Chapter 10

Anesthesia and Intensive Care Management for Cardiac Transplantation

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Additional information is available at the end of the chapter

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Abstract

Patient management in heart transplant is quite complex and includes multiple steps from preoperative recipient evaluation to postoperative ICU treatment. Monitoring, anesthesia induction, and cardiopulmonary bypass weaning strategies are discussed. The success of the operation also depends on right heart support especially in case of pulmonary hypertension. Many details like fluid management, well-timed respiratory weaning, and primary graft dysfunction management can make the difference in terms of outcome. Pediatric heart transplants represent a small group of total cardiac transplant, but the differences in anatomy and physiology make the surgical and anesthesiological management more complex in unique scenario that requires a specific knowledge at different stages of growth, from newborn through childhood up to adulthood.

Keywords: anesthesia, intensive care, monitoring, inotropic drugs, mechanical support

1. Intraoperative management

Intraoperative management in heart transplant is quite complex and includes multiple steps from preoperative evaluation to ICU admission.

1.1. Preoperative evaluation

During this phase, we need to collect the consent from the patient after having explained to him all the possible complications coming from surgery, anesthesia, and ICU stay.

Above all, we need to know the background history of the patient, any previous issue with general anesthesia, allergies, difficult airway management, and any possible contraindication to the transplant itself [**Table 1**].

A multiorgan analysis must be taken into account:

- Neurological history: syncopal episodes, carotid stenosis, ischemic or hemorrhagic stroke, transitory ischemic attack.
- Respiratory history: smoke, COPD, spirometry, DLCO test.
- Cardiovascular history:
  1. origin of cardiomyopathy: dilated/hypertrophic/ischemic cardiomyopathy
  2. noncompaction left ventricle (LV), sarcoidosis, amyloidosis, and others
  3. arrhythmias: episodes of sudden cardiac death syndrome, implantation of an ICD
  4. right side catheterization: pulmonary artery pressures (PAP), pulmonary capillary wedge pressure (PCWP), pulmonary vascular resistances (PVR), results of reversibility test with enoximone, origin of pulmonary hypertension (prepost capillary)
  5. presence of prosthetic valves in situ
  6. home medications: oral anticoagulants, ace inhibitors, b-blockers, diuretics
- Renal history: chronic or acute renal failure, preoperative serum level of creatinine and urea, creatinine clearance, history of renal replacement therapy.
- Hepatobiliary history: a systemic portal venous congestion can often derive from chronic congestive heart failure. In this case, high levels of transaminases and bilirubin may occur and this may influence the pharmacological and hemodynamic management during anesthesia.

Absolute contraindications	**Relative contraindications**
Significant COPD (FEV1 < 1 L/min)	Age > 72 years
Fixed pulmonary hypertension	Active infections
PAPs >60 mmHg	BMI > 35 kg/m^2 or <18 kg/m^2
GTP > 15 mmHg	Creatinine clearance < 25 ml/min
PVR > 6 wood units	Active mental illness or psychosocial instability
Irreversible renal or hepatic dysfunction	Severe peripheral vascular disease
AIDS/malignancy/lupus	Diabetes mellitus with end organ damage

Table 1. Contraindications to heart transplantation.

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- Metabolic history: surgical stress and corticosteroid therapy may dramatically increase glycemia levels and hyperglycemia may dramatically increase the lactate levels during and after surgery; this is the reason why we need to know if the patient has diabetes and plan a proper blood glucose control with continuous infusion insulin (usually 50 UI/50 ml gelatin starting with a speed of 2–3 ml/h, depending on glucose plasma levels, with a target of 80–150 mg/dl). Among metabolic disorders, hypothyroidism can be further impaired during and after heart transplantation because plasma levels of triiodothyronine are often decreased during long periods of cardiopulmonary bypass, so that it's important to plan an early replacement thyroid therapy.
- Preoperative fasting: the patient should fast from food at least 8 hours and from fluids 4–6 hours before the operation.
- Premedication: it's important to avoid any preoperative oversedation since hypoxia may increase the pulmonary vascular resistances (PVR). We usually do not exceed a dose of 10—15 drops per os of diazepam in adult patients before going to theater, but, if the patient is really critical, we avoid any premedication.

1.2. Recipient with pulmonary hypertension

Severe pulmonary hypertension in the recipient is one of the major contraindications to heart transplant [1, 2] due to high risk of right heart failure. When pulmonary hypertension persists up to 1 year from transplant, clinical outcomes and percentage of long-term survival are really poor [3]. For the above-mentioned reasons, a potential recipient must be evaluated with caution before being added to the waiting list. First of all, he needs to be sent for cath lab in order to evaluate his own pulmonary vascular resistances (PVR), mean pulmonary arterial pressure (m-PAP), pulmonary artery wedge pressure (PAWP), cardiac output (CO), cardiac index (CI), and the transpulmonary gradient (TPG).

This last equals the difference between mPAP and wedge pressure (TPG = mPAP − PAWP).

In case of high PVR (PVR > 3 wood units [WU]), it is important to perform the reversibility test with enoximone or dobutamine in order to quantify the reversibility degree of pulmonary hypertension. When postcapillary pulmonary hypertension (defined as mPAP ≥ 25 mmHg, PAWP > 15 mmHg and PVR > 3WU) is unresponsive to dobutamine reversibility test (i.e., PVR > 3 WU or mPAP > 35 mmHg with a TPG > 12 mmHg), a team made of cardiologists, anesthesiologists, and cardiac surgeons should seriously evaluate if the patient is suitable for receiving a new heart.

A preventive treatment with pulmonary vasodilators such as sildenafil should be considered since it has been shown to decrease the PVR in a period of few months [4].

A preventive treatment with sildenafil should also be considered when patients are scheduled for receiving an LVAD positioning as bridge to transplant, thanks to its effectiveness in long-term reduction of the PVR and major responsiveness to a further test with dobutamine [5].

2. Monitoring and induction of general anesthesia

Timing to get the patient ready to receive the new organ is crucial because the ischemia of the donor heart should be as short as possible to avoid the ischemia-reperfusion injury.

