE	transesophageal echocardiography
FFP	fresh frozen plasma
PC	platelet concentrates

Introduction

Although being a standard surgical procedure since decades, heart transplantation remains a challenge for the cardiac anesthetist as it requires a sophisticated monitoring and management of circulation, ventilation and hemostasis. The current article aims to provide a basic overview of anesthetic problems during heart transplantation and lines out areas of future investigation.

Induction of anesthesia and monitoring

Timing is always a critical issue in heart transplantation as the period of ischemia of the donor heart should be as short as possible to reduce ischemia- and reperfusion-injury. A postponement of the implantation due to a delay in the preparation/explantation of the native heart has to be avoided. Therefore, induction of anesthesia and insertion of moni-toring lines must be performed rapidly, which however can be a problem in these patients who often have experienced multiple intensive care unit stays including multiple previous punctures of arteries and central veins.

Usually the patient awaiting heart transplantation arrives into the anesthesia induction room before the organ is finally accepted. A peripheral venous access and an arterial catheter are inserted. Placement of an arterial catheter can be difficult in patients with an axial flow left ventricular assist device (LVAD) as no arterial pulse can be palpated. Imaging of the radial artery by ultrasound devices and image-guided puncture of the radial artery is helpful in this regard. However, if an ultrasound device is not available, stimulation of the native left ventricular output by administration of a small inotropic bolus of epinephrine (10-20 μg) helps to generate a radial or femoral pulse wave capable of being palpated. Viewing the pulse pressure curve of the patient, the anesthetist will get a good estimation of the cardiac output and can decide whether to start or increase inotropic therapy with dobutamine or epinephrine in order to maintain blood pressure and cardiac output during the   induction of anesthesia.

Induction of anesthesia normally starts just with the final acceptance of the donor organ. A rapid sequence induction of anesthesia with etomidate, a fast acting muscle relaxans, e.g. rocuronium 1 mg/kg, midazolam (3-5 mg) and morphine derivates is recommended as patients are in a vast stress situation and sometimes not present with an empty stomach. Maintenance of anesthesia is achieved with further continuous intravenous administration of morphins and propofol or volatile anesthetics.

Afterwards, a 3-4 line central venous catheter and an introducer set with a pulmonary artery catheter are placed in the right or left internal jugular vein. A placement of these access lines before the final approval of the organ should be avoided if possible to save the vessels in case the donor heart is not accepted for transplantation. However, it can

be considered if the conditions for the acceptance of the donor heart are optimal and the time frame for implantation rather narrow.

A second large bore central venous access, e.g. an introducer set or a double lumen hemofiltration catheter, should be inserted in the contra lateral jugular vein or the femoral vein in patients undergoing repeat cardiac surgery. Particularly in patients after implantation of a VAD system severe hemorrhage often occurs due to the large wound area and pretreatment of patient with multiple anticoagulants and platelet inhibitors so that severe bleeding can be expected.

Perioperative evaluation of pulmonary artery pressure and the transpulmonary gradient before transplantation

Before initiation of cardiopulmonary bypass (CPB), the pulmonary artery catheter should be shortly placed into the pulmonary artery to measure the actual pulmonary artery pressures (PAP) and cardiac output.

The calculation of the **PULMONARY ARTERY VASCULAR RESISTANCE (PAVR)** follows the equation: PAVR = [80 x (mean pulmonary artery pressure – pulmonary + capillary wedge pressure)/cardiac output (dynxs/cm^{-5}) (normal value approx. 100 dynxs cm^{-5})].

Under the condition of hyperoxygenation and deep anesthesia the **TRANSPULMONARY GRADIENT (TPG)** is calculated by: TPG = [mean pulmonary artery pressure – pulmonary capillary wedge pressure (mmHg) (normal value approx. 6 mmHg)].

Afterwards, before canulation for CPB, the catheter should be removed in the upper vena cava.

Patients with an increased systolic PAP of > 60mm Hg, and/or a PAVR > 200 dyn x s cm^{-5} and/or a TPG of >15 mmHg are considered to be of high risk to develop early perioperative right ventricular (RV) failure [1].

Pathophysiology and treatment of right ventricular failure

Right ventricular failure is the main contributor to early graft failure and of multifactorial etiology. The donor heart, especially when it is young and comparably small, can not easily adapt to the often observed pulmonary hypertension and increased PAVR of the recipient. Additionally, adaptation of the donor heart may be impaired by the ischemia- and reperfusion-injury associated with organ preservation and inflammation triggered by CPB. As a result, the RV dilates, becomes ischemic and further reduces contractility. The decrease in pulmonary blood flow and the leftward shift of the interventricular septum lead to a change of the LV shape, a lower LV preload and a reduction of systemic artery pressure and systemic cardiac output which further impair coronary perfusion.