Everyone in the theater should wear sterile surgical gown, hat, mask, and sterile gloves for any procedure on the patient especially because he will go under immune deficiency. Once the patient is in the theater, he will be connected to multiparametric monitor, with the 12 lead ECG and oximetry probe. Two peripheral venous lines are placed (generally 18G for iv sedation and 14G for rapid fluid infusion), and an arterial catheter, generally 20G, is placed into the radial or humeral artery. When the patient is very unstable, an arterial catheter is placed in the left femoral artery, to estimate central to peripheral arterial pressure gradients. Placement of an arterial line can be very difficult in patients with previous implantation of LVADs as bridge to transplant, due to the absence of arterial pulse. In such situations, ultrasound guidance can be very helpful (see **Table 2**).

Induction of general anesthesia usually starts just with the final acceptance of the donor organ. Drugs used for general anesthesia should impact the less possible on hemodynamics. A rapid sequence induction is preferred since recipients are always very stressed and sometimes not present with an empty stomach [6].

Midazolam (10–15 mg) or etomidate (20 mg) are preferred to propofol for hypnosis, due to the less impact on hemodynamics. Opioids like fentanyl or sufentanil are preferred for the same reason ("stress-free anesthesia"), with an induction dose of 0.2–0.4 mcg/kg for sufentanil and 2–4 mcg/kg for fentanyl. Continuous infusion analgesia remifentanil is preferable for the less impact on renal function since it is metabolized by plasmatic esterase. This is particularly important in patients with low cardiac output and preexisting renal failure. Remifentanil will be turned off and replaced by morphine or tramadol (30 mg/die and 300 mg/die, respectively), before moving to the intensive care unit. Mean term muscle relaxant rocuronium (1 mg/kg) is usually the first choice for rapid sequence induction. Sometimes short-term cisatracurium

Device	Measure
PA radial	Invasive arterial pressure (peripheral)
PA fem	Invasive arterial pressure (central)
CVP	Central venous pressure
ECG	12 lead electrocardiography
SpO2	Oxygen saturation levels
PAC	(pulmonary artery catheter) PAPs, PAPm, PAPd, sVO_2
TEE	Biventricular function, shape of ventricular septum, filling, air etc.
NIRS	$ScvO_2$ correlation, adequate tissue perfusion, brain perfusion
LAP	LV filling pressure

Table 2. Standard monitoring.

besylate (0.15–0.2 mg/kg for induction and 1–2 mcg/kg/min for continuous iv infusion during surgery) is a good alternative since it is metabolized by ester hydrolysis and Hofmann reaction, so the duration of block is not affected by renal or hepatic function. During induction of general anesthesia, severe hypotension can occur, so that a fluid iv bolus ad availability of rapid onset vasoconstrictors as metaraminol, phenylephrine, noradrenaline should be ensured. Cardioplegia is not administered in the recipient during heart transplantation, so that the risk of related hemodilution is less than routine cardiac surgery. On pump, sevoflurane or iv 2% propofol infusion (4 mg/kg/h) are the options for maintenance of general anesthesia. Monitoring the depth of anesthesia with bispectral index (BIS) should be routinely adopted in order to decrease the risk of awareness. Once having put the patient asleep, central lines must be placed (queen central venous pressure [CVP] line and 8 Fr line for the pulmonary artery catheter [PAC]). The ideal site for puncture (blind or ultrasound-guided) is the left internal jugular vein (IJV), since the right one can be reserved for eventual postoperative biopsy (necessary to evaluate the level of graft rejection). When this is not possible (presence of ICD on the left side), we can adopt the right subclavian vein. Sometimes, when the preoperative renal function is really compromised, we can already place into the femoral or subclavian vein a catheter for continuous renal filtration afterwards. The PA catheter is flown through the 8 Fr line up to the right atrium, and then, once the new heart is placed, it will be advanced by the cardiac surgeon up to the superior right pulmonary artery. Vigilance calibration will be done immediately before weaning from the CPB.

3. CPB and weaning

If the graft is not carried out into the organ care system (OCS), the ischemic time is crucial and the risk of ischemic/reperfusion injury is proportionally high, with possible dramatic increase of blood lactate levels and decrease of the graft global function. This is the reason why we must ensure adequate glycemia control, urine output, and, in general, an optimal tissue perfusion during CPB. This means to guarantee an adequate oxygen delivery (DO_2), which means to keep MAPs about 60–80 mmHg and Hb levels at least about 8–9 mg/dL. When the aorta is unclamped, VF can occur (50% of patients). A shock delivery (10–30 J) followed by lidocaine bolus (when VF is refractory to electrical therapy) will take to resolution of the arrhythmia and return to sinus rhythm. In case of sinus bradycardia, temporary epicardial pacing will ensure adequate heart rate (100–110 bpm). Due to limited muscular mass, the ability of the right ventricle (RV) to increase contractility is limited and a temporary pacing at about 110 bpm will increase RV output and will overpace possible arrhythmias. Surgeons will also place a left atrial catheter for continuous measurement of the left atrial pressure (LAP) as an indicator of the left ventricle performance and stiffness. This value, together with CVP, PAPs, MAPs, and SvO2, will influence the posttransplantation hemodynamic management. Throughout this period, it will be mandatory to ensure adequate MAPs and diastolic pressure to allow adequate coronary perfusion, while maintaining medium-low preload pressures (CVP < 12 mmHg, LAP/PCWP < 12 mmHg). The biventricular assessment with transesophageal echocardiography should be done simultaneously.

Pharmacological tools for CPB weaning will include the following [**Tables 3** and **4**]:

- Isoprenaline at low-moderate dose (0.02–0.04 mcg/kg/min): it is the first choice in heart transplantation due to the positive chronotropic effect; it helps to guarantee a heart rate of 100–110 bpm. If it does not work, do not go beyond 0.04 mcg/kg/min, in order to avoid hypotensive effects. In this case, switching to atrial pacing is the best choice.
- Adrenaline (0.02–0.2 mcg/kg/min): it provides inotropic support to the new heart, especially to the right ventricle, which is the one more at risk of failure.
- Milrinone (0.2–0.5 mcg/kg/min) or other phosphodiesterase inhibitors (enoximone at 5–8 mcg/kg/min): they increase contractility especially of the right ventricle, while decreasing pulmonary vascular resistances. They both increase intracellular levels of cAMP, but they also decrease the systemic vascular resistances (SVR), so that the patient may benefit from low-moderate noradrenergic support in addition. If systemic peripheral resistances are really low, selective pulmonary vasodilators, aimed to decrease RV afterload without affecting peripheral resistances, are a better choice: inhaled nitric oxide (iNO) at 20–40 ppm [9, 17]) or aerosolized prostaglandins (iloprost 20 mcg/15 min, repeated after 4 hours).

  Possible side effects of these selective inhalation drugs are inhibition of platelet activation and aggregation and inhibition of leucocyte adhesion.
- Levosimendan (0.1–0.2 mcg/kg/min) has also been reported to reverse low cardiac output after heart transplantation [10], although its use has not been shown to reduce cardiac surgery mortality [11].

After having unclamped the aorta and before weaning from CPB, about 1 hour of assistance to the new heart is provided. During this period, an adequate temperature is achieved (36–36.5°C measured by nasopharyngeal temperature probe). Vigilance calibration is performed by providing Hb levels and SvO_2 from gas analysis; it gives results about the indexed cardiac output, pulmonary vascular resistances, and systemic peripheral vascular resistances, indexed on the patient weight. PAPs are shown on the monitor together with CVP, LAP, MAPs, and ECG. The PAVR (pulmonary artery vascular resistance) equals: PAVR = [80 × (mean pulmonary artery pressure – pulmonary + capillary wedge pressure)/cardiac output] (normal value 100 dynes/cm^{-5}).

The TPG (transpulmonary gradient) equals: TPG = mPAP − PCWP (normal value 6 mmHg).

A TPG > 15 mmHg is considered at high risk to develop early postoperative RV dysfunction [7]. The reason for RV dysfunction development may be found in the background of the donor heart. Especially when young and comparably small, it may not easily adapt to the already existing pulmonary hypertension in the recipient. Furthermore, as a result of a long ischemia and CPB time, with ischemia-reperfusion injury, RV dilates, becomes ischemic, and further reduces its own contractility. In this case, we need to adjust the amount of inotropes, chronotropes, and pulmonary vasodilators given, basing also on transesophageal echocardiography that can show the biventricular systolic-diastolic function and fluid responsiveness. Once the patient is stable and the heart rate is appropriate, we can start ventilation and slowly decrease the pump flow until 0.5–1 L/min. At that point, we come out from bypass. During CPB weaning, the heart should be loaded with caution because RV is very sensitive to distension. Echocardiographic parameters to asses the RV behavior will be RVFAC (fractional area change), leftward shift of

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Sustain SVR and arterial pressure (if necessary)	Norepinephrine
	vasopressin
Maintain DO_2 level	Raise in pump flow
272 ml/min/m^2	Raise Hb level
	Raise O_2 sat
	Decrease body temp
Support graft	Milrinone (0.2–0.5 mcg/kg/min)
	Dopamine (4–6 mcg/kg/min)
	Epinephrine (0.05–0.25 mcg/kg/min)
Hb level	11 g/dl
Maintain regular rhythm	K^+/Mg^+
and A-V synchrony	Pacing
110 bpm	Isoprenaline (0.02–0.04 mcg/kg/min)
Pacing with 110–120 bpm	Increase of HR increases CI, avoid overload
Reduce PVR (if necessary)	iNO (20–40 ppm)
	Inhalatory iloprost (10–20 ng)
	Inhalatory milrinone (5 mg) for 15 min
Slowly reduce CPB flow (careful monitoring CVP, TEE, LAP)	Check/change drug infusion rate
	Check chamber filling
	Check contractility

Table 3. Practice guide to wean from CPB.

Drug	Average dosage	Advantages	Side effects
Epinephrine	0.05–0.25 mcg/kg/min	Support RV overload	Tachycardia, arrhythmias, raise O_2 demand
Norepinephrine	Up to 0.15 mcg/kg/min	Contrast vasodilatation	Increase PVR
Levosimendan	0.1–0.2 mcg/kg/min	Support RV overload	Vasodilation
Milrinone	0.2–0.5 mcg/kg/min	Support RV overload	Arrhythmias, raise O_2 demand, vasodilation
Vasopressin	2.5–5 U/h	Contrast vasodilatation	Increase SVR impair forward flow of LVAD
i-NO	20–40 ppm	Reduce PVR (if not fixed)	
i-Milrinone	5 mg/15 min	Reduce PVR (if not fixed)	
i-Iloprost	20–30 mcg/15 min	Reduce PVR (if not fixed)	
Methylene blue	0.5–2 mg/kg	Contrast vasodilation	

Table 4. Inotropes/vasoactive: average therapeutic dosage to support hemodynamics.

Inotropic score	Dopamine (μg/kg/min) + dobutamine (μg/kg/min) + 100 × epinephrine (μg/kg/min)
Vasoactive inotropic score (modified by Davidson et al. with inclusion of vasoactive medication	IS + 10 × milrinone (μg/kg/min) + 10 × vasopressin (U/kg/min) + 100 × norepinephrine (μg/kg/min
Vasoactive inotropic score plus levosimendan	VIS + 10 × levosimendan (mcg/kg/min)
Poor clinical outcome	VIS 20–24 (in the first 24 h) + VIS 15–19 (in the subsequent 24 h)

Table 5. Inotropic score.

IAS (interatrial septum) or "fluttering" of IVS (interventricular septum) during end-diastole, TAPSE(tricuspid annular plane systolic excursion), and MPI (myocardial performance index).

Basic ventilation strategies to reduce pulmonary artery resistances such as hyperoxia and moderate hyperventilation are mandatory. Ventilation should be set at 60–100% FiO_2, 6–8 ml/kg TV (tidal volume), and low-moderate PEEP (5–6 cmH_2O), after recruitment maneuver, with the intention to prevent lung atelectasis [12].

Chest closure can be very critical for hemodynamics. In some rare cases (i.e., 2.5%), primary graft failure can occur [13], and it is responsible for more than 30% of early deaths after cardiac transplantation. Clinical onset of primary graft failure is with hypotension, low cardiac output, high preload pressures (PVC, LAP, and wedge pressure), and biventricular failure. When necessary, a temporary IABP (intra-aortic balloon pump), as first step, and then peripheral (femoral vein-femoral artery) or central (left atrium, right atrium, aorta) VA-ECMO (venous-arteriosus extracorporeal membrane oxygenation) should be taken into account, whenever hemodynamics remain unsatisfactory despite high inotropic support (**Table 5**) [14].