Basic management strategies to optimize RV function and prevent RV failure include:
– *Reduction of the PAVR by optimal ventilation and pharmacological treatment*
– *Preservation of coronary perfusion by maintenance of adequate systemic artery pressures*
– *Improvement of RV function by inotropic support.*

Weaning from CPB

Shortly before weaning from CPB a transesophageal echocardiography (TEE) probe should be inserted to evaluate RV and LV function during and after weaning from CPB. (It is of practical importance that during this period and the following weaning period from CPB, the patient is deeply anesthetized as pain and awakening can result in excessive increase of the PAP and RV afterload).

The examination should focus on the RV function as well as LV ejection fraction and diastolic function. Measurement of RV fractional area change (RVFAC) in the apical 4 chamber view is relatively easy to perform

and a valid parameter of RV function [2]. The evaluation should be repeated when hemodynamic changes occur and particularly after closure of the chest. Ventilation should be started with an inspiratory oxygen concentration of 100%, small inspiratory tidal volumes (6 ml/kg) and a moderate positive end expiratory pressure (PEEP) of 5-6 mmHg. The intention is to prevent mechanical compression of the pulmonary capillary bed which may compromise pulmonary capillary blood flow and increase PAVR [3]. Moderate hyperventilation, high oxygenation and moderate alcalosis are basic strategies to reduce PAP and basic conditions before starting the weaning process from CPB and for the further course of the operation.

Inotropic therapy

Inotropic therapy should be initiated with a combination of beta-adrenergic agents such as dobutamine (3-8 µg/kg/min) or epinephrine (0.05-0.4 µg/kg/min). While dobutamine especially in higher dosages promotes arrhythmias and tachycardia, higher dosages of epinephrine lead to an increase of systemic vascular resistance and PAVR. The beta adrenergic drug therapy should be combined with a phosphodiesterase-3 inhibitor such as milrinone (bolus of 50µg/kg over 10 min and continuous infusion of 0.5 -0.75 µg/kg/min) or enoximone (bolus of 1 mg/kg over 10 min followed by a continuous infusion of 5-10 µg/kg/min). Both classes of agents improve contractility by increasing intracellular levels of cyclic adenylate monophosphate (cAMP) although cAMP levels are affected by different mechanisms [3]. As l-tyroxine also increases cAMP levels, this drug (0.8 µg/kg) should be considered especially during prolonged CPB courses which have been shown to be associated with decreased triiodthyronine levels [1;4;5].

Due to the reduced muscular mass the ability of the RV to increase contractility is limited. Therefore, the heart rate may be elevated by pacing to a frequency of approximately 110- 120 b/min in order to increase RV output and "overpace" possible arrhythmias. If further arrhythmias are observed, cautious treatment with amiodarone (150-300 mg over 10-20 min) should be initiated.

Inhalation of pulmonary artery vasodilators

In patients with an increased TPG, systolic PAP or PAVR preemptive ventilation should be initiated with inhaled nitric oxide (NO) (20-40 ppm) or inhalation of aerosolized prostaglandins (20-30 µg iloprost/15 min, repeated after 4 hours) before complete termination of CPB.

Nitric oxide reveals its strong vasodilator effect by increasing the concentrations of intracellular cGMP cells of the pulmonary artery bed which induces vasodilatation by a variety of mechanisms [6].

Iloprost exerts its vasodilator effects by binding to special subgroups of receptors of the group of prostanoid receptors in the pulmonary artery bed. However, the final intracellular effect of this prostanoid receptor activation is the increase of cAMP via stimulation of the guanylate cyclase. The transduced biological effects are vasodilatation, inhibition of platelet activation and aggregation, inhibition of leucocyte activation and adhesion and antiproliferation [7].

Both drugs have been demonstrated to be effective means to reduce PAP in heart transplantation. The inhalation of these agents appears to be superior to a systemic administration of prostaglandins or other pulmonary vasodilators as the pulmonary artery bed is widened more selectively and systemic vasodilation and consecutive systemic hypotension can be prevented [8]. As preferentially better ventilated lung areas are targeted, hypoxic pulmonary vasoconstriction is augmented and oxygenation improved. Particularly the inhalation of aerosolized prostaglandines is simply to achieve, as the small nebulization devices can be easily implemented into the inspiratory ventilation cir-

cuit and monitoring of drug and metabolites, such as needed when NO is inhaled, are not necessary.

Practically the heart should be cautiously loaded and the CPB flow reduced to approximately 50% to achieve a better perfusion of the pulmonary vascular bed so that the inhaled agents can exert its effects in the pulmonary artery bed. During this period the canula of the upper vena cava can be positioned into the right atrium and the pulmonary artery catheter directed into the pulmonary artery to monitor the PAP. After 10-15 minutes of inhalation and optimization of inotropic support cautious separation from CPB can be completed.