4. Fluid management

Fluid management should be "goal directed," that is, guided by the above-mentioned hemodynamic and echocardiographic parameters, and with the aim to avoid a fluid overload, which is very harmful for the lungs and the right ventricle, while providing adequate intravascular space filling. This should be done via balanced colloids and crystalloids in order to avoid electrolyte disorders and hyperchloremic hyperkalemic metabolic acidosis. Adequate oxygen delivery is ensured by maintaining the hemoglobin level around 10–11 g/dL and an adequate plasma oncotic power is ensured by giving the right amount of albumin.

5. Anticoagulation and hemostasis

To go on CPB, we need to provide an appropriate anticoagulation via unfractionated heparin (300–400 U/kg). A value of ACT at least of 480 s is enough to start the extracorporeal

circulation. In case of low response to a full dose of heparin, we can achieve an adequate ACT by administering antithrombin III (AT3), especially when AT3 plasma levels are less than 70%. From 0.5 to 5% of patients with end-stage heart disease can develop HIT (heparin-induced thrombocytopenia), due to repeated heparin exposures related to the placement of IABP, LVADs, or frequent catheter procedures. Alternative anticoagulation, with direct thrombin inhibitors (bivalirudin and argatroban), [8] is recommended in such patients. At the end of organ implantation, once the aortic and right atrium cannulas are removed, we need to guarantee an appropriate heparin reversal with protamine (50 mg of protamine every 50 mg of heparin). We also give the patient 2 g of tranexamic acid at the induction of general anesthesia and 2 g (25–50 mg/kg) with protamine in association with 1 g of gluconate calcium, to avoid hyperfibrinolysis and replace calcium deficiency. Severe bleeding is not a rare condition especially in patients with previous heart surgery. Particularly, in patients with LVADs as bridge to transplant, severe bleeding can often occur due to the large wound area and pretreatment with multiple anticoagulants and platelet inhibitors. If hemostasis is insufficient and the patient is still bleeding, we need to check for coagulation disorders via ROTEM (i.e., hyperfibrinolysis, coagulation factor deficiency, and hypofibrinogenemia) or via TEG and correct the specific deficiency (prothrombin complex concentrate for clotting factor deficiency or fibrinogen concentrate for hypofibrinogenemia). We prefer this approach instead of large dose of fresh frozen plasma, in order to avoid TACO (transfusion-associated circulatory overload), TRALI (transfusion-related lung injury), immune modulation, and increased risk of infections.

6. Intensive care management

Almost 90% of heart transplants are due to ischemic or dilatative cardiomyopathy and men over 40 years of age are the most involved. They all need a special care and a multimodal approach, even because not only cardiovascular balance but also respiratory care, fluid management, and immune system modulation impact on the overall survival.

6.1. ICU admission

Patients incoming from the operating room have to be placed in an isolated single bed room to avoid contamination, since they will undergo immunosuppressive therapy. Everyone in contact with them must wear mask, cup, and sterile gown and do routine sterile hand washing. Invasive hemodynamic monitoring, including systemic arterial pressure, right atrial pressure, pulmonary artery pressure through the PAC, and left atrial pressure, should be immediately reconnected in the room.

Twelve lead ECG at the arrival is mandatory to check heart rhythm disorders. Bradyarrhythmias and supraventricular arrhythmias are the most frequent and should be related to inotropic and chronotropic support, hypovolemia, and electrolyte disorders. If atrial fibrillation occurs, an acute rejection should be considered and a 500 mg bolus of methylprednisolone should be administered, eventually followed by amiodarone (300 mg iv bolus in 30 min) for pharmacological cardioversion and rate control. In case of failure of pharmacological cardioversion, we can try electrical cardioversion. Sinus bradycardia can be

treated with low-dose isoprenaline (0.01–0.04 mcg/kg/min), adrenaline (0.01–0.04 mcg/kg/min), and/or temporary atrial pacing, in order to ensure a heart rate about 100–110 bpm. In case of severe AV block, a sequential pacing is required. Anyway, if the patient is still pacing dependent after 2 weeks from the operation, implantation of a permanent pace maker should be considered. Then, you can proceed to request chest X-ray to check the lungs, endotracheal and nasogastric tube position, chest drains, and intravascular devices (CVP line, PAC, and pacing wires) and send for laboratory tests including standard coagulation, renal and liver function, platelets, red blood cell and white blood cell counts, troponin I, CK, albumin, viral markers, thyroid markers, and glycaemia. Blood samples should be sent for good practice also for coagulation tests (ROTEM or TEG) in case of excessive bleeding. A plan for immunosuppressive therapy (methylprednisolone, thymoglobulins, etc.) must be provided in collaboration with specialist immunologist and cardiologist. Antibiotic therapy must be tailored on the background history of donor and/or recipient.

7. Hemodynamic management

Hemodynamic stability, after heart transplant, may be impaired by several pathophysiological processes, including autonomic denervation, with subsequent chronotropic and inotropic failure, ischemia reperfusion injury, metabolic acidosis, and volume depletion. To support such effects, several endpoints must be taken into account:

7.1. Intravascular volume optimization

A goal-directed therapy is the ideal way to ensure adequate fluid filling. It means using the above-mentioned hemodynamic parameters coming from invasive monitoring and from echocardiographic evaluation, to be guided in the fluid replacement. Once the need of fluids is clear, the physician should decide the most ideal fluid in order to avoid peripheral organ oncotic damage (i.e., hyperoncotic kidney failure from hydroxyethyl starches [15]); hyperchloremic hyperkalemic acidosis, which can impact itself on kidney function; and fluid overload into the interstitial space. Crystalloids have a less oncotic power than colloids; however, albumin can cross the pulmonary capillary membrane, if damaged, and anyway it can recirculate through the pulmonary barrier 24 hours from the administration: then balanced crystalloids and balanced colloids (albumin solution at 5 or 20%) should be given at the right per kilo amount and the fluid responsiveness should be tested while they are given.

7.2. Narrow monitoring of hemodynamic parameters

During the recovery period (approximately 7–14 days), a narrow monitoring of hemodynamic and vital parameters is mandatory: IBP, CI, CO, ISVRI, IPVR, PAPs, HR, SvO_2, LAP/PCWP, TPG, SpO_2, ECG, body temperature, urine output, and lactate levels.