As the RV is particularly sensitive to distension, care should be taken that excessive preload of the right heart is avoided. The central venous pressure should not be increased about 10-12 mmHg and TEE performed online to assess RV function by measurement of RVFAC and recognize first indicators of right heart failure such as beginning tricuspid regurgitation, leftward shift of the interatrial septum or "flattening" of the interventricular septum during enddiastole and early systole [9-12]. Further, more sophisticated TEE derived parameters of RV performance including tricuspid annular plane systolic excursion (TAPSE) and myocardial performance index (MPI or Tei index) may better help to estimate RV function and response to therapy [2, 13, 14,15].

If an adequate systemic vascular pressure can not be established with this medication and direct measurement of the left atrial pressure and the TEE assessments indicate an unloaded LV with unimpaired function, a vasopressor such as norepinephrine should be added to provide adequate systemic arterial (diastolic) pressures and maintain coronary artery perfusion [6-9]. According to the experiences in the German Heart Institute Berlin a left ventricular enddiastolic diameter (LVEDD) of <30 mm in the TEE is a good indicator for impaired left ventricular filling.

If this pharmacological treatment remains unsatisfactory (low cardiac output, low sys-temic arterial pressures, continuous acidosis), use of the calcium sensitizer levosimendan (Simdax®), similar as phosphodiesterase-3-inhibitors an inodilator, should be considered. Although not studied adequately in this special indication, reports of larger patient series demonstrated reversal of the low output syndrome after heart transplantation when levosimendan therapy was initiated. Levosimendan is given with a bolus of 6-12 µg/kg (30-60 min) followed by a continuous infusion of 0.1 - 0.4 µg/kg/min [16, 17].

Even if hemodynamics are acceptable with open chest, the closure of the chest and compression of the often swollen heart by the lungs or sometimes small intrapericardial cavity (for example after explantation of a total artificial heart) sometimes has a tamponade like effect and might impair particularly right heart function. Therefore, chest closure has to be done very cautiously. If previously stable haemodynamics remain unsatisfactory in this situation, re-opening and leaving the chest open is an option (even it should be critically evaluated in the immune-suppressed patient) which should be discussed with the surgeon.

If all these strategies remain ineffective to achieve an adequate cardiac output, mechanical support by insertion of an intra aortic balloon pump (IABP) is the next step which can help to increase coronary perfusion pressures. If even this strategy fails, implantation of a right ventricular assist device (RVAD) or extracorporeal membrane oxygenation (ECMO) are ultimate strategies [18].

In the more rare case of biventricular failure, pharmacological management strategies remain similar. However, due to LV dysfunction, systemic vasoconstriction will be avoided and the decision to implant an IABP forwarded much earlier. Further mechanical assistance of the failing heart by temporary VAD placement or ECMO should be considered early.

Coagulation management

Use of a cell saver helps to reduce the amount of transfusions of red packed blood cells which might exert unfavorable side effects due to the low ph-value of the stored blood which might increase pulmonary vascular resistance. This particularly applies for older red blood cell concentrates (>14 days) which have been associated with an unfavorable outcome in patients after cardiac surgery [19]. Especially in patients undergoing heart transplantation after VAD support and other complex previous cardiac operations massive intraoperative bleeding can be expected. Administration of an antifibrinolytic agent during CPB, such as tranexamic acid (10mg/kg bolus, 500 mg in the CPB prime, continuous infusion of 1 mg/kg/hour until chest closure), to attenuate hemostatic activation and reduce perioperative blood loss is recommended [20].

The patient should be re-warmed to 36-37° C before weaning from CPB and all infusions and transfusions should be given via fluid warming systems since a physiological body temperature is a prerequisite to establish sufficient coagulation after CPB.

In patients with a higher risk of excessive hemorrhage the hemoglobin value should be elevated to values of 10-12 (14) g/dl before weaning from CPB. This will allow infusing larger amounts of fresh frozen plasma (FFP) and platelet concentrates (PC) early after protamine infusion in order to re-install coagulation even if impaired RV function may restrict additional transfusion of RBC to maintain hemoglobin levels. Another technique to replace coagulation factors and platelets adequately is a modified ultrafiltration after CPB (but still during heparinization) using FFP and PC for replacement of the filtrated volume [21]. This strategy is advisable when severely impaired right ventricular function requires a restriction in the amount of volume application and therefore aggravates adequate re-installation of coagulation. In patients with existing coumadine therapy, 2000-3000 IU of prothrombin complex concentrate should be given after conclusion of CPB and protamine administration.

Performance of a ROTEM analysis of the coagulation system helps to guide therapy with plasmatic coagulation factors, FFP and PCs [22].

In case of uncontrollable hemorrhage despite transfusion of coagulation factors, FFP and PC, administration of recombinant coagulation factor VIIa (Bolus of 90 µg/kg or 360 IU of Novo Seven® in the 70 kg patient) may be an ultimate option to establish hemostasis [23].

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Correspondence address
Andreas Koster, MD, PhD
Institute of Anesthesiology
Heart and Diabetes Center
Nordrhein-Westfalen
Georgstr. 11
32545 Bad Oeynhausen
akoster@hdz-nrw.de