Target values are: CVP ≤ 12 mmHg, MAP > 65 mmHg, LAP 8–12 mmHg, SvO_2 over 65%, HR about 100–110 bpm, urine output > 1.5 ml/kg, and lactate < 2 mmol/L.

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7.3. Pharmacological support

The goal is to ensure adequate CO, avoiding excessive increase of cardiac preload and afterload, while maintaining adequate heart rate. Chronotropic support is achieved through low-moderate dose of isoprenaline or by atrial-sequential external pacing. Inotropic effect is achieved through moderate-high dose of adrenaline and, when necessary, with phosphodiesterase inhibitors as milrinone that also decreases peripheral vascular resistances. Other pharmacological tools that are aimed to control arterial ventricle coupling are nitroglycerin and sodium nitroprusside, very helpful to decrease the afterload of the left ventricle and increase cardiac output, when used together with an inotropic drug. In case of preexistent pulmonary hypertension, inhalation of nitric oxide and imbrication with sildenafil can help to reduce pulmonary vascular resistances [14]. In the further postoperative course, addition of an upstream therapy including ace inhibitors, b-blockers, or calcium antagonists may be helpful as cardiac protection.

7.4. Support the right ventricle of the donor heart

The donor heart, particularly the right ventricle, in case of preexisting precapillary or postcapillary pulmonary hypertension, has to fight with high afterload [**Table 6**]. The preexisting conditions may be impaired in case of coexisting hypoxia or hypercapnia, prolonged extracorporeal circulation, and donor ischemia with consequent ischemia-reperfusion injury, blood transfusion, and protamine administration. Right ventricular failure may be challenging and really impacts on the overall survival of transplanted patients [18].

Early PA pressure monitoring at the time of CPB weaning is fundamental and has to be continued in the early postoperative period. The first aim in hemodynamic management of the graft is to offload the right ventricle, decreasing PA pressures and pulmonary vascular resistances while ensuring an adequate RV contractility. Inhaled nitric oxide at 20–40 ppm is a rapid onset tool to decrease PA pressures. It seems to improve early clinical outcomes in heart transplanted patients, but literature is still lacking in terms of overall survival [9].

This is the reason why it is often used preventively during weaning from the CPB. Alternatively, the prostacyclin analog iloprost (6 × 5–10 mcg) can be given.

After the very early postoperative period, inhaled nitric oxide can be substituted by the phosphodiesterase-5 inhibitor sildenafil at the dosage of 20 mg × 3/die via NG tube with very small effects on the systemic pressures, avoiding also the rebound phenomena coming from the discontinuation of inhaled nitric oxide therapy. Sildenafil has also been shown to decrease PA pressures during inhalation of nitric oxide, since they seem to activate different regulatory mechanisms of the vascular tone [19, 20]. Inotropic support of the RV should be guaranteed by moderate-high dose of adrenaline (0.05–0.1 mcg/kg/min) or low-moderate doses of phosphodiesterase inhibitors as milrinone (0.2–0.3 mcg/kg/min).

Clearly, while supporting the right ventricle, we need to ensure adequate oxygenation, avoid hypercapnia, maintain adequate lung recruitment by PEEP (not over 6 cmH_2O), and guarantee a negative fluid balance in order to reduce the preload and optimize the afterload [**Table 6**]. If all these maneuvers are not sufficient, we have to consider a temporary mechanical right ventricle support via peripheral VA-ECMO.

Monitor by PAC	CVP, MPAP, PCWP, CO, SvO_2
Mechanical ventilation	PaO_2 100 mmHg, pCO_2 30–35 mmHg, pH 7.5. Adequate peep level (5–10 cm H_2O) to recruit lung and optimize PVR
Restricted fluid therapy	Monitoring filling pressure CVP 10–12 mmHg, PCWP 12–15 mmHg
	Monitoring LVEDV, RVEDV by echocardiography
Inotropes to support RV contractility	Epinephrine 0.02–0.25 mcg/kg/min
Inodilator	Milrinone 0.2–0.5 mcg/kg/min
	Levosimendan 0.2 mcg/kg/min ± norepinephrine (up to 0.15 mcg/kg/min) to maintain right coronary perfusion pressure
iNO	5–40 ppm
Phosphodiesterase V inhibitor	Revatio 3 × 20 mg p.o.
Systemic vasodilators	Sodium nitroprusside, prostacyclin PGI_2 analogon iloprost (2 ng/kg/min)

Table 6. Pulmonary artery hypertension monitoring and right ventricular dysfunction prevention.

In case of concomitant LV insufficiency and signs of systemic hypoperfusion (with raising of LAP/PCWP and sudden reduction of CO, CI, and SvO_2), we will need to increase the inotrope support and try to compensate the peripheral vasoconstriction with peripheral vasodilators as nitroprusside, when the MAPs allow to do that, in order to reduce left ventricle afterload and facilitate the ejection. The conditioning with inodilators as levosimendan [10] can be very helpful and, in case of massive peripheral vasodilatory response, it can be compensated with mean dosage of noradrenaline to ensure adequate MAPs. When this is not enough, an additional support with IABP should be considered, but, when insufficient, a central or peripheral VA-ECMO will be placed. The simultaneous presence of the IABP will help avoid pulmonary edema by reducing the afterload of LV.

7.5. Avoid metabolic acidosis and monitor acid-base balance and kidney function

A patient undergoing heart transplant comes from a long period of low cardiac output, so the kidney dysfunction is often preexisting.

In the immediate postoperative period, urinary output may decrease for several reasons including intravascular volume depletion and kidney damage coming from long lasting extracorporeal support or from the use of unbalanced solutions for fluid challenge. In addition, a high use of colloidal molecules may damage directly the renal tubules with a process called "osmotic-nephrosis." If urine output is <0.5 ml/kg/h despite optimization of blood pressure, preload and CO, and use of standard diuretics (furosemide or torasemide), and the patient develops kidney failure with serum urea >200 mg/dL or hyperkalemia, kidney replacement therapy becomes mandatory.

We prefer early application of continuous venovenous hemofiltration (CVVH) for a complete hemodynamic and fluid rebalancing. In case kidney replacement therapy is

necessary in a long-term postoperative period, the change is made to intermittent dialysis (three times weekly).

7.6. Consider echocardiography as a main tool, together with PAC, to guide hemodynamic management, inotropic support, and fluid challenge

At first, we may exclude significant pericardial collection, assess left ventricle diastolic function of the new performing heart, related to its stiffness and hypertrophy, and think about which wedge pressure we are expected to find [21]. If the systolic function of the new heart is failing, we should exclude an acute graft rejection. Regarding the right ventricle, we must know the recipient preoperative pulmonary vascular resistances, if pre- or postcapillary pulmonary hypertension persists and if it is reversible with phosphodiesterase inhibitors.

RV dysfunction is identified early with a dilation of the right chambers, alteration of interventricular septum movement, and appearance of tricuspid valve insufficiency.

8. Respiratory weaning

A patient undergoing heart transplant should remain under mechanical ventilation until hemodynamic stability is ensured, lactate levels are stable, and immunosuppressive therapy is started. To protect the lungs, we have to limit peak pressures and use low tidal volumes (6 ml/kg) with adequate PEEP level (at least 3–5 cmH_2O).

However, disadvantages coming from permissive hypercapnia on the pulmonary vascular resistances and right ventricle afterload, myocardial function, and renal blood flow loads must be taken into account [16]. As a consequence, there are no universal evidences, but the choice must be tailored for the patient. The only certainty is we must avoid hypercapnia, hypoxia, and PEEP over 10 cmH_2O and keep peak pressure under 35–40 cmH_2O.

During mechanical ventilation, inhaled nitric oxide can be administered in order to reduce right PA pressures, pulmonary vascular resistances, and then right ventricle afterload, especially in the first 24 hours from CPB weaning at the maximum dosage of 20–40 ppm [17, 18]. Once mechanical ventilation is discontinued, inhaled nitric oxide can be substituted by iv or oral pulmonary vasodilators as sildenafil. The weaning criteria do not differ from those used in normal cardiosurgical patients, and the goal is the same: maintain adequate analgesia and sedation levels and wean the patient from the mechanical ventilation as soon as possible. If this is not possible, due to unstable hemodynamics, high inotropic score, respiratory failure, or neurological issues, a percutaneous dilatation tracheostomy will be packaged without further delay (within the first 5–7 days of mechanical ventilation).

Once the patient is awake and self-breathing and the LAP line is removed (generally 24–48 hours from surgery), the patient will need physiotherapy and mobilization.

Early feeding is important. It is initially given via NG tube (25–30 kcal/kg/day) and then self-feeding is achieved once there is no more gastrointestinal paresis.

9. Infection control

Standard prophylaxis is due to cefuroxime 2 g iv every 6 hours in the first 24 hours from heart transplantation (the first two boluses are given in the operating room, at the induction of general anesthesia and once CPB is started). The amount of antibiotic given in the ICU should be tailored for the patient's creatinine clearance, especially if the patient is not under renal filter. Further extension and change of antibiotic therapy should depend on microbiological results of the donor and on microbiological samples of the recipient once admitted in the ICU. Furthermore, in case of redo-operation with existing wound infection, the patient will receive vancomycin and meropenem as standard medication and vancomycin plasma levels should be tested daily. Obviously, due to the immunosuppressive therapy, transplanted patients are very prone to infections. Delivery of care should be done in sterile conditions and, besides standard iv antibiotic therapy, topical antifungal medications should be given in the early postoperative period.

10. Immunosuppressive therapy

A specific team is taking care of immunosuppressive therapy. It starts with 500 mg iv bolus of solumedrol at the CPB weaning. Once admitted in the ICU, the patient will receive 125 mg bolus of solumedrol every 8 hours, with a specific descending dose scheme.

Antithymocyte globulines (1.5 mg/kg iv) are usually given 4, 24, and 48 hours after the end of the transplantation. They will be adjusted based on eventual presence of high body temperature, bleeding, and thrombocytopenia. There are several possible immunosuppressive agents that will be tailored for the patient such as tacrolimus, cyclosporin A, everolimus, and mycophenolate.

11. Graft dysfunction

An international consensus conference in 2014 has classified the graft dysfunction into primary graft dysfunction (PDG) and secondary graft dysfunction (SGD). The first one occurs 24 h from heart transplant and can involve the left, the right ventricle, or both, with different degrees of dysfunction. Typical signs are severe deficit of systolic function, low cardiac output, and high filling pressures without evidence of acute graft rejection or cardiac tamponade. The SGD has a specific reason such as acute rejection, pulmonary hypertension, or surgical complications. Risk factors to develop PGD may be related to the recipient, donor, or technical factors [22].

Donor-related risk factors may be:

- Age (increased risk of 20% every decade)
- Sex (nearly doubled risk with female)

Recipient-related risk factors may be:

- High vasoactive or inotropic support (doubled risk)
- Uncontrolled diabetes (doubled risk)

Technical risk factors are:

- Warm ischemic time (= explant time + implant time); implant time was found to be a strong predictor of PGD.
- Resternotomy (it has been identified as a risk factor for severe PGD due to adherences and tissue fibrosis that can extend the explant time and increase the risk of infections).
- Prolonged CPB time, with subsequent systemic inflammatory response, vasoplegia, clotting and platelet dysfunction, leukocyte activation, free oxygen radical release, and larger amount of blood products given.

All these factors can increase the ischemic-reperfusion injury and the overall mortality [23].

The first step to treat a PDG is vasoactive and inotropic support. If it were not sufficient, an intra-aortic balloon pump (IABP) placement may help.

In case of very severe PGD, an extracorporeal membrane oxygenation (ECMO) becomes the only emergency treatment.

11.1. Anesthesia and intensive care management

11.1.1. For cardiac transplantation in pediatrics

Pediatric heart transplant represents a small subgroup (14%) of total cardiac transplant where the differences in anatomy and physiology make the surgical procedure and the management more complex and creates a unique scenario [24].

The management of pediatric patients undergoing cardiac transplantation differs from the adult patients because it requires a specific knowledge of physiology and physiopathology at different stages of growth, from the newborns through childhood up to adulthood.

This heterogeneous population with a wide range of age, genetic disorders, anatomical anomalies, and symptoms can be classified in four different groups based on the different etiology: 1—CHD (congenital heart disease); 2—DCM (dilated cardiomyopathy); 3—RETX (retransplant); 4—OTHER (**Table 7**) [25]; each of these has specific features.

11.1.2. Preoperative evaluation

The preoperative evaluation is an essential step in order to better analyze both the cardiac pathology and the possible related comorbidities.

Category (abbreviation)	Diagnoses in category
Congenital heart disease (CHD)	Congenital heart defects: HLHS-unoperated, with surgery, without surgery, valvular heart disease
Dilated cardiomyopathy (DCM)	Dilated myopathy due to alcohol, familiar, idiopathic, myocarditis, viral, postpartum, etc.
Retransplant (RETX)	Due to acute rejection, coronary artery disease, etc.
Other (OTHER)	Arrhythmogenic right ventricular dysplasia, cancer, coronary artery disease, myopathy-ischemia, hypertrophic cardiomyopathy, etc.

Table 7. Diagnosis for pediatric heart transplant.

Main preoperative features and examinations that must be considered are:

- Type of heart disease (CHD, DCM, RETX, and OTHER)
- Right heart catheterization (RHC): pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), pulmonary vascular resistances (PVR), and pulmonary hypertension etiology. Unfortunately, most patients with congenital heart defects have high PVR because of pulmonary vascular disease. However, the presence of systemic-to-pulmonary shunts, intra-pulmonary shunting, and caval pulmonary circulation does not allow a correct assessment of PVR. For these patients, RHC should be performed at 3–6 month interval in adult patients but is not advocated as routine surveillance in children unless a clinical change is noted [26].
- Numbers and types of previous operations (sternotomy and thoracotomy).
- Cyanotic congenital heart disease (secondary erythrocytosis, hyperviscosity, and coagulation deficit).
- Panel reactive antibody (PRA) identifies sensitized patients. It may be elevated in patients with allograft patch or with multiple redo-operations, due to the multiple transfusions. It may result in an increased risk of acute rejection [27].
- Variable anatomic substrates (isomerism, issues of situs, MAPCAs, aberrant right or left subclavian artery, and persistence of left superior vena cava).
- Previous venous or arterial thromboembolism (central venous catheter thrombosis).
- Previous neurological history: syncope, previous stroke, and cerebral arteriovenous malformation.
- Respiratory insufficiency: smoke, chronic obstructive pulmonary disease (COPD), anatomical anomalies of the pulmonary vessels, and presence of bronchial or pulmonary stents.
- Arrhythmias and previous ICD implantation.
- Liver disease: an evaluation of the patient's liver profile is extremely important. Chronic heart failure and in particular the univentricular heart physiology can lead to a liver dysfunction.

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Fontan-associated liver disease (FALD) is a liver dysfunction due to a chronic elevated central venous pressure, low cardiac output, persistent hypoxemia, and intrahepatic venous thrombosis. FALD can be expressed in different stages, from moderate hepatic congestion up to liver cirrhosis with portal hypertension. In several cases, liver function is preserved or is only slightly altered, with high international normalizer ratio (INR), low factor V levels, and elevated factor VIII levels [28].

- Kidney disease: acute or acute-on-chronic renal dysfunction.
- Coagulation anomalies may be present as result of chronic anticoagulation, liver disease, or as a result of cyanotic congenital heart disease (reduced levels of coagulation factors II, V, VII, IX, and X, accelerated fibrinolysis, and fibrinogen alterations).
- Gastrointestinal disorders: necrotizing enterocolitis in newborns or protein losing enteropathy (PLE), which is an excessive protein loss through the gastrointestinal tract that can be present after Fontan operation (even if its origins are poorly understood) [29]

12. Intraoperative management

The anesthetic management should consider that these patients have a poor cardiac reserve and that the premedication, general anesthesia, and the surgical manipulation after the sternotomy can lead to a destabilization of the hemodynamics.

Antibiotic therapy differs according to age and weight and background of both the donor and recipient (**Tables 8** and **9**).

Immunosuppression is started 1 hour before going to the operating room: thymoglobulin 1 mg/kg/12 h and methylprednisolone 7–10 mg/kg (max. 125 mg).

Premedication is performed, according to clinical condition, with low doses of benzodiazepines (midazolam 0.3–0.5 mg/kg orally or rectal in neonate) avoiding excessive sedation and consequently hypercapnia.

It is well known that in newborns and infants, placing an invasive monitoring before induction of anesthesia is not always possible; therefore, it is essential to have a noninvasive monitoring before starting the drug administration.

General anesthesia is induced by inhalation of sevoflurane/desflurane in newborns and infants and by intravenous injections of midazolam 0.3–0.5 mg/kg, fentanyl 2–4 mcg/kg, rocuronium 1 mg/kg, and propofol 2–4 mg/kg in adults and children. Moreover, for continuous infusion of the anesthesia, propofol 4–6 mg/kg/h in adults, while midazolam 0.2 mg/kg/h and fentanyl 2 mcg/kg/h in newborns and children are recommended. After induction, hydrocortisone 10–20 mg/kg is infused.

In all patients, regional cerebral monitoring is achieved with the use of near infrared spectroscopy (NIRS).

Newborn < 1200 g	20 mg q 12 h
Newborn ≥ 1200 g < 7 days of life	20 mg q 12 h
Newborn ≥ 1200 gr > 7 days of life	20 mg q 8 h
Infants and children	100 mg/kg/24 h in 3 doses

Table 8. Antibiotic therapy (cefazolin).

Newborn < 1200 g	5 mg q 12 h
Newborn = 2000 g < 7 days of life	5 mg q 12 h
Newborn = 2000 g > 7 days of life	5 mg q 8 h
Newborn > 2000 g < 7 days of life	5 mg q 8 h
Newborn > 2000 g > 7 days of life	5 mg q 6 h
Infants and children	15/40 mg/kg/24 h in 3–4 doses
In case of allergy to beta-lactams, clindamycin is administered.	

Table 9. Antibiotic therapy (clindamycin).

Different conditions may complicate the venous central catheter placing as: anatomical variables, possible occlusion due to previous repeated catheterizations, and previous positioning of central lines. In these cases, the echo-guided assistance is recommended. In smaller patients or in occluded jugular/subclavian veins, femoral veins can be also used. The sizing of the catheter and the numbers of lumens used depend on the weight and age of the patients. When possible, a pulmonary artery catheter (PAC) must be placed into the superior vena cava and then correctly repositioned by the cardiac surgeon before removing the aortic cross-clamp. In newborns and infants, placing PAC may be problematic or impossible due to the size of the patient. In these cases, it is possible to use the central venous oxygen saturation ($SCvO_2$) as a surrogate of SVO_2 even if the results are controversial [30].

As an alternative, the left atrial pressure (LAP) can be monitored with the insertion of a catheter through the right superior pulmonary vein.

Transesophageal echocardiography (TEE) is always recommended for a correct evaluation of biventricular function, after the CPB weaning, accordingly with the patient's weight.

After induction of the anesthesia, the ventilation management requires extreme attention since the hypoxia and the hypercapnia can increase PVR leading to a low cardiac output syndrome. In case of hypotension, before infusing, a bolus of colloid is essential to secure the correct ventilation, avoiding respiratory acidosis.

The majority of patients with CHD undergoing cardiac transplantation are reoperation candidates, so it is important to put into account long operative times, due to dissection of the adhesions and complex reconstruction of the anatomy.

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12.1. CPB and weaning

CPB management can be extremely complex and differs according to the patient's weight and age. The main aim is to maintain a correct medium arterial pressure (MAP) and a correct DO_2/VO_2 ratio.

Sometimes, this is difficult to be achieved, due to the possible presence of anatomical extracardiac shunts. The dose of unfractionated heparin for the CPB is 200 U/kg in newborns and infants or 300 U/kg in the child and adult, in order to have an ACT > 400 s. In case of reduced response to heparin, administration of ATIII at a dose of 100 mg/kg is recommended. Furthermore, in case of HIT or low response to heparin, direct thrombin inhibitors are administered (bivalirudin and argatroban) as in adult patients. After the aortic cross-clamp is removed, methylprednisolone is administered with the dose of 7–10 mg/kg (max. 125 mg/kg).

Weaning from CPB always requires inotropic support and the right ventricular failure is a possible complication, characterized by restrictive pattern that can be managed by inhaled nitric oxide (5–40 ppm) and inotropic support (milrinone 0.3–0.75 mcg/kg/min, adrenaline 0.02–0.1 mcg/kg/min, and isoprenaline 0.1–1 mcg/kg/min) in order to vasodilate the pulmonary circulation improving biventricular contractility and providing a chronotropic effect if bradycardia occurs. It is extremely important to keep normal PVR by providing a proper ventilation, avoiding hypoxia and maintaining normocapnia.

Once the patient has been weaned form CBP, the vigilance or $SCvO_2$ can monitor the hemodynamic profile and biventricular function can be evaluated with echocardiogram.

However, in case of poor CO, despite maximal inotropic support and correct ventilation, we should consider the support via an extracorporeal membrane oxygenation (ECMO).

12.2. Anticoagulation and hemostasis

At the end of CPB, heparin is antagonized with a ratio 2:1 or 1:1 with protamine based on the ACT values. Antifibrinolytic agents are administrated at the dosage of 50 mg/kg (25 mg/kg after general anesthesia induction and 25 mg/kg at the end of CPB). Severe bleeding is not uncommon in pediatric population. Main reasons of postoperative bleeding are previous heart surgery, cyanotic congenital heart disease, immature coagulation system, and excessive hemodilution due to the disproportionate ratio of CPB circuit volume to patient blood volume, especially in newborns and infants. Correct coagulation management is always achieved through ROTEM.

12.3. Intensive care

During the postoperative intensive care course, close monitoring of hemodynamic parameters, inotropes, ventilation, and acid base balance is required to predict pulmonary hypertension, biventricular failure, and LCOS. Normalization of the oxygenation and ventilation is the primary goal in these patients and ventilation support must be discontinued as soon as possible. The antibiotic therapy will be set according to microbiological surveillance. Immunotherapy during the postoperative course is managed by the cardiologist as follows: methylprednisolone, thymoglobulin, tacrolimus, and mycophenolate.

12.4. Peculiar problems

In the postoperative setting, the main problems for pediatric patients are comorbidities related to chronic decompensation and univentricular physiology.

- Cyanotic congenital heart disease: patients with long standing hypoxemia often develop severe alteration of whole blood viscosity and alteration of coagulation profiles with high risk of postoperative bleeding [31].
- Plastic bronchitis: it is a rare complication of univentricular physiology characterized by the formation of exudative airway casts that can occlude airways and cause respiratory failure. The etiology is still not well identified, but it seems to relate to an increased central venous pressure or lymphatic drainage alterations [32].
- Protein losing enteropathy (PLE): it is defined as a possible complication of the univentricular circulation. It can arise after the Fontan operation (5–15% of the patients) [33]. It is characterized by the abnormal loss of proteins into the enteral lumen, which results in hypoproteinemia and hypoalbuminemia. This leads to an increase of lymphatic drainage and a dilation of intestinal lymphatic system with an impaired fat absorption resulting in steatorrhea. Moreover, the hypoproteinemia may result also in ascites, peripheral edema, and pleural/pericardial effusion. Therapy consists of diuretics, corticosteroids, and albumin supplementation.

Abbreviations

BIS	bispectral index
CI	cardiac index
CO	cardiac output
COPD	chronic obstructive pulmonary disease
CPB	cardiopulmonary bypass
CVC	central venous catheter
CVP	central venous pressure
CVVH	central venovenous hemofiltration
DLCO	carbon monoxide lung diffusion
ECMO	extracorporeal membranous oxygenation
HIT	heparin-induced thrombocytopenia
IABP	intra-aortic balloon pump
ICD	implantable cardioverter defibrillator

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ISVR	indexed systemic vascular resistance
LAP	left atrial pressure
LV	left ventricle
LVAD	left ventricular assist device
NGT	nasogastric tube
NO	nitrogen oxide
OCS	organ care system
PAC	pulmonary artery catheter
PAP	pulmonary arterial pressure
PCWP	pulmonary capillary wedge pressure
PEEP	positive end expiratory pressure
PPM	parts per millions
PGD	primary graft dysfunction
PVR	pulmonary vascular resistance
RAP	right atrial pressure
RV	right ventricle
SIRS	systemic inflammatory response syndrome
SVR	systemic vascular resistance
TACO	transfusion-associated circulatory overload
TPG	transpulmonary pressure gradient
TRALI	transfusion-associated lung injury
TV	tidal volume
VAD	ventricular assist device
WU	wood unit

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